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Antithrombin alternatives in STEMI

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Restoration of effective myocardial perfusion by percutaneous coronary intervention (PCI) in ST-segment elevation myocardial infarction (STEMI) is a life-saving therapy. Selection of the optimum anticoagulation regimen to support primary PCI is essential. Unfractionated heparin, low molecular weight heparins, the factor Xa inhibitor fondaparinux, and the direct thrombin (factor IIa) inhibitor bivalirudin have all been studied in this setting. These agents have different mechanisms of action, binding specificity, pharmacokinetic and pharmacodynamic consistency, risks of heparin-induced thrombocytopenia, and half-lives (table). Paradoxically, unfractionated heparin, low molecular weight heparins, and fondaparinux activate platelets by binding to the platelet glycoprotein IIb/IIIa integrin receptor.[1] By inhibiting the aggregation of activated platelets, glycoprotein IIb/IIIa inhibitors reduce the rate of ischaemic complications when primary PCI is done with unfractionated heparin, at the cost of increased bleeding.[2] Fondaparinux as a stand-alone agent during primary PCI results in an unacceptably high rate of catheter thrombosis,[3] and is not recommended. Conversely, bivalirudin reduces thrombin generation and both thrombin-dependent and collagen-dependent platelet activation.[4] In the HORIZONS-AMI trial,[5] bivalirudin during primary PCI substantially decreased bleeding and thrombocytopenia while suppressing ischaemic complications compared with unfractionated heparin plus glycoprotein IIb/IIIa inhibitors, thereby reducing all-cause and cardiac mortality. These findings were replicated in a registry of more than 100 000 people.[6] These data emphasise the importance of both platelet and thrombin inhibition during PCI, and the delicate balance between safety and efficacy that has to be achieved for optimum outcomes.

Low molecular weight heparin has been increasingly studied as an anticoagulant during PCI. The most widely used low molecular weight heparin is enoxaparin, which has shown varying safety and efficacy compared with unfractionated heparin in previous trials, depending on the clinical setting and mode of administration. In the ExTRACT-TIMI-25 trial,[7] intravenous followed by subcutaneous enoxaparin reduced the 30-day composite rate of death or reinfarction, but increased major bleeding in patients with STEMI receiving fibrinolysis. In the SYNERGY trial,[8] subcutaneous enoxaparin compared with unfractionated heparin did not reduce the 48-h

	Unfractionated heparin	Enoxaparin	Fondaparinux	Bivalirudin
Factor Xa:IIa inhibition	1:1	3–4:1	100% Xa	100% IIa
Action independent of antithrombin	No	No	No	Yes
Non-specific binding	Yes	Partial	No	No
Variable PK/PD measures	Yes	Less	No	No
Inhibits fibrin-bound thrombin	No	No	No	Yes
Activates or aggregates platelets	Yes	Yes	Yes	Inhibits
Half-life	Variable with dose, about 60 min IV	300 min SC; 90–120 min IV (0·5 mg/kg)	17 h SC	25 min IV
PF-4 complexing and risk of HIT	Yes	Reduced	Low	No

PK/PD=pharmacokinetic and pharmacodynamic. PF-4=platelet factor 4. HIT=heparin-induced thrombocytopenia. SC=subcutaneous. IV=intravenous.

Table: **Comparative properties of unfractionated heparin, enoxaparin, fondaparinux, and bivalirudin**

rate of death or myocardial infarction in patients with non-ST-segment elevation acute coronary syndromes treated with an invasive strategy, and resulted in increased bleeding. Conversely, 0·5 mg/kg intravenous enoxaparin resulted in reduced rates of major bleeding and similar ischaemic outcomes in stable patients undergoing elective PCI in the STEEPLE trial.[9]

In *The Lancet*, Gilles Montalescot and colleagues[10] report the results of the ATOLL trial, in which 910 patients with STEMI were randomly assigned to unfractionated heparin versus 0·5 mg/kg intravenous enoxaparin before primary PCI. Enoxaparin did not significantly reduce the 30-day composite primary endpoint of death, complication of myocardial infarction, procedure failure, or major bleeding (relative risk [RR] 0·83, 95% CI 0·68–1·01, p=0·06), and nor did it reduce major bleeding alone (RR 0·92, 95% CI 0·51–1·66, p=0·79), but did reduce the main secondary endpoint of death, recurrent acute coronary syndrome, or urgent revascularisation (RR 0·59, 0·38–0·91, p=0·015). How should these results inform clinical practice?

ATOLL, led by a highly qualified investigator group, has numerous strengths. Exclusion of antithrombin therapy before enrolment provides clarity in the effect of the randomised treatments. Randomisation and treatment were initiated by the mobile emergency medical service in 71% of patients, which, although not yet possible in most locations, is clearly forward-looking. Intravenous enoxaparin is also a convenient, inexpensive treatment. Several caveats of the study deserve mention, however. In view of the small sample size, to achieve adequate power the primary endpoint was an atypical composite of 12 events, some clinical, some angiographic, and some procedural. Since the principal hypothesis tested was not met, the results of secondary endpoints are hypothesis-generating rather than conclusive, needing additional study before informing labelling or guidelines with confidence. Radial access was used in more than two-thirds of patients, a strategy which minimises access-related bleeding. Equivalence in haemorrhagic complications between the two agents thus cannot be assumed for the femoral approach.

Without a large comparative randomised trial, bivalirudin (with use of glycoprotein IIb/IIIa inhibitors reserved for refractory thrombotic complications) remains the gold standard to optimise outcomes during primary PCI, with a class IB level of evidence for use during primary PCI in both European and US guidelines. An unfractionated heparin bolus can be administered in the emergency department (or earlier) before initiation of bivalirudin in the catheterisation laboratory just before PCI without loss of safety or efficacy—a regimen consistent with most systems of care.[11] Can smarter pharmacotherapy decisions further improve primary PCI outcomes? Stent implantation in ruptured plaques is inherently thrombogenic, and high rates of early and late stent thrombosis have been reported in STEMI.[5] Bivalirudin monotherapy has been associated with a 1% increase in stent thrombosis within the first 5 h in STEMI compared with heparin plus glycoprotein IIb/IIIa inhibitors (although after the first 24 h stent thrombosis rates were decreased in bivalirudin-treated patients).[5] Potent platelet ADP receptor inhibition with prasugrel and ticagrelor reduces thrombotic events (including stent thrombosis) in acute coronary syndromes, although bleeding concerns have restricted their widespread adoption.[12,13] In view of the favourable bleeding profile of bivalirudin,[5] the early administration of prasugrel or ticagrelor before primary PCI with bivalirudin might be highly synergistic; surprisingly, such a combination has not yet been formally studied. In appropriate patients in whom the likelihood of atherothrombotic complications exceeds the risk of major bleeding, harnessing the potency of these agents could further improve survival in acute coronary syndromes.[14]

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Why not screen for subclinical atherosclerosis?

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Although preventable, atherosclerotic cardiovascular disease remains a leading global cause of death and disability.[1] Despite, or rather because of, major improvements in survival after myocardial infarction and stroke, the prevalence, burden, and costs of the disease continue to rise.[2] In high-income countries, cardiovascular disease is the most costly disease—more costly than all cancers combined.[3] Furthermore, sudden and unexpected death is still a common first manifestation of cardiovascular disease.[3] The only effective approach to restrict this undue loss of life, and the health burden and use of resources, is to prevent the disease from developing in the first place—ie, primary prevention. Public health initiatives are important but so is personalised prevention for those at highest risk.

Causal risk factors for cardiovascular disease constitute important therapeutic targets, but their usefulness as predictors for developing the disease is limited.[4,5] Most heart attacks and strokes occur in people at average risk-factor level who are misclassified by traditional risk-factor scoring, as low or intermediate risk.[6] Conversely, others are misclassified as high risk and advised to take drugs to reduce their risk factor(s), drugs that are not needed. These facts remind us that, although exposure to causal factors is important, susceptibility to these factors and the disease in question might be more important. Despite great promise, genetic testing for susceptibility has not proven useful for risk stratification.[7]

Atherosclerosis develops silently over decades before symptoms eventually occur, offering unique opportunities for timely detection and personalised prevention. Subclinical atherosclerosis can be detected and quantified non-invasively, to show the cumulative effect of all risk and susceptibility factors combined—known and unknown.[4,5] Three measures of disease burden have proven useful for

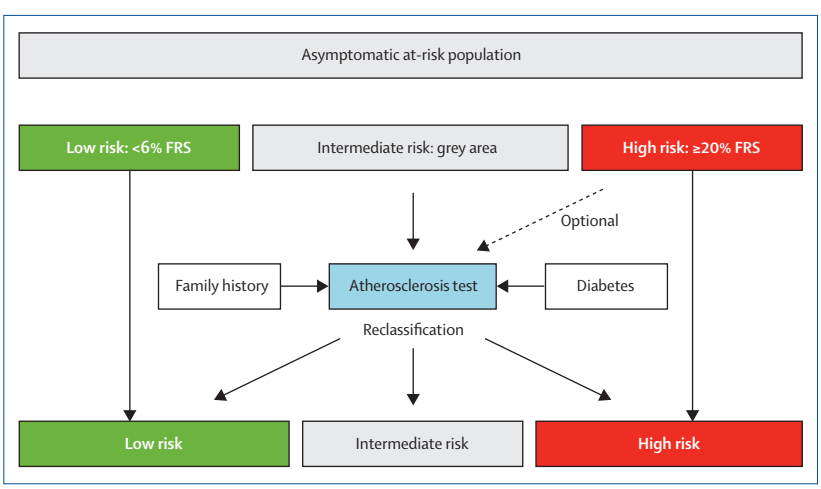

Figure: **Flow chart of how non-invasive tests for subclinical atherosclerosis can be implemented in cardiovascular risk assessment**
FRS=Framingham risk score. Inspired by SHAPE (Society for Heart Attack Prevention and Eradication),[4,5] 2010 ACCF/AHA (American College of Cardiology Foundation/American Heart Association) cardiovascular risk-assessment guideline,[8] and 2010 appropriate-use criteria for cardiac CT.[9]

Intravenous enoxaparin or unfractionated heparin in primary percutaneous coronary intervention for ST-elevation myocardial infarction: the international randomised open-label ATOLL trial

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Summary

Background Primary percutaneous coronary intervention (PCI) for ST-elevation myocardial infarction has traditionally been supported by unfractionated heparin, which has never been directly compared with a new anticoagulant using consistent anticoagulation and similar antiplatelet strategies in both groups. We compared traditional heparin treatment with intravenous enoxaparin in primary PCI.

Methods In a randomised open-label trial, patients presenting with ST-elevation myocardial infarction were randomly assigned (1:1) to receive an intravenous bolus of 0·5 mg/kg of enoxaparin or unfractionated heparin before primary PCI. Wherever possible, medical teams travelling in mobile intensive care units (ambulances) selected, randomly assigned (using an interactive voice response system at the central randomisation centre), and treated patients. Patients who had received any anticoagulant before randomisation were excluded. Patients and caregivers were not masked to treatment allocation. The primary endpoint was 30-day incidence of death, complication of myocardial infarction, procedure failure, or major bleeding. The main secondary endpoint was the composite of death, recurrent acute coronary syndrome, or urgent revascularisation. Analysis was by intention to treat. This trial is registered at ClinicalTrials.gov, number NCT00718471.

Findings 910 patients were assigned to treatment with enoxaparin (n=450) or unfractionated heparin (n=460). The primary endpoint occurred in 126 (28%) patients after anticoagulation with enoxaparin versus 155 (34%) patients on unfractionated heparin (relative risk [RR] 0·83, 95% CI 0·68–1·01, p=0·06). The incidence of death (enoxaparin, 17 [4%] *vs* heparin, 29 [6%] patients; p=0·08), complication of myocardial infarction (20 [4%] *vs* 29 [6%]; p=0·21), procedure failure (100 [26%] *vs* 109 [28%]; p=0·61), and major bleeding (20 [5%] *vs* 22 [5%]; p=0·79) did not differ between groups. Enoxaparin resulted in a significantly reduced rate of the main secondary endpoint (30 [7%] *vs* 52 [11%] patients; RR 0·59, 95% CI 0·38–0·91, p=0·015). Death, complication of myocardial infarction, or major bleeding (46 [10%] *vs* 69 [15%] patients; p=0·03), death or complication of myocardial infarction (35 [8%] *vs* 57 [12%]; p=0·02), and death, recurrent myocardial infarction, or urgent revascularisation (23 [5%] *vs* 39 [8%]; p=0·04) were all reduced with enoxaparin.

Interpretation Intravenous enoxaparin compared with unfractionated heparin significantly reduced clinical ischaemic outcomes without differences in bleeding and procedural success. Therefore, enoxaparin provided an improvement in net clinical benefit in patients undergoing primary PCI.

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Introduction

Anticoagulation during primary percutaneous coronary intervention (PCI) for ST-elevation myocardial infarction (STEMI) has traditionally been supported by unfractionated heparin, largely on the basis of evidence extrapolated from studies of elective angioplasty. The Joint STEMI/PCI Guidelines Update[1] produced by the American College of Cardiology, American Heart Association, and Society for Cardiovascular Angiography and Interventions as well as guidelines from the Task Force on Myocardial Revascularization of the European Society of Cardiology[2] continue to afford unfractionated heparin a class 1 recommendation for this indication while recognising that evidence is limited (level of evidence C).

In recent studies with new anticoagulants in primary PCI, such as OASIS-6 (Organization for the Assessment of Strategies for Ischemic Syndromes),[3] the subgroup undergoing primary PCI had no clinical benefit with the indirect factor Xa inhibitor fondaparinux and had an excess of catheter thrombosis. In the HORIZONS-AMI (Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction) trial,[4] the direct thrombin inhibitor bivalirudin alone, as compared with

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unfractionated heparin plus glycoprotein IIb/IIIa inhibitors, significantly reduced 30-day rates of major bleeding and mortality, but there was increased stent thrombosis within the first 24 h (not at 30 days; class I-B recommendation). Most noteworthy is that in both studies a large proportion of patients received a full dose of unfractionated heparin before randomisation, precluding a real comparison between two anticoagulant drugs. Therefore, there has thus far been no comparison between two anticoagulants in primary PCI that is not confounded by prerandomisation anticoagulation therapy or differing antiplatelet strategy, which can both affect clinical outcomes.[2,3,5–9]

Subcutaneous enoxaparin provides more predictable anticoagulation than does unfractionated heparin[10] and has an established role in the management of non-ST-elevation acute coronary syndromes and in STEMI treated with thrombolysis.[6,11,12] The excess bleeding reported in these studies might have been due to the prolonged treatment with therapeutic doses of subcutaneous enoxaparin or the concomitant administration of unfractionated heparin, or both. The clinical usefulness of intravenous enoxaparin has been shown recently in elective PCI at a dose of 0·5 mg/kg, which provides immediately an adequate level of anticoagulation with the short half-life of the drug, adapted to interventional procedures.[13–17] Enoxaparin was also compared with unfractionated heparin in several non-randomised studies that reported significantly better results with enoxaparin in PCI of STEMI,[18–22] but there has been no randomised evaluation of intravenous enoxaparin in primary PCI.

The ATOLL (Acute Myocardial Infarction Treated with Primary Angioplasty and Intravenous Enoxaparin or Unfractionated Heparin to Lower Ischemic and Bleeding Events at Short- and Long-term Follow-up) study is a randomised comparison of intravenous enoxaparin and unfractionated heparin in primary PCI, excluding patients who received any anticoagulation before randomisation and requiring no crossover from one drug to the other during or after the procedure.

Methods

Participants

ATOLL was an international, randomised, open-label trial evaluating intravenous enoxaparin versus intravenous unfractionated heparin in patients undergoing primary PCI for STEMI. Patients were enrolled at 64 sites in four countries (Austria, France, Germany, USA). Wherever possible, medical teams travelling in mobile intensive care units (ambulances) were regarded as study sites and were allowed to select, randomly assign, and treat patients. STEMI was defined as continuous ischaemic chest pain for at least 20 min plus an ST elevation of 2 mm or more in two or more contiguous precordial electrocardiogram (ECG) leads, or greater than 1 mm ST elevation in two or more contiguous limb ECG leads, or new left bundle branch block. Patients with STEMI were eligible to enter the study if they were older than 17 years (without an upper age limit) and had an indication for primary PCI within 12 h of symptom onset. Patients presenting between 12 h and 24 h of symptom onset with persistent ischaemic symptoms or persistent or recurrent ST elevation on ECG, or both, and an indication for primary PCI were also eligible, as were patients with shock or cardiac arrest (<10 min) in the setting of STEMI.

In both groups, the use of concomitant drugs, including glycoprotein IIb/IIIa inhibitors, was at the discretion of the treating clinicians. Patients who received anticoagulant of any type (unfractionated heparin, low molecular weight heparin, fondaparinux, warfarin) before randomisation were excluded. Other major exclusion criteria were the administration of thrombolytic agents for the present episode, a short life expectancy, childbearing potential, and known contraindications to treatment with aspirin, thienopyridines, or heparins. Written informed consent was required from all patients. The study was undertaken according to the Declaration of Helsinki and in keeping with local regulations. The protocol was approved by national or institutional ethical review boards as required in each participating country.

Randomisation and masking

Anticoagulation-naive patients who were eligible for the study were randomly assigned to receive an intravenous bolus of either enoxaparin or unfractionated heparin in an open-label fashion. Study drug was always administered before sheath insertion and before transfer whenever possible. Patients were assigned via an interactive voice response system at the central randomisation centre, in a 1:1 ratio. Randomisation was stratified according to centre and random permuted blocks were used. We used the standard operating procedure of the clinical research department to avoid any knowledge of the randomisation list by the participants of the trial. All patients received aspirin (75–500 mg/day), thienopyridines, and glycoprotein IIb/IIIa inhibitors according to local practice.

Procedures

All patients assigned to the enoxaparin group received a similar intravenous bolus of 0·5 mg/kg enoxaparin without anticoagulation monitoring. This dose has been shown to provide immediately an anti-Xa level of about 0·9 IU/mL with an elimination half-life of antifactor Xa activity ranging from 1 h to 2 h, which is three-to-four times shorter than the half-life obtained with subcutaneous injections.[13,14,16] When procedures were prolonged by more than 2 h, or if the investigator needed stronger anticoagulation to manage per-procedural complications, an additional intravenous bolus of enoxaparin (at half the original dose, 0·25 mg/kg) was allowed.[13,16] No adjustment of the intravenous dose was

recommended based on renal function.[13,16,23] After primary PCI, prolongation of anticoagulation was left to the physician's discretion; when full anticoagulation was clinically indicated (eg, atrial fibrillation, left-ventricular thrombus, intra-aortic balloon pump), anticoagulation was done with enoxaparin (1 mg/kg subcutaneous twice a day with dose adjustment to renal function) until replacement by a vitamin K antagonist when necessary. Otherwise, when anticoagulation was continued, prophylactic doses were recommended (enoxaparin 40 mg subcutaneously once a day).

According to current recommendations, patients randomly assigned to unfractionated heparin who were not receiving concurrent glycoprotein IIb/IIIa inhibitors were given an initial intravenous bolus of 70–100 IU/kg; patients who received concurrent glycoprotein IIb/IIIa inhibitors were given an initial bolus of 50–70 IU/kg.[2,24] During the procedure, additional boluses were allowed to maintain an activated clotting time of 300–350 s without glycoprotein IIb/IIIa inhibitors, or 200–300 s with glycoprotein IIb/IIIa inhibitors. After the procedure, prolongation of anticoagulation was at the physician's discretion. If continued, prophylactic anticoagulation was recommended with intravenous or subcutaneous unfractionated heparin unless full anticoagulation was clinically indicated.

Radial access was allowed, as was use of arterial closure devices after femoral access. Femoral sheath removal in the absence of closure devices was authorised with an activated clotting time between 150 s and 180 s in the unfractionated heparin group,[2,24] and immediately after the end of PCI in the enoxaparin group.[16] All technical aspects concerning mechanical reperfusion, thrombectomy, choice of stents, or haemodynamic support were left to the discretion of the treating clinicians. Clinical follow-up took place at 30 days (within 2 days).

The primary endpoint of the trial was the occurrence of the composite endpoint of death, complication of myocardial infarction, procedure failure, or major bleeding. Death was defined as all-cause mortality within 30 days. Complication of myocardial infarction was defined as resuscitated cardiac arrest, recurrent acute coronary syndrome, urgent revascularisation, stroke, or peripheral or pulmonary embolism within 30 days. Procedure failure was defined as definite stent thrombosis (according to the Academic Research Consortium definition[25]), bailout use of glycoprotein IIb/IIIa inhibitors for an angiographic or a clinical complication occurring after guidewire crossing of the lesion, non-TIMI 3 flow, or ST-segment resolution of less than 50% after PCI. Non-coronary-artery-bypass-graft (CABG) major bleeding during hospital stay was defined according to the STEEPLE definition[16] as fatal bleeding, documented retroperitoneal, intracranial, or intraocular bleeding, bleeding resulting in haemodynamic compromise requiring specific treatment,

	Enoxaparin (n=450)	Unfractionated heparin (n=460)
Patient characteristic		
Age		
Median (years)	59 (52–71)	60 (52–70)
≥75 years	85 (19%)	80 (17%)
Range (years)	28–91	24–93
Women	97 (22%)	101 (22%)
Weight (kg)	75·0 (67·0–85·0)	75·5 (67·0–86·5)
Medical history		
Present smoking	199 (44%)	218 (47%)
Diabetes mellitus, all	63 (14%)	69 (15%)
Diabetes mellitus, insulin-requiring	58 (13%)	65 (14%)
Dyslipidaemia	180 (40%)	184 (40%)
Hypertension	205 (46%)	207 (45%)
Previous CABG	4 (1%)	6 (1%)
Previous MI	28 (6%)	44 (10%)
Previous PCI	33 (7%)	53 (12%)
Previous PAD	16 (4%)	22 (5%)
Previous stroke	12 (3%)	10 (2%)
Previous cancer	25 (6%)	28 (6%)
Respiratory insufficiency	9 (2%)	18 (4%)
Killip class II, III, or IV	35 (8%)	51 (11%)
Place of randomisation		
Mobile emergency medical service	318 (71%)	325 (71%)
Hospital emergency room	19 (4%)	26 (6%)
Cardiac care unit	20 (4%)	17 (4%)
Catheterisation laboratory	93 (21%)	92 (20%)
Time from symptom onset to randomisation		
Median (min)	153 (89–290)	139 (86–277)
≤6 h	345 (77%)	382 (83%)
≤12 h	407 (90%)	423 (92%)
Time from randomisation to sheath insertion (min)	43 (22–58)	42 (22–57)
Haemodynamic failure before sheath insertion		
Cardiogenic shock, Killip class IV	13 (3%)	13 (3%)
Resuscitated cardiac arrest	8 (2%)	13 (3%)
Heart rate (beats per min)	75 (65–85)	75 (66–88)
Systolic blood pressure (mm Hg)	139 (120–156)	140 (120–159)
Concomitant treatments		
Aspirin	433 (96%)	439 (95%)
Clopidogrel		
Any	418 (93%)	428 (93%)
Loading dose	..	..
Median (mg)	600 (300–675)	600 (300–675)
≤300 mg*	168 (37%)	171 (37%)
>300 mg and ≤600 mg	174 (39%)	172 (37%)
>600 mg and ≤900 mg	101 (22%)	113 (25%)
>900 mg	7 (2%)	4 (1%)
Maintenance dose during hospitalisation (mg)	75 (75–150)	75 (75–150)
Maintenance dose after discharge (mg)	75 (75–75)	75 (75–75)
Glycoprotein IIb/IIIa inhibitors		
Any	347 (77%)	382 (83%)
Abciximab	301 (67%)	317 (69%)

(Continues on next page)

	Enoxaparin (n=450)	Unfractionated heparin (n=460)
(Continued from previous page)		
Eptifibatide	45 (10%)	57 (12%)
Tirofiban	2 (<1%)	8 (2%)
β blocker	398 (88%)	385 (84%)
Statin	401 (89%)	394 (86%)
ACE inhibitor or ARB	348 (77%)	346 (75%)
Procedure characteristics		
Time from sheath insertion to sheath removal (min)	40 (25–65)	40 (30–65)
Arterial access		
Radial	309 (69%)	305 (66%)
Other or multiple access	141 (31%)	155 (34%)
Angiographic findings, culprit artery†		
Left main trunk	7 (2%)	4 (1%)
Left anterior descending artery	162 (43%)	157 (40%)
Circumflex artery	40 (10%)	66 (17%)
Right coronary artery	171 (45%)	162 (41%)
Coronary bypass graft	0	2 (1%)
Revascularisation		
Thromboaspiration†	184 (48%)	173 (44%)
Stent implanted†	364 (96%)	366 (94%)
Drug-eluting stent‡	64 (18%)	66 (18%)
CABG surgery	5 (1%)	3 (1%)

Data are n (%), median (IQR), or range. CABG=coronary artery bypass graft. MI=myocardial infarction. PCI=percutaneous coronary intervention. PAD=peripheral artery disease. ACE=angiotensin-converting enzyme. ARB=angiotensin receptor blocker. *Including 58 and 60 patients without any loading dose in enoxaparin and heparin groups, respectively. †In PCI patients (381 enoxaparin, 391 heparin). ‡In stented patients (364 enoxaparin, 366 heparin).

Table 1: **Baseline and procedure characteristics**

bleeding requiring surgical intervention or decompression of a closed space to control the event, any transfusion, or a haemoglobin drop of 30 g/L or more.

The main secondary efficacy endpoint was the composite of any death, recurrent acute coronary syndrome, or urgent revascularisation and was the first endpoint tested after the primary endpoint. Other prespecified efficacy objectives included death or complication of myocardial infarction, death, or resuscitated cardiac arrest, and each component of the primary objective. The main safety objective was non-CABG-related major bleeding during hospital stay. Another secondary safety objective was the composite of major and minor bleeding during hospital stay (STEEPLE definitions).[16]

See Online for webappendix

The net clinical benefit endpoint was prespecified as the combination of death, complication of myocardial infarction, or major bleeding. All cinefilms were read in a central angiographic core laboratory by two readers who were unaware of the treatment assignments. All ECGs were also blindly analysed in a central ECG core laboratory. All clinical events were adjudicated by an independent clinical events committee that was unaware of the treatment assignments.

Statistical analysis

A sample size of 850 patients was initially calculated on the basis of an incidence of the primary composite endpoint at 30 days in the unfractionated heparin group of 30%. The superiority design of the study had 80% power to detect the difference between a group unfractionated heparin proportion, π_1, of 0·30 and a group enoxaparin proportion, π_2, of 0·216 (relative risk [RR] reduction 28%, odds ratio 0·643). A dropout rate of 8% was expected, and the final sample size was adjusted accordingly to 910 patients. The possibility of a sample size reassessment after 75% recruitment on the basis of a conditional power calculation was also allowed by the protocol (Addplan software), but no change in sample size was done after this analysis.

All analyses included the intention-to-treat population (all patients randomly assigned to treatment groups, analysed as randomised). Analysis of observed cases and multiple imputation procedures for missing values were done for sensitivity analysis of the primary and main secondary criteria (Proc MI SAS). χ^2 test for frequency comparisons and log-rank for survival analysis were used (SAS version 9.2). All subgroup analyses presented were prespecified. An independent data and safety monitoring board periodically reviewed the data.

The trial is registered at ClinicalTrials.gov, number NCT00718471.

Role of the sponsor and of the funding source

The trial was led by the non-profit Academic Research Organization ACTION (Allies in Cardiovascular Trials, Initiatives and Organized Networks), located at Pitié-Salpêtrière Hospital (University Paris 6, Paris, France). The trial was sponsored and partly funded by the Direction de la Recherche Clinique at Assistance Publique-Hôpitaux de Paris (AP-HP). An unrestricted research grant was obtained from Sanofi-Aventis, which had no involvement in the design of the study, site selection, data collection, analysis, or writing of the report. The trial was designed and the protocol written by the principal investigator and modified and approved by the steering committee (see webappendix). Data were gathered by Pierrel Research-Hyperphar (Milano, Italy) using electronic case report forms. Data were maintained at the Unité de Recherche Clinique (Lariboisière Hospital, University Paris 7), which independently undertook all statistical analyses. The principal investigator had unrestricted access to the data after the database was locked, prepared the first draft of the report, and controlled the decision to publish. The steering committee vouches for the integrity and completeness of the data and the statistician for the accuracy of the data analysis.

Results

Between July, 2008, and January, 2010, 910 patients were randomly assigned to receive enoxaparin (450 patients)

or unfractionated heparin (460 patients) before primary PCI. Diagnosis of STEMI, randomisation, and initial treatment were done in the field by the mobile emergency medical service in 643 (71%) cases. Baseline characteristics were well balanced between treatment groups (table 1). Patients were mainly male (n=712, 78%), 165 (18%) were older than 75 years, 86 (9%) had signs of heart failure, 21 (2%) had presented with a resuscitated cardiac arrest, and 26 (3%) were in shock at the time of randomisation. After emergency angiography, significant left main coronary disease was identified in 43 (6%) and triple vessel disease in 145 (19%) patients. 775 (85%) patients underwent primary PCI (figure 1).

Procedural characteristics were much the same in both treatment groups (table 1). The infarct-related vessel was the left main trunk or the left anterior descending artery in 330 (43%) patients. Thrombus aspiration was done in 357 (46%) patients (table 1). None of the patients received anticoagulant before randomisation and compliance with protocol-specified study drugs was high. Intravenous enoxaparin was the only anticoagulant given before or at the time of catheterisation to 96% (n=433) of patients who were assigned to that treatment. Similarly, intravenous unfractionated heparin was the only anticoagulant given for catheterisation in 97% (n=444) of patients allocated this treatment. After the revascularisation procedure, 33 (7%) of 450 patients in the enoxaparin group and 49 (11%) of 460 patients in the heparin group crossed over to the other study treatment (a protocol violation). Finally, 400 (89%) patients in the enoxaparin group and 395 (86%) patients in the heparin group were consistently treated across the whole hospital stay with enoxaparin or unfractionated heparin according to randomisation. In 108 (14%) of 767 patients with available data for treatment duration, anticoagulation was stopped on the day of admission, whereas other patients needed more prolonged anticoagulation; the average duration of treatment was 4·1 days for patients on unfractionated heparin and 4·6 days for those on enoxaparin. Intense antiplatelet therapy was administered (often before hospital admission) to most patients as shown by the 571 (63%) patients who received high-dose clopidogrel (600 mg or more) and the 729 (80%) patients who received glycoprotein IIb/IIIa inhibitors. The two groups were well matched for antiplatelet therapy and other treatments.

The primary endpoint occurred in 126 (28%) patients after anticoagulation with enoxaparin versus 155 (34%) with unfractionated heparin (relative risk [RR] 0·83, 95% CI 0·68–1·01, p=0·063). The enoxaparin group had a significantly reduced rate of the main secondary endpoint evaluating ischaemic outcome (30 [7%] patients *vs* 52 [11%]; RR 0·59, 95% CI 0·38–0·91, p=0·015). The number of missing data was low (n=15 for enoxaparin and n=12 for heparin). Sensitivity analyses (observed cases and multiple imputation procedures) confirmed conclusions for both the primary and main secondary endpoints. Death or complication of myocardial infarction, as well as the net

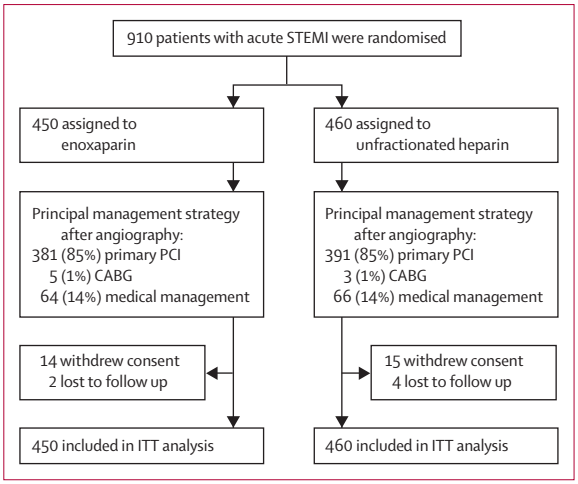


Figure 1: **Trial profile**
STEMI=ST-elevation myocardial infarction. PCI=percutaneous coronary intervention. CABG=coronary artery bypass graft.

	Enoxaparin (n=450)	Unfractionated heparin (n=460)	Relative risk (95% CI)	p value
Death, complication of MI, procedure failure, or major bleeding (primary endpoint)	126 (28%)	155 (34%)	0·83 (0·68–1·01)	0·063
Death, recurrent MI or ACS, or urgent revascularisation (main secondary endpoint)	30 (7%)	52 (11%)	0·59 (0·38–0·91)	0·015
Death , complication of MI, or major bleeding (net clinical benefit)	46 (10%)	69 (15%)	0·68 (0·48–0·97)	0·030
Death or complication of MI	35 (8%)	57 (12%)	0·63 (0·42–0·94)	0·021
Death, recurrent MI, or urgent revascularisation	23 (5%)	39 (8%)	0·60 (0·37–0·99)	0·044
Death or recurrent MI	20 (4%)	32 (7%)	0·64 (0·37–1·10)	0·1026
Death, any cause	17 (4%)	29 (6%)	0·6 (0·33–1·07)	0·082
Complication of MI				
Any	20 (4%)	29 (6%)	0·7 (0·4–1·23)	0·21
Resuscitated cardiac arrest	2 (<1%)	3 (1%)	..	..
Recurrent MI or ACS	10 (2%)	20 (4%)	..	..
Urgent revascularisation	5 (1%)	7 (2%)	..	..
Stroke	3 (1%)	1 (<1%)	..	..
Procedure failure*				
Any	100 (26%)	109 (28%)	0·94 (0·75–1·19)	0·61
Stent thrombosis, definite	4 (1%)	2 (1%)	..	..
Bailout use of glycoprotein IIb/IIIa inhibitors	10 (3%)	8 (2%)	..	..
Non-TIMI 3 flow after procedure	44 (12%)	46 (12%)	..	..
ST resolution <50% after procedure	61 (16%)	62 (16%)	..	..
Bleeding endpoints†				
Major bleeding	20 (5%)	22 (5%)	0·92 (0·51–1·66)	0·79
Minor bleeding	31 (7%)	40 (9%)	0·79 (0·50–1·23)	0·29
Major or minor bleeding	49 (11%)	54 (12%)	0·92 (0·64–1·32)	0·65
Blood transfusion	8 (2%)	10 (2%)	0·81 (0·32–2·04)	0·65

Data are n (%). MI=myocardial infarction. ACS=acute coronary syndrome. TIMI=thrombolysis in myocardial infarction. *In patients who underwent percutaneous coronary intervention (381 enoxaparin, 391 heparin). †Study definitions of bleeding were the STEEPLE definitions for patients exposed to at least one administration of the drug (444 enoxaparin, 450 heparin).

Table 2: **Clinical outcomes at 30 days**

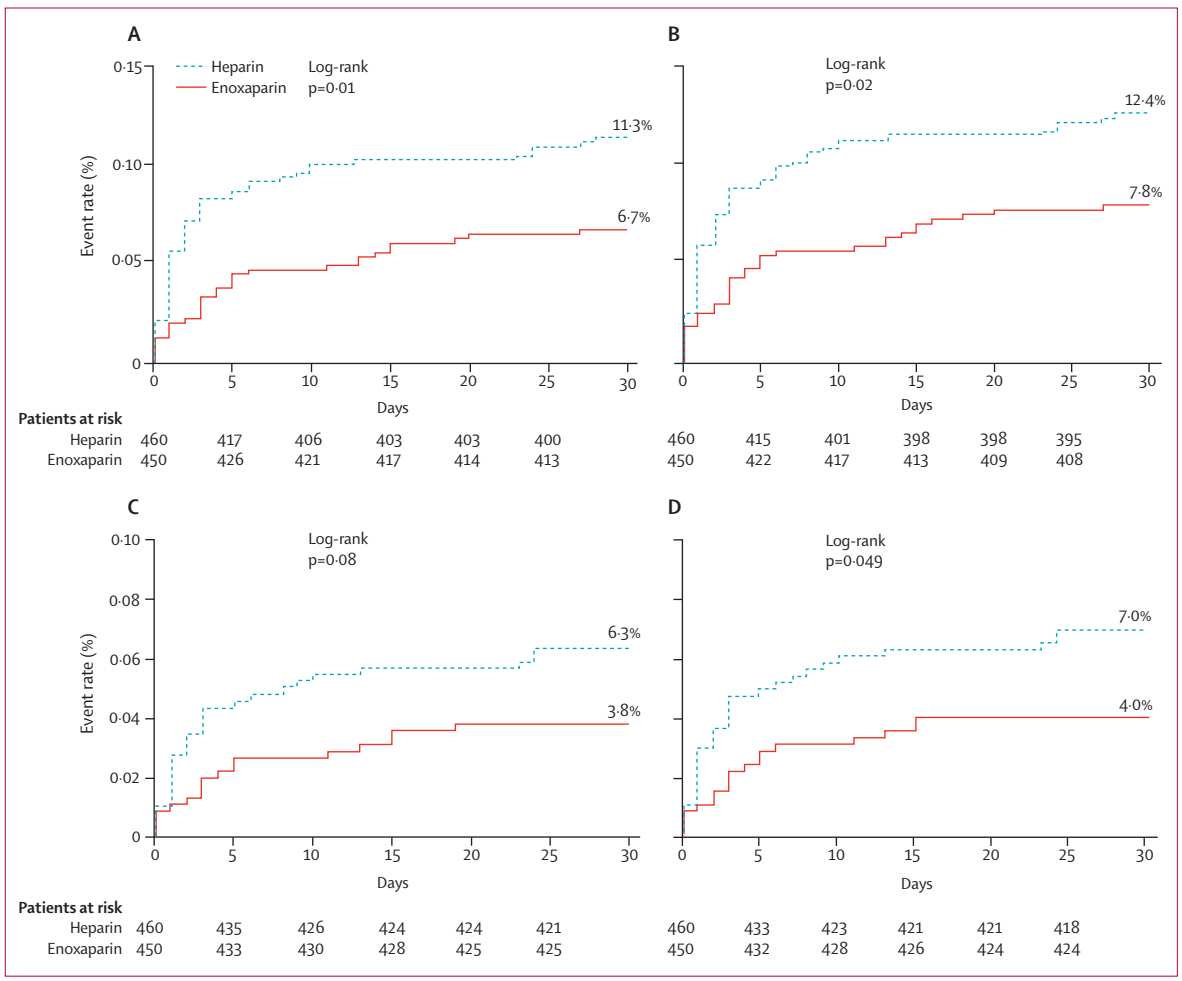


Figure 2: **Clinical outcomes at 30 days in patients on enoxaparin or unfractionated heparin**
Time-to-event curves through 30 days are shown for (A) the main secondary endpoint of death, recurrent acute coronary syndrome, or urgent revascularisation, (B) death or complication of myocardial infarction, (C) any death, and (D) death or resuscitated cardiac death. All these endpoints were prespecified.

clinical benefit evaluated by the composite of death, complication of myocardial infarction, or major bleeding, were significantly reduced with enoxaparin (table 2). Death or resuscitated cardiac death also favoured enoxaparin over unfractionated heparin (figure 2).

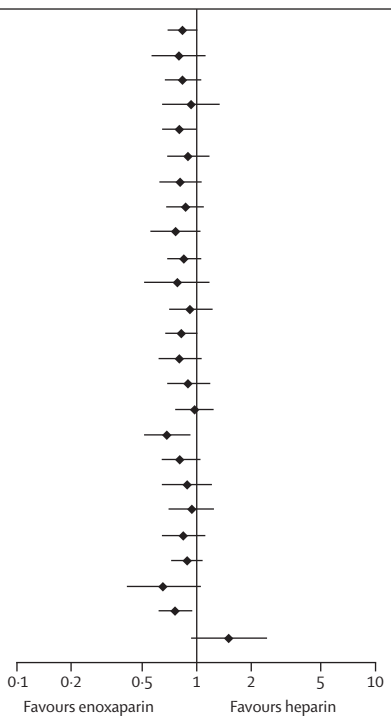
The composite endpoint of non-CABG-related major and minor bleeding was not significantly reduced with enoxaparin compared with unfractionated heparin (table 2). Although not prespecified, bleeding according to TIMI and GUSTO criteria was also assessed. The rates of TIMI bleeding did not differ significantly between the two groups (TIMI major or minor: 4% enoxaparin [n=18] *vs* 4% heparin [n=20], p=0·77), nor were the rates of GUSTO bleeding (severe or moderate: 2% enoxaparin [n=10] *vs* 3% heparin [n=12], p=0·69). The two most common overt bleeding complications were gastrointestinal and access-site bleeding events, which were equally split between the two groups; there were two retroperitoneal bleeds, two intracranial haemorrhages (one in each group) and one fatal bleed (tamponade in the enoxaparin group).

Among complications of myocardial infarction, the largest treatment effect was on recurrent acute coronary syndrome (2% enoxaparin [n=10] *vs* 4% heparin [n=20], p=0·07). Urgent revascularisation was done in five (1%) patients on enoxaparin versus seven (2%) on unfractionated heparin (p=0·59), and 30-day definite stent thrombosis occurred in four patients (1%) on enoxaparin and two patients on heparin (1%, p=0·45). The absence of ST resolution was the most common reason for procedure failure (123 [16%] patients). Catheter thrombosis occurred in two patients, one in each group.

Consistent results were obtained across all prespecified subgroups for both the primary and main secondary endpoints (no significant interaction), with the exception of the group of patients who were administered more than one heparin (protocol violation). Administration of one heparin versus more

A

	Enoxaparin		Unfractionated heparin		Relative risk (95% CI)	$p_{interaction}$
	n	%	n	%		
Full population	450	28%	460	34%	0·83 (0·68–1·01)	
Age ≥75 years	85	38%	80	48%	0·79 (0·55–1·13)	0·66
Age <75 years	365	26%	380	31%	0·84 (0·66–1·05)	
Women	97	34%	101	37%	0·93 (0·64–1·35)	0·56
Men	353	26%	359	33%	0·80 (0·64–1·01)	
Weight ≥75 kg	200	31%	208	35%	0·90 (0·68–1·18)	0·65
Weight <75 kg	236	27%	240	33%	0·81 (0·61–1·07)	
Prehospital randomisation	318	27%	325	31%	0·87 (0·68–1·11)	0·47
Intrahospital randomisation	132	31%	135	41%	0·76 (0·55–1·06)	
No diabetes	379	27%	384	32%	0·85 (0·68–1·06)	0·14
Diabetes	63	35%	69	45%	0·78 (0·51–1·19)	
Shock	13	85%	13	92%	0·92 (0·69–1·21)	0·70
No shock	437	26%	447	32%	0·82 (0·67–1·01)	
Time to randomisation	184	32%	167	40%	0·80 (0·60–1·06)	0·51
Time to randomisation	248	26%	284	29%	0·89 (0·68–1·18)	
Anterior MI	195	38%	189	39%	0·97 (0·75–1·25)	0·12
Other MI	255	20%	271	30%	0·68 (0·50–0·92)	
Radial access	309	26%	305	32%	0·81 (0·63–1·03)	0·71
No radial access	127	34%	142	38%	0·89 (0·65–1·23)	
Thrombus aspiration	184	32%	173	34%	0·94 (0·70–1·27)	0·58
No thrombus aspiration	197	30%	218	36%	0·84 (0·64–1·11)	
Use of GPI IIb/IIIa	347	30%	382	34%	0·89 (0·71–1·10)	0·24
No use of GPI IIb/IIIa	103	22%	78	35%	0·65 (0·40–1·03)	
Only one heparin	402	26%	398	34%	0·76 (0·61–0·94)	<0·02
More than one heparin	48	44%	62	29%	1·51 (0·91–2·50)	



B

	Enoxaparin		Unfractionated heparin		Relative risk (95% CI)	$p_{interaction}$
	n	%	n	%		
Full population	450	7%	460	11%	0·59 (0·38–0·91)	
Age ≥75 years	85	11%	80	25%	0·42 (0·21–0·87)	0·23
Age <75 years	365	6%	380	8%	0·68 (0·40–1·16)	
Women	97	9%	101	13%	0·72 (0·32–1·61)	0·59
Men	353	6%	359	11%	0·55 (0·33–0·91)	
Weight ≥75 kg	200	8%	208	13%	0·59 (0·33–1·06)	0·86
Weight <75 kg	236	6%	240	9%	0·63 (0·32–1·23)	
Prehospital randomisation	318	6%	325	10%	0·61 (0·35–1·05)	0·83
Intrahospital randomisation	132	8%	135	15%	0·56 (0·28–1·13)	
No diabetes	379	6%	384	11%	0·57 (0·35–0·93)	0·02
Diabetes	63	10%	69	14%	0·66 (0·25–1·70)	
Shock	13	69%	13	77%	0·90 (0·56–1·44)	0·73
No shock	437	5%	447	9%	0·51 (0·31–0·85)	
Time to randomisation	184	7%	167	12%	0·59 (0·30–1·15)	0·90
Time to randomisation	248	6%	284	10%	0·55 (0·30–1·02)	
Anterior MI	195	10%	189	13%	0·81 (0·46–1·41)	0·11
Other MI	255	4%	271	10%	0·38 (0·19–0·77)	
Radial access	309	6%	305	10%	0·62 (0·36–1·05)	0·79
No radial access	127	7%	142	13%	0·56 (0·26–1·20)	
Thrombus aspiration	184	7%	173	9%	0·81 (0·40–1·66)	0·43
No thrombus aspiration	197	6%	218	11%	0·55 (0·28–1·08)	
Use of GPI IIb/IIIa	347	6%	382	10%	0·65 (0·39–1·09)	0·29
No use of GPI IIb/IIIa	103	8%	78	19%	0·40 (0·18–0·90)	
Only one heparin	402	4%	398	12%	0·37 (0·22–0·63)	<0·0001
More than one heparin	48	25%	62	6%	3·88 (1·33–11·26)	

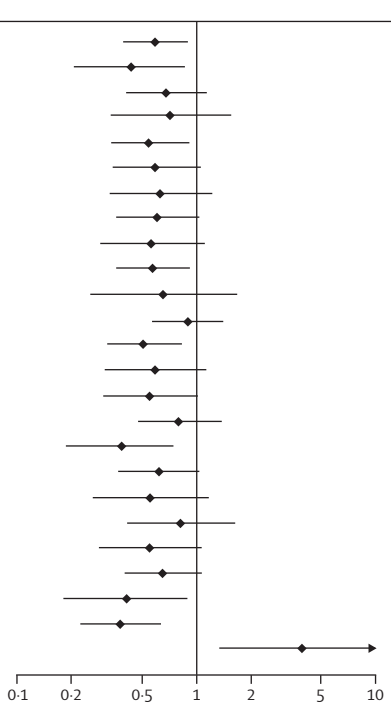


Figure 3: **Rates of (A) the primary endpoint and (B) the main secondary endpoint in prespecified subgroups at 30 days**
MI=myocardial infarction. GPI=glycoprotein inhibitors.

than one heparin affected outcomes. When both the primary and main secondary endpoints were considered, enoxaparin was significantly better than unfractionated heparin in the subgroup of patients treated consistently with the study drug. By contrast, crossover to the other anticoagulant (in either group) or simultaneous administration of both anticoagulants was associated with worsened clinical outcome (interaction p values were p=0·02 for the primary endpoint and p<0·0001 and main secondary endpoint; figure 3).

Discussion

The ATOLL trial evaluated the efficacy and safety of intravenous enoxaparin versus unfractionated heparin in the contemporary interventional management of STEMI, which in most patients included prehospital diagnosis and treatment, intense antiplatelet therapy, and radial artery access for thrombus aspiration and primary stenting (panel). In this trial, data suggested fewer primary endpoint events with intravenous enoxaparin 0·5 mg/kg than with heparin, but the difference was not significant (p=0·06). The other endpoints, including the main secondary (ischaemic) endpoint, the composite endpoint of death or complication of myocardial infarction, and the endpoint of death or resuscitated cardiac death, were significantly reduced by 37–42%. Safety of the two drugs was similar and the net clinical benefit significantly favoured enoxaparin.

To recruit a population that was as close as possible to real life, we had few clinical exclusion criteria and we randomly assigned patients to treatment groups early (as reflected by the short time from symptom onset to randomisation), accepting high-risk participants including elderly patients, patients with reduced renal function, and patients in shock or cardiac arrest. Consequently, the mortality and ischaemic event rates were higher than those reported in recent randomised studies,[3,4] but were similar to those of registries.[20–22] Patients who had received anticoagulation before randomisation were excluded, and no crossover between anticoagulation regimens was allowed during or after the procedure. Antiplatelet therapy was the same in the two groups.

The improvement in efficacy outcomes was consistent for each evaluated manifestation of coronary ischaemia, and the reduction in death or resuscitated cardiac death could be attributable to the prevention of ischaemic complications as we noted for complications of myocardial infarction and recurrent myocardial infarction or acute coronary syndrome. Our findings are in keeping with recently reported non-randomised data.[18–22,26] In the formal prospective enoxaparin substudy nested in the large FINESSE study,[18] 2452 patients with STEMI received intravenously either 0·5 mg/kg enoxaparin or 40 U/kg unfractionated heparin according to centres' prespecified use. Enoxaparin reduced the composite ischaemic endpoint of death, reinfarction, urgent revascularisation, or refractory ischaemia (similar to the ATOLL main secondary endpoint) by 53% (versus 41% in ATOLL), the triple endpoint of death, reinfarction, or urgent revascularisation by 37% (versus 40% in ATOLL), and mortality by 41% (versus 40 % in ATOLL).

Similar significant reductions of ischaemic events have been reported with enoxaparin in recent registries of primary PCI for STEMI.[19–22] In these publications, enoxaparin has been consistently associated with significant reductions of mortality of similar or greater magnitude than we recorded in ATOLL, the only large randomised trial testing enoxaparin in primary PCI. In our study, the superiority of enoxaparin was obtained with a background of intense antiplatelet therapy—80% of patients received glycoprotein IIb/IIIa inhibitors and 63% received 600 mg or more of clopidogrel—which suggests additional mechanisms of protection against coronary ischaemic events, as suggested in mechanistic studies.[27,28] By comparison with unfractionated heparin, enoxaparin has a weaker affinity for endothelial cells, anti-inflammatory properties, and favourable effects on von Willebrand factor release and glycoprotein Ib/IX receptors; these factors play a key part in the pathogenesis of myocardial infarction and are all affected favourably by enoxaparin. These factors along with a superior bioavailability and a consistent reliable anticoagulant effect of the drug could account for the benefits seen on ischaemic events.

Surprisingly, there was no reduction of severe haemorrhages using the same definitions as in the STEEPLE study,[16] which reported a significant 57% reduction of major bleeding with enoxaparin 0·5 mg/kg. This finding also contrasts with the FINESSE results, which showed a 41% reduced rate of TIMI major bleeding with the same drug regimen.[18] Two-thirds of our patients underwent PCI using the radial approach, whereas femoral access was the rule in the STEEPLE and FINESSE studies. This approach eliminates femoral access site complications, a common source of bleeding after PCI, and is the most likely explanation for the absence of a significant safety benefit with enoxaparin in our study.[29] It had also a direct effect on the magnitude of effect measured for the primary endpoint, which included major bleeding. This recent change in practice concerning the access site for PCI was unexpected and to our knowledge ATOLL is the first international randomised study to report a predominant use of radial access for primary PCI.

Although enoxaparin has been used subcutaneously for many years in acute coronary syndromes, its intravenous use is quite recent though pharmacologically well adapted to PCI and emergency situations, since it provides immediate and predictable anticoagulation and is fully effective for 2 h.[13,14] This advantage is achieved with a protocol that is simpler than that typically used for unfractionated heparin: one intravenous bolus without anticoagulation monitoring,

at the same dose with or without glycoprotein IIb/IIIa inhibitors, and immediate sheath removal after radial or femoral PCI.[30] Although stacking or switching of drugs was forbidden in our study, it nonetheless occurred in a few patients, mostly after the procedure when patients were moved to an intensive care unit, and was associated with worsened clinical outcomes in this prespecified analysis. Although this finding could be confounded by the fact that this information is postrandomisation and possibly related to imbalance in underlying risk or evolution, it confirms previous reports.[5–7] Nine of ten patients were treated consistently with the same anticoagulant, which is a major difference compared with recent trials in which mixing of drugs was frequent and difficult to interpret; in patients on consistent therapy in ATOLL, both the primary and main secondary endpoints were significantly improved by enoxaparin versus unfractionated heparin, recognising that there is little randomised evidence of the magnitude of benefit offered by heparin over placebo in this situation.

Panel: Research in context

Systematic review

We searched Medline and the Cochrane databases from 1980 to 2011. A full electronic search strategy was done, and the terms used for research were: "enoxaparin", "unfractionated heparin", and "PCI" [percutaneous coronary intervention]. Four clinical studies including the ATOLL study have compared intravenous 0·5 mg/kg enoxaparin with unfractionated heparin in PCI. Two, including the ATOLL study, were randomised studies comparing enoxaparin with unfractionated heparin,[16] one was a formal prospective substudy of a randomised study,[18] and the last one was a non-randomised comparison between enoxaparin and unfractionated heparin.[22] One study was done in elective PCI[16] and three in primary PCI.[18,22] To further evaluate the effect of intravenous 0·5 mg/kg enoxaparin, we did a meta-analysis of all four PCI studies using the original study definitions (figure 4). The net clinical benefit was the primary objective of this meta-analysis, defined as the composite of death, myocardial infarction, or major bleeding. To give a global estimation of the treatment effect, the results of all studies were combined with a fixed effect model. The Q Cochran test was used to look for heterogeneity between groups.

Interpretation

In this pooled analysis, enoxaparin was superior to unfractionated heparin with a relative risk (RR) reduction of 26% of the net clinical benefit endpoint. The composite of death or myocardial infarction was reduced with enoxaparin 0·5 mg/kg (RR 0·75, 95% CI 0·60–0·93, p=0·009) as well as major bleeding (0·66, 95% CI 0·50–0·88, p=0·006). Mortality was also significantly reduced with enoxaparin (RR 0·68, 95% CI 0·51–0·91, p=0·009).

Our study has several strengths, including the recruitment of a broad risk, real world population managed with current, guidelines-supported drugs and techniques, and comparison of two consistent anticoagulation strategies combined with similar antiplatelet therapy. Nevertheless, several limitations should be noted. First, an open-label design was imposed by several logistical complexities: emergency nature of the treatment, need for different doses of unfractionated heparin according to the use of glycoprotein IIb/IIIa inhibitors and activated clotting time results obtained in the catheterisation laboratory, and consistent anticoagulation to be continued after the procedure. Second, the study was underpowered for low frequency events. However, the endpoints presented were prespecified, the reductions were consistent across all ischaemic criteria including the hardest endpoints, the findings were plausible on the basis of the known mechanistic effects of enoxaparin,[5,16,27,28] and the data were in line with recent reports in the field. Third, a screening log was not kept, and thus the extent to which these results can be generalised is not known. The next logical step would be a large randomised trial comparing enoxaparin with bivalirudin, allowing the use of the new P2Y12 antagonists.

In conclusion, intravenous enoxaparin compared with unfractionated heparin did not significantly reduce the ATOLL primary endpoint; however, significance was present in patients consistently treated with the study drug. Intravenous enoxaparin did reduce secondary endpoints of adverse ischaemic events without a significant difference in bleeding endpoints compared with unfractionated heparin. Therefore, the net clinical benefit was improved with enoxaparin in patients undergoing primary PCI.

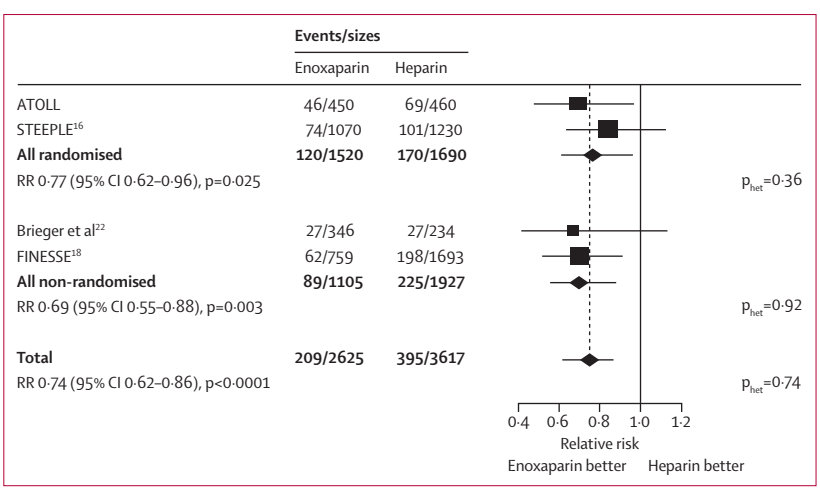


Figure 4: Meta-analysis of the four studies that compared intravenous enoxaparin 0·5 mg/kg with intravenous unfractionated heparin in percutaneous coronary intervention

Meta-analysis of four studies evaluating net clinical benefit defined as death, myocardial infarction, or major bleeding. The upper panel presents studies that randomly assigned patients to receive intravenous enoxaparin 0·5 mg/kg or intravenous unfractionated heparin. The lower panel presents non-randomised studies. The final line is the global analysis of all four studies. RR=relative risk.

Contributors

GM, UZ, MC, PG, KH, CP, and EV designed the study, analysed and interpreted data, and revised the report. JS, BB, PE, XC, J-FB, OS, EF, ET, GC, SE, FA, TC, SG, AG, MA, and J-PC contributed to implementation of the study, enrolment and follow-up of patients, and reviewed the report. MA and EV did all statistical analysis. JS did the meta-analysis. GM wrote the first draft and submitted the final version of the report. All authors have seen the final submitted Article and agree with its contents.

Conflicts of interest

GC reports receiving a research grant from la Fédération Française de Cardiologie; consultant fees from Abbott Vascular, AstraZeneca, CLS Behring, Daiichi Sankyo, and Eli Lilly; and lecture fees from Abbott Vascular, AstraZeneca, Biotronik, CLS Behring, Daiichi Sankyo, Eli Lilly, and Iroko Cardio. MC reports receiving grant support and speakers' honoraria from Sanofi-Aventis, Bristol-Myers Squibb, and Merck. J-PC reports receiving research grants from Bristol-Myers Squibb, Sanofi-Aventis, Eli Lilly, Guerbet Medical, Medtronic, Boston Scientific, Cordis, Stago, Fondation de France, INSERM, Fédération Française de Cardiologie, and Société Française de Cardiologie; consulting fees from Sanofi-Aventis, Eli Lilly, and Bristol-Myers Squibb; and lecture fees from Bristol-Myers Squibb, Sanofi-Aventis, Eli Lilly, and AstraZeneca. PG reports receiving consulting or board fees and lecture fees from AstraZeneca, Boehringer Ingelheim, Daiichi-Sankyo, Eli-Lilly, Sanofi-Aventis, and The Medicines Company. KH reports receiving lecture fees from AstraZeneca, Bayer, Bristol-Myers Squibb, Boehringer Ingelheim, Daiichi Sankyo, Eli Lilly, Pfizer, Sanofi-Aventis, Schering-Plough, and The Medicines Company. GM reports receiving grant support from Abbott Vascular, Boston Scientific, Cordis, Eli Lilly, Fédération Française de Cardiologie, Fondation de France, Guerbet Medical, INSERM, ITC Edison, Medtronic, Pfizer, Sanofi-Aventis, Société Française de Cardiologie, and Stago; consulting or board fees and lecture fees from AstraZeneca, Bayer, Boehringer Ingelheim, Cardiovascular Research Foundation, Cleveland Clinic Research Foundation, Daiichi-Sankyo, Duke Institute, Eli Lilly, Europa, Lead-up, GlaxoSmithKline, Institut de Cardiologie de Montreal, Menarini, Nanospheres, Novartis, Pfizer, Portola, Sanofi-Aventis, The Medicines Company, and the TIMI study group. CP reports receiving research support and consulting fees from Sanofi-Aventis and The Medicines Company. JS reports receiving research grants from Sanofi-Aventis, Daiichi-Sankyo, Eli Lilly, Brahms, INSERM, Fédération Française de Cardiologie, and Société Française de Cardiologie; consulting fees from Daiichi-Sankyo and Eli Lilly; and speakers' honoraria from AstraZeneca, Daiichi Sankyo, Eli Lilly, and Servier. ET reports speakers' honoraria from Eli Lilly and Daiichi Sankyo and consulting fees and lectures fees from Medtronic and Cordis. EV reports receiving consulting fees and lecture fees from Abbott, Amgen, Eli Lilly, Pfizer, Sanofi-Aventis, and Servier. UZ reports receiving research grants and speakers' honoraria from Bristol-Myers Squibb, Eli Lilly, and Sanofi-Aventis and consulting fees and lecture fees from AstraZeneca, Bayer, Boehringer Ingelheim, Daiichi Sankyo, Portola, and The Medicines Company. All other authors declare that they have no conflicts of interest.

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