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ORIGINAL ARTICLE

Low-molecular-weight heparins vs. unfractionated heparin in the setting of percutaneous coronary intervention for ST-elevation myocardial infarction: a meta-analysis

E. P. NAVARESE,* G. DE LUCA,† F. CASTRIOTA,‡ M. KOZINSKI,* P.A. GURBEL,§ C. M. GIBSON,¶ F. ANDREOTTI,** A. BUFFON,** J. M. SILLER-MATULA,†† A. SUKIENNIK,* S. DE SERVI‡‡ and J. KUBICA*

**Department of Cardiology and Internal Medicine, Ludwik Rydygier Collegium Medicum, Nicolaus Copernicus University, Bydgoszcz, Poland; †Department of Cardiology, ''Maggiore della Carità'' Hospital, Eastern Piedmont University ''A. Avogadro'', Novara; ‡Interventional Cardio-Angiology Unit, GVM Care and Research, Cotignola, Italy; §Sinai Center for Thrombosis Research, Sinai Hospital of Baltimore, Baltimore, MD; ¶Institute of Cardiology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA; **Department of Cardiovascular Medicine, Catholic University of the Sacred Heart, Rome, Italy; ††Department of Cardiology, Medical University of Vienna, Vienna, Austria; and ‡‡Department of Cardiovascular Diseases, Civic Hospital, Legnano, Italy*

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Summary. *Background:* The aim of the current study was to perform two separate meta-analyses of available studies comparing low-molecular-weight heparins (LMWHs) vs. unfractionated heparin (UFH) in ST-elevation myocardial infarction (STEMI) patients treated (i) with primary percutaneous coronary intervention (pPCI) or (ii) with PCI after thrombolysis. *Methods:* All-cause mortality was the prespecified primary endpoint and major bleeding complications were recorded as the secondary endpoints. Relative risk (RR) with a 95% confidence interval (CI) and absolute risk reduction (ARR) were chosen as the effect measure. *Results:* Ten studies comprising 16 286 patients were included. The median follow-up was 2 months for the primary endpoint. Among LMWHs, enoxaparin was the compound most frequently used. In the pPCI group, LMWHs were associated with a reduction in mortality [RR (95% CI) = 0.51 (0.41–0.64), $P < 0.001$, ARR = 3%] and major bleeding [RR (95% CI) = 0.68 (0.49–0.94), $P = 0.02$, ARR = 2.0%] as compared with UFH. Conversely, no clear evidence of benefits with LWMHs was observed in the PCI group after thrombolysis. Meta-regression showed that patients with a higher baseline risk had greater benefits from LMWHs ($r = 0.72$, $P = 0.02$). *Conclusions:* LMWHs were associated with greater efficacy and safety than UFH in STEMI patients treated with pPCI, with a significant relationship between risk profile and clinical benefits. Based on this meta-analysis, LMWHs may be considered as a preferred anticoagulant among STEMI patients undergoing pPCI.

Keywords: low-molecular-weight heparin, percutaneous coronary intervention, ST-elevation myocardial infarction, unfractionated heparin.

Correspondence: Eliano Pio Navarese, Department of Cardiology and Internal Medicine, Ludwik Rydygier Collegium Medicum, Nicolaus Copernicus University, Skodowskiej-Curie Street No 9, 85-094 Bydgoszcz, Poland.
Tel.: +48 52 585 40 23; fax: +48 52 585 40 24.
E-mail: eliano.navarese@alice.it

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Introduction

Unfractionated heparin (UFH) is regarded as standard anticoagulant therapy for the treatment of ST-elevation myocardial infarction (STEMI) patients, including those treated with percutaneous coronary intervention (PCI). Guidelines from the American College of Cardiology and European Society of Cardiology recommend the use of UFH with a level of evidence C [1,2]. However, this recommendation is not based on comparison data with a placebo, but only on the strong belief that anticoagulation therapy is required during the procedure. There is evidence of efficacy for the low-molecular-weight heparins (LMWHs) in STEMI patients treated with fibrinolytics [3], but their use in STEMI patients treated with PCI has been controversial because of the scant available data up to a few years ago.

More recently, several observational studies, analyses of large randomized trials (RCTs) or ad hoc RCTs have compared LMWHs with UFH in STEMI populations treated with primary PCI (pPCI) or PCI performed after thrombolysis.

The aims of this investigation were: (i) to perform two separate meta-analyzes of available studies comparing

LMWHs vs. UFH in STEMI patients treated with either pPCI or PCI after thrombolysis; and (ii) to assess whether the effects of different anticoagulation regimens on mortality may be related to the patients' baseline risk profile.

Methods

The present meta-analysis was performed according to established methods, according to the guidelines of the Cochrane Collaboration [4], the guidelines of the MOOSE group [5] and the updated guidelines on systematic reviews of non-randomized studies [6].

Search strategy

A systematic investigation was performed of all the published and unpublished literature, including oral presentations, to minimize the risk of bias. A search covering the period from January 1993 to March 2011 was conducted by two independent investigators using MEDLINE, CENTRAL and Google Scholar databases. Proceedings from the Scientific Sessions of the American College of Cardiology [http://www.acc.org], American Heart Association [http://www.a-ha.org], European Society of Cardiology [http://www.escardio.org], Transcatheter Cardiovascular Therapeutics [http://www.tctmd.com] and EuroPCR [http://www.europcr.com] were also considered. The following keywords were applied: 'low-molecular-weight-heparins', 'unfractionated heparin', 'angioplasty' and 'ST-elevation myocardial infarction'. References of retrieved studies were searched manually for additional trials. Efforts to contact authors were performed to obtain further details or additional references. No language restrictions were applied.

Study endpoints

All-cause mortality was the primary pre-specified endpoint; major bleeding complications were recorded as a secondary endpoint. Mortality was evaluated at long-term follow-up, if available; otherwise, in-hospital or 30-day data were included. Data on major bleeding (at 30 days if available, otherwise at shorter follow-up) were managed according to the TIMI criteria, when available; if not, by study protocol definition.

Selection criteria and internal validity

RCTs and non-randomized studies were selected based on the following inclusion criteria: studies comparing LMWHs vs. UFH in STEMI patients treated either with pPCI or with thrombolysis followed by PCI. Main exclusion criteria were: (i) comparison between LMWHs and UFH in patients with NSTEMI [29–34], with STEMI treated with thrombolysis only [35–40] or undergoing elective PCI [25,27–28]; (ii) absence of comparator treatment group (i.e. UFH) [41]; (iii) combined data (pPCI and thrombolysis) with no separate data on pPCI [42]; and (iv) duplicate reporting [43–44] (Fig. 1). The quality of the included studies was appraised by two unblinded reviewers. Non-randomized studies were evaluated using the validated Newcastle–Ottawa Scale [4]. Data were abstracted on pre-specified forms by two independent investigators, neither involved in any of the retrieved studies; divergences were resolved by discussion with a third investigator. Pre-specified extracted data included: trial name/first author, publication year, study design, study-inclusion and exclusion criteria, the number of patients, dose of LMWH/UFH, type of LMWH used, clinical outcome (mortality, major bleeding), major bleeding definition, glycoprotein (Gp) IIb/IIIa inhibitor use,

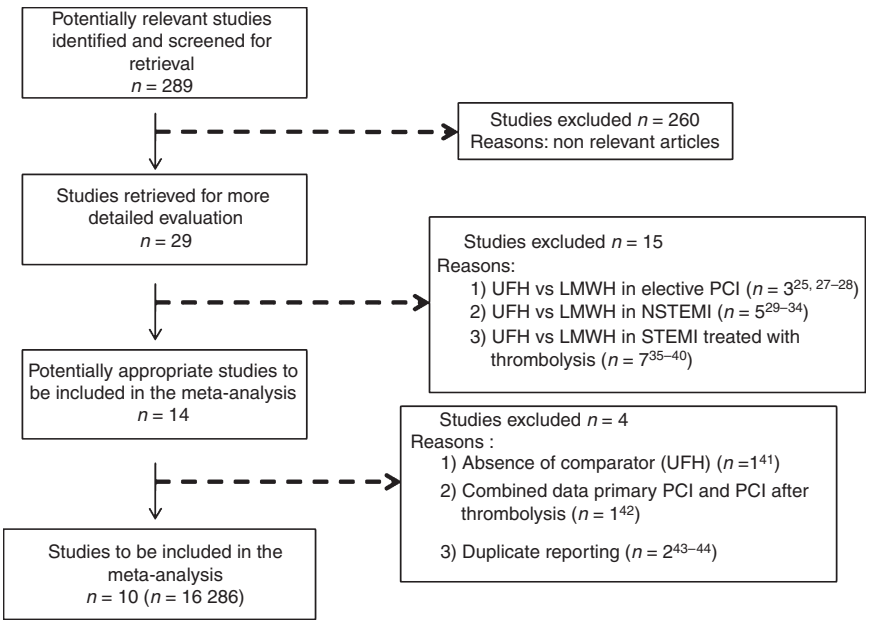


Fig. 1. Flow diagram of the reviewing process.

Table 1 Characteristics of the included studies

Study	Journal/ Meeting	Year	UFH + LMWH Patients (*N*)	Study design	Inclusion criteria	Exclusion criteria	PCI setting	Main outcomes	Major bleeding definition
ASSENT-3 [12]	*J Am Coll Cardiol*	2003	533	RCS	PCI subgroup analysis: patients undergoing PCI after treatment with a fibrinolytic agent	Clopidogrel before enrollment, age > 75 years, cardiogenic shock, creatinine > 2.5 mg mL^{-1}	PCI after thrombolysis	Death, major bleeding, composite	Protocol
ATOLL [http://spo.escardio.org/eslides/view.aspx?eevtid=40&fp=2042]	*ESC Congress*	2010	910	RCT	STEMI patients with included real life population (shock, cardiac arrest)	Thrombolysis before pPCI, previous anticoagulation before pPCI	pPCI	Death, major bleeding, composite	Protocol, TIMI, GUSTO
Brieger *et al.* [13]	*Catheter Cardiovasc Interv*	2010	580	NRCT	STEMI patients treated with pPCI and known anticoagulant regimen	Patients receiving both UFH and therapeutic dose of enoxaparin	pPCI	Death, MI, major bleeding, composite	TIMI, STEEPLE, protocol
CLARITY-TIMI 28 [14]	*Circulation*	2005	1677	NRCT	PCI subgroup analysis: patients undergoing PCI after treatment with a fibrinolytic agent	Patients who weighed < 67 kg and had received a > 4000 IU bolus or who weighed > 67 kg and had received a > 5000 IU bolus of UFH and patients who had received enoxaparin > 30 mg i.v. or > 1.1 mg kg^{-1} per s.c.	PCI after thrombolysis	Major bleeding, composite	TIMI
PCI ExTRACT-TIMI 25 [15]	*J Am Coll Cardiol*	2005	4676	NRCT	PCI subgroup analysis: patients undergoing PCI after treatment with a fibrinolytic agent	Patients undergoing coronary artery bypass grafting	PCI after thrombolysis	Death, MI, major bleeding, composite	TIMI

Dose of UFH	Dose of LMWH	Type of LMWH	Gp IIb/IIIa inhibitors (%)	Female gender (%)	Anterior MI (%)	Mortality Follow-up (months)	Major bleeding follow-up (months)
60 IU kg^{-1} i.v. bolus, then 12 IU kg^{-1} per h i.v.	30 mg i.v. bolus, then 1 mg kg^{-1} s.c. b.i.d.	Enoxaparin	NA	27 UFH, 23 LMWHs	36 UFH, 34 LMWHs	12	In-hospital
50–70 IU i.v. bolus with Gp 11 b/111 a inhibitors, 70–100 IU i.v. bolus without Gp 11 b/111 a inhibitors, then UFH recommended (i.v. or s.c.), restarted after sheath removal	0.5 mg kg^{-1} i.v. bolus with or without Gp 11 b/111 a inhibitors, then 40 mg s.c. after sheath removal	Enoxaparin	77 UFH, 71 LMWHs	NA	NA	1	In-hospital
68 IU kg^{-1} i.v. bolus	1 mg kg^{-1} s.c. at first medical contact or 0.50 mg kg^{-1} i.v. bolus in the cath- lab	Enoxaparin	74.4 UFH, 75.7 LMWHs	18.8 UFH, 24.27 LMWHs	44.4 UFH, 41.6 LMWHs	1	In-hospital
60 IU kg^{-1} i.v. bolus, then 12 IU kg^{-1} per h i.v.	30 mg i.v. bolus, then first s.c. dose of 1.0 mg kg^{-1}, then additional s.c. doses of 1.0 mg kg^{-1} b.i.d. (enoxaparin); 30 IU kg^{-1} i.v. bolus, then first s.c. dose of 90 IU kg^{-1}, then additional s.c doses of 120 IU kg^{-1} b.i.d. (dalteparin); 86-anti-Xa IU kg^{-1} i.v. bolus, then 86-anti-Xa IU kg^{-1} s.c. b.i.d. (nandroparin)	Enoxaparin, dalteparin nadroparin, tinzaparin, certoparin	21 UFH, 16 LMWHs	18.5 UFH, 19.45 LMWHs	42 UFH, 39 LMWHs	1	1
60 IU kg^{-1} i.v. bolus, then 12 IU kg^{-1} per h i.v.	30 mg i.v. bolus, then 1 mg kg^{-1} s.c. b.i.d. if age < 75 years or 0.75 mg kg^{-1} s.c. b.i.d. if age > 75 years	Enoxaparin	19.2 UFH, 15.4 LMWHs	17.2 UFH, 17.82 LMWHs	40.2 UFH, 40.9 LMWHs	1	1

Table 1 Continued

Study	Journal/ Meeting	Year	UFH + LMWH Patients (*N*)	Study design	Inclusion criteria	Exclusion criteria	PCI setting	Main outcomes	Major bleeding definition
FINESSE [16]	JACC Cardiov Interv	2010	1609	NRCT	STEMI patients presenting within 6 h of symptom onset treated with pPCI or PCI after thrombolysis	Patients receiving any UFH within 24 h of randomization or who had a history of allergy to enoxaparin or reduced CrCl < 30 mL min^{-1}	pPCI and PCI after thrombolysis	Death, major bleeding, composite	TIMI
Galeote *et al.* [17]	*Med Intensiva*	2009	191	NRCT	STEMI patients treated with pPCI	Patients with cardiogenic shock	pPCI	Death, major bleeding	Protocol
Khoobiar *et al.* [18]	*J Thromb Thrombolysis*	2008	83	RCS	STEMI patients treated with pPCI	Previous thrombolysis, pPCI delayed more than 12 h	pPCI	Death, major bleeding	TIMI, GUSTO
Li *et al.* [19]	*Am Heart J*	2010	3372	NRCT	STEMI patients who undergo pPCI with DES	NSTEMI, STEMI treated with pPCI and BMS or without stenting	pPCI	Death, MI, major bleeding, composite	Protocol
Zeymer *et al.* [20]	*Eurointervention*	2008	2655	RCS	STEMI patients treated with pPCI	Patients treated with therapeutic dose of both UFH and enoxaparin or with LMWH other than enoxaparin	pPCI	Death, MI, major bleeding, composite	Protocol

b.i.d., twice a day; BMS, bare metal stent; CrCl, creatinine clearance; DES, drug eluting stent; Gp IIb/IIIa inhibitors, glycoprotein IIb/IIIa inhibitors; GUSTO, Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries; h, hours; i.v., intravenous; LMWH, low-molecular weight-heparin; NA, not available; MI, myocardial infarction; NRCT, non-randomized study; NSTEMI, non-ST-elevation myocardial infarction; PCI, Percutaneous Coronary Intervention; pPCI, primary Percutaneous Coronary Intervention; RCS, retrospective cohort study; RCT, randomized controlled trial, s.c., subcutaneous; STEMI, ST-elevation myocardial infarction; TIMI, Thrombolysis in Myocardial Infarction; UFH, unfractionated heparin. In the majority of trials, UFH was weight adjusted according to the results of the activated partial thromboplastin (ACT) time.

female gender, anterior MI, the longest follow-up available for mortality and major bleeding.

Comparative studies were classified into three categories according to study design according to the *Cochrane Intervention Meta-analysis Handbook* [4]: (1) non-randomized controlled trials (NRCTs) (patients with STEMI treated with pPCI/PCI after thrombolysis who were non-randomly allocated to UFH or LMWH treatment); (2) retrospective cohort studies (RCS) (patients with STEMI treated with pPCI/PCI after thrombolysis who were retrospectively identified and in whom outcomes after LMWH or UFH treatment were assessed; and (3) RCTs (patients with STEMI treated with pPCI/PCI after thrombolysis who were randomly allocated to LMWH or UFH treatment). Categories 1 and 2 were considered as non-randomized comparative studies.

Statistical analysis

Relative risk (RR) and 95% confidence intervals (95% CI) were used as summary statistics. Heterogeneity was assessed using Cochran's Q test, with a two-tailed $P = 0.1$, as conventionally recommended [7]. The statistical inconsistency test (I^2) $[(Q - \mathrm{df})/Q] \times 100\%$, where Q is the χ^2 statistic and

Dose of UFH	Dose of LMWH	Type of LMWH	Gp IIb/IIIa inhibitors (%)	Female gender (%)	Anterior MI (%)	Mortality Follow-up (months)	Major bleeding follow-up (months)
40 IU kg^{-1} i.v. bolus	0.5 mg kg^{-1} i.v. bolus and 0.3 mg kg^{-1} s.c.	Enoxaparin	100 UFH and LMWHs	25.9 UFH, 26.9 LMWHs	47.4 UFH, 48.9 LMWHs	3	Discharge or day 7
70–100 IU kg^{-1} i.v. bolus	0.75–1 mg kg^{-1} i.v. bolus	Enoxaparin	81 UFH, 87.9 LMWHs	36 UFH, 33 LMWHs	41 UFH, 51.6 LMWHs	In-hospital	In-hospital
60 IU kg^{-1} i.v. bolus, then 12 IU kg^{-1} per h i.v.	30 mg i.v. bolus, then 1 mg kg^{-1} s.c. b.i.d. if age < 75 years or 0.75 mg kg^{-1} s.c. b.i.d. if age > 75 years	Enoxaparin	89 UFH, 97 LMWHs	36.3 UFH, 33.33 LMWHs	34 UFH, 44 LMWHs	15	In-hospital
5000 IU i.v. bolus at emergency department, then 50–70 IU kg^{-1} i.v. during primary PCI, then 24 000 IU per day i.v.	1 mg kg^{-1} s.c. b.i.d. of enoxaparin, plus reduced dose of UFH, 50 UI kg^{-1} i.v. during PCI	Enoxaparin	21.5 UFH, 18 LMWHs	24.8 UFH, 2.6.71 LMWHs	52. 2 UFH, 52.6 LMWHs	8	In-hospital
NA	NA	Enoxaparin	64.4 UFH, 52.9 LMWHs	27.4 UFH, 22.7 LMWHs	27.4 UFH, 22.5 LMWHs	In-hospital	In-hospital

d.f. is its degrees of freedom, was also employed to overcome the low statistical power of Cochran's Q test [8].

Pre-specified analyses are presented separately for the pPCI and PCI after thrombolysis groups. Separate pre-specified analyses were also performed with or without the RCT and a P for interaction was calculated to formally explore any statistical difference between the two analyses.

To increase the accuracy of the meta-analysis, we reported the analysis of both crude and adjusted estimates when available from the retrieved studies, according to the Cochrane Guidelines [4].

For the crude estimate computation, the pooled RR was calculated using a Fixed-Effect model with the Mantel–Haenszel method.

The adjusted estimates were pooled by the inverse variance method using the log RR available from the retrieved studies; in case of availability of the odds ratio (OR) only, we converted this into the RR using the following equation according to the Cochrane Guidelines [4]: $RR = OR/1 - ACR \times (1 - OR)$, where ACR is the assumed control risk. Adjusted hazard ratios were accepted as RR.

In case of significant benefits from one or another strategy, the absolute risk reduction (ARR) was also calculated.

Potential publication bias for the subgroups was examined by constructing a 'funnel plot', in which the standard error (SE) of the ln RR was plotted against the RR (mortality or major bleeding). In addition, a mathematical estimate of the asymmetry of this plot was provided using a linear regression approach [9]. The Duval and Tweedie non-parametric trim and fill method was used to obtain symmetry in the funnel plot and to determine the impact of hypothetical negative or imputed studies on the pooled estimate [10].

The following sensitivity analyses were also performed: (i) the influence of each study was assessed by testing whether, deleting each in turn, would have significantly changed the pooled results of the meta-analyses (sensitivity analysis); and (ii) separate pre-specified analyses were carried out for the NRCT or RCS to test the potential influence on the results of the non-randomized studies' design.

The relationship between the effect on mortality of LMWHs vs. UFH and the patients' risk profile in each study (study level variable) was evaluated using a Fixed-Effect meta-regression analysis, regressing ARR against the control group event rate as a proxy for the risk of mortality using the inverse variance of the ARR as a weight [11]; the related number needed to treat (NNT) as the inverse of the ARR for the different risk profiles in the meta-regression was also computed.

Finally, survival and major bleeding after Gp IIb/IIIa inhibitors as concomitant antithrombotic therapy with UFH or LMWHs were evaluated using meta-regression, regressing the rate of Gp IIb/IIIa inhibitor use against the log RR from the included studies.

Review Manager 5.1 (The Nordic Cochrane Center, Købehvn, Denmark), Stata/SE, version 10, for Windows (StataCorp, Houston, TX, USA) and SPSS for Windows version 15 (SPSS, Chicago, IL, USA) were used for statistical computations.

Results

Eligible studies

Nine non-randomized studies [12–20] and one RCT [http://spo.escardio.org/eslides/view.aspx?eevtid=40&fp=2042] were included in the meta-analysis that involved a total of 16 286 patients: 6622 and 9664 allocated to the LMWH and UFH group, respectively. Among LMWHs, enoxaparin was the compound most frequently used. Table 1 lists the study characteristics. Six non-randomized studies had a prospective design; three were retrospective analyses. The majority of the included studies reported until 1-month follow-up for mortality outcome, whereas four studies reported a longer follow-up (range 3–15 months); the median follow-up was 2 months. Concerning major bleeding complications, data were mostly available up to hospital discharge, whereas two studies reported data at 30 days.

The FINESSE (Facilitated INtervention with Enhanced reperfusion Speed to Stop Events) trial [16] reported separate results for pPCI and PCI after thrombolysis, which were computed separately in the meta-analysis as pre-specified. In the CLARITY TIMI-28 (CLopidogrel as Adjunctive ReperfuIion TherapY – Thrombolysis in Myocardial Infarction 28) trial [14] 50% of patients received a LMWH, with enoxaparin administered to the majority of these (85%) and nadroparin, dalteparin, tinzaparin or certoparin to the remaining 15%. PCI exTRACT TIMI-25 (EnoXaparin and Thrombolysis Reperfusion for ACute myocardial infarction Treatment, Thrombolysis In Myocardial Infarction 25) [15] is a subgroup analysis of a RCT, including patients who underwent PCI after thrombolysis. It was considered as a non-randomized study, in compliance with the Cochrane Guidelines for systematic reviews and meta-analyzes [4].

Risk of bias of included studies

Table 2 summarizes quality ratings and risk of bias assessment for the non-randomized studies. Overall, the quality of the studies was good and high scores were achieved. Most of the studies reported adjusted estimates for the primary endpoint and when not available (two studies) the baseline clinical characteristics were found to be well matched between the two arms (LMWHs vs. UFH). In the majority of the included studies the accuracy of the data was checked by (i) an independent Clinical Events Committee, (ii) using standardized case report forms completed by a trained study coordinator [19], (iii) by source documents for completeness and for internal consistency [12] or (iv) by social security indices [20].

Primary endpoint

Mortality Nine studies (including 14 620 patients) reported the mortality outcome in the group treated with LMWHs vs. UFH (Fig. 2A). In the overall cohort of patients there were a total of 694 deaths, 3.61% (211/5842) in the LMWH group and 5.50% (483/8778) in the UFH group. No heterogeneity or statistical inconsistency was observed in the results.

LMWHs were associated with a marked reduction in mortality in the pPCI group: RR_{fixed} (95% CI) = 0.51 (0.41–0.64), $P < 0.001$, ARR = 3% (NNT = 33) (Fig. 2A, upper panel), whereas no significant reduction in mortality was found in STEMI patients undergoing PCI after thrombolysis: RR_{fixed} (95% CI) = 1.01 (0.78–1.32), $P = 0.92$ (Fig. 2A, lower panel).

In the pPCI group, the pre-specifed meta-analysis of non-randomized studies conducted excluding the only RCT ATOLL (Acute STEMI Treated with primary angioplasty and intravenous enoxaparin Or UFH to Lower ischemic and bleeding events at short- and Long-term follow-up) [http://spo.escardio.org/eslides/view.aspx?eevtid=40&fp=2042] confirmed the benefits of LMWHs found in our overall analysis and in the dataset coming from the randomized study [RR_{fixed} (95% CI) = 0.50 (0.40–0.63), $P < 0.001$].

In the adjusted estimates' analysis, the benefits of LMWHs were strongly maintained in the pPCI group [RR (95% CI) = 0.50 (0.39–0.63), $P < 0.001$], and they became signif-

Table 2 The Newcastle Ottawa Scale for non-randomized studies assigns star for three area of study quality: selection, comparability and outcome. Each criterion is worth one star, with the exception of comparability. In this area, a study can receive up two stars for two or more important factors

Non-randomized comparative studies	Selection	Comparability	Outcome	Score	Adjusted estimates/Methods of adjustment
ASSENT-3	★★★★	★★	★★★	9/9	Multivariate and propensity score analysis
Brieger *et al.* [13]	★★★★	★★	★★	8/9	Multivariate analysis
CLARITY TIMI-28	★★★★	★★	★★★	9/9	Multivariate analysis
EXTRACT TIMI-25	★★★★	★★	★★★	9/9	Multivariate analysis
FINESSE	★★★★	★★	★★★	9/9	Multivariate and propensity score analysis
Galeote *et al.* [17]	★★★★	–	★★	6/9	No adjusted estimates available*
Khoobiar *et al.* [18]	★★★★	–	★★	6/9	No adjusted estimates available*
Li *et al.* [19]	★★★★	★★	★★★	9/9	Multivariate and propensity score analysis
Zeymer *et al.* [20]	★★★★	★★	★★★	9/9	Propensity score analysis

*Adjustment method was probably unnecessary since baseline characteristics were well matched.

icant in favour of LMWHs in the PCI after the thrombolysis group [RR_{fixed} (95% CI) = 0.76 (0.64–0.90), $P = 0.001$] (Fig. 2B).

In the pPCI group, stratified analyses of studies with 1-month follow-up or longer follow-up (range 3–15 months) were also performed and the results were found consistent in favour of LMWH treatment: (i) 1-month follow-up RR_{Fixed} (95% CI) = 0.43 (0.29–0.63), $P < 0.001$; (ii) longer follow-up RR_{Fixed} (95% CI) = 0.56 (0.43–0.73), $P < 0.001$.

The funnel plot for mortality for the pPCI group demonstrated a slight asymmetry between the right- and left-hand sides of the plot, however, the Egger's test was not significant ($P = 0.07$). We therefore further explored any potential bias using the Duval and Tweedie trim and fill method, whereby the asymmetric studies from the left-hand side of the plot were trimmed to locate the unbiased effect; the plot was then filled by reinserting the trimmed studies on the left as well as their imputed counterparts to the right of the mean effect, producing a symmetric plot. The overall effect on mortality reported in the forest plot appeared valid with trivial publication bias effect because the observed estimates were similar to the adjusted estimates (Fig. 3).

As shown in Fig. 4, using meta-regression, a significant relationship between benefits in mortality reduction with LMWHs compared with UFH and patients' risk profile was found ($r = 0.72$; $P = 0.02$); the greater the risk, the higher the associated benefit from the administration of LMWHs. The related NNT to prevent one death decreased in favour of LMWHs at increasing risk profiles.

Major bleeding Ten studies, including 16 286 patients, reported the rate of major bleeding complications. No publication bias was found on the funnel plot. The overall incidence of major bleeding was 1.73% (115 out of 6622 patients) in the LMWH group and 3.22% (312 out of 9664 patients) in the UFH group.

LMWH treatment was associated with a significant reduction in the rate of major bleeding complications in the pPCI group: RR_{fixed} (95% CI) = 0.68 (0.49–0.94), $P = 0.02$, ARR = 2.0% (NNT = 50) (Fig. 5, upper panel). However, no significant differences were observed between the two agents in the PCI after thrombolysis group: RR_{fixed} (95% CI) = 0.91 (0.66–1.25), $P = 0.56$ (Fig. 5, lower panel).

In the pPCI group, the results did not change after the exclusion of the ATOLL study: RR_{fixed} (95% CI) = 0.60 (0.42–0.85), $P = 0.004$.

Overall sensitivity analyses

Sensitivity analysis, performed by removing each of the studies one at a time, demonstrated that no single study influenced the overall results.

Test for interaction

The interaction test yielded $\chi^2 = 0.05$, d.f. = 1, $P = 0.82$, showing no significant difference between the results for mortality in the pPCI group when obtained from the RCT vs. non-randomized studies. The effects of the two non-randomized study type categories were similar (NRCS vs. RCS) with $\chi^2 = 2.61$, d.f. = 1, $P = 0.11$. These concordant results applied also to major bleeding outcomes for the pPCI and the PCI after thrombolysis groups, suggesting that the summary effect was robust and justified.

Discussion

The main finding of the meta-analysis is that the use of LMWHs in patients undergoing pPCI for STEMI is associated with a reduction in rates of mortality and major bleeding as compared with the use of UFH.

LMWHs have several pharmacological properties that may theoretically explain their greater efficacy. As compared with UFH, LMWHs have a four-fold greater activity against activated factor X that is crucial to promote the production of thrombin. LMWHs also possess a much more predictable anticoagulant response than UFH as they do not bind to plasma proteins. Moreover, pleiotropic effects such as blunting the increase in von Willebrand factor and a relative lack of associated platelet activation might influence its antithrombotic properties in addition to superior anticoagulant effects [21–23]. Based on these pharmacokinetic and pharmacodynamic characteristics, LMWHs provide a pharmacologic-

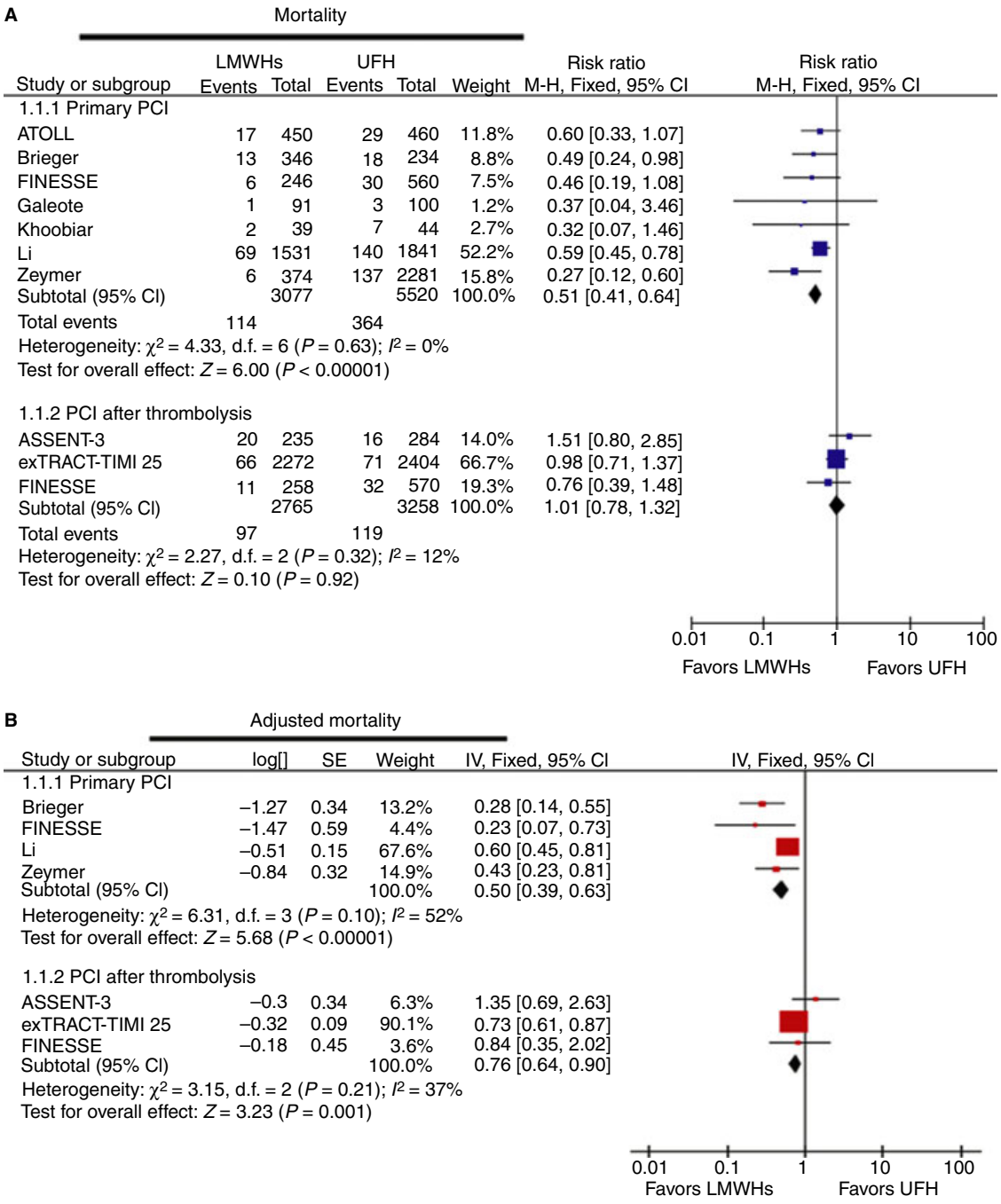
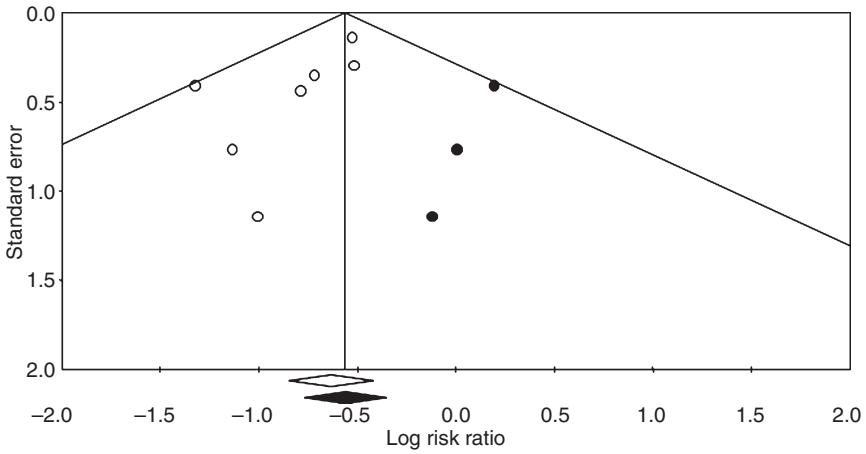


Fig. 2. (A) Individual and summary relative risks (risk ratios) for mortality in patients treated with low-molecular-weight heparins (LMWHs) vs. unfractionated heparin (UFH). (B) Individual and summary adjusted relative risks (risk ratios) for mortality in patients treated with LMWHs vs. UFH.

profile that may be better suited for PCI in STEMI than UFH.

Currently, increasing data suggest benefits associated with LMWHs in elective patients [24] and acute patients undergoing PCI, as shown in the sub-analysis of the FINESSE trial [16]. In FINESSE lower rates of death, MI, urgent revascularization, or refractory ischemia through 30 days were associated with LMWHs vs. UFH in patients treated with primary or facilitated PCI (5.3% vs. 8.0%, respectively), as well as lower all-cause mortality at 90 days in patients treated with pPCI or facilitated PCI (3.8% vs. 5.6%, respectively). The incidence of non-intracranial TIMI major bleeding was also lower with enoxaparin (2.6% vs. 4.4%).

A sub-analysis of the ExTRACT-TIMI-25 (EnoXaparin and Thrombolysis Reperfusion for ACute myocardial infarction Treatment, Thrombolysis In Myocardial Infarction 25) trial included 2272 patients in the LMWH arm and 2404 in the



Duval and Tweedie's trim and fill

		Fixed effects			Random effects			Q value
	Studies trimmed	Point estimate	Lower limit	Upper limit	Point estimate	Lower limit	Upper limit	
Observed values		0.53185	0.42811	0.66073	0.53185	0.42811	0.66073	4.21958
Adjusted values	3	0.57062	0.46405	0.70165	0.57062	0.46405	0.70165	8.69431

Fig. 3. Funnel plot for mortality outcome in the primary percutaneous coronary intervention (pPCI) group. The standard error of each study was plotted against the log risk ratio for overall mortality. Open circles represent original studies. Solid circles represent hypothetical or imputed studies. Open diamonds represent the pooled treatment effects from the original studies. The solid diamonds represent the pooled treatment effects incorporating the imputed studies. The adjusted estimate is close to the original observed estimate suggesting validity of the reported effect on mortality from LMWHs vs. UFH.

UFH treatment group who underwent PCI [15]. It provides one of the largest cohorts to date of STEMI patients receiving thrombolysis and anticoagulants. In this PCI subgroup, the primary endpoint of death and non-fatal MI occurred in 10.7% of patients treated with enoxaparin compared with 13.8% of patients in the UFH-treated group. There was a non-significant increase in bleeding in the enoxaparin group: TIMI major bleeding occurring in 1.6% and 1.4% in the enoxaparin and UFH arms, respectively. The reduced rate of death or recurrent MI outweighed the trend towards increased rates in major bleeding and resulted in a net clinical benefit associated with enoxaparin compared with UFH.

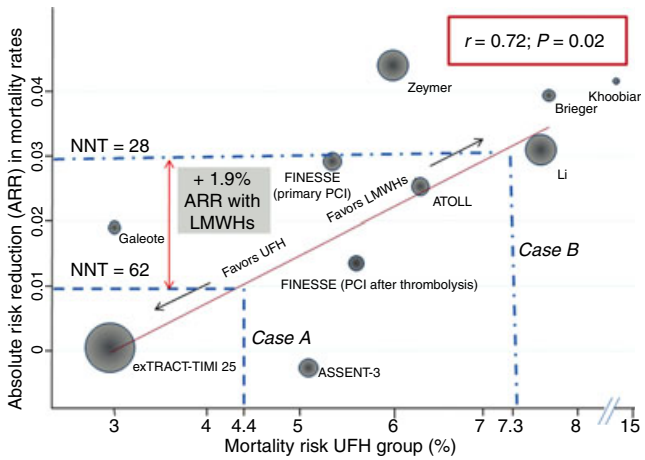


Fig. 4. Meta-regression shows survival advantage of low-molecular-weight heparins (LMWHs) over unfractionated heparin (UFH) therapy as a function of the UFH event rate (proxy for the risk) in two clinical scenarios: the thrombolysis in myocardial infarction (TIMI) risk score (http://www.mdcalc.com/ stemitimiscore) of a 50-year-old hemodynamically stable, male, diabetic patient, with an anterior myocardial infarction (MI), and time to treatment > 4 h (case A) is 3 (4.4% of risk of mortality), whereas the TIMI risk score of a 50-year-old male with an anterior MI and hemodynamic instability (case B) is 4 (7.3% of risk of mortality). Our meta-regression showed that in case A, the number needed to treat (NNT) using LMWHs is 62, whereas for the case B it is less than the half of the case A (NNT = 28). The sizes of the circle are proportional to their statistical weight in the meta-regression.

The only RCT comparing LMWHs with UFH in pPCI is the ATOLL trial (450 patients randomized to enoxaparin, 460 patients randomized to UFH). Preliminary results of this previous study, presented at the 2010 European Society of Cardiology Congress, showed a reduction of the composite endpoint (death, recurrent MI/ACS or Urgent Revascularization) in the enoxaparin arm (6.7% vs. 11.3% in the UFH group, $P = 0.001$) without increased bleeding complications. However, the study was underpowered to assess the effect on individual outcomes.

The current meta-analysis is the first aimed at assessing the safety and efficacy of LMWHs vs. UFH in the setting of PCI (pPCI and after thrombolysis) for STEMI patients.

In our meta-analysis, the benefits in survival associated with LMWH use were evident in the pPCI group, in whom there was also a significant decrease in the rates of major bleeding complications. These data provide further support to the benefits observed with enoxaparin in the ATOLL trial, the only RCT available to date in pPCI.

The present results are consistent with those reported in the RIVIERA study [25], a large prospective observational

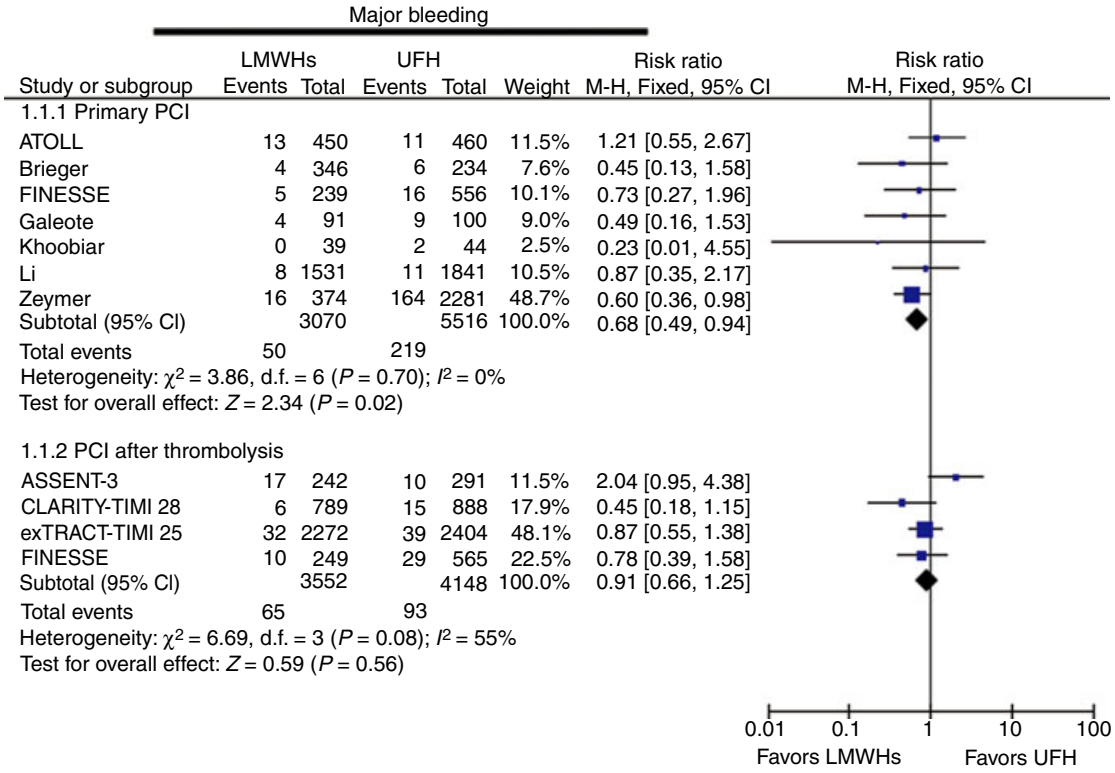


Fig. 5. Individual and summary relative risks (risk ratios) for major bleeding in patients treated with low-molecular-weight heparins (LMWHs) vs. unfractionated heparin (UFH).

registry involving patients undergoing either elective or pPCI, where anticoagulation with enoxaparin was associated with a lower risk of death or MI and a reduced rate of major bleeding complications as compared with UFH treatment.

It should be pointed out that some of the studies included in the current meta-analysis have used different dosing regimens of LMWHs as well as a different length of LMWH treatment. Accordingly, a potential explanation for the success of LMWHs in the setting of pPCI found in our meta-analysis might be the predominantly intravenous and short LMWH regimen vs. the predominantly subcutaneous and prolonged regimen in the lytic studies. However, no single study with its specific regimen was demonstrated to influence the overall results for pPCI, as showed in the sensitivity analyses performed by removing each study and assessing the related changes in the pooled estimates.

Notably, baseline risk differed across the included studies: in the ExTRACT-TIMI 25 trial [15], patients underwent PCI approximately 5 days after thrombolysis for STEMI and were possibly at a lower risk for periprocedural complications than in the FINESSE trial [16] where patients underwent PCI approximately 2 h after presentation and treatment with thrombolytics.

This finding is supported by our risk profile meta-regression; the higher the risk, the greater the benefit associated with LMWH therapy, indicating that the baseline advantage of LMWHs is increased in more complex patients undergoing interventions.

Limitations

There are several limitations that must be acknowledged. A limitation of this meta-analysis, common to all the meta-analyses based on study-level data, is the lack of individual patient data that would have further improved the results of the present study. Pooling data from non-randomized studies may be subject to confounders. However, observational data come from the 'real world' and reflect current practice without selection of populations for randomized studies which often include patients who are far from representative of the patients that are actually going to be treated with the drugs.

On the other hand, some factors may contribute to support the robustness of our findings, such as the high-quality score of included studies (Table 2), the stable results in the sensitivity analyses, in and the absence of heterogeneity among trials.

Some patients in the LMWH group received a mixed treatment with UFH and LMWHs, as reported in one study [19], as well as it is not possible to quantify the precise number of patients undergoing mixed treatment because this information was not available in many of the included studies. In the CLARITY-TIMI 28 different LMWHs were given, even although enoxaparin was the LMWH most frequently administered.

Follow-up time was different across the included studies for the selected endpoints; on the other hand, the longest follow-up available was chosen and stratified analyses for mortality in the pPCI group were performed with 1 month or longest follow-up data, showing consistent benefits in favour of LWMHs.

Patients from the UFH group were more likely to receive adjunctive antithrombotic medications such as IIb/IIIa inhibitors. Therefore, it is possible that patients in the UFH group were at a higher baseline risk, which might have influenced the interventionalist's choice of therapy. On the other hand, additional meta-regressions, performed using as covariate the rate of Gp IIb/IIIa inhibitors reported in the included studies, showed that the use of Gp IIb/IIIa inhibitors did not influence results on mortality and major bleeding outcomes. Almost 100% of the patients in the pPCI group and the vast majority of patients in the PCI after thrombolysis group were on dual antiplatelet therapy: aspirin and clopidogrel (300–600 mg as loading dose). Currently, there are no data regarding the effects of LMWHs vs. UFH in the pPCI setting with concomitant use of new antiplatelet agents such as prasugrel or ticagrelor.

Conclusions

This meta-analysis indicates that LMWHs are associated with a reduction in mortality and major bleeding rates in STEMI patients treated with pPCI as compared with UFH, and that patients at the greatest risk derive the maximum benefit.

Addendum

E.P. Navarese: conception, design, data analysis and interpretation, drafting and revision of the manuscript. G. De Luca interpretation, revision of the manuscript. F. Castriota: interpretation, drafting of the manuscript. M. Kozinski: interpretation, drafting the manuscript. P.A. Gurbel: interpretation, drafting and revision of the manuscript. C.M. Gibson: interpretation, drafting and revision of the manuscript. F. Andreotti: interpretation, drafting and revision of the manuscript. A. Buffon: interpretation, revision of the manuscript. J.M. Siller-Matula: interpretation, revision of the manuscript. A. Sukiennik: interpretation, revision of the manuscript. S. De Servi: interpretation and revision of the manuscript. J. Kubica: interpretation, drafting and revision of the manuscript.

Disclosure of Conflict of Interests

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