RESEARCH

Efficacy and safety of enoxaparin versus unfractionated heparin during percutaneous coronary intervention: systematic review and meta-analysis

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Abstract

Objective To determine the efficacy and safety of enoxaparin compared with unfractionated heparin during percutaneous coronary intervention.

Design Systematic review and meta-analysis.

Data sources Medline and Cochrane database of systematic reviews, January 1996 to May 2011.

Study selection Randomised and non-randomised studies comparing enoxaparin with unfractionated heparin during percutaneous coronary intervention and reporting on both mortality (efficacy end point) and major bleeding (safety end point) outcomes.

Data extraction Sample size, characteristics, and outcomes, extracted independently and analysed.

Data synthesis 23 trials representing 30 966 patients were identified, including 10 243 patients (33.1%) undergoing primary percutaneous coronary intervention for ST elevation myocardial infarction, 8750 (28.2%) undergoing secondary percutaneous coronary intervention after fibrinolysis, and 11 973 (38.7%) with non-ST elevation acute coronary syndrome or stable patients scheduled for percutaneous coronary intervention. A total of 13 943 patients (45.0%) received enoxaparin and 17 023 (55.0%) unfractionated heparin. Enoxaparin was associated with significant reductions in death (relative risk 0.66, 95% confidence interval 0.57 to 0.76; $P<0.001$), the composite of death or myocardial infarction (0.68, 0.57 to 0.81; $P<0.001$), and complications of myocardial infarction

(0.75, 0.6 to 0.85; $P<0.001$), and a reduction in incidence of major bleeding (0.80, 0.68 to 0.95; $P=0.009$). In patients who underwent primary percutaneous coronary intervention, the reduction in death (0.52, 0.42 to 0.64; $P<0.001$) was particularly significant and associated with a reduction in major bleeding (0.72, 0.56 to 0.93; $P=0.01$).

Conclusion Enoxaparin seems to be superior to unfractionated heparin in reducing mortality and bleeding outcomes during percutaneous coronary intervention and particularly in patients undergoing primary percutaneous coronary intervention for ST elevation myocardial infarction.

Introduction

The use of unfractionated heparin during percutaneous coronary intervention is limited by its unpredictable effect, the need for close monitoring, and the uncertainty around optimal levels of activated clotting time.¹⁻⁴ Moreover, the drug exhibits prothrombotic properties related to platelet activation, poor control of von Willebrand factor release, and rebound of thrombin generation after discontinuation.⁵⁻⁶ Despite these limitations and the absence of relevant randomised placebo controlled trials, anticoagulation during elective and primary percutaneous coronary intervention has traditionally been supported by unfractionated heparin, based largely on historical practice. The current updated guidelines for anticoagulation in patients requiring percutaneous coronary intervention for ST

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Characteristics of included studies

Death or myocardial infarction in participants

Complications of myocardial infarction (or myocardial infarction) in participants

segment elevation myocardial infarction produced by the American College of Cardiology, American Heart Association, and Society of Cardiac Angiography and Intervention as well as guidelines from the Task Force on Myocardial Revascularization of the European Society of Cardiology continue to afford unfractionated heparin a class I recommendation for this indication, despite limited supporting evidence (level of evidence C).^{7 8}

Enoxaparin is the leading low molecular weight heparin with the largest volume of published information on use in the setting of percutaneous coronary intervention. It provides predictable anticoagulation without the need for monitoring^{9 10} and it can be administered predominantly by subcutaneous injection, as in the management of non-ST elevation acute coronary syndromes and ST elevation myocardial infarction treated with thrombolysis, in both cases with a scheduled invasive strategy (American College of Cardiology and American Heart Association class IIa and I, respectively). Enoxaparin can also be used with intravenous injections for immediate anticoagulation in patients undergoing primary percutaneous coronary intervention or elective percutaneous coronary intervention, as shown recently in several randomised studies.¹¹⁻¹⁴ Although studies have evaluated enoxaparin during percutaneous coronary intervention in several clinical settings,¹⁵⁻³³ none was powered for mortality.

We pooled the data from all the studies that compared enoxaparin with unfractionated heparin during percutaneous coronary intervention to gain sufficient power to evaluate potential differences in mortality and safety.

Methods

Two researchers (JS and GM) searched PubMed and the Cochrane database of systematic reviews from January 1996 to May 2011 using the search terms “enoxaparin”, “unfractionated heparin”, “angioplasty”, and “percutaneous coronary intervention”. In addition, we contacted experts in the specialty and reviewed abstracts from selected major cardiology scientific meetings (American Heart Association, American College of Cardiology, European Society of Cardiology, and Transcatheter Cardiovascular Therapeutics). The meta-analysis included cohort studies and clinical trials that compared the efficacy and safety of enoxaparin with unfractionated heparin among patients undergoing primary, secondary (post-fibrinolysis), or scheduled percutaneous coronary intervention according to a predefined protocol. We restricted our analysis to trials that met all of the following inclusion criteria: patients with coronary heart disease undergoing percutaneous coronary intervention, considering the whole study population or at least a predominant subset of this population; a control group using unfractionated heparin for comparison with enoxaparin; and publications reporting data at least on mortality and major bleeding. To focus on the direct comparison of enoxaparin with unfractionated heparin, we excluded studies that used a low molecular weight heparin other than enoxaparin, with the exception of one study in which other low molecular weight heparins were used in a few of the patients.³⁴

A total of 229 studies were identified as potentially relevant and were screened for inclusion. Of the 34 studies that fulfilled the inclusion criteria and were screened in detailed, we subsequently excluded 11 because they did not include data on efficacy outcomes³⁵ did not include data on the percutaneous coronary intervention subgroup,³⁶⁻⁴¹ published details of the percutaneous coronary intervention subgroup in a separate article,^{42 43} or studied a low molecular weight heparin other than

enoxaparin.^{44 45} From the 23 studies remaining for the analysis, two reviewers (JS and OB) independently extracted outcome data and recorded the information on a standardised case report form. When available we extracted the following data from each trial: year of publication, trial design, population characteristics, number of patients (per group), dose and mode of enoxaparin administered, dose of unfractionated heparin, use of antiplatelet drugs (aspirin, thienopyridine, and platelet glycoprotein IIb/IIIa inhibitors), duration of follow-up, efficacy end points, and safety end points (see web extra table).

Assessment and reporting risk of bias in included studies

Two independent reviewers determined the quality score of non-randomised studies and subanalysis and retrospective analysis of randomised controlled trials according to the Newcastle-Ottawa scale for cohort studies (www.ohri.ca/programs/clinical_epidemiology/oxford.htm). We also carried out a validity assessment according to the Cochrane Collaboration's tool for assessing risk of bias. Randomised clinical trials were graded based on sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other sources of bias. For each trial we summarised the global assessment of risk of bias as low, unclear, or high. We entered data into a centralised database for analysis and resolved discrepancies by consensus of two authors (JS and OB). If additional data or clarification was necessary we contacted the study authors. When necessary, research associates with the relevant language helped to interpret non-English manuscripts.²⁴

Endpoint definitions

The main objective of this study was to evaluate the impact of enoxaparin and unfractionated heparin on mortality (main efficacy end point) and major bleeding (main safety end point) during percutaneous coronary intervention. We considered all cause mortality except in studies where only cardiovascular mortality was reported. The bleeding definitions used for this analysis were those corresponding to the main safety end point of each study (see web extra table). Other efficacy end points analysed were the composite ischaemic end point of death or myocardial infarction and complications of myocardial infarction (or post-procedure myocardial infarction when this was the only reported complication) as defined in each study. Major bleeding was the main safety end point, although we also collected and analysed data on minor bleeding. We considered all end points at the longest follow-up available in each study. Firstly, we carried out a global meta-analysis of all the studies, including all patients after percutaneous coronary intervention regardless of the clinical presentation. Secondly, we carried out a meta-analysis for the same end points, restricting the analyses to predefined types of percutaneous coronary intervention: primary, secondary (post-fibrinolysis), and scheduled (patients with non-ST elevation acute coronary syndromes or stable patients).

Statistical analysis

From each publication we obtained the raw numbers of patients experiencing the outcomes of interest among all patients in each treatment group. We obtained the common effect calculation by analysis of all patients. Using a random model we carried out several analyses to obtain a global estimation of the treatment effect and to minimise heterogeneity between groups. We used the EasyMa software (Department of Clinical

Pharmacology and Biostatistic, EA643, university hospital of Lyon, France) to calculate relative risks with 95% confidence intervals.⁴⁶ An α risk of 5% was used. Finally, the number of patients needed to treat (NNT) to avoid one event was calculated using the overall weighted risk difference: $NNT=1/(\text{absolute risk difference})$.

Confirmatory evaluation of potential bias

We carried out a confirmatory analysis using the “meta” package of R software (R version 2.13.0, R Foundation for Statistical Computing) and arcsine transformation. This analysis accounts for heterogeneity, particularly when effect sizes are small and heterogeneity is high, and allows inclusion of trials with zero events in each arm.

Subgroup analysis and investigation of heterogeneity

Although the random effect model accommodated variability among studies, we examined the extent of heterogeneity in the individual trials. We used the Q Cochran test to look for heterogeneity between groups, with heterogeneity tests set at 0.1.⁴⁷ Potential small study bias or publication bias (that is, the likelihood of small yet nominally significant studies being published selectively) was examined by visual inspection of constructed funnel plots and analytically using Egger’s test.⁴⁸ Egger’s method plots linearly the standard normal deviate (natural logarithm of relative risk/standard error (SE) of relative risk) and precision ($1/SE$ of relative risk) as independent variables, with test results based on the P value of the regression constant.

Sensitivity analysis

We carried out a sensitivity analysis by removing each study in turn from the overall data to evaluate the influence of a single study on the pooled analysis and by restricting the meta-analysis to several subgroups: patients with ST elevation myocardial infarction undergoing percutaneous coronary intervention (primary or secondary), published (full length) studies, small (<500 patients) versus large studies (≥ 500 patients), intravenous versus subcutaneous enoxaparin, and high quality (randomised controlled trials) or low quality studies (registry based).

Results

Twenty three trials, totalling 30 966 patients, met the inclusion criteria (fig 1). Twelve randomised controlled trials and 11 non-randomised trials (including four subanalyses of randomised controlled trials) compared enoxaparin with unfractionated heparin during percutaneous coronary intervention. The average follow-up of the studies was 2.4 months, but most ($n=19$) had only short term follow-up (in hospital or at 30 days). A total of 13 943 patients (45.0%) received enoxaparin and 17 023 (55.0%) unfractionated heparin. In seven trials, totalling 10 243 patients (33.1%), primary percutaneous coronary intervention was carried out for ST elevation myocardial infarction; in three trials, totalling 8750 patients (28.2%), percutaneous coronary intervention was carried out after initial reperfusion with lytics; and in 13 trials, totalling 11 973 patients (38.7%), percutaneous coronary intervention was carried out in an elective setting. In 15 of these trials, enoxaparin was used as an intravenous bolus just before percutaneous coronary intervention; at a low dose (0.5 mg/kg) in four studies and at a higher dose (0.75 mg/kg or 1 mg/kg) in 12 studies (including the 0.75 mg/kg arm of the STEEPLE trial). In six trials, patients underwent percutaneous coronary intervention under a regimen of enoxaparin

administered subcutaneously, and in two trials^{20 33} no mention was made of the enoxaparin dose or mode in which it was administered. The dose range for unfractionated heparin was 60 to 100 IU/kg bolus according to the concomitant use of platelet glycoprotein IIb/IIIa inhibitors or not, with further adjustments based on measurement of activated clotting time. Table 1 outlines the details of the trials, the settings of the percutaneous coronary intervention, and length of follow-up (see web extra table for anticoagulation protocols, concomitant use of antiplatelet therapies, and major baseline characteristics of each study). Within each randomised trial, the baseline characteristics of patients treated with enoxaparin or with unfractionated heparin were similar, but some of the main characteristics in the registry based studies differed (see web extra table).

Summary of end points

Figure 2 summarises all studied end points for the total population of the meta-analysis, as well as the subgroup of patients undergoing primary percutaneous coronary intervention. The Cochrane P value for heterogeneity is included.

Mortality

In the overall cohort of patients ($n=30\,966$), enoxaparin was associated with a 34% relative risk reduction (0.66, 95% confidence interval 0.58 to 0.77; $P<0.001$) and a 1.66% absolute risk reduction of mortality (NNT=60; fig 3). Heterogeneity between trials was not significant ($P=0.46$) and evidence of publication bias using the funnel plot and Egger’s regression test was lacking ($P=0.82$). In the higher risk group of patients with ST elevation myocardial infarction undergoing primary percutaneous coronary intervention ($n=10\,243$), enoxaparin was associated with a significant 48% relative risk reduction in mortality (3.12% enoxaparin v 6.03% unfractionated heparin) and a 2.91% absolute relative risk reduction ($P<0.001$; NNT=34). Heterogeneity between trials was not significant ($P=0.53$) and evidence of publication bias in the primary percutaneous coronary intervention subgroup was lacking ($P=0.90$). In the smaller and lower risk group of patients with non-ST elevation acute coronary syndromes and stable coronary artery disease undergoing scheduled percutaneous coronary intervention (relative weight 12.5%; mortality rate 0.88%) mortality rates did not differ significantly between the enoxaparin and unfractionated heparin cohorts, with a trend towards a reduction in mortality with enoxaparin.

Safety outcomes

In the overall cohort of patients with reported major bleeding ($n=30\,775$), enoxaparin was associated with a 20% relative risk reduction (0.80, 95% confidence interval 0.67 to 0.95; $P=0.009$) and an absolute risk reduction of 1.20% (NNT=83; fig 4). Heterogeneity between trials was not significant ($P=0.58$) and evidence of publication bias was lacking. The reduction in major bleeding seemed to be greater in patients with ST elevation myocardial infarction undergoing primary percutaneous coronary intervention, with enoxaparin treatment compared with unfractionated heparin treatment resulting in relative and absolute risk reductions of 28% and 1.9%, respectively (NNT=53), $P=0.01$.

Although the incidence of minor bleeding was numerically lower in patients treated with enoxaparin than with unfractionated heparin, this difference was not significant in the overall percutaneous coronary intervention cohort or in the setting of primary percutaneous coronary intervention (fig 2).

Ischaemic end points

Compared with unfractionated heparin, enoxaparin was associated with a 32% relative risk reduction and 2.01% absolute risk reduction of death or myocardial infarction (relative risk 0.68, 95% confidence interval 0.57 to 0.81; $P<0.001$, NNT=50; see web extra figure 1). Similarly, enoxaparin was associated with a significant 25% relative risk reduction and 1.52% absolute risk reduction in complications of myocardial infarction (0.75, 0.66 to 0.85; $P<0.001$; NNT=66; see web extra figure 2). Heterogeneity between trials for these two composite end points was not significant ($P=0.42$ and $P=0.55$, respectively) and evidence of publication bias using the funnel plot was not found. The magnitude of the enoxaparin effect was largest in patients with ST elevation myocardial infarction undergoing primary percutaneous coronary intervention, with a 44% relative risk reduction and a 3.6% absolute risk reduction of death or myocardial infarction (0.56, 0.42 to 0.76; NNT=28; $P<0.001$), with a consistent significant reduction of complications of myocardial infarction compared with unfractionated heparin (0.76, 0.60 to 0.96; $P=0.022$; see web extra figure 1).

Sensitivity and subgroups analyses

A series of sensitivity analyses confirmed the same directionality for the primary efficacy end point (mortality) and the primary safety end point (major bleeding, tables 2 and 3). None of the studies individually affected the overall results either for mortality or for major bleeding. The reduction in mortality associated with enoxaparin was consistent across all subgroups, with the single exception of the subgroup of small sized studies (<500 patients), which showed a reduction of similar magnitude that did not reach significance (relative risk 0.59, 95% confidence interval 0.20 to 1.78; $P=0.35$). No subgroup analyses showed heterogeneity, and the superiority of enoxaparin on mortality was significant in both randomised controlled studies ($n=16$) and registry based studies ($n=7$). Results were consistent for major bleeding across all subgroups except for route of administered enoxaparin. In the subgroup of studies (14 studies, 10 260 patients) using intravenous enoxaparin, major bleeding was reduced by 34% compared with unfractionated heparin (0.66, 0.52 to 0.83; $P<0.001$, P for heterogeneity 0.9; absolute risk reduction 1.52%; NNT=66). This favourable effect was not observed in the subgroup of studies that used subcutaneous enoxaparin (six studies, 16 527 patients), with no difference between the two anticoagulants (1.04, 0.80 to 1.35, $P=0.7$, P for heterogeneity 0.4). Finally, the arcsine test for binary outcomes confirmed the results of the primary additive summary models for all end points.

Discussion

In this meta-analysis, enoxaparin was superior to unfractionated heparin in reducing mortality and bleeding outcomes during percutaneous coronary intervention, particularly in patients undergoing primary percutaneous coronary intervention for ST elevation myocardial infarction. Since early 2000 data have accumulated on enoxaparin in varied percutaneous coronary intervention settings. This current meta-analysis, with information on more than 30 000 patients, showed a 34% statistically significant reduction in mortality (1.66% absolute risk reduction) in patients receiving enoxaparin during percutaneous coronary intervention compared with unfractionated heparin. This survival benefit is supported by concomitant reductions in both ischaemic and major bleeding complications. All sensitivity analyses of mortality confirmed a genuine difference between the two drugs. Subgroup analyses

suggested that the benefits on mortality and ischaemic complications were largely driven by the superiority measured in patients undergoing primary percutaneous coronary intervention for ST elevation myocardial infarction, whereas the better safety outcomes might be driven by the intravenous (versus subcutaneous) use of enoxaparin.

This meta-analysis confirms the results recently reported in the ATOLL (Acute ST-elevation 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) randomised trial.¹⁴ Compared with unfractionated heparin, intravenous enoxaparin at a dose of 0.5 mg/kg reduced death or resuscitated cardiac death in patients undergoing primary percutaneous coronary intervention by 42% ($P=0.049$) and death or myocardial infarction by 37% ($P=0.02$).¹⁴ Although the 40% relative risk reduction in all cause mortality associated with enoxaparin in ATOLL was not significant ($P=0.08$) owing to lack of power, it is consistent with the 38% reduction in mortality found in the group with ST elevation myocardial infarction in the current meta-analysis ($P<0.001$), and more specifically with the 48% reduction of mortality in patients undergoing primary percutaneous coronary intervention ($P<0.001$). The survival benefit associated with enoxaparin was present in both risk of bias subgroups in our meta-analysis; in low risk of bias studies (randomised trials and retrospective analysis of randomised trials) and in those showing higher risk of bias (non-randomised studies).

This reduction in mortality is likely to be related to the favourable effects of enoxaparin in the prevention of ischaemic complications, which were also shown in this meta-analysis. Consistent reductions in ischaemic end points were observed in the overall analysis as well as in the five largest randomised studies,^{13 14 30 35 42} which together represented two thirds of the weight of ischaemic events in our meta-analysis. In comparison with unfractionated heparin, enoxaparin has been shown to be more stable and have more predictable pharmacokinetics,¹ providing an optimal level of anticoagulation at the time of the procedure in more than 90% of patients, by whatever route the drug is administered.^{9 49-51} These optimal levels of anticoagulation have also been related to better ischaemic and survival outcomes.¹⁰ Moreover, additional endothelial and anti-inflammatory properties of enoxaparin⁶ may play an additional part in the prevention of ischaemic complications of acute coronary syndrome.

Improved safety might also contribute to the reduction in mortality rates. Previous studies have shown that bleeding and red blood cell transfusion have deleterious effects⁵² and have an effect on ischaemic outcomes as well as on mortality.⁵³ Therefore the 20% reduction in major bleeding associated with enoxaparin might also have affected ischaemic and mortality outcomes. This result is consistent among all subgroups, with the exception of studies in which subcutaneous enoxaparin was used in comparison with unfractionated heparin, when no difference was seen. It seems that the reduction in major bleeding was mostly observed with intravenous enoxaparin, but the P value for interaction was not significant probably because of the heterogeneity in risk levels of populations in the two subgroups (subcutaneous versus intravenous). Indeed, the intravenous route provides immediate anticoagulation, with rapid clearance,⁴⁹ avoiding exposure to prolonged anticoagulation after percutaneous coronary intervention, and in this study was associated with a 34% reduction in major bleeding (absolute risk reduction 1.52%) compared with unfractionated heparin. Therefore this meta-analysis confirms the benefit of enoxaparin measured in the individual randomised

STEEPLE¹(elective angioplasty) and ATOLL¹⁴(primary angioplasty) studies, with enough power to show a reduction in mortality. Patients with ST elevation myocardial infarction obviously gain a large benefit from enoxaparin on ischaemic end points and mortality. Although favourable, the magnitude of these effects seems less important in other clinical situations.

Comparisons with other reviews

Other new anticoagulants have been compared with unfractionated heparin in the setting of percutaneous coronary intervention. Bivalirudin alone compared with unfractionated heparin plus glycoprotein IIb/IIIa inhibitors has consistently shown improved safety in percutaneous coronary intervention, associated with a reduction in mortality in one trial.⁵⁴⁻⁵⁷ Head to head comparisons of unfractionated heparin alone in percutaneous coronary intervention have also suggested a better safety profile of bivalirudin, but without significant advantage on the net clinical benefit or mortality.⁵⁸⁻⁶⁰ Finally, a recent meta-analysis of nine trials, totalling almost 30 000 patients, confirmed the reduction in major bleeding complications from use of bivalirudin compared with unfractionated heparin, but failed to show any benefit on mortality, whereas a trend for higher risk of myocardial infarction was noted.⁶¹ In contrast with this, a meta-analysis of nine studies, totalling 16 286 patients, comparing low molecular weight heparin with unfractionated heparin in the setting of percutaneous coronary intervention for ST elevation myocardial infarction reported a reduction in both mortality and major bleeding consistent with our findings.⁶²

An alternative anticoagulant, the synthetic factor Xa inhibitor fondaparinux, has been tested in acute coronary syndromes.⁶³ Results were not favourable in patients with ST elevation myocardial infarction undergoing primary percutaneous coronary intervention⁶⁴ and the drug has been tested only sparingly in elective percutaneous coronary intervention.⁶⁵ A significant increase in catheter related thrombosis with fondaparinux prompted guidelines committees on both sides of the Atlantic to recommend unfractionated heparin as adjunctive treatment at the time of percutaneous coronary intervention. The recent results of the randomised Fondaparinux Trial With Unfractionated Heparin During Revascularization in Acute Coronary Syndromes (FUTURA) suggest that a standard unfractionated heparin dose of 85 IU/kg bolus, with an additional bolus if needed to achieve activated clotting time of 300 to 350 seconds, is preferable to a lower dose in patients previously treated with subcutaneous fondaparinux.³ In a pooled analysis of 19 085 patients with acute coronary syndrome invasively managed, fondaparinux reduced major bleeding compared with a heparin based strategy, with similar rates of ischaemic events and no reduction in mortality.⁶⁶

Strengths and limitations of this meta-analysis

Our meta-analysis has limitations and was not carried out on individual patients' data, which if possible would have strengthened the results, especially for subgroup analyses. Although differences in trial designs and definitions should be considered when interpreting the overall results, mortality is a hard end point not affected by study definitions. Duration and dose of study drugs also differed between trials, as did the use of concomitant treatments and types of revascularisation. Of note, many of the non-randomised studies were not pure head to head comparisons of the two anticoagulants. However, the absence of heterogeneity in the overall analysis and the sensitivity and subgroup analyses all showing consistent

reductions in mortality, suggest that the results are robust. Regarding safety, it seems that the intravenous route for administering enoxaparin drives the reduction in major bleeding, confirming previous information from randomised trials.^{11 14 67} Duration of anticoagulation is a possible confounder for this problem, although this information is usually not available in published data.

Meaning of the study and implications for policymakers

The profound reduction in mortality found in this meta-analysis could be explained by the additional reductions of serious ischaemic events and major bleeding. The global reduction in ischaemic events and mortality was driven by the major effect observed in the setting of primary percutaneous coronary intervention for ST elevation myocardial infarction and is in line with the results of the ATOLL randomised trial.¹⁴ This effect was obtained from anticoagulation using intravenous enoxaparin and the favourable pharmacodynamic profile of the 0.5 mg/kg dose. A similar benefit on mortality has been seen recently in other studies of ST elevation myocardial infarction using bivalirudin⁵⁶ or radial access.^{68 69} In lower risk populations the same interventions did not reduce mortality.^{1 54 69} The results of this meta-analysis should influence the next guidelines dealing with anticoagulation in percutaneous coronary intervention or in ST elevation myocardial infarction. The superiority of enoxaparin over unfractionated heparin is now well documented in the setting of percutaneous coronary intervention, by randomised controlled trials, registry based studies, and this meta-analysis, building the case for an update of current guidelines on anticoagulation. This is particularly true for primary percutaneous coronary intervention, where the benefit is most striking.

Unanswered questions and future research

Two new anticoagulants (bivalirudin and enoxaparin) have proved to be superior to unfractionated heparin during percutaneous coronary intervention, particularly in patients with ST elevation myocardial infarction undergoing primary percutaneous coronary intervention. A head to head comparison between intravenous enoxaparin and intravenous bivalirudin is needed in the setting of primary percutaneous coronary intervention using contemporary techniques (radial access, last generation of stent, and thromboaspiration) and new antiplatelet agents such as prasugrel or ticagrelor.

Conclusions

During percutaneous coronary intervention, enoxaparin seems to be superior to unfractionated heparin in reducing all cause mortality and ischaemic and bleeding end points. This superiority was particularly evident in patients with ST elevation myocardial infarction undergoing primary percutaneous coronary intervention. Given the relatively low cost of enoxaparin (and its wide availability), this seems to be an attractive strategy to improve outcomes in the large number of patients undergoing percutaneous coronary intervention worldwide.

Contributors: JS, OB, and GM designed the study; acquired, analysed, and interpreted the data; and revised the manuscript. JS, OB, FB, CP, MC, KH, UZ, GC, J-PC, and EV helped implement the study and made critical revision of the manuscript. JS did the statistical analysis, which was reviewed by OB, EV, and FB. JS wrote the first draft and submitted the final version of the manuscript under the supervision of GM. All

What is already known on this topic

Enoxaparin has a more stable and predictable anticoagulant effect than unfractionated heparin, which requires tight monitoring and dose adjustment

In randomised studies, intravenous enoxaparin 0.5 mg/kg was superior to unfractionated heparin in elective percutaneous coronary intervention (reduction of bleeding) and primary percutaneous coronary intervention (reduction of ischaemic events)

What this study adds

Enoxaparin use during percutaneous coronary intervention reduced mortality by 34% (absolute risk reduction 1.66%) compared with unfractionated heparin

The mortality benefit was particularly noticeable in patients with ST elevation myocardial infarction undergoing primary percutaneous coronary intervention

This survival benefit is supported by concomitant reductions in both ischaemic and major bleeding complications

authors have seen the final submitted manuscript and agree with its contents. JS and GM are the guarantors.

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Ethical approval: Not required.

Data sharing: The dataset, statistical code, and review protocol are available from the corresponding at gilles.montalescot@psl.aphp.fr.

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Tables

Table 1 | Description of studies included in meta-analysis

Study	Journal	No of patients in enoxaparin/unfractionated heparin groups	Study design (quality score*or risk of bias)	Study population/PCI setting	Follow-up
ATOLL 2011 ¹⁴	<i>Lancet</i>	450/460	Randomised controlled trial (low risk)	Primary PCI (STEMI)	1 month
Brieger et al 2011 ¹⁶	<i>Catheter Cardiovascular Intervention</i>	346/234	Registry (8/9)	Primary PCI (STEMI)	1 month
Li et al 2010 ²⁸	<i>American Heart Journal</i>	1531/1841	Registry (9/9)	Primary PCI (STEMI)	8 months
FINESSE Enox 2010 ¹³	<i>JACC. Cardiovascular Interventions</i>	759/1693	Prospective substudy of randomised controlled trial (9/9)	Primary PCI (STEMI) with 33% of patients receiving half dose thrombolysis	3 months
Galeote et al 2009 ¹⁹	<i>Medicina Intensiva</i>	91/100	Registry (6/9)	Primary PCI (STEMI)	In-hospital
Khoobiar et al 2008 ²⁹	<i>Journal of Thrombosis and Thrombolysis</i>	39/44	Registry (6/9)	Primary PCI (STEMI)	15 months
Zeymer et al 2008 ⁴³	<i>Eurointervention</i>	374/2281	Registry (9/9)	Primary PCI (STEMI)	In-hospital
ExTRACT-TIMI 25 2007 ³⁴	<i>Journal of the American College of Cardiology</i>	2272/2404	Retrospective analysis of randomised controlled trial (9/9)	Post-fibrinolysis PCI (STEMI)	1 month
CLARITY-TIMI 28 2005 ³⁰	<i>Circulation</i>	1429/1431	Retrospective analysis of randomised controlled trial (9/9)	Post-fibrinolysis PCI (STEMI)	1 month
ASSENT-3 2003 ³²	<i>Journal of the American College of Cardiology</i>	590/624	Retrospective analysis of randomised controlled trial (9/9)	Post-fibrinolysis PCI (STEMI)	12 months
ZEUS 2010 ¹⁵	<i>Eurointervention</i>	436/440	Randomised controlled trial (low risk)	Elective or urgent PCI	1 month
Diez et al 2009 ¹⁷	<i>Texas Heart Institute Journal</i>	222/271	Registry (8/9)	Elective or urgent PCI	In-hospital
Zeymer et al 2006 ²⁰	<i>American Journal of Cardiology</i>	339/994	Registry (8/9)	Early PCI	In-hospital
STEEPLE 2006 ¹¹	<i>New England Journal of Medicine</i>	2298 (2 doses)/1230	Randomised controlled trial (low risk)	Elective PCI	1 month
SYNERGY 2006 ³¹	<i>American Heart Journal</i>	2028/2293	Retrospective analysis of randomised controlled trial (9/9)	Elective or urgent PCI	1 month
Her et al 2006 ²¹	<i>Korean Circulation Journal</i>	68/71	Randomised controlled trial (unclear risk)	Elective PCI	1 month
ACTION 2005 ²²	<i>American Journal of Cardiology</i>	100/100	Randomised controlled trial (low risk)	Elective PCI	1 month
CRUISE 2003 ²³	<i>Journal of the American College of Cardiology</i>	129/132	Randomised controlled trial (low risk)	Elective or urgent PCI	1 month
Galeote et al 2002 ²⁴	<i>Revista Espanola de Cardiologia</i>	50/49	Randomised controlled trial (unclear risk)	Elective or urgent PCI	In-hospital
Drozd et al 2001 ¹⁸	<i>Kardiologia Polska</i>	50/50	Randomised controlled trial (unclear risk)	Elective PCI	1 month
Dudek et al 2000 ²⁷	<i>American Journal of Cardiology</i>	200/200	Randomised controlled trial (low risk)	Elective or urgent PCI	In-hospital
Dudek et al 2000 ²⁶	<i>Journal of the American College of Cardiology</i>	112 (2 doses)/50	Randomised controlled trial (unclear risk)	Elective PCI	In-hospital
Rabah et al 1999 ²⁵	<i>American Journal of Cardiology</i>	30/30	Randomised controlled trial (low risk)	Elective PCI	1 month

PCI=percutaneous coronary intervention; STEMI=ST elevation myocardial infarction.

*Non-randomised controlled trials.

Table 2| Subgroup analysis for mortality

Subgroup	No of studies	No of patients	No of deaths/No in group		Relative risk (95% CI)	P values	
			Enoxaparin group	Unfractionated heparin group		Overall	For heterogeneity
Overall	23	30 966	278/13 943	622/17 023	0.66 (0.57 to 0.76)	<0.001	0.46
Published (full length report)	21	30 404	278/13 631	621/16 773	0.66 (0.56 to 0.77)	<0.001	0.56
Large size (≥500)	12	28 778	275/12 852	615/15 923	0.65 (0.52 to 0.81)	<0.001	0.43
Small size (<500)	11	2188	3/1091	7/1097	0.59 (0.20 to 1.78)	0.35	0.46
Patients with STEMI	10	18 993	237/7881	557/11 112	0.62 (0.48 to 0.78)	<0.001	0.52
High quality studies: RCT*	16	22 259	211/11 001	325/11 258	0.78 (0.66 to 0.93)	0.006	0.97
Low quality studies: registries	7	8707	67/2943	297/5765	0.43 (0.33 to 0.57)	<0.001	0.86
Subcutaneous enoxaparin	6†	16 527	197/7889	314/8638	0.70 (0.53 to 0.94)	0.017	0.57
Intravenous enoxaparin	15†	10 451	74/5341	151/5110	0.66 (0.50 to 0.88)	0.004	0.99

STEMI=ST elevation myocardial infarction; RCT=randomised controlled trial.

*Including substudies of RCTs.

†Two studies did not mention mode in which drug was administered.^{20 33}

Table 3| Subgroup analysis for major bleeding

Subgroup	No of studies	No of patients	No with major bleeding/No in group		Relative risk (95%CI)	P values	
			Enoxaparin group	Unfractionated heparin group		Overall	For heterogeneity
Overall	22*	30 775	295/13 852	564/16 923	0.80 (0.68 to 0.95)	0.009	0.58
Published (full length report)	20	30 213	295/13 540	564/16 673	0.80 (0.66 to 0.96)	0.022	0.62
Large size (≥500)	12	28 778	288/12 852	549/15 926	0.80 (0.50 to 0.99)	0.041	0.55
Small size (<500)	10	1997	7/1000	15/997	0.62 (0.27 to 1.42)	0.26	0.98
Patients with STEMI	9	18 802	170/7790	384/11 012	0.80 (0.66 to 0.97)	0.026	0.44
High quality studies: RCTs†	16	22 259	226/11 001	299/11 258	0.83 (0.66 to 1.04)	0.11	0.70
Low quality studies: registry based	7	8516	69/2851	265/5665	0.73 (0.55 to 0.96)	0.026	0.80
Subcutaneous enoxaparin	6	16 527	149/7889	154/8638	1.04 (0.80 to 1.35)	0.75	0.43
Intravenous enoxaparin	14	10 260	114/5250	185/5010	0.66 (0.52 to 0.83)	<0.001	0.90

RCT=randomised controlled trial; STEMI=ST elevation myocardial infarction.

*One study did not report major bleeding in both groups and was excluded from analysis.²⁴

Figures

Fig 1 Flow of studies through review

Fig 2 Pooled event rates and relative risk ratios for major end points in overall cohort of patients undergoing percutaneous coronary intervention (PCI) and in subgroup of patients undergoing primary percutaneous coronary intervention. STEMI=ST elevation myocardial infarction

Fig 3 All cause mortality in patients undergoing percutaneous coronary intervention (PCI) treated with enoxaparin or unfractionated heparin. STEMI=ST elevation myocardial infarction; non-STE ACS=non-ST elevation acute coronary syndrome

Fig 4 Major bleeding in patients undergoing percutaneous coronary intervention (PCI) treated with enoxaparin or unfractionated heparin. STEMI=ST elevation myocardial infarction; non-STE ACS=non-ST elevation acute coronary syndrome