Intravenous Low-Molecular-Weight Heparins Compared With Unfractionated Heparin in Percutaneous Coronary Intervention: Quantitative Review of Randomized Trials

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Background: Despite its limitations, unfractionated heparin (UFH) is the recommended anticoagulant during percutaneous coronary intervention (PCI). Few randomized trials have compared low-molecular-weight heparin (LMWH) and UFH, and most lacked the power to detect a difference between the 2 anticoagulants in terms of safety or efficacy. Our objective was to perform a meta-analysis of randomized trials comparing the efficacy and safety of LMWH vs UFH as anticoagulants in the setting of PCI.

Methods: We used MEDLINE, randomized trials presented at major cardiology conferences, and journal article bibliographies from January 1998 and September 2006. Two reviewers independently identified randomized studies comparing the intravenous administration of LMWH vs UFH among patients undergoing PCI. Data on sample size, baseline characteristics, and outcomes of interest were independently extracted and analyzed.

Results: Thirteen trials including 7318 patients met the inclusion criteria. A total of 4201 patients (57.4%) received LMWH, and 3117 patients (42.6%) received UFH. Intravenous LMWH use was associated with a significant reduction in the risk of major bleeding compared with UFH (odds ratio [OR], 0.57; 95% confidence interval [CI], 0.40-0.82; P = .002). A trend toward a reduction in minor bleeding was also observed among LMWH-treated patients (OR, 0.75; 95% CI, 0.47-1.20; P = .24). Similar efficacy was observed between LMWH and UFH regarding the double end point of death or myocardial infarction (OR, 0.99; 95% CI, 0.79-1.24; P = .93). There were no significant differences in death, myocardial infarction, and urgent revascularization between patients receiving LMWH and those receiving UFH.

Conclusion: The use of intravenous LMWH during PCI is associated with a significant reduction in major bleeding events compared with UFH, without compromising outcomes on hard ischemic end points.

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Low-molecular-weight heparins (LMWHs) have demonstrated several well-established potential advantages over unfractionated heparin (UFH) as antithrombin agents. In percutaneous coronary intervention (PCI), the use of UFH is limited by its unpredictable stability, the need for close monitoring of anticoagulation levels, and the absence of well-determined target anticoagulation levels. Moreover, UFH exhibits prothrombotic properties related to poor control of von Willebrand factor release, as well as platelet activation and rebound of thrombin generation after discontinuation. In contrast, LMWHs have a more predictable pharmacological profile than UFH, removing the need for close therapeutic drug monitoring. This is mainly because of reduced nonspecific protein binding and reduced neutralization by platelet factor 4. Other properties, such as reduced induction of von Willebrand factor release and reduced platelet activation, are of importance in PCI, during which endothelial denudation, plaque disruption, and implantation of stents are systematically followed by platelet activation and aggregation. Furthermore, LMWHs exhibit a greater inhibition of thrombin generation compared with UFH due to a higher anti-Xa to anti-IIa ratio; they also produce an enhanced release of tissue factor pathway inhibitor. Heparin-induced thrombocytopenia is also much less common with LMWH than UFH.

Despite its limitations, UFH remains widely used during PCI. Several randomized studies have sought to assess the ef-
Efficacy and safety of intravenous administration of LMWH during PCI compared with UFH, but their small sample size did not allow any definitive conclusions.7-14 Recently, the large randomized Safety and Efficacy of Enoxaparin in PCI (STEPPLE) trial demonstrated a better safety profile of the LMWH enoxaparin over UFH with similar efficacy on ischemic end points, although the power of the trial was not sufficient to draw definitive conclusions on death or myocardial infarction (MI). The present meta-analysis evaluates the safety of LMWH in more than 7000 patients undergoing PCI with sufficient power to examine efficacy (death or MI).

OBJECTIVE AND CRITERIA FOR STUDY SELECTION

The objective of this meta-analysis was to assess the efficacy and safety of intravenous LMWH compared with UFH among patients undergoing elective or urgent PCI. Studies eligible for this meta-analysis had to include patients undergoing PCI and randomized to receive either single-bolus intravenous LMWH or intravenous UFH during the procedure. In addition, data regarding efficacy and/or safety end points had to be available. No restriction criteria were imposed regarding the setting of PCI, the rate and type of stent placement, or the use of concomitant antplatelet therapies.

DATA SOURCES

We searched MEDLINE for reports of studies in which intravenous LMWH was used as an anticoagulant agent during PCI. Studies were included if treatment with LMWH was initiated at the start of PCI. The search aimed to identify work published or presented between January 1998 and September 2006 and used the following keywords: percutaneous coronary intervention; coronary angioplasty; low-molecular-weight heparin; enoxaparin; nadroparin; dalteparin; reviparin; and tinzaparin. In addition, we reviewed reference lists from relevant reviews and other publications, considered conference proceedings from major international cardiology meetings (including the American Heart Association, American College of Cardiology, and European Society of Cardiology meetings), and consulted experts and trial investigators to complete a comprehensive search of data.

DATA COLLECTED AND END POINT DEFINITIONS

The following information, when available, was abstracted from eligible studies: year of publication, trial design, population characteristics, number of patients (per group), type and dose of LMWH, dose of UFH, use of antplatelet drugs (eg, glycoprotein [GP] IIb/IIIa inhibitors), efficacy, and safety end points.

Safety end points included major bleeding, minor bleeding, and the composite of major and minor bleeding. Bleeding definitions were those used in the trials. The Coronary Revascularization Using Integrilin and Single Bolus Enoxaparin (CRUISE) study,8 Actinomycin-Eluting Stent Improves Outcomes by Reducing Neointimal Hyperplasia (ACTION) study,16 Protection Against Post-PCI Microvascular Dysfunction and Post-PCI Ischemia Among Antiplaatle and Antithrombotic Agents–Thrombolysis in Myocardial Infarction 30 (PROTECT-TIMI 30) study,17 and Zuerich Enoxaparin versus Unfractionated Heparin Study (ZEUS)18 used the Thrombolysis in Myocardial Infarction (TIMI) bleeding definitions for major and minor bleeding. The STEPPLE trial used the definitions for major and minor bleeding described previously.13 The studies by Dudek al11,12 and Drodz et al13 did not provide a detailed definition for major bleeding. In these studies, minor bleeding was classified as local hematoma. The REDUCE (Reduction of Restenosis After PTCA, Early Administration of Reviparin in a Double-blind Unfractionated Heparin and Placebo-Controlled Evaluation) study7 and the study by Natarajan et al14 defined major bleeding as intracranial or retroperitoneal bleeding, bleeding of a critical site, or clinically evident bleeding and a decrease in hemoglobin level greater than 3 g/dL (to convert to grams per liter, multiply by 10) or requiring transfusion of at least 2 units of blood. The study by Natarajan et al14 classified minor bleeding as local hematoma. In the study by Galeote et al15 major bleeding was defined as bleeding resulting in death, intracranial or retroocular hemorrhage, or in a decrease in hemoglobin level greater than 5 g/dL. The studies by Rabah et al16 and Her et al17 did not make a distinction between major and minor bleeding. In the study by Rabah et al,9 bleeding was defined as a decrease in hemoglobin level greater than 3 g/dL, need for blood transfusion, and any systemic bleeding and groin bleed as well as local vascular injury, and these events were classified as major bleeding in the present meta-analysis. In the study by Her et al, the only bleeding events reported were hematoma at the puncture site, and these were classified as minor bleeding in the present meta-analysis.

Efficacy end points included ischemic events (death or MI) and the individual end points of death, MI, and urgent target vessel revascularization. Global efficacy assessment was expressed as a composite efficacy end point as defined in each individual study, when available.1-13 The composite of efficacy and safety end points included the composite efficacy end point and major bleeding.

STATISTICAL ANALYSIS

The results from each trial were those obtained on an intention-to-treat basis. Odds ratios (ORs) with 95% confidence intervals (CIs) were computed as summary statistics. To compensate for potential variability of treatment effect across trials, the pooled OR was calculated using a random effect model. The efficacy and safety of LMWH compared with UFH was assessed using a χ² test on the pooled OR. The Cochran Q test based on the pooled OR was performed to explore heterogeneity across trials. Results were considered statistically significant at P < .05, for both association and heterogeneity tests. Publication bias was analyzed by funnel plots. The statistical analysis was performed using EasyMA software.21

The weight of each trial on the overall results of the study was calculated as a percentage of the number of patients in a given trial over the 7318 patients included in the analysis.

RESULTS

TRIAL PATIENT CHARACTERISTICS AND STUDY DESIGNS

Thirteen randomized trials comparing intravenous LMWH with UFH among patients undergoing PCI were identified.7-18,20 Among the 7318 patients included in the analysis, 4201 (57.4%) received LMWH and 3117 patients (42.6%) received UFH.

In 11 trials, PCI was performed either in an urgent or an elective setting.7,14,17,18,20 In 2 trials, only elective PCI was performed.15,16 The LMWH compared with UFH was
<table>
<thead>
<tr>
<th>Source</th>
<th>Study Population</th>
<th>No. of Patients (LMWH-UFH)</th>
<th>LMWH IV Dose</th>
<th>UFH IV Dose</th>
<th>Additional Antiplatelet Drugs</th>
<th>Efficacy End Point</th>
<th>Safety End Point</th>
<th>Weight of Each Study, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>REDUCE, 1996</td>
<td>PCI w/stable/unsy stable angina</td>
<td>306/306</td>
<td>Reviparin (7,000 IU, anti-Xa)</td>
<td>UFH (10,000 IU)</td>
<td>Aspirin</td>
<td>Death, MI, need for reintervention (re-PCI, CABG) at 30 wk</td>
<td>Major + minor bleeding</td>
<td>8.36</td>
</tr>
<tr>
<td>Rabah et al, 1999</td>
<td>PCI w/stable angina</td>
<td>30/30</td>
<td>Enoxaparin (1-mg/kg bolus, then titrated to ACT &gt; 300 s)</td>
<td>UFH (10,000 IU), then titrated to ACT &gt; 300 s</td>
<td>Aspirin</td>
<td>Death, MI, need for reintervention (re-PCI, CABG) at 30 wk</td>
<td>Major + minor bleeding</td>
<td>0.82</td>
</tr>
<tr>
<td>CRUISE, 2003</td>
<td>Urgent or elective PCI</td>
<td>129/132</td>
<td>Enoxaparin (0.75-mg/kg bolus)</td>
<td>UFH (60-IU/kg bolus, then titrated to ACT &gt; 200 s)</td>
<td>Eptifibatide, aspirin, clopidogrel</td>
<td>Death, MI, urgent revascularization (including re-PCI, CABG) at 30 d</td>
<td>TI-MI major + minor bleeding</td>
<td>3.57</td>
</tr>
<tr>
<td>Galeote et al, 2002</td>
<td>PCI w/stable/unsy stable angina or AMI PCI</td>
<td>50/49</td>
<td>Enoxaparin (0.75-mg/kg bolus)</td>
<td>UFH (70-IU/kg bolus, then titrated to ACT &gt; 200 s)</td>
<td>Abciximab</td>
<td>Death, MI, urgent revascularization in hospital</td>
<td>Major bleeding</td>
<td>1.35</td>
</tr>
<tr>
<td>Dudek et al, 2000</td>
<td>PCI complex lesions</td>
<td>112 (2 doses: 50)</td>
<td>Enoxaparin (1-mg/kg bolus), enoxaparin (0.75-mg/kg bolus) + abciximab</td>
<td>UFH (treated to ACT &gt; 300 s)</td>
<td>Aspirin, ticlopidine, abciximab</td>
<td>Death, MI, urgent revascularization, need for bailout GPIIb/IIIa inhibitors at 30 d</td>
<td>Major + minor bleeding</td>
<td>5.47</td>
</tr>
<tr>
<td>Drozd et al, 2001</td>
<td>PCI for stable angina</td>
<td>50/50</td>
<td>Enoxaparin (1-mg/kg)</td>
<td>UFH (100 IU/kg)</td>
<td>Aspirin, ticlopidine</td>
<td>Death, MI, need for reintervention (re-PCI, CABG) at 30 d</td>
<td>Major + minor bleeding</td>
<td>1.37</td>
</tr>
<tr>
<td>Natarajan et al, 2006</td>
<td>Elective or urgent PCI</td>
<td>160/161 (2 doses of each medication)</td>
<td>Dalteparin (100 IU/kg), dalteparin (70 IU/kg) + GPIIb/IIIa inhibitor</td>
<td>UFH (100 IU/kg), UFH (70 IU/kg) + GPIIb/IIIa inhibitors</td>
<td>Aspirin, clopidogrel</td>
<td>Death, MI, urgent CABG/PCI, need for bailout GPIIb/IIIa inhibitors at 24 h or hospital discharge</td>
<td>Major bleeding</td>
<td>4.39</td>
</tr>
<tr>
<td>STEEPLE, 2006</td>
<td>Elective PCI</td>
<td>2298 (2 doses: 1230)</td>
<td>Enoxaparin (0.75-mg/kg bolus), enoxaparin (0.5-mg/kg bolus)</td>
<td>UFH (if GPIIb/IIIa inhibitors were not used: 70-100 IU/kg bolus, then titrated to ACT 300-350 s; if GPIIb/IIIa inhibitors were used: 50-70 IU/kg bolus, then titrated to ACT 200-300 s)</td>
<td>Aspirin, clopidogrel or ticlopidine, use of GPIIb/IIIa inhibitors per physician choice (40%)</td>
<td>Death, MI, urgent revascularization at 30 d</td>
<td>Major + minor bleeding</td>
<td>48.21</td>
</tr>
<tr>
<td>ACTION, 2005</td>
<td>Elective PCI</td>
<td>100/100</td>
<td>Enoxaparin (0.75-mg/kg bolus)</td>
<td>UFH (60-IU/kg bolus, then titrated to ACT 200-300 s)</td>
<td>Aspirin, clopidogrel, eptifibatide (50%) or tirofiban (50%)</td>
<td>Death, MI, urgent revascularization at 30 d</td>
<td>TIMI major + minor bleeding</td>
<td>2.73</td>
</tr>
<tr>
<td>Her et al, 2005</td>
<td>PCI</td>
<td>68.71</td>
<td>Enoxaparin (0.75-mg/kg bolus)</td>
<td>UFH (100-IU/kg bolus)</td>
<td>None</td>
<td>Angiographic complications, rise in cardiac biomarkers, clinical outcomes at 30 d</td>
<td>Bleeding</td>
<td>1.90</td>
</tr>
<tr>
<td>PROTECT-TIMI 30, 2006</td>
<td>Non-ST-segment elevation acute coronary syndrome</td>
<td>262/298</td>
<td>Enoxaparin (0.5-mg/kg bolus)</td>
<td>UFH (50-IU/kg bolus, then titrated to ACT 200-250 s)</td>
<td>Aspirin, clopidogrel or ticlopidine, eptifibatide</td>
<td>Coronary flow reserve, composite of death, MI and occurrence of any ischemia within 48 h</td>
<td>TIMI major bleeding</td>
<td>7.65</td>
</tr>
<tr>
<td>ZEUS, 2006</td>
<td>Elective or urgent PCI</td>
<td>436/440</td>
<td>Enoxaparin (0.75-mg/kg bolus)</td>
<td>UFH (treated to ACT 300 s or 250 s if GPIIb/IIIa inhibitors were used)</td>
<td>Occasional use of GPIIb/IIIa (22%)</td>
<td>All cause death, MI, unplanned revascularization</td>
<td>TIMI major + minor bleeding</td>
<td>11.97</td>
</tr>
</tbody>
</table>

Abbreviations: ACT, activated clotting time; AMI, acute myocardial infarction; CABG, coronary artery bypass graft; GP, glycoprotein; IV, intravenous; LMWH, low-molecular-weight heparin; MI, myocardial infarction; PCI, percutaneous coronary intervention; TIMI, thrombolysis in myocardial infarction; UFH, unfractionated heparin.

Additional antiplatelet medication used prior to or during PCI in some or all patients.
enoxaparin in 11 trials,8,13,15-18,20 and in 4 of those trials, an intravenous bolus of enoxaparin was administered at the dose of 1 mg/kg during the procedure.8,11-13 In 7 trials, an intravenous bolus of 0.75-mg/kg enoxaparin was used,9,10,12,15,16,18,20 and a dose of 0.5-mg/kg intravenous bolus of enoxaparin was administered in 2 trials.9,17 One trial compared reviparin at a dose of 7000-IU anti-Xa with UFH; another trial compared dalteparin (at a dose of 70 or 100 IU/ kg) with UFH.14

The Table summarizes trial settings and concomitant antplatelet therapies administered. Within each trial, baseline characteristics were comparable among LMWH-treated patients and UFH-treated patients.

**SAFETY OUTCOMES**

The incidence of major bleeding was significantly reduced by 43% with LMWH compared with UFH (OR, 0.57; 95% CI, 0.40-0.82 [P = .002]) (Figure 1). There was no significant heterogeneity between trials (P = .77) and no evidence of publication bias using the funnel plot (figure not shown). A series of sensitivity analyses were performed that confirmed the same directionality for all the end points independent of which study was removed from the analysis. Treatment with LMWH was associated with a 0.87% absolute risk reduction for major bleeding compared with UFH. The incidence of minor bleeding tended to be lower among LMWH-treated patients compared with UFH-treated patients (OR 0.75; 95% CI, 0.47-1.20 [P = .24]). Similarly, there was a nonsignificant trend toward a reduction in the incidence of major and minor bleeding with LMWH compared with UFH (OR, 0.73; 95% CI, 0.50-1.05 [P = .09]) (Figure 2).

**EFFICACY OUTCOMES**

There was no significant difference in the composite of death and MI between patients receiving LMWH and those receiving UFH (OR, 0.99; 95% CI, 0.79-1.24; [P = .93]) (Figure 3). There was no significant heterogeneity between trials (P = .47) and no evidence of publication bias using the funnel plot (figure not shown). There was no difference in the incidence of the individual end points of death, MI, and urgent target vessel revascularization between patients receiving LMWH and those receiving UFH (Figure 2). There was no difference between treatment groups in the incidence of the composite efficacy end point as defined in each study (OR, 1.02; 95% CI, 0.85-1.22 [P = .87]) (Figure 2).

**COMPOSITE EFFICACY AND SAFETY END POINT**

The use of LMWH was associated with a nonsignificant 9% reduction in the incidence of the combined efficacy and safety end point compared with UFH (OR, 0.91; 95% CI, 0.78-1.08 [P = .29]) (Figure 2). The absolute risk reduction associated with LMWH for the composite efficacy and safety end point was 1.71%.

A series of sensitivity analyses were performed that confirmed the same directionality for all the end points regardless of which study was removed from the analysis. Analysis of only the trials using enoxaparin vs UFH showed that the results were closely correlated with the results from all studies, using any LMWH. For all end points, there was no statistical evidence of heterogeneity among the trials.

**COMMENT**

This meta-analysis on 7318 patients from 13 randomized trials demonstrates that the use of intravenous LMWH during PCI is associated with a significant reduction in major bleeding compared with the use of UFH, without compromising efficacy outcomes on hard ischemic end points. These findings confirm results from a previous meta-analysis by Boretain et al,22 which analyzed data from both randomized and nonrandomized studies, as well as results from the largest randomized study that occurred after this first pooled analysis.15
Despite the improvement of procedural techniques, bleeding remains a common and costly complication of PCI, often resulting in increased hospital stay, patient pain and discomfort, and short- and long-term mortality. Periprocedural bleeding was shown to occur in approximately 3% to 10% of patients undergoing elective or primary PCI in recently published randomized trials. Bleeding severity was shown to be independently associated with in-hospital mortality in patients with non–ST-segment elevation MI undergoing PCI, whereas Yusuf et al. found that less bleeding during PCI translated into less long-term mortality and morbidity. Moreover, a large proportion of major bleeds require transfusion, which has been shown to be an independent risk factor for long-term mortality in patients with acute coronary syndrome undergoing PCI. Therefore, the finding that intravenous LMWH is associated with reduced major bleeding rates compared with UFH is of clinical importance and should be considered when determining the appropriate anticoagulation regimen for use during PCI.

The use of UFH as an antithrombotic agent during PCI has several limitations, including the need for monitoring of anticoagulant activity. The optimal level of activated clotting time–adjusted UFH therapy during PCI has not been determined. Guidelines from the American Heart Association, American College of Cardiology, European Society of Cardiology, and American College of Chest Physicians recommend alternative activated clotting time target levels depending on the type of measurement device and whether therapy is concomitant with the use of GPIIb/IIIa inhibitors. Moreover, conflicting evidence from meta-analyses suggests that these guideline recommendations for optimal activated clotting time are either too low or too high depending on the study, as well as on the use of GPIIb/IIIa inhibitors. These discrepancies have caused confusion and have led to variations in standard practice of UFH use during PCI. In contrast, LMWHs have a more stable and predictable anticoagulant activity compared with UFH, which removes the need for routine monitoring of anticoagulant activity during PCI. Although results from this meta-analysis show enoxaparin to be associated with a reduced risk for major bleeding compared with UFH, it should be noted that the anticoagulant effect of LMWH is only partially reversible with protamine. However, other new anticoagulants such as bivalirudin and fondaparinux and all antiplatelet agents have no antidotes at all.

This meta-analysis included data from more than 7000 patients. The large sample size provides enough statistical power to detect differences between LMWH and UFH in the prevention of ischemic events. However, no significant difference was measured for each of the efficacy end points. There have been no placebo-controlled trials of UFH in PCI, and UFH does not have approval from the Food and Drug Administration for this indication. It is therefore difficult to define a non-inferiority margin for the treatment effect. An OR for death or MI below 1 and an upper limit of the 95% CI below 1.25 supports the hypothesis that UFH and LMWH are equally effective to prevent ischemic events. Although previous studies have provided data suggesting comparable efficacy of LMWH compared with UFH, this is an important finding because none had such power in estimating the efficacy of LMWH compared with UFH. The largest of such studies was the recent STEEPELE trial. Despite the large number of patients included in the STEEPELE trial, the relatively low number of ischemic events did not provide enough power to draw definitive conclusions regarding the efficacy of LMWH compared with UFH. The low rate of ischemic events during PCI was most likely affected by procedure-related factors rather than by treatment. However, the comparable efficacy of LMWH and UFH observed in the present well-powered meta-analysis is important in demonstrating that the significant benefit measured on major bleeding does not translate in any trade-off on ischemic outcomes.

Use of LMWH for the treatment of ST-segment elevation MI and non–ST-segment elevation MI is associated with improved efficacy and
an increased risk for bleeding compared with UFH. In contrast, this meta-analysis suggests that in the setting of PCI, LMWH is associated with comparable efficacy and less bleeding compared with UFH. It is likely that this discrepancy is mainly owing to the different modes of administration of the drug: multiple subcutaneous injections in acute coronary syndrome trials vs a single intravenous injection in PCI trials. The prolonged subcutaneous treatment in a high-risk population is a good situation to demonstrate the superior efficacy of LMWH compared with UFH; however, it runs the risk of drug accumulation in patients with renal failure (when there is no dose adjustment) and of crossover with UFH (pretreatment or at the time of PCI), both being associated with excessive anticoagulation. A single intravenous injection of enoxaparin is not associated with drug accumulation and provides all the pharmacokinetic advantages of the drug with its excellent predictability of anticoagulation (compared with UFH, which has a poor bioavailability), translating into better safety in elective PCI, a situation in which it is more difficult to show differences in efficacy.

There is now a large set of convincing data showing that LMWHs are a safe and effective alternative to UFH during PCI. Recently, 2 trials compared UFH with the direct thrombin inhibitor bivalirudin and the synthetic factor-Xa inhibitor fondaparinux in the setting of elective PCI. These studies, along with the STEEPLE trial and the present meta-analysis, suggest that the new anticoagulant drugs offer attractive alternatives to UFH for use during PCI. Safety and efficacy of LMWHs have been proved in a range of clinical settings through a large and convincing set of data. In elective PCI, intravenous enoxaparin was shown to be a safer alternative to UFH regardless of patient age, weight, renal function, and whether the use of GPIIb/IIIa inhibitors was planned.

This meta-analysis is subject to certain limitations. As for any meta-analysis, some heterogeneity may exist between the trials analyzed regarding their design, study populations, definitions of end points, and time of end point or follow-up. For example, the studies had different definitions of end points, which were used in the meta-analysis trial rather than using a common definition. However, all trials included in this meta-analysis were randomized and controlled, and all studies compared a single bolus of intravenous LMWH with intravenous UFH in patients undergoing urgent or elective PCI. Also, LMWH have different biochemical and pharmacological properties and, therefore, do not necessarily confer the same benefits. However, most trials in this meta-analysis compared enoxaparin with UFH. The influence of the STEEPLE trial on the results of this meta-analysis should be noted; patients in the STEEPLE trial accounted for approximately 50% of the patients analyzed in the present study. Finally, although a wide range of enoxaparin doses were studied, the majority were high doses, which reinforces the safety profile of enoxaparin in PCI.

In conclusion, the present meta-analysis demonstrates that intravenous LMWH significantly reduces the incidence of major bleeding compared with UFH among patients undergoing PCI. The safety benefit does not compromise efficacy, and LMWHs appear to be as effective as UFH in preventing hard ischemic end points. Therefore, LMWHs are an attractive alternative to UFH for patients undergoing PCI.

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Figure 3. Odds ratios (ORs) and 95% confidence intervals (CIs) for composite of death and myocardial infarction in the trials. LMWH indicates low-molecular-weight heparin; UFH, unfractionated heparin.

<table>
<thead>
<tr>
<th>Study</th>
<th>LMWH*</th>
<th>UFH*</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>REDUCE</td>
<td>13/306</td>
<td>8/306</td>
<td>1.63 (0.67-3.95)</td>
</tr>
<tr>
<td>Rabah et al</td>
<td>0/30</td>
<td>1/30</td>
<td>0.19 (0.00-14.61)</td>
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<tr>
<td>CRUISE</td>
<td>11/129</td>
<td>10/132</td>
<td>1.13 (0.47-2.75)</td>
</tr>
<tr>
<td>Galeote et al</td>
<td>5/50</td>
<td>3/49</td>
<td>1.65 (0.39-6.99)</td>
</tr>
<tr>
<td>Dudek et al</td>
<td>10/200</td>
<td>8/200</td>
<td>1.26 (0.49-3.21)</td>
</tr>
<tr>
<td>Dudek et al</td>
<td>0/112</td>
<td>0/50</td>
<td>0.45 (0.00-115.71)</td>
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<td>Drozd et al</td>
<td>0/50</td>
<td>2/50</td>
<td>0.11 (0.00-6.78)</td>
</tr>
<tr>
<td>Natarajan et al</td>
<td>12/160</td>
<td>12/161</td>
<td>1.01 (0.44-2.30)</td>
</tr>
<tr>
<td>ACTION</td>
<td>8/100</td>
<td>14/100</td>
<td>0.54 (0.22-1.34)</td>
</tr>
<tr>
<td>STEEPLE</td>
<td>138/2298</td>
<td>70/1230</td>
<td>1.06 (0.79-1.42)</td>
</tr>
<tr>
<td>Her et al</td>
<td>1/68</td>
<td>2/71</td>
<td>0.57 (0.06-5.23)</td>
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<tr>
<td>ZEUS</td>
<td>4/436</td>
<td>14/440</td>
<td>0.29 (0.10-0.88)</td>
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<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td>0.99 (0.78-1.24)</td>
</tr>
</tbody>
</table>

P = .93

Better LMWH | UFH Better

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Author Contributions: Dr Dumeaine had full access to all the data in the study and takes responsibility for the integrity of the data analysis and the accuracy of the data analysis. Study concept and design: Dumeaine, Boretain, Gallo, Collet, and Montalescot. Acquisition of data: Dumeaine, Bertel, Gallo, White, and Steinhubl. Analysis and interpretation of data: Dumeaine, Bertel, Bode, Gallo, White, Collet, and Montalescot. Drafting of the manuscript: Dumeaine, Boretain, Bertel, Bode, White, and Montalescot. Critical revision of the manuscript for important intellectual content: Dumeaine, Bertel, Bode, Gallo, Collet, Steinhubl, and Montalescot. Statistical analysis: Dumeaine, Boretain, and Collet. Obtained funding: Montalescot. Administrative, technical, and material support: Gallo, Collet, and Montalescot. Study supervision: Bode, Gallo, and Montalescot.

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