Enoxaparin Versus Unfractionated Heparin in Elective Percutaneous Coronary Intervention

1-Year Results From the STEEPLE (SafeTy and Efficacy of Enoxaparin in Percutaneous coronary intervention patients, an international randomized Evaluation) Trial

Gilles Montalescot, MD, PhtD,* Richard Gallo, MD,† Harvey D. White, MB, ChtB, DSc,‡ Marc Cohen, MD,§ Ph. Gabriel Steg, MD,‖ Philip E. G. Aylward, MB, ChtB, PhtD,¶ Christoph Bode, MD, PhtD,# Massimo Chiariello, MD,** Spencer B. King III, MD,†† Robert A. Harrington, MD,‡‡ Walter J. Desmet, MD, §§ Carlos Macaya, MD, PhtD,||| Steven R. Steinhubl, MD,¶¶## for the STEEPLE Investigators

Paris, France; Montreal, Canada; Auckland, New Zealand; Newark, New Jersey; South Australia, Australia; Freiburg, Germany; Naples, Italy; Atlanta, Georgia; Durham, North Carolina; Leuven, Belgium; Madrid, Spain; Danville, Pennsylvania; and Zurich, Switzerland

Objectives Our purpose was to evaluate long-term mortality and identify factors associated with 1-year mortality in patients who underwent elective percutaneous coronary intervention (PCI).

Background While long-term outcomes in PCI patients have been reported previously, limited data are currently available regarding the comparative long-term outcomes in PCI patients who receive enoxaparin versus intravenous unfractionated heparin (UFH).

Methods We conducted a follow-up analysis of clinical outcomes at 1 year in patients enrolled in the STEEPLE (SafeTy and Efficacy of Enoxaparin in Percutaneous coronary intervention patients, an international randomized Evaluation) trial of 3,528 patients undergoing elective PCI. Patients were randomized to receive either intravenous 0.50-mg/kg or 0.75-mg/kg enoxaparin or intravenous UFH during elective PCI procedures. All-cause mortality at 1 year after index PCI was the main outcome measure.

Results Mortality rates were 1.4%, 2.0%, and 1.5% from 1 month to 1 year, and 2.3%, 2.2%, and 1.9% from randomization to 1 year, after index PCI in patients receiving 0.50 mg/kg enoxaparin, 0.75 mg/kg enoxaparin, and UFH, respectively. Multivariate analysis identified nonfatal myocardial infarction and/or urgent target vessel revascularization up to 30 days after index PCI (hazard ratio: 3.5, 95% confidence interval: 1.7 to 7.3; \( p < 0.001 \)), and major bleeding within 48 h (hazard ratio: 3.0, 95% confidence interval: 1.1 to 8.5; \( p = 0.04 \)) as the strongest independent risk factors for 1-year mortality.

Conclusions The 1-year mortality rates were low and comparable between patients receiving enoxaparin and UFH during elective PCI. Periprocedural ischemic or bleeding events were the strongest independent predictors of 1-year mortality. (The STEEPLE Trial; NCT00077844) (J Am Coll Cardiol Intv 2009;2:1083–91) © 2009 by the American College of Cardiology Foundation

From the *Institut du Cœur, Centre Hospitalier Universitaire Pitié-Salpêtrière, Paris, France; †The Montreal Heart Institute, University of Montreal, Montreal, Canada; Auckland City Hospital, Auckland, New Zealand; §Division of Cardiology, Newark Beth Israel Medical Center, Newark, New Jersey; INSERM U-698, Université Paris 7 and AP-HP, Paris, France; ¶Cardiology Research, Flinders Medical Centre, South Australia, Australia; #Abteilung Innere Medizin III, Universitätsklinikum Freiburg, Freiburg, Germany; **Division of Cardiology, Federico 2nd University, Naples, Italy; ††St Joseph’s Heart and Vascular Institute, Atlanta, Georgia; ‡‡Duke Clinical Research Institute, Duke University Medical Center, Durham, North Carolina; §§University Hospital Gasthuisberg, Leuven, Belgium; || Servicio de Cardiología, Hospital Universitario, Madrid, Spain; ¶¶Geisinger Clinic, Geisinger Center for Health Research, Danville, Pennsylvania; and ##The Medicines Company, Zurich, Switzerland. The STEEPLE trial was funded by sanofi-aventis. The authors received editorial support in the preparation of this manuscript, funded by sanofi-aventis. The authors, however, were fully responsible for content and editorial decisions for this manuscript. For full author disclosures, please see the end of this article.
The safety and efficacy of intravenous low-molecular-weight heparin (LMWH) anticoagulation in patients undergoing either emergent or elective percutaneous coronary intervention (PCI) has previously been demonstrated in a number of trials (1–8). The largest of these trials in elective PCI was the STEEPLE (SafeTy and Efficacy of Enoxaparin in PCI patients, an international randomized Evaluation) trial, which was a prospective, open-label, parallel-group study evaluating intravenous enoxaparin (0.50 mg/kg or 0.75 mg/kg) and unfractionated heparin (UFH) in patients with stable coronary artery disease (7). The study found that enoxaparin was associated with reduced bleeding rates, compared with UFH. Notably, the beneficial effect of enoxaparin was primarily driven by a significant 57% reduction in noncoronary artery bypass graft-related major bleeding in the first 48 h compared with UFH (7). Although the STEEPLE study was not powered to make definitive conclusions regarding efficacy, a subsequent meta-analysis of 13 randomized studies, which was sufficiently powered, reported similar efficacy between UFH and LMWH (6).

However, none of 13 published randomized studies has examined the long-term outcomes of PCI in patients receiving intravenous LMWH or UFH. In this study, we present data from a 1-year follow-up of the STEEPLE trial, during which we evaluated patient outcomes and identified factors associated with long-term mortality.

Methods

Between January 2004 and December 2004, a total of 3,528 patients were enrolled into the STEEPLE trial. Briefly, 1,070 were randomly assigned to receive enoxaparin 0.50 mg/kg intravenously, 1,228 to enoxaparin 0.75 mg/kg intravenously, and 1,230 to activated clotting time (ACT)-adjusted UFH (7). Randomization was stratified according to the medical center and planned use of glycoprotein IIb/IIIa inhibitors. Regardless of weight or renal function, patients were eligible for the study if they were age ≥17 years, were scheduled to undergo elective PCI with a femoral approach, did not meet any of the exclusion criteria, and gave informed consent. The exclusion criteria included recent thrombolysis, a planned staged procedure, an increased risk of bleeding, treatment with a parenteral anti-thrombotic agent before PCI, or a known hypersensitivity to the drugs used in the study. The study complied with the Declaration of Helsinki, and locally appointed ethics committees approved the research protocol.

A follow-up analysis of clinical outcomes in patients enrolled in the STEEPLE trial, which was not part of the original study protocol, was initiated in December 2005—1 year after the closure of the primary study. From the original 124 centers, 25 did not participate in this analysis and 892 patients were lost to follow-up beyond day 30. Reasons for the loss of follow-up data were: no internal review board approval (n = 154); contractual issues (n = 435); lengthy administrative procedures (n = 115); unwillingness to participate (n = 113); other reasons (n = 75). Treatment protocol. Patients were treated with aspirin (75 to 500 mg/day) and thienopyridines according to local practice. Before PCI, 46% of patients had received long-term treatment with thienopyridine. On the day of PCI, approximately 40% of patients in each treatment arm had received a glycoprotein IIb/IIIa inhibitor and 94% a thienopyridine. Patients in the control arm, who were not receiving concurrent glycoprotein IIb/IIIa inhibitors, were given an initial intravenous bolus of 70 to 100 IU/kg UFH to achieve a target ACT of 300 to 350 s. Patients who received concurrent glycoprotein IIb/IIIa inhibitors were given an initial bolus of 50 to 70 IU/kg of UFH to achieve a target ACT of 200 to 300 s. Additional boluses of UFH (before the start of PCI and during the procedure) were given to 16.5% of patients when ACT measurements dropped below the recommended range. Patients receiving enoxaparin were not routinely monitored for anticoagulation levels, and neither dose regimen was adjusted according to the concomitant use of glycoprotein IIb/IIIa inhibitors.

In the original study, a nonsignificant increase in mortality up to 30 days after index PCI was observed in patients receiving 0.50 mg/kg enoxaparin, compared with UFH, which resulted in early closure of the low-dose enoxaparin arm (7).

End points at 1 year. The primary end point for this analysis was all-cause mortality at 1 year. Data on all-cause mortality at 1 year were gathered by telephone or by visiting participating sites; no information on cause of mortality or other adverse events was collected.

Statistical analyses. All-cause mortality at 1 year was analyzed using a Cox proportional hazard model. All patients enrolled in the initial STEEPLE trial, whatever the duration of follow-up, were included in this model. Each enoxaparin dose was compared with UFH separately. The Simes adjustment for multiplicity was applied to ensure a global type 1 error rate of 0.05: if both p values were 0.05 or
less, both were considered as statistically significant; if the highest p value was >0.05, the other p value had to be 0.025 or less to be considered statistically significant. Kaplan-Meier curves were used to present the calculated probability of mortality over time.

Univariate and stepwise multivariate (significance level 0.05) Cox proportional hazard models were used to identify risk factors associated with all-cause mortality at 1 year. The following variables were included in these analyses: subjects’ characteristics (age, sex, obesity, diabetes, measured hypertension, smoking habits, hypercholesterolemia, renal insufficiency [creatinine clearance ≤60 ml/min], peripheral arterial disease, family history of coronary heart disease, unstable angina or myocardial infarction [MI] within the previous 7 days, low hemoglobin at entry [≤10 g/dl and ≤11 g/dl for female and male patients, respectively]); PCI characteristics (number of diseased arteries, number of dilated arteries, maximum sheath size, use of closure device, time from end of PCI to sheath removal, drug-eluting stent, Thrombolysis In Myocardial Infarction flow grade [pre-procedure]); previous medication within 1 week before enrollment (beta-blocker, calcium-channel blocker, angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, statin, warfarin, or other vitamin K antagonists); concomitant medication (glycoprotein IIb/IIIa inhibitor, thrombytic during PCI, dose of aspirin on the day of PCI, clopidogrel loading dose, and glycoprotein IIb/IIIa inhibitor and clopidogrel dose on the day of PCI); anticoagulant crossover during the index hospitalization; country; nonfatal MI or urgent target vessel revascularization (UTVR), considered as a time-dependent covariate; creatine kinase (CK) and creatine kinase-myocardial/brain mass (CK-MB); and major bleeding up to 48 h.

Nonfatal MI was defined by a new Q-wave in 2 or more leads, or a total CK level or CK-MB fraction that was ≥3× the upper limit of the normal range (ULNR) during hospitalization for the index PCI, or ≥2× ULNR after discharge. Nonfatal MI was defined by a new Q-wave in 2 or more leads, or a total CK level or CK-MB fraction that was ≥3× ULNR during hospitalization for the index PCI, or ≥2× ULNR after discharge. The definition for major bleeding and the associated time point were used as reported previously (7).

### Results

In total, 3,528 patients were randomized to receive either 0.50-mg/kg or 0.75-mg/kg enoxaparin, or UFH. Of these patients, 1-year follow-up data were available for 2,636 patients. The baseline characteristics of patients included in this study were well balanced between treatment groups (Table 1). Importantly, these baseline characteristics were similar in patients evaluated in the 1-year follow-up compared with those who were not (Table 1). The only significant differences in patient populations included in this study and those lost to follow-up were the number of patients with diabetes in the UFH treatment arm and the number of patients with moderate renal impairment in the 0.75-mg/kg enoxaparin arm.

**Table 1. Baseline Characteristics of Patients in 1-Year Follow-Up Subanalysis**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Enoxaparin 0.50 mg/kg (n = 792)</th>
<th>Enoxaparin 0.75 mg/kg (n = 915)</th>
<th>UFH (n = 929)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean age, yrs</strong></td>
<td>63.7 ± 10.3</td>
<td>63.8 ± 10.1</td>
<td>63.5 ± 10.2</td>
</tr>
<tr>
<td><strong>Age ≥75 yrs</strong></td>
<td>138 (17.4)</td>
<td>134 (14.6)</td>
<td>143 (15.4)</td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td>590 (74.5)</td>
<td>685 (74.9)</td>
<td>685 (73.7)</td>
</tr>
<tr>
<td><strong>Mean weight, kg</strong></td>
<td>83.7 ± 16.3</td>
<td>83.8 ± 16.0</td>
<td>83.1 ± 15.8</td>
</tr>
<tr>
<td><strong>Body mass index ≥30 kg/m²</strong></td>
<td>295 (37.5)</td>
<td>308 (34.1)</td>
<td>319 (34.6)</td>
</tr>
<tr>
<td><strong>Creatinine clearance, ml/min</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;30–≤60</td>
<td>141 (18.1)</td>
<td>175 (19.5)</td>
<td>161 (17.7)</td>
</tr>
<tr>
<td>≤30</td>
<td>10 (1.3)</td>
<td>6 (0.7)</td>
<td>17 (1.9)</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td>229 (28.9)</td>
<td>257 (28.1)</td>
<td>269 (29.0)</td>
</tr>
<tr>
<td><strong>Prior MI</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;48 h to ≤7 days</td>
<td>12 (1.5)</td>
<td>15 (1.6)</td>
<td>17 (1.8)</td>
</tr>
<tr>
<td>≤48 h</td>
<td>2 (0.3)</td>
<td>6 (0.7)</td>
<td>3 (0.3)</td>
</tr>
<tr>
<td><strong>Prior unstable angina</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;48 h to ≤7 days</td>
<td>57 (7.2)</td>
<td>60 (6.6)</td>
<td>64 (6.9)</td>
</tr>
<tr>
<td>≤48 h</td>
<td>37 (4.7)</td>
<td>51 (5.6)</td>
<td>39 (4.2)</td>
</tr>
<tr>
<td><strong>Prior PCI</strong></td>
<td>274 (34.6)</td>
<td>329 (36.0)</td>
<td>358 (38.5)</td>
</tr>
<tr>
<td><strong>Prior CABG</strong></td>
<td>113 (14.3)</td>
<td>125 (13.7)</td>
<td>142 (15.3)</td>
</tr>
</tbody>
</table>

Values expressed as mean ± SD or n (%). CABG = coronary artery bypass graft; MI = myocardial infarction; PCI = percutaneous coronary intervention; UFH = unfractionated heparin.
ences between the treatment arms for all-cause mortality evaluated between 1 month and 1 year after index PCI: 1.4% for enoxaparin 0.50 mg/kg (p = 0.86 vs. UFH); 2.0% for enoxaparin 0.75 mg/kg (p = 0.45 vs. UFH); and 1.5% for UFH (Fig. 1A). Subsequently, we observed comparable rates of all-cause mortality at 1 year in the 3 treatment groups: 2.3% for enoxaparin 0.50 mg/kg (hazard ratio [HR]: 1.3, 95% confidence interval [CI]: 0.70 to 2.41; p = 0.41); 2.2% for enoxaparin 0.75 mg/kg (HR: 1.12, 95% CI: 0.60 to 2.08; p = 0.72); and 1.9% for UFH (Fig. 1B).

**Predictors of mortality at 1 year.** After univariate analysis, mortality was significantly higher in patients who had an ischemic event (nonfatal MI and/or UTVR) up to day 30, compared with those who did not (Fig. 2A). Nonfatal MI
up to 30 days after PCI was independently associated with mortality when this event was considered separately from UTVR (5.7% vs. 2.0%, respectively; \( p < 0.008 \)). In addition, a strong relationship was observed between post-procedural CK or CK-MB fraction release and 1-year mortality. Rates of mortality were significantly increased in patients with raised levels of total CK or CK-MB (Fig. 2B). This relationship remained strong and significant regardless of the threshold for significant CK increase used. Mortality was significantly higher in patients who experienced major bleeding compared with those who did not (Fig. 2C).
Multivariate analysis indicated that ischemic events (MI or UTVR) in the first 30 days after PCI, and major bleeding within 48 h after index PCI were the 2 strongest independent predictors for all-cause mortality at 1 year, with similar HRs of 3.5 and 3.0, respectively (Fig. 3). When MI was considered independently of UTVR, an odds ratio of 3.29 (95% CI: 1.53 to 7.05; \(p = 0.002\)) was obtained. The number of diseased coronary arteries and the presence of peripheral arterial disease were also significant predictors of mortality (Fig. 3). The presence of diabetes and baseline renal insufficiency as well as age \(\geq 75\) years were also associated with increased 1-year mortality. Interestingly, the investigators’ choice of using \(\geq 100\) mg of aspirin at the time of PCI was the only variable associated with improved mortality.

**Discussion**

This update of the STEEPLE trial showed that all-cause mortality at 1 year was low in patients undergoing elective PCI. Mortality rates were similar in enoxaparin and UFH treatment groups, although this study was not powered to draw final conclusions on mortality. Mortality rates increased sharply in patients with a periprocedural ischemic or bleeding event.

These data are consistent with studies performed in the context of patients with acute coronary syndromes (ACS); enoxaparin and UFH are associated with similar efficacy (in terms of the reduction of ischemic events) and long-term mortality \((6,8,9)\). Although the original analysis showed a nonsignificant trend towards increased short-term mortality with enoxaparin 0.50 mg/kg over the first 30 days after index PCI, resulting in enrollment in this arm being stopped prematurely (lower mortality rates were observed in patients receiving enoxaparin 0.75 mg/kg \([7]\)), this trend was reversed in mortality rates from 1 month to 1 year, with a lower mortality rate being observed in the 0.50-mg/kg enoxaparin arm (a higher mortality rate was observed in the 0.75-mg/kg arm).

The observed trends in mortality across treatment groups reflect variations in rare events in a low-risk population recruited in a trial not powered to assess mortality, with chance being the most likely explanation for these variations. Furthermore, reductions in both in-hospital mortality combined with nonfatal reinfarction, and in-hospital mortality alone, have been observed in ST-segment elevation MI patients receiving enoxaparin \((10,11)\), and more recently in a trial using the same dose of intravenous enoxaparin \((0.50\ \text{mg/kg})\) in primary PCI \((12)\).

Major bleeding is a hard clinical end point associated with increased long-term mortality. Its importance is underlined in the guidelines for the management of patients with non–ST-segment elevation ACS, which recommend the risk stratification of patients according to bleeding \((13)\), and in a recent subanalysis of the ACUITY (Acute Catheterization and Urgent Intervention Triage strategy) ACS trial, which reported a significant association between major
bleeding and 1-year mortality (14). The STEEPLE trial demonstrated that in patients undergoing elective PCI, fewer major bleeding complications occurred at 30 days with intravenous enoxaparin than with UFH. Periprocedural major bleeding is increasingly being recognized as a substantial cause of short-term morbidity and mortality in elective PCI (15–17). The association between major bleeding and morbidity or mortality has been reported to be temporal (with the greatest risk during the first 30 days, and markedly reduced risk if patients survive at least 30 days after a major bleed), and linked to severity (with a higher risk of death in those with more severe degrees of bleeding) (16,17). Our data suggest that this relationship between major bleeding and mortality extends at least up to 1 year after PCI.

One of several explanations for the relationship between major bleeding and 1-year mortality is that major bleeding might lead physicians to discontinue effective antithrombotic drugs such as aspirin, clopidogrel, heparin, LMWH, and warfarin, which in turn could increase the risk of MI, stroke, and cardiovascular death. These data suggest significant clinical benefits can be achieved by using novel strategies based on the use of new antithrombotic agents (7,12,18,19), and/or of new techniques (such as radial approach for PCI) capable of reducing major bleeding (20–22).

Our analysis also shows that even with the use of drug-eluting stents, thienopyridines, and glycoprotein IIb/IIIa inhibitors, ischemic events as measured in the first 30 days after PCI, remain the most important predictor of mortality at 1 year. Periprocedural CK release was also strongly associated with 1-year mortality, regardless of the cutoff value defining increased CK or CK-MB release. These findings confirm observations from previous studies, which reported periprocedural myonecrosis as a predictor of major adverse cardiac events and death (23–25) and support the new “universal definition of MI” (26).

Consistent with findings from previous studies, we identified multivessel coronary disease, peripheral arterial disease, diabetes mellitus, and renal disease, as well as advancing age (≥75 years) as major risk factors for poor clinical outcomes (27–29). These factors are markers of the extent of the atherothrombotic process exposing the patient to further ischemic events and death. Questions remain regarding the safety and efficacy of PCI for patients presenting with several of these independent markers of mortality, indicating chronic, systemic, and diffuse disease in different vascular beds. Tailoring the intensity of antithrombotic therapy acutely, and after discharge as secondary prevention to individual risk, could become an important goal for the future (29,30).

Although all study sites participating in the STEEPLE trial were contacted, 25 centers did not participate in this analysis, and overall 892 patients were lost to follow-up. Despite the limitations of this incomplete follow-up, there was no evidence for selection bias as the baseline characteristics of patients included in this subanalysis matched well with both the overall STEEPLE study population and those who were lost to follow-up. A key limitation of this study was the loss of statistical power resulting from the incompleteness of follow-up data availability. Full data on adverse clinical events, such as cardiac death, MI, and repeat revascularization up to 1 year, were not collected during this study.

**Conclusions**

In summary, the data from the STEEPLE study show that 1-year mortality rates were low and comparable between patients receiving enoxaparin (0.50 mg/kg or 0.75 mg/kg) and UFH during elective PCI. Periprocedural major bleeding and ischemic events were the most serious independent predictors of death at 1 year. Reduction in major bleeding over the first 48 h after PCI and prevention of CK release are important to improve the long-term survival of patients undergoing PCI.

**Author Disclosures**

Dr. Montalescot reports receiving grant support, consulting fees, and lecture fees from sanofi-aventis, Eli Lilly, and Bristol-Myers Squibb, consulting fees from Schering-Plough and The Medicines Company, and lecture fees from GlaxoSmithKline. Dr. Gallo reports having received grant support, consulting fees from AstraZeneca, Biovail Pharmaceuticals, sanofi-aventis, and Schering-Plough, and lecture fees from Abbott Interventional, Biovail Pharmaceuticals, and sanofi-aventis. Dr. White reports receiving grant support, consulting fees, and lecture fees from sanofi-aventis and The Medicines Company, and grant support from Proctor and Gamble, Alexion, Schering-Plough, and Eli Lilly. Dr. Cohen reports receiving grant support from Aventis Pharmaceuticals, consulting fees from sanofi-aventis and AstraZeneca, and lecture fees from sanofi-aventis, Merck, and Schering-Plough. Dr. Steg reports receiving grant support from sanofi-aventis, consulting fees from sanofi-aventis, Takeda, AstraZeneca, Bristol-Myers Squibb, Endotis, Lilly, Merck Sharpe & Dohme, GlaxoSmithKline, Pfizer, Servier, and The Medicines Company, and is on the Speakers’ Bureau of AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, GlaxoSmithKline, Merck Sharpe & Dohme, Novartis, Nycoderm, sanofi-aventis, Sankyo, Servier, The Medicines Company, and ZLB Behring. Dr. Aylward reports receiving grant support from sanofi-aventis, Proctor and Gamble, Alexion, The Medicines Company, Schering-Plough, and Eli Lilly, as well as consulting fees and lecture fees from sanofi-aventis and Bristol-Myers Squibb. Dr. Bode reports receiving consulting fees and
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Reprint requests and correspondence: Dr. Gilles Montalescot, Institut du Cœur, Bureau 2-236, Centre Hospitalier Universitaire Pitié-Salpêtrière, 47 Boulevard de l’Hôpital, 75013 Paris, France. E-mail: gilles.montalescot@psl.aphp.fr.

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