Economic Assessment of Low-Molecular-Weight Heparin (Enoxaparin) Versus Unfractionated Heparin in Acute Coronary Syndrome Patients
Results From the ESSENCE Randomized Trial

Daniel B. Mark, MD, MPH; Patricia A. Cowper, PhD; Scott D. Berkowitz, MD; Linda Davidson-Ray, BA; Elizabeth R. DeLong, PhD; Alexander G.G. Turpie, MB; Robert M. Califf, MD; Beth Weatherley, MS; Marc Cohen, MD

Background—In the ESSENCE trial, subcutaneous low-molecular-weight heparin (enoxaparin) reduced the 30-day incidence of death, myocardial infarction, and recurrent angina relative to intravenous unfractionated heparin in 3171 patients with acute coronary syndrome (unstable angina or non–Q-wave myocardial infarction). No increase in major bleeding was seen.

Methods and Results—Of the 936 ESSENCE patients randomized in the United States, 655 had hospital billing data collected. For the remainder, hospital costs were imputed with a multivariable linear regression model ($R^2 = .86$). Physician fees were estimated from the Medicare Fee Schedule. During the initial hospitalization, major resource use was reduced for enoxaparin patients, with the largest effect seen with coronary angioplasty (15% versus 20% for heparin, $P = .04$). At 30 days, these effects persisted, with the largest reductions seen in diagnostic catheterization (57% versus 63% for heparin, $P = .04$) and coronary angioplasty (18% versus 22%, $P = .08$). All resource use trends seen in the US cohort were also evident in the overall ESSENCE study population. In the United States, the mean cost of a course of enoxaparin therapy was $155, whereas that for heparin was $80. The total medical costs (hospital, physician, drug) for the initial hospitalization were $11,857 for enoxaparin and $12,620 for heparin, a cost advantage for the enoxaparin arm of $763 ($P = .18$). At the end of 30 days, the cumulative cost savings associated with enoxaparin was $1172 ($P = .04$). In 200 bootstrap samples of the 30-day data, 94% of the samples showed a cost advantage for enoxaparin.

Conclusions—In patients with acute coronary syndrome, low-molecular-weight heparin (enoxaparin) both improves important clinical outcomes and saves money relative to therapy with standard unfractionated heparin. (Circulation. 1998;97:1702-1707.)

Key Words: anticoagulants ▪ angina ▪ coronary disease ▪ cost-benefit analysis

Standard care for patients hospitalized with unstable angina includes daily aspirin and a 2- to 5-day infusion of intravenous unfractionated heparin. While these therapies have been shown to improve short-term outcomes, they do not fully eliminate the risk of recurrent ischemic events. Thus opportunities remain for new, more potent therapies to diminish the incidence of adverse events in acute coronary disease. However, because both aspirin and unfractionated heparin are quite inexpensive, such new therapies may achieve improved clinical effectiveness and still have difficulty demonstrating economic attractiveness (ie, incremental costs over current standard therapies that are proportionate to the incremental benefits produced).

The low-molecular-weight heparins have recently been proposed as an antithrombin therapy potentially superior to unfractionated heparin. ESSENCE (Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q wave Coronary Events [unstable angina or non–Q-wave myocardial infarction]) was a multicenter, double-blind, randomized controlled trial that recently reported a 16% reduction in the 14-day incidence of death, myocardial infarction, or recurrent angina with enoxaparin relative to unfractionated heparin. We conducted a prospective, detailed economic analysis of the ESSENCE results in the United States.

Methods

Patient Population
Between October 1994 and May 1996, 3171 patients with rest unstable angina or non–Q-wave myocardial infarction were enrolled.
in the ESSENCE trial at 176 centers in the United States, Canada, South America, and Europe. Enrolled patients were required to have (1) recent onset of rest angina lasting >10 minutes and occurring within 24 hours of randomization and (2) underlying ischemic heart disease as evidenced by (a) new ST-segment depression ≥0.1 mV or transient ST-segment elevation or T-wave changes in at least two contiguous leads, (b) prior documented myocardial infarction, (c) prior revascularization procedure, or (d) noninvasive or invasive testing results consistent with ischemic heart disease. Exclusions included contraindications to anticoagulation and advanced renal insufficiency. For the present analysis, patients were also excluded if procedures or hospitalizations recorded on the case report form could not be confirmed by source documentation from the individual enrolling sites. Of the 3171 randomized patients, 120 (4%) were excluded for this reason (13 US patients, 107 non-US patients). Of the remaining 3051 patients, 923 were enrolled in the United States and make up the primary study population for this report.

Overview of ESSENCE Protocol and Summary of Major Clinical Outcomes

All patients received daily aspirin at a dose of 100 to 325 mg. Patients were randomized to either weight-adjusted enoxaparin 1 mg/kg subcutaneously at 12-hour intervals plus placebo intravenous heparin bolus and infusion, or placebo subcutaneous enoxaparin plus intravenous heparin bolus and infusion adjusted with serial activated partial thromboplastin time (aPTT) values. The aPTT was measured at baseline and 4 to 6 hours after initiation of study drug. Adjustment of heparin dosing according to aPTT values (with general target of 55 to 85 seconds) was done by an unblinded observer at each institution who was independent from the study investigators. Study drug was administered for a minimum of 48 hours and a maximum of 8 days. Aside from the foregoing, the study protocol did not alter institutional usual care in any other way.

As reported elsewhere, enoxaparin therapy was associated with a reduction in the study primary end point, the 14-day incidence of death, myocardial (re-)infarction, or recurrent angina (16.6% versus 19.8% with unfractionated heparin, \(P = 0.019\)). At 30 days, 19.8% of the enoxaparin patients had one of these three events versus 23.3% of the heparin patients (\(P = 0.016\)). Major bleeding was equivalent in the two arms at 30 days (6.5% for enoxaparin versus 7.0% for heparin), but minor bleeding was increased with enoxaparin (13.8% versus 8.8%, \(P < 0.001\)). Most of the excess minor bleeds were injection site ecchymoses.

Overview of Economic Substudy

As part of the ESSENCE research effort, we conducted a prospective economic substudy of trial patients randomized in the United States. We estimated medical costs starting with the initial hospital admission (during which the patient was enrolled in the trial) and extending through the 30-day follow-up. For hospital costs, we collected copies of the relevant hospital bills. Both itemized and summary ledger forms of the bill were collected along with a UB-92 bill form. During analysis, hospital charges were converted to costs by using the department level correction factors contained in each hospital’s annual Medicare Cost Report. Physician fees were assigned from the 1995 Medicare Fee Schedule for the following services: daily follow-up (intensive care unit [ICU], non-ICU), cardiac catheterization, coronary angioplasty, and coronary bypass surgery. Inpatient consultations were not recorded, and outpatient follow-up care (aside from cardiac catheterization) was not assessed.

While the initial protocol for the ESSENCE economic substudy was constructed before patient enrollment, administrative issues delayed the initiation of hospital cost data collection until May 1996, after patient enrollment had been completed. Thus for some patients enrolled earlier in the trial, hospital bill data could not be collected because the data had already been archived by the hospital in question. Of the total 923 potential economic substudy patients enrolled in ESSENCE in the United States, 151 were enrolled at Veterans Administration hospitals that do not generate hospital bills, and 117 were enrolled at hospitals unable to provide billing data. Thus 655 patients had collection of complete baseline hospital cost data (85% of the patients with collectable hospital bill data). Because of the concern that patients with hospital billing data collected might reflect a biased sample of the total United States enrollment in ESSENCE, we used a resource-based regression model developed in study patients with cost data (see “Data Analysis”) along with medical resource use data from the case report forms to impute hospital costs for all baseline US hospitalizations in which billing data could not be collected. Furthermore, because hospital identity was not included on the study case report forms, we were unable to collect hospital billing data for follow-up admissions and costs were imputed in a similar manner for all of these hospitalizations.

In the ESSENCE Trial, the randomized study treatments (heparin, enoxaparin) were provided without cost to study participants. Therefore we were required to estimate these costs separately. For this indication, enoxaparin is provided in a multidose vial (similar to insulin vials) with a drug cost to hospitals of $0.38 per mg of drug. With two daily doses of enoxaparin at 1 mg/kg each, the mean enoxaparin cost per day of treatment (including pharmacy preparation costs) was $69 for US patients. In the United States, the mean treatment duration was 2.25 days, thus yielding a mean total enoxaparin cost of $155.

Heparin therapy involves the cost of the drug (with pharmacy preparation costs), along with the rental cost of the infusion pump, the costs of the aPTT laboratory determinations, and nursing and physician time associated with monitoring and adjusting the infusion. In assigning those costs, we chose to adopt a conservative position favoring the heparin arm by assuming that the medical personnel labor costs associated with heparin therapy would not be recoverable (ie, switching from heparin to enoxaparin would not generate cost savings from reduced personnel work). Consequently, only disposable supply costs, the cost of infusion pump rental, and the cost of the aPTTs were used in developing a daily cost for heparin therapy. Unit costs for these items were obtained from the Duke Transition One Cost Accounting System and from the Duke Medical Center Pharmacy.

Data Analysis

Descriptive statistics are presented as percentages for discrete variables and median and interquartile ranges (25th to 75th percentiles) or means and standard deviations for continuous variables. Given the skewness typically present in the distribution of medical cost data, no individual descriptive statistic is completely satisfactory. Thus we present both mean costs (reflecting the cost of the treatment program expressed on a per patient basis) and median costs (reflecting the costs of the “typical” patient). Treatment groups were compared by intention to treat for medical costs (hospital plus physician) of the initial hospitalization and by cumulative costs to 30 days. We tested differences with either the Wilcoxon rank sum test (for continuous variables) or the \(\chi^2\) test (for discrete variables).

To impute hospital costs for US patients without hospital billing data, we developed a multivariable linear regression model in the 655 patients on whom we had collected such data. Candidate variables were selected from the clinical case report form and included length of stay (both ICU and non-ICU), number of cardiac catheterizations, number of coronary angioplasty procedures, and coronary artery bypass graft surgery. The \(R^2\) value for this model was .86. Cost comparisons by intention to treat restricted to patients with hospital bill data were similar to those that included all US patients (including imputed hospital cost data). Thus our presentation of results emphasizes the use of complete US patient resource and cost data.

Because ESSENCE was an international trial, the possibility existed that the treatment-related resource patterns (and associated costs) seen in the United States might differ from those seen outside the United States. As a sensitivity analysis to evaluate this possibility, we used the cost regression model described above to impute US costs for all non-US patients and compared medical costs for the overall study cohort by intention to treat.
Because statistical hypothesis testing of cost data addresses a relatively narrow question ("Is the cost difference between the two treatment arms equal to $0?"), we supplemented standard statistical testing with a bootstrap analysis. We created 200 bootstrapped samples from the US study cohort and calculated the mean cost difference by intention to treat for each sample. The results of this analysis, displayed as a cumulative distribution function, describes the distribution of a net difference in medical costs between these two treatment strategies. Thus the proportion of bootstrap replications with a cost difference $\geq$500, $\geq$1000, or any other threshold of interest can be calculated.

### Results

#### Baseline Characteristics

The baseline study population characteristics and 14- and 30-day outcomes from ESSENCE have been previously reported. The two treatment groups were well balanced with regard to baseline characteristics. Overall, the US cohort had a median age of 63 years with 65% male enrollment (Table 1). Coronary disease was established by diagnostic catheterization in 55%, by a documented myocardial infarction in 46%, by a prior coronary artery bypass grafting in 27%, by a prior percutaneous transluminal coronary angioplasty in 30%, and by a positive exercise test in 27%. Transient ST-segment elevation was present on the enrollment ECG in 6% of the study population, whereas 19% had ST depression and 31% had T-wave inversions. Compared with the non-US ESSENCE cohort, the US patients were heavier and had more hypertension, hypercholesterolemia, and diabetes (Table 1). US patients also had a higher prevalence of coronary disease documented by diagnostic catheterization and of prior revascularization.

#### Medical Resource Consumption

During the initial (enrollment) hospitalization, enoxaparin patients in the United States used fewer major medical resources than heparin patients (Table 2). The largest effect was a 5% absolute reduction in the use of coronary angioplasty. Samples from the US study cohort and calculated the mean cost difference by intention to treat for each sample. The results of this analysis, displayed as a cumulative distribution function, describes the distribution of a net difference in medical costs between these two treatment strategies. Thus the proportion of bootstrap replications with a cost difference $\geq$500, $\geq$1000, or any other threshold of interest can be calculated.

### Medical Resource Consumption

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plasty (15% versus 20% for heparin, P=.04). Trends with diagnostic catheterization and coronary bypass surgery favored enoxaparin but were not statistically significant. There were also nonsignificant trends toward shorter ICU and total hospital stays with enoxaparin. All these trends in the US patients were also seen in the overall study cohort (Table 2).

At the 30-day follow-up point, the resource use differences observed were equivalent to those seen at baseline or increased slightly in favor of enoxaparin (Table 2). Reductions in the use of diagnostic catheterization (57% versus 63% for heparin, P=.04) and coronary angioplasty (18% versus 22%, P=.08) with enoxaparin were accompanied by a reduction in intensive care unit length of stay (2.4 versus 2.8 days for heparin, P=.05). As with the initial hospitalization, all these trends were also evident in the total ESSENCE study population (Table 2). The rehospitalization rate out to 30 days in the US patients was 14% in the enoxaparin arm versus 16% in the heparin arm (P=.37), whereas in the overall study population 13.1% were rehospitalized in the enoxaparin arm versus 12.3% in the heparin arm (P=.50).

**Medical Costs**

In the US ESSENCE patients, the differences in resource consumption described in the previous section produced a $600 hospital cost saving for enoxaparin and a $237 saving in physician fees (Table 3). For US patients, the mean duration of study drug administration was 2.3 days. The associated costs of enoxaparin therapy were $155, whereas those for heparin were $80. Thus the total medical cost for the initial hospital admission was $11 857 for enoxaparin and $12 620 for heparin, a $763 savings with enoxaparin therapy (P=.18) (Table 3). At the end of 30 days, the trends in cost figures that had favored enoxaparin were all statistically significant (Table 3). The cumulative total cost savings associated with enoxaparin at 30 days was $1172 (P=.04).

The total baseline hospitalization costs in the subset of 655 US patients who had hospital bill data collected were $12 425 in the heparin arm and $11 269 in the enoxaparin arm, a $1156 difference favoring enoxaparin (P=.16). The 30-day cost difference in these patients was $1636 in favor of enoxaparin (P=.03).

When US cost weights were applied to the resource use patterns observed in the non-US ESSENCE countries and the results then summed with the US cost data, the cost advantage for enoxaparin persisted. Outside the United States, the mean duration of study drug treatment was longer than in the United States (range, 2.5 to 5.0 days), so that the associated costs of treatment outside the Unites States were somewhat higher. For the total ESSENCE cohort with resource data available (n=3051), estimated baseline medical costs were $14 653 in the heparin arm and $13 992 in the enoxaparin arm (P=.09). At the end of 30 days, cumulative estimated costs for the heparin arm were $15 960 versus $15 272 for enoxaparin (P=.10).

In 200 bootstrap samples of the US initial hospitalization cost data (ie, hospital, physician and drug cost), net costs for the enoxaparin arm were lower than the heparin arm in 86% of samples, were >$500 lower in 63% of samples, >$750 lower in 51% of samples, and >$1000 in 43% of samples (Figure 1). In a similar bootstrap analysis of the 30-day cost data, the corresponding sample proportions favoring the enoxaparin arm by any amount, and by >$500, >$750, and >$1000 were 94%, 77%, 69%, and 58%, respectively (Figure 2).

**Discussion**

The ESSENCE trial demonstrated that improved antithrombin activity with the low-molecular-weight heparin enoxap-

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**TABLE 3. Initial Hospitalization and Cumulative 30-Day Medical Costs for US Cohort**

<table>
<thead>
<tr>
<th></th>
<th>Heparin (n=459)</th>
<th>Enoxaparin (n=464)</th>
<th>P</th>
</tr>
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<tbody>
<tr>
<td><strong>Initial hospitalization costs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital costs, $</td>
<td>10 056±9499</td>
<td>9 456±11 921</td>
<td>.11</td>
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<tr>
<td>Median</td>
<td>6753</td>
<td>6323</td>
<td></td>
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<tr>
<td>Physician fees, $</td>
<td>2483±2231</td>
<td>2246±2038</td>
<td>.17</td>
</tr>
<tr>
<td>Median</td>
<td>1553</td>
<td>1479</td>
<td></td>
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<tr>
<td>Study drug, $</td>
<td>80±36</td>
<td>155±86</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Median</td>
<td>78</td>
<td>141</td>
<td></td>
</tr>
<tr>
<td>Total costs, $</td>
<td>12 620±11 587</td>
<td>11 857±13 630</td>
<td>.18</td>
</tr>
<tr>
<td>Median</td>
<td>8282</td>
<td>7966</td>
<td></td>
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<tr>
<td><strong>Cumulative 30-day costs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital costs, $</td>
<td>11 443±9955</td>
<td>10 514±12 295</td>
<td>.02</td>
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<tr>
<td>Median</td>
<td>7753</td>
<td>6984</td>
<td></td>
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<tr>
<td>Physician fees, $</td>
<td>2833±2353</td>
<td>2516±2190</td>
<td>.03</td>
</tr>
<tr>
<td>Median</td>
<td>1853</td>
<td>1579</td>
<td></td>
</tr>
<tr>
<td>Total costs (including drug), $</td>
<td>14 357±12 171</td>
<td>13 185±14 151</td>
<td>.04</td>
</tr>
<tr>
<td>Median</td>
<td>9655</td>
<td>8797</td>
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</tbody>
</table>
Figure 2. Cumulative distribution function of mean differences in 30-day medical costs between the enoxaparin arm and the heparin arm in 200 bootstrap samples. In 94% of samples, enoxaparin was cost saving.

Enoxaparin yielded sustained clinical advantage out to 30 days over standard unfractionated heparin. Enoxaparin reduced the 30-day incidence of death, myocardial infarction, or recurrent angina from 23.3% with heparin to 19.8% (P = .016). The present study has demonstrated that this improved clinical effectiveness was associated with a complete recoup of the $75 incremental cost of administering enoxaparin rather than heparin plus additional cost savings of $763 at hospital discharge and $1172 at 30 days. Thus enoxaparin joins the ranks of a select group of therapies that both improve important clinical outcomes and reduce net treatment costs relative to the therapies they propose to replace. There have been several previous trials of low-molecular-weight heparin in acute coronary syndrome patients, but none reported both a clinical and economic benefit for this therapy.

ESSENCE was a double-blind trial. Thus the reductions in resource use seen in the enoxaparin arm are not due to investigator expectations or biases but rather to effects of the drug on the clinical manifestations of acute coronary disease. This is important to keep in mind when reviewing the treatment-related differences in medical resource use, some of which did not achieve statistical significance (Table 2). The consistency of the trends—all favoring enoxaparin—suggest that the modest reduction in individual resources (eg, 4 per 100 fewer diagnostic catheterizations, 5 per 100 fewer coronary angioplasties, 2 per 100 fewer coronary artery bypass surgeries) would have been significant with a larger sample size. Indeed some of the resource shifts that were not significant in the US cohort were significant in the overall study cohort despite a slightly smaller absolute reduction in resource use in non-US patients.

The most substantial resource effect of enoxaparin was a reduction in the use of coronary angioplasty, which was consequent to the clinical reduction in recurrent ischemic events. Few coronary stents were used in the ESSENCE trial, and no difference in stent use was observed by treatment group (data not shown). If current US coronary stenting practices had been in effect during the ESSENCE trial, the observed economic results probably would have been unchanged or might have even increased the cost advantage of enoxaparin, given the higher costs of stenting versus balloon angioplasty.

Both of the agents studied in ESSENCE are inexpensive by modern pharmaceutical standards. Enoxaparin is given twice daily as a weight-adjusted subcutaneous dose. The mean cost was $69 per day for US ESSENCE patients, and the entire course of therapy was $155. Heparin is even less expensive but is somewhat more complex to administer. The drug must be given as a continuous intravenous infusion to achieve reliable and sustained therapeutic effect and dosage must be monitored and periodically adjusted with aPTT determinations. The pharmacy and laboratory costs of heparin therapy (ie, heparin bag, infusion pump, aPTTs) in this study was estimated at $80. There are also labor components to the use of heparin, particularly nursing time involved in monitoring and adjusting the heparin infusions. In comparing treatment strategies, one should count reduced labor requirements as a cost savings only if the new therapy allows some personnel to be sent home without pay because they are not needed or allows them to be diverted to other revenue generating activities. In the case of heparin therapy, the estimated time savings per shift in even a high-volume Cardiac Care Unit were too small and fragmented to allow a reduction in personnel requirements or a diversion to other productive activities. Instead, nurses probably would spend more time performing their primary care-giving activities for their existing patient load. For these reasons, we chose the conservative strategy of including only drug and laboratory costs of heparin therapy in our analysis.

To supplement standard statistical hypothesis testing, we performed a bootstrap replication to evaluate more fully the likely magnitude of cost differences between the two treatment arms. This analysis demonstrated that for the index hospitalization, 86% of replications showed that the enoxaparin arm had lower total medical costs than did the heparin arm. In 63% of samples the net cost advantage for enoxaparin was >$500. At 30 days, 94% of replications showed a cost saving for enoxaparin, and in 77% the cost advantage exceeded $500.

Economic analysis of international clinical trials can be challenging because of substantial intercountry differences in patterns of resource use. In ESSENCE, US patients received more invasive procedures and had shorter hospital stays than their non-US counterparts. Despite these differences, however, we found substantial consistency of treatment effect on resource use between US patients and the total ESSENCE cohort (Table 2). Thus we feel that the US economic substudy fairly reflects what would have been observed had the entire trial been conducted solely in the United States.

Several caveats about the present study should be considered. First, we did not measure outpatient care, but we consider it highly unlikely that these small additional costs would have changed our results materially. Second, we did not evaluate productivity costs related to loss of employment. Given the short time frame of ESSENCE follow-up (30 days) and the mean age of the study population (63 years), these costs would not be likely to alter our primary results. Finally, the limited follow-up of ESSENCE (30 days) leaves open the question of whether the observed clinical and economic benefits would be preserved...
over a longer time span. For example, it is theoretically possible that by saving the sickest patients, enoxaparin therapy might be associated with extra downstream costs and narrowing of the observed cost advantage.

Economists refer to a therapy that improves outcomes at a net cost equivalence (or a cost savings) as “dominant.” From a policy point of view, such therapies are virtually always preferable to the therapies they have improved on. The ESSENCE trial suggests that enoxaparin therapy is dominant over unfractionated heparin for acute coronary syndrome patients. If the ESSENCE results are confirmed by the on-going TIMI 11b Trial, the two trials together will undoubtedly establish enoxaparin as the new standard of care for this disorder.

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