Prior aspirin users with acute non-ST-elevation coronary syndromes are at increased risk of cardiac events and benefit from enoxaparin

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Background The aim of this article was to investigate whether prior aspirin use in patients with acute coronary syndromes affects clinical outcome. The Efficacy Safety Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events Study (ESSENCE) and Thrombolysis in Myocardial Infarction (TIMI) 11B trials have shown superiority of enoxaparin over unfractionated heparin (UFH) in patients with unstable angina and non-ST-segment elevation myocardial infarction (UA/NSTEMI). However, the treatment effect of enoxaparin in the subset of patients reporting prior aspirin use has not been determined.

Methods The rate of death, myocardial infarction, and urgent revascularization at days 8 and 43 after randomization was compared among patients who received aspirin within the week before randomization with those who did not receive aspirin in the TIMI 11B trial. A total of 3275 patients (84%) were prior aspirin users.

Results The admission diagnosis was similar for prior and nonprior aspirin users. At both day 8 and day 43 the event rate was higher for prior aspirin users than for nonprior aspirin users (odds ratio 1.6 [1.24-2.08], P = .0004 at day 43), even after correction for baseline characteristics. Compared with those prior aspirin users taking UFH, enoxaparin-treated prior aspirin users had a reduced rate of the composite end point of death, myocardial infarction, and urgent revascularization at day 8 (odds ratio 0.82 [0.67-1.00], P = .046) and day 43 (odds ratio 0.83 [0.70-0.98], P = .032).

Conclusion Patients with UA/NSTEMI and prior aspirin use had a 60% higher risk of death and cardiac ischemic events compared with nonprior aspirin users. On the basis of this subanalysis, enoxaparin is superior to UFH in all patients. In prior aspirin users the benefit is more clearly demonstrated. (Am Heart J 2001;141:566-72.)

Over the past 10 years major changes have occurred in our understanding of the pathophysiologic mechanisms underlying vascular occlusion.1-3 The first stage in this process involves rupture of a vulnerable plaque, which leads to activation, adhesion, and aggregation of platelets and activation of the clotting cascade. This sequence eventually leads to the formation of an occlusive thrombus. Aspirin is the most widely prescribed agent to reduce platelet-mediated coronary thrombosis, having been shown to reduce the incidence of death and recurrent ischemia in patients with acute coronary syndromes.4 In the last decade data from placebo-controlled trials have demonstrated that aspirin in doses of 75 to 1200 mg per day reduced the risk of death or nonfatal myocardial infarction in patients with unstable angina by as much as 50%.5,6 In addition, the Antithrombotic Trialists’ meta-analysis showed a 25% reduction in the incidence of cardiovascular events with the use of aspirin.4 Despite the remarkable properties of aspirin, there are several scenarios in which it may fail to provide a full antithrombotic benefit.7 A 2-year follow-up study investigated outcomes for poststroke patients who were defined as aspirin responders on the basis of a consistent reduction in platelet reactivity after repeated aspirin use and compared them with outcomes for poststroke patients defined as nonresponders.8 The study demonstrated that aspirin responders had a reduced rate of stroke, myocardial infarction, and death compared with nonresponders. In addition, unexpected and discordant effects of aspirin on platelet reactivity have been reported in a study detecting P selectin expression and platelet activation and aggregation in healthy subjects before and after 5 days of aspirin treatment.9 Response to two dosages of aspirin was discordant, with 45% of patients being consistent nonresponders, 33% consistently responding, and 22% of patients show-
ing decreased platelet activation with an 81 mg daily regimen but increased activation with an higher dosage of 325 mg daily. It should be noted that a substantial number of patients have recurrent events despite aspirin use. These patients are by definition clinical aspirin failures and some of them may be aspirin resis-
tant. This "uncontrolled" prothrombotic activity may be improved by better or more powerful antithrom-
botic therapy with enoxaparin independent of the rates of events. The combination of unfractionated heparin (UFH) and aspirin therapy in unstable angina and non-
ST-segment elevation myocardial infarction (UA/NSTEMI) in nonprior aspirin users has been shown to signi-
cantly reduce recurrent ischemic events in the early phase of unstable angina at day 14 (10.5% vs 27%, \( P = .04 \)) compared with patients taking aspirin alone.\(^{10}\) The use of a stable antithrombotic treatment could improve the outcome of this particular group of patients. Between 30% and 80% of patients with UA/NSTEMI have been reported to take aspirin before admis-
sion.\(^{11,12}\)

The aim of this article was to investigate whether prior aspirin use is associated with worse outcome and, because the Thrombolysis in Myocardial Infarction (TIMI) 11B trial has shown the superiority of enoxa-
parin over UFH in patients with UA/NSTEMI,\(^{12}\) to com-
pare the treatment effect of enoxaparin in patients reporting prior aspirin use and in patients not reporting prior aspirin use.

Material and methods

Study design

This multicenter, randomized, double-blind, parallel-group clinical trial was designed to evaluate the efficacy and safety of long-term subcutaneous treatment with enoxaparin in patients with UA/NSTEMI. The inclusion criteria have been described elsewhere.\(^{12}\) All patients received aspirin throughout the study. By use of a centralized telephone system, eligi-
ble patients were randomly allocated either enoxaparin or UFH in a 1:1 ratio. Blinded treatment started as soon as possible and within 1 hour of randomization. Patients received at least 72 hours of treatment with either enoxaparin and placebo or UFH and placebo. \(\beta\)-Blockers, calcium-channel blockers, intravenous nitroglycerin, and aspirin were given at the physician’s discretion. Two strategies of antithrombotic therapy were compared: UFH during the acute phase fol-
lowed by placebo subcutaneous injections during the chronic phase and uninterrupted therapy with subcutaneous enoxa-
parin during both the acute and chronic phases. The acute phase began with enrollment and ended either at hospital discharge or at day 8 (whichever came first). An initial 30 mg intravenous bolus of enoxaparin was given followed by a dose of 1 mg/kg every 12 hours and intravenous UFH with a bolus of 70 IU/kg followed by an infusion of 15 IU/kg per hour titrated to an activated thromboplastin time 1.5 to 2.5 times the control. The infusion of UFH/placebo was maintained for a minimum of 72 hours, whereas subcutaneous injections of enoxaparin/placebo were maintained until hospital discharge or day 8. The chronic treatment phase began at hospital discharge or day 8, with a fixed dose (40 mg for patients weighing <65 kg or 60 mg for those weighing ≥65 kg), and ended 35 days thereafter.

Assessments of efficacy, adverse events, and safety end points were carried out daily. All patients were followed up at day 8 or discharge and at days 14 and 43. They were also con-
tacted by telephone 3 months and 12 months later.

We defined prior aspirin users as those patients who had taken aspirin on a regular basis during the week before the onset of the qualifying event. The primary efficacy end point was a composite of all-cause mortality, nonfatal myocardial infarction, or severe recurrent ischemia requiring urgent revascularization. The analysis of end point data stratified by prior aspirin use was part of the design of the TIMI 11B trial.

Statistical analysis

Baseline characteristics were compared by chi-square analy-
sis for categorical variables and the Student \( t \) test for continu-
ous variables. Analyses of efficacy end points used chi-square tests and were performed on an intention-to-treat basis. Two-
sided \( P \) values less than .05 indicated statistical significance. Statistical correction for confounding factors was done by logistic regression analysis. A Breslow-Day test was used to assess the homogeneity of the treatment effect in aspirin and nonaspirin users.

Results

A total of 3910 patients admitted with the initial diag-
nosis of UA/NSTEMI were randomly assigned treatment with enoxaparin or UFH. A total 3275 patients (84%) were prior aspirin users and 635 patients (16%) were not prior aspirin users. The population profile was consis-
tent with that of high-risk patients (Table I). Overall, prior aspirin users had a higher risk profile before ran-
donization (Table I), with a greater proportion reporting prior myocardial infarction (34.4% vs 17.6%, \( P = .0001 \)), coronary artery bypass grafting (15.0% vs 5.4%, \( P = .0001 \)), percutaneous transluminal coronary angio-
plasty (12.9% vs 5.0%, \( P = .0001 \)), and angina class III/IV (13.4% vs 9.9%, \( P = .02 \)).

A total of 39.1% of prior aspirin users had elevated car-
diac biomarkers compared with 36.9% of those not prior aspirin users—the between-groups difference was not statistically significant. Prior and nonprior aspirin user patient groups had a similar number of patients with UA and NSTEMI (UA: 59.4% vs 58.4%, \( P \) not signifi-
cant; NSTEMI: 32.1% vs 34.5%, \( P \) not significant). Fewer patients had Q-wave myocardial infarction in the prior aspirin users group compared with the nonprior aspirin users (3.4% vs 5.0% respectively, \( P = .04 \)) (Table II).

The triple end point of death, myocardial infarction, and urgent revascularization was evaluated at days 8 and 43 stratified by prior or nonprior aspirin use and by treatment. At day 8 no significant differences were found in the rate of death, but fewer myocardial infar-
cptions and urgent revascularizations were observed in
those not prior aspirin users. At day 8 a statistically significant higher rate of combined events was observed for prior aspirin users than was seen in those who were not prior aspirin users (14.4% vs 8.5%, odds ratio [OR] 1.81 [95% confidence interval (CI) 1.35–2.43], \( P < .0001 \); Figure 1). At day 43, no differences were found in the number of deaths, but increased rates of myocardial infarction and urgent revascularization were observed in prior aspirin users. There was a statistically significant higher event rate for the composite endpoint in the group of prior aspirin users compared with the nonprior aspirin users (19.7% vs 12.3%, OR 1.6 [95% CI 1.24–2.08], \( P = .0004 \); Figure 2).

Because there were some differences in the risk profile of prior and nonprior aspirin users, multiple logistic regression was used to adjust for differences in baseline characteristics, including age, sex, diabetes, family history, prior angina, prior coronary stenosis (>50%), prior \( \beta \)-blocker usage, hypertension and prior myocardial infarction, coronary artery bypass grafting, or percutaneous coronary intervention. After adjustment, the increased risk for prior aspirin users was unchanged (adjusted OR 1.57 [95% CI 1.21–2.03], \( P = .0003 \)).

Event rates stratified by previous aspirin use are shown in Figure 3. In prior aspirin users, there was a significant reduction in the composite endpoint of death, myocardial infarction, and urgent revascularization in the enoxaparin group compared with UFH (21.1% vs 18.2%; OR 0.83 [95% CI 0.70–0.98]). In the nonprior aspirin group a benefit of enoxaparin was not apparent; however, the size of the nonprior aspirin group was inadequate for a definitive analysis of the benefit of enoxaparin within that subgroup. Event rates stratified by enoxaparin and UFH were similar, but there was no evidence that the overall benefit of enoxaparin seen in the TIMI 11B patients as a whole was different for patients without prior aspirin use (Breslow-Day test for homogeneity of OR of the aspirin and nonaspirin groups, \( P = .376 \)).

There were no statistically significant differences in the incidence of major bleeding for patients administered enoxaparin compared with patients given UFH.

### Table I. Baseline characteristics of all randomized patients by prior aspirin use

<table>
<thead>
<tr>
<th></th>
<th>No prior aspirin use</th>
<th>Prior aspirin use</th>
<th>Significance (aspirin vs nonaspirin usage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>635</td>
<td>3275</td>
<td></td>
</tr>
<tr>
<td>Mean age (y)</td>
<td>64.6</td>
<td>64.3</td>
<td>NS</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>379 [59.7]</td>
<td>2153 [65.7]</td>
<td>( P = .003 )</td>
</tr>
<tr>
<td>Female</td>
<td>256 [40.3]</td>
<td>1122 [34.3]</td>
<td></td>
</tr>
<tr>
<td>Mean weight [kg]</td>
<td>76.4</td>
<td>78.5</td>
<td>NS</td>
</tr>
<tr>
<td>Risk factor for CAD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family history</td>
<td>184 [29]</td>
<td>1169 [35.7]</td>
<td>( P = .001 )</td>
</tr>
<tr>
<td>Hypertension</td>
<td>313 [49.3]</td>
<td>1629 [49.7]</td>
<td>NS</td>
</tr>
<tr>
<td>Four or more risk factors</td>
<td>19 [3]</td>
<td>150 [4.6]</td>
<td>( P = .06 )</td>
</tr>
<tr>
<td>Elevated cardiac markers</td>
<td>233 [36.7]</td>
<td>1279 [39.1%]</td>
<td>NS</td>
</tr>
<tr>
<td>Prior coronary stenosis &gt;50</td>
<td>79 [12.4]</td>
<td>949 [29]</td>
<td>( P &lt; .0001 )</td>
</tr>
<tr>
<td>Prior heart failure</td>
<td>25 [3.9]</td>
<td>180 [5.5]</td>
<td>( P = .107 )</td>
</tr>
<tr>
<td>Prior CABG</td>
<td>34 [5.4]</td>
<td>491 [15]</td>
<td>( P &lt; .0001 )</td>
</tr>
<tr>
<td>Prior documented MI</td>
<td>112 [17.6]</td>
<td>1128 [34.4]</td>
<td>( P &lt; .0001 )</td>
</tr>
</tbody>
</table>

Percentages shown in parentheses. NS, Not significant; CAD, coronary artery disease; PTCA, percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass grafting; MI, myocardial infarction.

### Table II. Final diagnosis of presenting symptoms of all randomized patients, by prior aspirin use

<table>
<thead>
<tr>
<th></th>
<th>No prior aspirin use</th>
<th>Prior aspirin use</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unstable angina</td>
<td>59.4</td>
<td>58.4</td>
<td>NS</td>
</tr>
<tr>
<td>NSTEMI</td>
<td>32.1</td>
<td>34.5</td>
<td>NS</td>
</tr>
<tr>
<td>QMI</td>
<td>5.0</td>
<td>3.4</td>
<td>( P = .04 )</td>
</tr>
<tr>
<td>Noncardiac</td>
<td>3.5</td>
<td>3.7</td>
<td>NS</td>
</tr>
</tbody>
</table>

Percentages shown in parentheses. NS, Not significant; QMI, Q-wave myocardial infarction.
stratified by prior aspirin use, at 72 hours, and throughout the index hospitalization (hemorrhage incidence at 72 hours: prior aspirin users 0.7% vs 0.7%, P not significant; nonprior aspirin users 1.2% vs 0.7%, P not significant) (Table III).

Discussion

The clinical efficacy of aspirin (75–650 mg/d) for the primary and secondary prevention of occlusive cardiovascular disease in different vascular territories and in different risk profile patients has been established.4,13,14
However, some subgroups of patients still experience events regardless of prior aspirin use; for example, approximately 10% of patients in prospective registry studies have new nonfatal myocardial infarction or death at 6 months and approximately 13% of patients have refractory angina over the same period of time.15 Almost half these events occur within the first 7 days, highlighting the need for more effective therapy in this time frame. There is convincing evidence for combining UFH with aspirin in the treatment of acute coronary syndromes.16 Recently, in TIMI 11B and Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events (ESSENCE) studies, enoxaparin has shown a greater treatment benefit than UFH in the treatment of acute coronary syndromes.16 Recently, in TIMI 11B and Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events (ESSENCE) studies, enoxaparin has shown a greater treatment benefit than UFH in the treatment of acute coronary syndromes.16 Recently, in TIMI 11B and Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events (ESSENCE) studies, enoxaparin has shown a greater treatment benefit than UFH in the treatment of acute coronary syndromes.16 Recently, in TIMI 11B and Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events (ESSENCE) studies, enoxaparin has shown a greater treatment benefit than UFH in the treatment of acute coronary syndromes.16 Recently, in TIMI 11B and Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events (ESSENCE) studies, enoxaparin has shown a greater treatment benefit than UFH in the treatment of acute coronary syndromes.16 Recently, in TIMI 11B and Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events (ESSENCE) studies, enoxaparin has shown a greater treatment benefit than UFH in the treatment of acute coronary syndromes.16 Recently, in TIMI 11B and Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events (ESSENCE) studies, enoxaparin has shown a greater treatment benefit than UFH in the treatment of acute coronary syndromes.16 Recently, in TIMI 11B and Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events (ESSENCE) studies, enoxaparin has shown a greater treatment benefit than UFH in the treatment of acute coronary syndromes.16 Recently, in TIMI 11B and Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events (ESSENCE) studies, enoxaparin has shown a greater treatment benefit than UFH in the treatment of acute coronary syndromes.16 Recently, in TIMI 11B and Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events (ESSENCE) studies, enoxaparin has shown a greater treatment benefit than UFH in the treatment of acute coronary syndromes.16 Recently, in TIMI 11B and Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events (ESSENCE) studies, enoxaparin has shown a greater treatment benefit than UFH in the treatment of acute coronary syndromes.16 Recently, in TIMI 11B and Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events (ESSENCE) studies, enoxaparin has shown a greater treatment benefit than UFH in the treatment of acute coronary syndromes.16 Recently, in TIMI 11B and Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events (ESSENCE) studies, enoxaparin has shown a greater treatment benefit than UFH in the treatment of acute coronary syndromes.16 Recently, in TIMI 11B and Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events (ESSENCE) studies, enoxaparin has shown a greater treatment benefit than UFH in the treatment of acute coronary syndromes.16 Recently, in TIMI 11B and Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events (ESSENCE) studies, enoxaparin has shown a greater treatment benefit than UFH in the treatment of acute coronary syndromes.16

In a review of two clinical studies exploring the effectiveness of antithrombotic therapy in prior/nonprior aspirin users, Lancaster et al19 investigated the impact of prior aspirin usage on the treatment effect of enoxaparin in the ESSENCE trial17 and of tirofiban in the Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited to Unstable Signs and Symptoms (PRISM-PLUS) trial.20 In both studies prior aspirin users had higher event rates and higher rates of failure of medical therapy compared with nonprior aspirin users. In addition, in the Platelet Ilb/IIIa in Unstable angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) study, a significantly higher event rate was reported in patients reporting prior aspirin use, and the patients had less severe disease on admission.21 Garcia Dorado et al22 showed a better evolution in acute coronary syndromes with less incidence of myocardial infarction and death in prior aspirin users admitted with the diagnosis of UA/NSTEMI. Q-wave myocardial infarction was more common in nonprior aspirin users, but despite an apparently more severe disease profile on admission in the non-prior aspirin users a higher event rate was reported for prior aspirin users. One reason for the initially less severe clinical characteristics of aspirin users could be that aspirin may act as a protective agent limiting myocardial damage, by the limitation of thrombus formation and progression. Our results differ from earlier studies: in TIMI 11B patients there were no differences in admission diagnosis with regard to UA and NSTEMI and less Q-wave myocardial infarction was reported in prior aspirin users. This discrepancy could be partially explained by the small number of patients in the nonaspirin group leading to a reduced statistical power to show such a difference in admission disease profile. This may be a limitation of our subanalysis. In TIMI 11B patients, prior aspirin use is a marker of a more severe disease profile on admission than no prior aspirin use, and a significantly higher number of serious ischemic events in follow up, both at day 8 and at day 43, which could be the explanation for the worse outcome.

Additionally, a clear treatment benefit of enoxaparin over UFH can be seen in prior aspirin users. A treatment benefit of enoxaparin was not observed in non-prior aspirin users; however, the sample size was low, when tested, and there was no evidence of a difference in the treatment effect of enoxaparin in aspirin users when compared with non-aspirin users, although the power to discern a difference in enoxaparin’s treat-

| Table III. Hemorrhage incidence at 72 hours and throughout the index hospitalization stratified by prior use of aspirin |
|------------------|------------------|------------------|------------------|------------------|
|                  | 72 h             |                   | Index hospitalization |                   |
|                  | UFH % | ENOX % | UFH % | ENOX % |
| Prior aspirin use| 0.7 | 0.7 | 1 | 1.4 |
| No prior aspirin use | 0.7 | 1.2 | 1 | 1.8 |

ENOX, Enoxaparin.
ment effect stratified by aspirin use is low because of the small sample size of the nonprior aspirin group. We have to point out that a significant proportion of patients with a clear indication for the use of aspirin who had an acute cardiac event were not taking aspirin on admission, but the reasons for actually not taking aspirin at the time of randomization in TIMI 11B are not clear (Table I). It is possible that it had been prescribed but was not being taken by the patient. It is also possible that the treating physician recognized the need for aspirin but had not yet written the order at the time of enrollment into TIMI 11B.

The observation that prior aspirin users have a worse clinical outcome could be used as a prognostic tool. A history of aspirin use, coupled with clinical and electrocardiographic data may allow for better "tailoring" and targeting of aggressive combination treatment regimens, consisting of perhaps one or more antiplatelet agents or a more intense antithrombotic regimen plus glycoprotein IIb/IIIa inhibitors. The identification of the mechanism of aspirin failure (if one exists) could aid the initial selection of a treatment regimen in the prior aspirin user. The effect of prior aspirin use must be analyzed and confirmed in future trials before recommendations concerning different routine clinical practice in management of acute non-ST-elevation coronary syndromes in aspirin users can be made.

Conclusion

Prior aspirin users have a higher risk profile, and prior aspirin use can be considered as an independent risk factor for worse prognosis. In the TIMI 11B trial, the majority of prior aspirin users had a prior cardiac event, evidenced by a higher prevalence of previous myocardial infarction, prior revascularization, and β-blocker use. Prior aspirin users have a 60% higher rate of death, myocardial infarction, and urgent revascularization, even after adjustment for other confounding factors. As previously reported, enoxaparin is significantly superior to UFH in reducing the rate of combined end points in all patients. In prior aspirin users, this superiority is clearly seen, both at day 8 and day 43, likely because of the larger sample size and the play of chance compared with nonprior aspirin users. Furthermore, enoxaparin can be administered subcutaneously, offering advantages in terms of ease of use and thus the treatment does not require the use of an infusion pump. There were no differences in the incidence of major hemorrhage in the group of patients treated with enoxaparin or UFH stratified by prior aspirin use at 72 hours and throughout the index hospitalization.

References


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