Efficacy of hirudin in reducing cardiovascular events in patients with acute coronary syndrome undergoing early percutaneous coronary intervention

S. R. Mehta 1,2, J. W. Eikelboom 2,3, H.-J. Rupprecht 4, B. S. Lewis 5, M. K. Natarajan 1,2, C. Yi 2, J. Pogue 2 and S. Yusuf 1,2

Aims Although hirudin is superior to unfractionated heparin for prevention of death, myocardial infarction, or refractory ischaemia in patients with non-ST-elevation acute coronary syndrome, it is not clear whether hirudin is also of benefit in acute coronary syndrome patients undergoing early percutaneous coronary intervention.

Methods and Results In the OASIS 2 trial, 10,141 patients with non-ST-elevation acute coronary syndrome were randomized to 72 h of intravenous hirudin or unfractionated heparin. Percutaneous coronary intervention was performed at the discretion of the investigator. One hundred and seventeen patients underwent percutaneous coronary intervention within the first 72 h (‘early percutaneous coronary intervention’). In patients undergoing early percutaneous coronary intervention, hirudin compared with unfractionated heparin was associated with a significantly lower incidence of death or myocardial infarction at 96 h (6.4% vs 21.4%, OR 0.30; 95% CI: 0.10–0.88) and 35 days (6.4% vs 22.9%, OR 0.25; 95% CI: 0.07–0.86). In the unfractionated heparin group, death or myocardial infarction was significantly higher at 35 days in patients undergoing early percutaneous coronary intervention compared with those managed conservatively (22.9% vs 7.3%, OR 3.14, P<0.001) but this early percutaneous coronary intervention-related hazard was not observed in hirudin-treated patients (6.4% vs 6.8%, OR 0.94, P=1.0). A time-dependent covariate for percutaneous coronary intervention was not significant in a Cox regression model, suggesting a similar treatment benefit with hirudin before and after percutaneous coronary intervention. After adjustment for percutaneous coronary intervention propensity, the benefits of hirudin remained significant. There were three major bleeds in patients undergoing early percutaneous coronary intervention, all in patients randomized to hirudin.

Conclusion In patients with non-ST-elevation acute coronary syndrome undergoing early percutaneous coronary intervention, a direct thrombin inhibitor such as hirudin may be more effective than heparin in reducing the incidence of ischaemic complications.

Key Words: Hirudin, unfractionated heparin, coronary artery disease.

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Introduction

Patients with acute coronary syndrome undergoing early percutaneous coronary intervention are at increased risk of early ischaemic complications[1–3]. This early hazard appears to be the result of a thrombin-mediated and platelet-dependent process that is initiated by mechanical plaque disruption and culminates in thrombus formation at the site of vessel injury[4–8]. Distal embolization of atherothrombotic debris into the coronary microcirculation may also occur. Conventional anticoagulants (e.g. unfractionated heparin) and antiplatelet therapies (e.g. aspirin) reduce the risk of ischaemic complications[9]; however, a substantial burden still remains. It has recently been shown that the addition of glycoprotein IIb/IIIa receptor inhibitors to
unfractionated heparin and aspirin further improves clinical outcomes\(^1\)\(^2\), but the role of the direct thrombin inhibitors during early percutaneous coronary intervention in the context of acute coronary syndrome remains unclear.

Recently, hirudin has been evaluated as a substitute for unfractionated heparin in patients with acute coronary syndromes. A potent and specific inhibitor of thrombin, hirudin binds directly with thrombin and, unlike unfractionated heparin, inhibits fibrin-bound and circulating thrombin equally well\(^1\)\(^3\). In animal models, hirudin markedly inhibits platelet and fibrinogen deposition onto fresh mural thrombus\(^1\)\(^2\), inhibits growth of thrombus, and causes dissolution of a pre-existing mural thrombus\(^1\)\(^3\)\(^4\). Because fibrin-bound thrombin may be an important trigger of thrombus growth, its inhibition by hirudin may explain why this agent is superior to unfractionated heparin for the prevention of death and major cardiovascular events in patients with acute coronary syndromes\(^1\)\(^5\). However, it is unclear whether hirudin is also of benefit in acute coronary syndrome patients undergoing early percutaneous coronary intervention.

To address this issue, we examined clinical outcomes in patients undergoing early percutaneous coronary intervention in the OASIS-2 study, a trial that randomized patients with unstable angina or non-Q-wave myocardial infarction to receive either intravenous hirudin or unfractionated heparin.

**Methods**

**Patients**

The OASIS-2 study was an international, double-blind, randomized trial of 10,141 patients with acute coronary syndrome without ST elevation randomized to intravenous hirudin (lepirudin) or unfractionated heparin. The inclusion and exclusion criteria, study interventions and primary efficacy outcomes have been previously published\(^1\)\(^5\). Briefly, patients were eligible for inclusion in this study if they were within 12 h of onset of chest pain suspected to be due to unstable angina or myocardial infarction without ST-segment elevation. Patients with contraindications to unfractionated heparin or hirudin, renal impairment (i.e. creatinine >175 \(\mu\)mol\(\cdot\)l\(^{-1}\) or >2.0 mg\(\cdot\)dl\(^{-1}\)), at high risk of bleeding complications or with significant thrombocytopenia at baseline, were excluded.

**Study treatment**

Patients were randomized to a double-blind, double-dummy, 72-h intravenous infusion of either hirudin or unfractionated heparin. Hirudin was given as an initial bolus of 0.4 mg\(\cdot\)kg\(^{-1}\) followed by an infusion of 0.15 mg\(\cdot\)kg\(^{-1}\)\(\cdot\)h\(^{-1}\), and unfractionated heparin was given as an initial bolus of 5000 units followed by an infusion of 15 units\(\cdot\)kg\(^{-1}\)\(\cdot\)h\(^{-1}\). Doses of hirudin and unfractionated heparin were adjusted according to predefined rules to maintain the activated partial thromboplastin time (APTT) between 60 and 100 s. Aspirin (80–325 mg\(\cdot\)d\(^{-1}\)) was recommended in all patients.

**Percutaneous coronary intervention**

Percutaneous coronary intervention was performed at the discretion of the attending physician. However, the protocol recommended that early percutaneous coronary intervention be performed only in the presence of a clear clinical indication (e.g. continuing chest pain with ECG changes despite optimal medical therapy). Use of blinded study drug infusion during percutaneous coronary intervention was encouraged, while glycoprotein IIb/IIIa antagonists were discouraged. Where a decision was made to use open-label unfractionated heparin during the intervention, the study drug infusion was temporarily discontinued.

**Outcomes**

Data on the following outcomes were documented during the 6 month study period: death; new myocardial infarction, defined as recurrent symptoms with either new electrocardiogram changes or new elevations of enzymes; refractory ischaemia, defined as recurrent ischaemic pain lasting at least 5 min with documented new ECG changes occurring despite optimum medical treatment and requiring an additional intervention before the end of the next calendar day; and percutaneous coronary intervention, defined as early if it occurred during the period of study drug infusion (<72 h). All outcomes were adjudicated by a central committee blinded to treatment allocation.

**Statistical analyses**

Baseline characteristics of patients undergoing early percutaneous coronary intervention versus those not undergoing early percutaneous coronary intervention, and of patients undergoing early percutaneous coronary intervention randomized to hirudin versus unfractionated heparin, were compared using a chi-squared test for categorical variables and a Student’s t-test for continuous variables.

The incidence of the composite outcome of death or myocardial infarction and of death, myocardial infarction or refractory ischaemia in hirudin versus unfractionated heparin-treated patients undergoing early percutaneous coronary intervention was compared using a chi-squared test or a Fisher exact test. The relationship between early percutaneous coronary intervention and event-free survival was further explored by use of time-dependent covariates in a Cox regression model.
potential interaction between randomized treatment allocation and percutaneous coronary intervention was examined by use of an interaction term in the model.

Adjustment for selection bias

Patients undergoing percutaneous coronary intervention differ systematically from those not undergoing percutaneous coronary intervention. Therefore, to minimize the impact of selection bias, a propensity score for the likelihood of undergoing early percutaneous coronary intervention was developed\(^\text{[16-19]}\) and included in a Cox regression model comparing the treatment effect of hirudin and unfractionated heparin in patients undergoing early percutaneous coronary intervention. The propensity score model was developed using logistic regression to identify baseline factors (including treatment allocation) predictive of early percutaneous coronary intervention in a sample of 5000 randomly selected patients from the OASIS-2 database, and was validated in the remaining ~5000 patients. The validated model was used to determine the probability for early percutaneous coronary intervention for each patient in the OASIS-2 study, and finally was included in the Cox regression model together with a time dependent co-variate for percutaneous coronary intervention. This approach allowed us to determine the relationship between early percutaneous coronary intervention, treatment allocation and clinical outcomes after adjustment for selection bias, while still preserving the integrity of the randomized treatment allocation.

Results

Of the 10,141 patients randomized in the OASIS-2 study, 1565 (15.4\%) underwent percutaneous coronary intervention during the 6-month trial period. One hundred and seventeen procedures (7.5\%) were performed within the first 72 h (‘early percutaneous coronary intervention’), 360 (23.0\%) between 72 h and 7 days, 708 (45.3\%) between 7 days and 35 days, and 378 (24.2\%) between 30 days and 6 months. During early (<72 h) percutaneous coronary intervention, 27\% of patients received open-label unfractionated heparin and 34\% underwent intracoronary stent placement, 14\% in the hirudin group and 20\% in the unfractionated heparin group.

Baseline characteristics

Compared with patients who did not undergo early percutaneous coronary intervention, patients undergoing early percutaneous coronary intervention were younger, more likely to be male, smokers, have ST segment changes on an ECG, or non-Q-wave myocardial infarction. They were also more likely to have a past history of hypertension, diabetes, percutaneous coronary intervention, heart failure, stroke or myocardial infarction (Table 1). Among patients undergoing early percutaneous coronary intervention, there were no significant differences in baseline characteristics between hirudin and unfractionated heparin-treated patients (Table 2).

Early percutaneous coronary intervention

Fewer patients requiring early percutaneous coronary intervention during blinded-treatment were randomized to hirudin compared with unfractionated heparin (47/117 vs 70/117, \(P=0.03\)).

Table 1 Baseline characteristics of patients undergoing early percutaneous coronary intervention compared with patients not undergoing percutaneous coronary intervention

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Early PCI (n=117)</th>
<th>No early PCI (n=10,024)</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years</td>
<td>60.8</td>
<td>64.2</td>
<td>(&lt;0.001)</td>
</tr>
<tr>
<td>Males, %</td>
<td>43.1</td>
<td>50.1</td>
<td>(&lt;0.001)</td>
</tr>
<tr>
<td>Previous MI, %</td>
<td>35.0</td>
<td>39.4</td>
<td>0.04</td>
</tr>
<tr>
<td>ST depression, %</td>
<td>2.7</td>
<td>3.4</td>
<td>0.008</td>
</tr>
<tr>
<td>ST elevation, %</td>
<td>14.3</td>
<td>18.1</td>
<td>0.07</td>
</tr>
<tr>
<td>Diagnosis NQMI, %</td>
<td>23.2</td>
<td>19.2</td>
<td>0.11</td>
</tr>
<tr>
<td>Previous PCI, %</td>
<td>14.5</td>
<td>15.0</td>
<td>0.18</td>
</tr>
<tr>
<td>Previous CABG, %</td>
<td>16.2</td>
<td>14.5</td>
<td>0.23</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>14.5</td>
<td>15.1</td>
<td>0.08</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>33.9</td>
<td>33.9</td>
<td>1.0</td>
</tr>
<tr>
<td>Previous CHF, %</td>
<td>1.7</td>
<td>1.7</td>
<td>0.01</td>
</tr>
<tr>
<td>Previous stroke, %</td>
<td>8.3</td>
<td>8.9</td>
<td>0.95</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>70.9</td>
<td>62.5</td>
<td>0.06</td>
</tr>
</tbody>
</table>

CABG=coronary artery bypass graft surgery; CHF=congestive heart failure; MI=myocardial infarction; NQMI=non-Q-wave myocardial infarction; PCI=percutaneous coronary intervention.

Table 2 Baseline characteristics of patients undergoing percutaneous coronary intervention treated with hirudin or unfractionated heparin

<table>
<thead>
<tr>
<th></th>
<th>Hirudin (n=47)</th>
<th>Heparin (n=70)</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years</td>
<td>64.2</td>
<td>64.1</td>
<td>0.32</td>
</tr>
<tr>
<td>Males, %</td>
<td>68.1</td>
<td>81.4</td>
<td>0.37</td>
</tr>
<tr>
<td>Previous MI, %</td>
<td>23.4</td>
<td>35.7</td>
<td>0.76</td>
</tr>
<tr>
<td>ST depression, %</td>
<td>36.2</td>
<td>34.3</td>
<td>0.43</td>
</tr>
<tr>
<td>ST elevation, %</td>
<td>10.6</td>
<td>5.7</td>
<td>0.42</td>
</tr>
<tr>
<td>Diagnosis NQMI, %</td>
<td>21.3</td>
<td>24.3</td>
<td>0.62</td>
</tr>
<tr>
<td>Previous PCI, %</td>
<td>12.8</td>
<td>15.7</td>
<td>0.28</td>
</tr>
<tr>
<td>Previous CABG, %</td>
<td>12.8</td>
<td>18.6</td>
<td>0.87</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>19.2</td>
<td>11.4</td>
<td>0.13</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>57.5</td>
<td>51.4</td>
<td>0.50</td>
</tr>
<tr>
<td>Previous stroke, %</td>
<td>4.3</td>
<td>4.3</td>
<td>0.80</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>23.4</td>
<td>35.7</td>
<td>0.09</td>
</tr>
</tbody>
</table>

CABG=coronary artery bypass graft surgery; MI=myocardial infarction; NQMI=non-Q-wave myocardial infarction; PCI=percutaneous coronary intervention.
Among patients undergoing early percutaneous coronary intervention, hirudin therapy significantly reduced the risk of death or myocardial infarction at 96 h (OR 0.30; 95% CI: 0.10–0.88, \(P=0.036\)) and 35 days (OR 0.25; 95% CI: 0.07–0.86, \(P=0.02\)) compared with unfractionated heparin (Fig. 1).

Kaplan–Meier survival estimates for patients undergoing early percutaneous coronary intervention are presented in Fig. 2. Compared with patients randomized to unfractionated heparin, hirudin-treated patients undergoing early percutaneous coronary intervention experienced a significant reduction in death or myocardial infarction (\(P=0.02\)) as well as in death, myocardial infarction or refractory ischaemia (\(P=0.02\)) during follow-up to 30 days.

There were three major bleeds in patients undergoing early percutaneous coronary intervention, one of which was life-threatening. Each of these bleeds occurred in patients randomized to hirudin therapy.

**Timing of events in relation to early percutaneous coronary intervention**

In patients undergoing early percutaneous coronary intervention the majority of clinical outcomes occurred prior to the intervention. However, inclusion of a time-dependent covariate for percutaneous coronary intervention in the Cox regression model was not significant which suggests that there was a similar treatment benefit with hirudin both prior to and after early percutaneous coronary intervention (Fig. 3).

In patients randomized to unfractionated heparin there was a significant hazard for death or myocardial infarction at 35 days associated with early percutaneous coronary intervention compared with conservative treatment (22.9% vs 7.3%, OR 3.14, 95% CI 1.99–4.95, \(P<0.001\)) but this early hazard associated with percutaneous coronary intervention was attenuated with use of hirudin (6.4% vs 6.8%, OR 0.94, 95% CI 0.31–2.82, \(P=1.0\)).

**Propensity to perform early percutaneous coronary intervention**

The propensity score was highly predictive of the likelihood of early percutaneous coronary intervention (chi-squared=231, \(P<0.0001\)). Males, patients with a previous history of percutaneous coronary intervention

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**Figure 1** Death or myocardial infarction in hirudin and unfractionated heparin-treated patients who did or did not undergo early percutaneous intervention. (a) Death/MI <96 h; (b) death/MI <35 days. □=Hirudin; ▶=heparin.

**Figure 2** Kaplan–Meier estimates of the likelihood of death or myocardial infarction and of death, myocardial infarction or refractory ischaemia in patients undergoing early percutaneous coronary intervention treated with hirudin or unfractionated heparin.
and patients in North America were more likely to undergo early percutaneous coronary intervention (Table 3).

After adjustment for propensity to undergo early percutaneous coronary intervention in the time-dependent Cox model, randomization to hirudin therapy remained associated with a significant reduction in death or myocardial infarction and in death, myocardial infarction and refractory ischaemia (Table 4). There was no evidence of an interaction between treatment allocation and early percutaneous coronary intervention, suggesting that the treatment benefit of hirudin was similar in medically treated patients and patients undergoing early percutaneous coronary intervention.

### Discussion

The results of this study demonstrate that hirudin is associated with a reduction in ischaemic events, including death, myocardial infarction, and refractory ischaemia in patients with acute coronary syndrome undergoing early percutaneous coronary intervention. This treatment benefit was evident both before and after early percutaneous coronary intervention and persisted after adjustment for propensity to undergo early intervention. However, the benefits of hirudin were achieved at a cost of increased major bleeding.

Our findings are consistent with the results of two major randomized trials evaluating the use of direct thrombin inhibitors during percutaneous coronary intervention. In patients with unstable angina undergoing percutaneous coronary intervention in the HELVETICA study, randomization to hirudin compared with unfractionated heparin was associated with a 39% reduction in major ischaemic events at 96 h (OR 0.61, 95% CI 0.41–0.90) after percutaneous coronary intervention, with no impact in preventing late restenosis. The lack of benefit on restenosis in this largely unstented population should not detract from the large impact of hirudin in reducing procedural ischaemic events. In the Hirulog Angioplasty Study involving more than 4000 patients with unstable angina or post-infarction angina, bivalirudin was at least as effective as
heparin for the prevention of ischaemic complications (OR 0·9, 95% CI 0·8–1·1), and superior to heparin in the subgroup with post-infarction angina (OR 0·6, 95% CI 0·4–0·9). Similarly, a recent preliminary report from the GUSTO IIb trial demonstrated a significant 44% risk reduction in death or myocardial infarction at 30 days in hirudin-treated patients undergoing percutaneous coronary intervention.

There is a strong biological rationale for the use of direct thrombin inhibitors to prevent ischaemic complications in patients undergoing early percutaneous coronary intervention. By blocking thrombin activity, hirudin not only inhibits blood coagulation but also indirectly inhibits platelet activation since thrombin is the most powerful platelet agonist. By contrast, unfractionated heparin may paradoxically activate platelets, which could explain its limited efficacy in preventing ischaemic complications in patients undergoing early percutaneous coronary intervention. Despite being routinely used, the efficacy of unfractionated heparin in patients undergoing percutaneous coronary intervention has never been clearly demonstrated in randomized trials.

Glycoprotein IIb/IIIa antagonists have recently been shown to prevent major ischaemic complications, including death and myocardial infarction, in patients with acute coronary syndromes undergoing percutaneous coronary intervention. However, to achieve maximal benefit, these agents must be used in combination with an inhibitor of thrombin such as unfractionated heparin. By contrast, our results suggest that hirudin is beneficial when used as monotherapy, thus obviating the need for an additional anticoagulant such as unfractionated heparin. Nevertheless, the relative efficacy and safety of direct thrombin inhibitors and glycoprotein IIb/IIIa antagonists will remain unclear until the results of randomized comparisons between these two treatments are available. Also, the benefits of direct thrombin inhibitors in the context of thienopyridine pre-treatment remain yet to be evaluated.

Why do antithrombotic agents appear to have an exaggerated benefit in patients undergoing percutaneous coronary intervention compared with patients treated medically? This phenomenon also has been observed in trials of glycoprotein IIb/IIIa antagonists. One possible explanation may be that plaque rupture in patients presenting with an acute coronary syndrome is spontaneous and occurs in the absence of antithrombotic therapy, which is generally delayed for at least several hours. By contrast, mechanical plaque rupture in patients undergoing percutaneous coronary intervention is deliberate and occurs only after antithrombotic therapy has been started, which may result in incremental benefits of these agents in the setting of percutaneous coronary intervention.

A potential limitation of our study is that patients were not randomized to undergo percutaneous coronary intervention, making the decision to perform early intervention subject to selection bias. Our data confirm the results of previous studies suggesting that there are systematic differences between patients with acute coronary syndrome who undergo or do not undergo percutaneous coronary intervention. However, even after adjustment for an individual’s propensity to undergo percutaneous coronary intervention, there was a clear benefit of hirudin, further supporting the validity of our conclusions. Furthermore, although the numbers of patients in our study is modest, our results demonstrating a substantial and highly statistically significant treatment benefit of hirudin during early percutaneous coronary intervention are both internally consistent across all clinical outcomes as well as externally consistent with the results of previous studies using hirudin and bivalirudin.

Moreover, open-label unfractionated heparin was used in 27% of patients undergoing early percutaneous coronary intervention. However, a similar proportion of patients randomized to hirudin compared with unfractionated heparin received open-label therapy (31·9% vs 23·2%, P=0·32) and there were no differences in death or myocardial infarction among those receiving procedural open-label heparin versus blinded study medication in the hirudin-allocated group (P=0·96) or in the heparin-allocated group (P=0·63). The likely impact of lack of adherence to treatment allocation in a randomized trial is to reduce the contrast between the treatment groups and, thereby, reduce the power of the study to detect a significant difference. Despite this, our study demonstrated a significant reduction in death or myocardial infarction with hirudin compared with unfractionated heparin.

Our results lend credence to the hypothesis that direct thrombin inhibitors are more effective than unfractionated heparin as adjunctive pharmacological therapy in patients undergoing moderate to high risk percutaneous coronary intervention. Further randomized trials evaluating the efficacy and safety of direct thrombin inhibitors, including hirudin and bivalirudin, are needed to further clarify the role of these agents in the setting of percutaneous coronary intervention.

References


