Direct thrombin inhibitors in acute coronary syndromes: effect in patients undergoing early percutaneous coronary intervention

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KEYWORDS
Direct thrombin inhibitors; Percutaneous coronary intervention; Acute coronary syndromes

Aims We evaluated the effect of direct thrombin inhibitors (DTIs) in patients undergoing early percutaneous coronary intervention (PCI), using the DTI Trialists’ Collaboration database of 35 970 patients from 11 randomized trials of DTIs vs. heparin.

Methods and results We performed a Cox proportional hazards regression analysis with PCI as a time-dependent covariate to assess the independent impact of DTIs according to the performance of early PCI. PCI was performed in 7049 patients in the first 72 h after randomization. In trials in which PCI was not planned, DTIs were associated with a 10% relative risk reduction in death or myocardial infarction at 30 days (HR = 0.90, 95% CI: 0.84–0.97). This benefit was found to be greater in patients undergoing early PCI (HR = 0.66, 95% CI: 0.48–0.91) than those undergoing non-early PCI (HR = 0.94, 95% CI: 0.86–1.03). After adjustment for baseline characteristics and propensity to undergo PCI, the risk of death or myocardial infarction remained lower with DTI (HR = 0.62, 95% CI: 0.44–0.89).

Conclusion After adjustment for baseline differences and propensity to undergo early PCI, DTIs appeared to be more effective than heparin in reducing death or re-infarction among patients undergoing early PCI.

Introduction

Thrombin generation contributing to intracoronary thrombus formation at the site of spontaneous plaque rupture plays a pivotal role in the pathogenesis of unstable angina or myocardial infarction. Thrombin also triggers ischaemic complications after mechanical plaque disruption in percutaneous coronary interventions (PCIs). Although aspirin and heparin are effective in reducing recurrent ischaemic events in these settings, a substantial risk of death or myocardial infarction persists. Compared with standard unfractionated heparin, direct thrombin inhibitors (DTIs) have been shown to be superior for the prevention of the combined endpoint of death or myocardial infarction in patients with acute coronary syndromes (ACS). DTIs offer several advantages over conventional unfractionated heparin.

DTIs inhibit thrombin activity better than heparin, and present better protection against reactivation of thrombin after discontinuation of therapy. Clot-bound thrombin is also protected from inactivation by heparin-antithrombin III, but can still be inactivated by DTI. Likewise, thrombin bound to soluble fibrin degradation products is not inhibited by heparin, but remains susceptible to inactivation by DTI.

Patients with ACS undergoing PCI appear to have greater benefit from DTIs. In the 1410 patients in GUSTO-IIb undergoing PCI during study drug infusion, hirudin was associated with a reduction in death or re-infarction. The benefits of hirudin occurred both before and immediately after PCI. Likewise, hirudin was also associated with a reduction in ischaemic events in patients with ACS undergoing early PCI ( <72 h) in the OASIS-2 trial, and this effect was also apparent both before and after PCI. However, no interaction was observed between treatment allocation and early PCI after adjustment for time-dependent covariate and propensity to undergo early PCI.
indicating that the treatment benefit of hirudin was similar for patients undergoing PCI and patients treated medically. Thus, it remains unclear whether DTI protects against ischaemic complications to a greater extent in patients undergoing PCI than in those not undergoing PCI. In this analysis, we studied the effect of DTIs in patients undergoing early PCI.

**Methods**

The protocol, detailing the methods and pre-specified analyses, has been published previously,\(^{11}\) while the rationale and selection of qualifying trials have been reported with the primary results.\(^4\) Briefly, the DTI Trialists’ Collaborative Group database comprises 35,970 patients from 11 randomized controlled trials of DTIs vs. heparin including more than 200 patients or 100 controls (Table 1). Nine trials were carried out in patients with ACS\(^{12–20}\) and two trials in patients with ACS undergoing percutaneous intervention (Helvetic\(^{21}\) and Bivalirudin Angioplasty Study\(^{22,23}\)). Also, data from three studies (GUSTO-IIa, HIT-III, and TIMI-9A) were not used because they were considered to have used excessive doses of DTI.\(^{24–26}\) In this analysis, individual patients’ data including baseline entry characteristics, dates of randomization, and end of treatment, outcomes, and use of PCI were used.

**Statistical methods**

The primary efficacy endpoint was the composite of death and myocardial infarction before 30 days. To focus on the interaction of PCI and antithrombotic agents, only patients with an early intervention (within 72 h of randomization, the standard duration of antithrombotic therapy) were included in the early-PCI group. Late PCI was defined as PCI between 72 h and 7 days after randomization. Myocardial infarction was also differentiated in events that occurred either before or after the PCI, with only patients from the ACS trials being used to assess treatment benefit prior to PCI. The DTI Trialists’ database only includes dates of events, not the exact timing. A censored analysis was performed to evaluate the effect of DTIs according to the timing of PCI. If the timing of the myocardial infarction relative to the start of the PCI was not recorded, and both occurred on the same day (\(n = 17\) for the trials in which PCI was an option and \(n = 1\) in the PCI trials), then the MI was assumed to occur after the PCI. For analyses of events that occurred after the intervention, patients from the two PCI trials were also included. A Significance level of 0.05 was used.

Continuous variables were compared using a Wilcoxon rank-sum test, and categorical variables were compared using a Pearson \(\chi^2\) test. A random-effects meta-analysis of DTIs vs. heparin in patients with early PCI was performed, with death or myocardial infarction up to 30 days as endpoints. The individual patients’ data were analysed by Cox proportional hazards regression analysis with PCI as a time-dependent covariate to assess the independent impact of DTIs according to the performance and timing of PCI. Adjustments were made for baseline characteristics (age, past history of ischaemic heart disease, previous PCI or CABG, diabetes, creatinine, heart rate, gender, smoking, systolic and diastolic blood pressures, weight, height, and the studies included in the analyses).

Also, to further reduce the impact of selection bias, a propensity score for the likelihood of undergoing early PCI was used.\(^{27}\) Propensity analysis aims to identify patients with similar probability of undergoing PCI based on their clinical characteristics. Using a multivariable logistic regression model that included the baseline characteristics as independent variables, the probability of being assigned to early PCI was determined. Covariates in the model were: gender, history of ischaemic heart disease, hypertension, previous PCI, previous CABG, diabetes, smoking, pulse, diastolic BP, systolic BP, body weight, and height. Restricted cubic spline transformations were used to evaluate the linearity assumption relative to the need for PCI. Appropriate transformations were made to continuous variables as needed. Linear splines were found to adequately fit when the linear factor itself was not.

**Table 1** Trial characteristics

<table>
<thead>
<tr>
<th>Trial Ref.</th>
<th>Year</th>
<th>Eligibility</th>
<th>Total number of patients</th>
<th>DTI</th>
<th>Control</th>
<th>Treatment duration</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>16</td>
<td>1996</td>
<td>AMI</td>
<td>3002</td>
<td>Hirudin 0.1 mg/kg bolus; 0.1 mg/(kg/h) infusion</td>
<td>UFH 5000 IU bolus; 1000 IU/h infusion</td>
<td>96 h</td>
<td>30 days</td>
</tr>
<tr>
<td>20</td>
<td>1997</td>
<td>AMI</td>
<td>404</td>
<td>Bivalirudin 0.125–0.250 mg/kg bolus; 0.125–0.500 mg/(kg/min) infusion</td>
<td>UFH 5000 IU bolus; 1000–1200 IU/h infusion</td>
<td>72 h</td>
<td>35 days</td>
</tr>
<tr>
<td>17</td>
<td>1998</td>
<td>AMI</td>
<td>1200</td>
<td>Argatroban 20–60 mg/kg bolus; 2–4 μg/(kg/min) infusion</td>
<td>UFH 5000 IU bolus; 1000 IU/h infusion</td>
<td>72 h</td>
<td>30 days</td>
</tr>
<tr>
<td>19</td>
<td>1999</td>
<td>AMI</td>
<td>1210</td>
<td>Hirudin 0.2 mg/kg bolus; 0.5 mg/kg twice daily</td>
<td>Placebo bolus, UFH 12 500 IU twice daily</td>
<td>5–7 days</td>
<td>30 days</td>
</tr>
<tr>
<td>12</td>
<td>1996</td>
<td>UA or AMI</td>
<td>12 142</td>
<td>Hirudin 0.1 mg/kg bolus; 0.1 mg/(kg/h) infusion</td>
<td>UFH 5000 IU bolus; 1000 IU/h infusion</td>
<td>3–5 days</td>
<td>1 year</td>
</tr>
<tr>
<td>13</td>
<td>1997</td>
<td>UA</td>
<td>909</td>
<td>Hirudin 0.2–0.4 mg/kg bolus; 0.1–0.15 mg/(kg/h) infusion</td>
<td>UFH 5000 IU bolus; 1000–1200 IU/h infusion</td>
<td>72 h</td>
<td>6 months</td>
</tr>
<tr>
<td>14</td>
<td>1997</td>
<td>UA</td>
<td>12 209</td>
<td>Inogatran 0.1–5.5 mg bolus; 2.0–10.0 mg/h infusion</td>
<td>UFH 5000 IU bolus; 1200 IU/h infusion</td>
<td>72 h</td>
<td>30 days</td>
</tr>
<tr>
<td>18</td>
<td>1999</td>
<td>UA</td>
<td>300</td>
<td>Eferatran 0.1–0.3 mg/kg bolus; 0.105–1.200 mg/(kg/min) infusion</td>
<td>UFH 5000 IU bolus; 1000 IU/h infusion</td>
<td>48 h</td>
<td>30 days</td>
</tr>
<tr>
<td>15</td>
<td>1999</td>
<td>UA</td>
<td>10 141</td>
<td>Hirudin 0.4 mg/kg bolus; 0.15 mg/(kg/h) infusion</td>
<td>UFH 5000 IU bolus; 15 IU/(kg/h) infusion</td>
<td>72 h</td>
<td>6 months</td>
</tr>
<tr>
<td>22,23</td>
<td>1995</td>
<td>PCI</td>
<td>4 312</td>
<td>Bivalirudin 1 mg/kg bolus; 2.5 mg/(kg/h) infusion for 4 h, then 0.2 mg/(kg/h) infusion</td>
<td>UFH 175 IU bolus; 15 IU/(kg/h) infusion</td>
<td>24 h</td>
<td>6 months</td>
</tr>
<tr>
<td>21</td>
<td>1995</td>
<td>PCI</td>
<td>1 141</td>
<td>Hirudin 40 mg bolus; 0.2 mg/(kg/h) infusion for 24 h, then 40 mg twice daily</td>
<td>UFH 10 000 IU bolus; 15 IU/(kg/h) infusion for 24 h, then placebo twice daily</td>
<td>72 h</td>
<td>6 months</td>
</tr>
</tbody>
</table>
adequate. The main factors that are used in deciding who will receive a PCI are not available, as we have seen in previous studies. The c-statistic for this model is 0.647. Patients were then divided into quintiles according to the propensity score, which was then included in the Cox proportional hazards regression analysis. Data from two studies in which PCI within the first 72 h was discouraged \(^\text{18,19}\) and the two PCI studies \(^\text{21,22}\) were not included in this analysis.

**Results**

Thirty-five thousand nine hundred and seventy patients from 11 trials (Table 1) were randomized to treatment with a DTI or heparin and followed up to at least 30 days. \(^\text{12-22}\) Of the 30 164 patients in the nine non-PCI trials, 1596 patients underwent PCI within 72 h of randomization, which is the usual duration of treatment with DTI or heparin (Figure 1 and Table 1), whereas 1752 patients had a PCI between 72 h and 7 days. In two ACS trials, \(^\text{18,19}\) no patient underwent PCI within the first 72 h. In the overall study population, 9420 patients (26%) had a catheterization within 7 days.

**Baseline characteristics**

In the ACS trials, 15% of all patients had a catheterization within 72 h of randomization (15.6% in the heparin group and 14.5% in the DTIs group, \(P = 0.008\)). Of these, 5.8% in the heparin group and 4.8% in the DTIs group underwent a PCI (\(P < 0.001\)) (Table 2). Of note, in both non-hirudin-non-bivalirudin trials, an excess in PCI was observed. In patients having early PCI, mean time from randomization to intervention was 1.5 days (median: 2 days). Study drug use during the intervention was recorded in GUSTO-IIb and TIMI-9b; in these trials, 67.3% received study drug during the revascularization procedure.

Patients who underwent early PCI were more likely to be male, older, and current or former smoker. They also had a higher rate of a past history of previous PCI, but they were less likely to have a previous history of ischaemic heart disease, diabetes, or hypertension (Table 3). There were no significant differences between the DTI and heparin groups regardless of undergoing early PCI or not.

**Percutaneous coronary intervention**

In the seven non-PCI trials in which early PCI was permitted, the rate of the composite endpoint of death or myocardial infarction was not different with DTIs when compared with heparin in patients without early PCI (8.00 vs. 8.30%, OR 0.96, 95% CI: 0.88–1.05). In all patients undergoing early PCI, however, the rate of death or re-infarction was 9.50% in DTI-treated patients compared with 13.86% with heparin (OR 0.64, 95% CI: 0.47–0.89). This difference was mainly driven by a significant reduction of myocardial infarction in patients treated with DTI (6.63 vs. 10.71% for heparin, OR 0.59, 95% CI: 0.41–0.85). When only taking the two PCI trials and the PCI arm of GUSTO-IIb into account, death or MI was also found to be lower with DTI than with heparin (4.51 vs. 5.54%, OR 0.77, 95% CI: 0.61–0.97). In the two non-PCI studies in which early PCI (<72 h) was discouraged, however, death or MI was not significantly different (8.85 vs. 9.77% for heparin, OR 0.89, 95% CI: 0.63–1.27).

In a Cox proportional hazards model with PCI as a time-dependent covariate, DTIs were not associated with a significant decrease in 30-day mortality either with or without PCI. In contrast, treatment with DTI had a significant effect on death or myocardial infarction to 30 days in the overall patient population (HR = 0.90, 95% CI: 0.84–0.97, \(P = 0.007\)), and this benefit remained after adjustment for baseline characteristics (\(P = 0.0167\)). We found a significant interaction between early PCI and treatment (\(P = 0.009\)), which remained after adjustment for baseline characteristics and propensity to undergo PCI (\(P = 0.021\)). After adjustment for baseline characteristics and propensity to undergo PCI, DTIs also appeared to be

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**Table 2 Number of patients with early PCI per trial**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Total (n)</th>
<th>PCI ≤ 72 h (n)</th>
<th>Unfractionated heparin (%)</th>
<th>DTI (%)</th>
<th>(P)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARGAMI-2</td>
<td>1 200</td>
<td>55</td>
<td>3.8</td>
<td>5.2</td>
<td>0.24</td>
</tr>
<tr>
<td>HERO-1</td>
<td>404</td>
<td>84</td>
<td>22.5</td>
<td>19.9</td>
<td>0.55</td>
</tr>
<tr>
<td>TIMI-9b</td>
<td>3 002</td>
<td>242</td>
<td>8.7</td>
<td>7.5</td>
<td>0.24</td>
</tr>
<tr>
<td>GUSTO-IIb</td>
<td>12 142</td>
<td>1001</td>
<td>9.1</td>
<td>7.4</td>
<td>0.001</td>
</tr>
<tr>
<td>OASIS-1</td>
<td>909</td>
<td>13</td>
<td>1.6</td>
<td>1.3</td>
<td>0.69</td>
</tr>
<tr>
<td>OASIS-2</td>
<td>10 141</td>
<td>188</td>
<td>2.0</td>
<td>1.7</td>
<td>0.23</td>
</tr>
<tr>
<td>TRIM</td>
<td>1 209</td>
<td>13</td>
<td>0.7</td>
<td>1.2</td>
<td>0.41</td>
</tr>
<tr>
<td>Overall</td>
<td>1596</td>
<td>5.8</td>
<td>4.8</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

In two non-PCI trials \(^\text{18,19}\), no patient underwent PCI within 72 h of randomization.
superior to heparin in patients undergoing early PCI (HR = 0.62, 95% CI: 0.44–0.89) but not in those treated conservatively (HR = 0.96, 95% CI: 0.87–1.06) or undergoing PCI between 3 and 7 days (HR = 0.73, 95% CI: 0.51–1.04) (P = 0.024 for heterogeneity) (Figure 2). Taken together, these results indicate that DTIs are associated with a lower rate of the combined endpoint of death or myocardial infarction than heparin, especially in early-PCI patients.

**Efficacy of DTI with respect to timing of PCI**

In patients undergoing early PCI, the benefit of DTI appears to be driven mainly by a reduction of myocardial infarction on the day of the intervention, although a trend towards better outcome with DTI can also be observed during medical treatment before and after the intervention (Figure 3). The Kaplan–Meier event estimates for the combined endpoint of death or myocardial infarction diverged early and remained separated through 30 days in patients with early PCI (Figure 4). The censored analyses showed a significant benefit for DTIs during the period between randomization and the intervention (Figure 5A). A similar benefit for DTI over heparin was observed during medical treatment after the intervention (Figure 5B) and after stopping treatment until the end of the follow-up period (Figure 5C). Thus,
the benefit of DTI over heparin in early-PCI patients appears to occur at least in part before the intervention.

Bleeding complications
The rate of major bleeding complications and stroke is reported in Table 4. In the non-PCI trials, major bleeding complications and stroke were not significantly different between heparin and DTI (4.27 vs. 4.88%, OR 1.15, 95% CI: 0.71–1.85 and 0.61 vs. 0.81%, OR 1.34, 95% CI: 0.41–4.40, respectively). In the PCI trials, DTIs were associated with a lower incidence of major bleeding complications.

Discussion
In this large database of trials comparing DTIs with heparin, early PCI was associated with a lower likelihood of death and MI at 30 days. After adjustment for baseline differences and propensity to undergo early intervention, DTIs appeared to be more effective than heparin in reducing death or re-infarction in patients undergoing early PCI. This benefit was primarily driven by a lower incidence of MI on the day of PCI. Also, we observed a significant interaction between early PCI and treatment allocation, indicating a greater benefit of DTI with PCI than without.

Previous studies have suggested that DTI might be superior to heparin in patients undergoing early coronary intervention. Hirudin was found to be associated with a reduction in ischaemic events in patients with ACS undergoing early PCI in the OASIS-2 trial.9 Patients receiving hirudin in the Helvetica trial experienced less ischaemic events early after the intervention.21 Also, in patients in the PCI arm of GUSTO-IIb, hirudin was associated with a reduction in non-fatal re-infarction and death or re-infarction.10 In contrast, bivalirudin was not associated with a reduction in ischaemic events in the entire patient cohort in the Hirulog Angioplasty Study.22 In both GUSTO-IIb and OASIS-2, the benefit of DTI seemed to be greater in PCI patients than in those treated conservatively. Nevertheless, no significant interaction between treatment allocation and early PCI after adjustment for time-dependent covariate and propensity to undergo early PCI was observed in the OASIS-2 trial, indicating that the treatment benefit of hirudin was similar for patients undergoing PCI and patients treated medically. In contrast, we found a significant interaction between treatment and PCI after adjustment for time-dependent covariate and propensity to undergo early PCI in the present meta-analysis, providing evidence that patients undergoing early PCI benefit more from DTI than patients treated conservatively.

The chronological relationship between treatments with DTI, timing of PCI, and treatment effect in ACS appears to be complex. Some of the benefit of hirudin in the GUSTO-IIb trial apparently occurs before the intervention.10 Similar temporal findings have been observed for...
glycoprotein (GP) IIb/IIIa antagonists. In combined data from the CAPTURE, PURSUIT, and PRISM-PLUS trials, part of the beneficial effect of GP IIb/IIIa antagonists in patients with ACS undergoing early coronary intervention was found to occur before the intervention. Similarly, DTIs were also associated with fewer ischaemic events in patients undergoing PCI before the intervention in the present meta-analysis. Taken together with the significant interaction of treatment and PCI, the current analysis suggests that at least part of the effect is because patients with ACS undergoing PCI are the ones who get benefit from DTI.

It remains uncertain why DTIs are more beneficial than heparin in patients undergoing early intervention. Patients undergoing PCI in the DTI and heparin groups differ: the use of early PCI was associated with allocated treatment, with fewer patients receiving DTI having an early PCI. Also, patients undergoing PCI constitute a highly selected subgroup, almost all likely to have substantial coronary stenosis. Moreover, in contrast with only a subset of conservatively treated patients, nearly all PCI patients have extensive (mechanical) plaque rupture. As thrombin generation triggered by plaque rupture contributes to subsequent ischaemic events, early efficient direct thrombin inhibition might be superior to heparin use.

In the REPLACE-2 trial of bivalirudin compared with heparin and GP IIb/IIIa antagonist therapy, there was evidence of non-inferiority for the 30-day endpoint of death, myocardial infarction, and the need for urgent target vessel revascularization after the index PCI. Efficacy with bivalirudin remained comparable with that of heparin and GP IIb/IIIa during long-term follow-up. A large proportion of the REPLACE-2 trial patients had ACS at presentation, and there was evidence of non-inferiority of bivalirudin in this group as well. These findings in a prospective trial of over 6000 patients appear to validate the current meta-analysis interpretation.

**Limitations**

Although these results are derived from a meta-analysis of patients randomized to DTI vs. heparin, the patients undergoing PCI are not strictly randomized and the confounding effects of post-randomization events cannot be completely accorded for. However, each analytical approach provides consistent findings. A large proportion of patients in the early-PCI group were derived from two PCI trials; the low event rate in both PCI studies might have biased the results in this meta-analysis.
Timing of PCI with regard to events on the day of PCI was not exactly known. Finally, most of the trials included in this meta-analysis have included patients in the pre-stent era.

Conclusion

In conclusion, these results indicate that DTIs have a greater effect on reducing death or myocardial infarction than heparin in early-PCI patients than in conservatively treated patients. Whether this is due to the PCI itself or because patients who undergo early PCI are getting more benefit from DTIs remains unclear. Thus, while certainly there is a bigger treatment effect of DTI in patients undergoing PCI, whether this is due to the PCI itself or due to a better effect of DTI in patients undergoing early PCI cannot be determined with certainty.

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Conflict of interest: none declared.

Appendix

Direct Thrombin Inhibitor Trialists’ Collaborative Group

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Efegatran Study—M.L. Simoons.


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Helveticas—P.W. Serruys.

HERO—J.D. White.


NHMRC Clinical Trials Centre—J. Simes.

Novartis—with S. Close, S. Edwards, P. Gallo, and M. Henis.


Quintiles—W. Kimball.

The Medicines Company—C. Meanwell and J. Villiger.

TIMI-9B—E.M. Antman, E. Braunwald, M. Gibson, and S. Murphy.

TRIM—L. Grip and P. Held.

References


