Bivalirudin vs. unfractionated heparin during percutaneous coronary interventions in patients with stable and unstable angina pectoris: 1-year results of the ISAR-REACT 3 trial

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Aims

In ISAR-REACT 3, 30-day outcomes in 4570 biomarker negative patients undergoing percutaneous coronary intervention (PCI) ≥ 2 h after pre-treatment with 600 mg of clopidogrel revealed less bleeding with bivalirudin compared with unfractionated heparin, but no difference in 30-day net clinical benefit. The objective of the present analysis was to assess the impact of bivalirudin vs. heparin on 1-year outcomes in ISAR-REACT 3.

Methods and results

The primary outcome for this analysis was the composite of death, myocardial infarction, or target vessel revascularization 1 year after randomization. The composite of death or myocardial infarction was a secondary outcome. At 1 year, the primary outcome occurred in 17.1% of patients assigned to bivalirudin vs. 17.5% assigned to heparin [hazard ratio (HR), 0.98; 95% confidence interval (CI), 0.86–1.13; \( P = 0.816 \)]. The combined incidence of death or myocardial infarction was 7.7% in the bivalirudin group vs. 6.7% in the heparin group (HR, 1.15; 95% CI, 0.93–1.43; \( P = 0.200 \)). The mortality rate was 1.9% in the bivalirudin group and 1.7% in the heparin group (HR, 1.10; 95% CI, 0.71–1.70; \( P = 0.667 \)). At 1 year, no significant differences in the primary outcome were observed with bivalirudin and heparin in any of the subgroups analysed.

Conclusion

Bivalirudin and unfractionated heparin during PCI provide comparable outcomes at 1 year in biomarker negative patients undergoing PCI after pre-treatment with 600 mg of clopidogrel.

Clinical trial registration information: URL www.clinicaltrials.gov; Unique identifier NCT00262054.

Keywords

Bivalirudin • Heparin • Clopidogrel • Stent

Adjunctive antithrombotic therapy is a prerequisite for the safe performance of percutaneous coronary interventions (PCIs). The direct thrombin inhibitor bivalirudin has been evaluated as an alternative to unfractionated heparin in a broad spectrum of patients undergoing PCI.1–6 Most of these trials, however, have compared bivalirudin vs. heparin with a glycoprotein IIb/IIIa inhibitor.2–6 The Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment (ISAR-REACT) 3 trial was a multicentre, randomized, double-blind, placebo-controlled trial designed to determine whether bivalirudin was
superior to unfractionated heparin in 4570 biomarker negative patients with stable and unstable coronary artery disease undergoing PCI after pre-treatment with 600 mg clopidogrel. Although bivalirudin therapy significantly reduced in-hospital bleeding, it did not provide net clinical benefit at 30 days, defined as the quadruple endpoint of death, myocardial infarction, target vessel revascularization (TVR), or in-hospital major bleeding. Peri-procedural bleeding has been shown to be a strong and independent predictor of short- and long-term clinical outcome after PCI. Measures to reduce haemorrhagic complications during PCI procedures may have the potential to improve patients’ prognosis. Thus, the 30-day endpoint in ISAR-REACT 3 trial might have been too short to thoroughly evaluate the potential benefit associated with the use of bivalirudin. Therefore, we performed this analysis of 1-year follow-up of patients enrolled in ISAR-REACT 3 to evaluate whether peri-procedural therapy with bivalirudin was associated with a clinical benefit compared with unfractionated heparin after a longer duration of follow-up.

Methods

Study patients

details of the ISAR-REACT 3 trial design have been published previously. In brief, the trial was conducted from September 2005 through January 2008 and included 4570 biomarker negative patients with stable and unstable angina undergoing PCI after pre-treatment with 600 mg clopidogrel at least 2 h prior to the intervention. All patients included in the study had given their written, informed consent. The study protocol was approved by the ethics committees of the participating centres and adhered to the Declaration of Helsinki.

Details of study protocol

All patients received 600 mg clopidogrel prior to PCI, as well as 325–500 mg aspirin. After the decision to perform the PCI but before the guide wire had crossed the lesion, patients were randomly assigned in a double-blind manner to receive either bivalirudin or unfractionated heparin using sealed opaque envelopes containing the block randomization sequence for each participating centre. Patients in the bivalirudin arm (n = 2289) received a 0.75 mg per kilogram body weight bolus of bivalirudin, followed by an infusion of 1.75 mg per kilogram per hour for the duration of the intervention. Patients in the heparin arm (n = 2281) received a bolus of 140 units per kilogram body weight followed by a placebo infusion for the duration of the procedure. At one centre, where 42 patients were enrolled, an initial dose of 100 units of heparin per kilogram was given and a monitor of activated clotting time who was unaware of the treatment assignments administered additional boluses of heparin or placebo if the activated clotting time was less than 250 s. All caregivers were unaware of the values for activated clotting time. Double blinding was achieved by using identically appearing vials in both study groups.

Post-interventional antithrombotic therapy consisted of aspirin 80–325 mg indefinitely and clopidogrel 75 mg twice daily for the remainder of the hospitalization (but not more than 3 days) followed by 75 mg a day for at least 1 month after bare metal stent implantation and at least 6 months after deployment of a drug-eluting stent. Other cardiac medications were prescribed at the discretion of the patient’s physician. More details of the study protocol were reported in the primary publication.

Follow-up, study definitions, and endpoints

Electrocardiograms and laboratory measurements (including cardiac enzymes, haemoglobin, and platelet count) were performed every 8 h for the first 24 h after the procedure and daily afterwards, until discharge. All patients were either seen by their physician or interviewed by phone at 30 days, 6 months, and 1 year. Those with cardiac complaints underwent a complete clinical, electrocardiographic, and laboratory evaluation. If patients suffered a qualifying event at another hospital, the appropriate source documents were solicited (including discharge summaries, laboratory values, and angiograms). Family doctors, referring cardiologists, patients, or their relatives were contacted for additional information if necessary.

The primary endpoint of the ISAR-REACT 3 trial was the composite of death, myocardial infarction, TVR within 30 days after randomization, or in-hospital major bleeding. Results have previously been published. The primary outcome of the present analysis was the combined incidence of death from any cause, myocardial infarction, or TVR at 1 year after randomization. This was a pre-specified secondary endpoint in the ISAR-REACT 3 trial protocol. The composite of death or myocardial infarction was a secondary outcome of this analysis. Information on deaths was obtained from hospital records, death certificates, or phone contact with relatives of patients or their attending physicians. The diagnosis of myocardial infarction required the presence of new pathologic Q waves (>30 ms in duration and ≥0.1 mV in depth) in ≥2 contiguous or adjacent electrocardiographic leads, or elevation of creatine kinase myocardial band (CK-MB) isoenzyme (or total CK if CK-MB was not available) greater than or equal to two times the upper limit of normal. Stent thrombosis was considered to have occurred when the criteria for definite stent thrombosis of the Academic Research Consortium were met. Target vessel revascularization was defined as any ischaemia-driven repeat PCI or bypass surgery of the target vessel. Bleeding was defined according to criteria used in the Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events (REPLACE) 2 trial. In addition, bleeding events were evaluated according to the Thrombolysis in Myocardial Infarction (TIMI) definition. All events were adjudicated and classified by an event adjudication committee blinded to the treatment assignments.

Statistical analysis

Data are presented as counts (%), median (range), or Kaplan–Meier estimates (%). We calculated the hazard ratios (HRs) with 95% confidence intervals (CIs) associated with therapy with bivalirudin vs. therapy with unfractionated heparin by the use of Cox proportional hazard models. The proportional hazards assumption was checked by the method of Grambsch and Therneau and was fulfilled in all cases in which we used Cox proportional hazards models. Data for patients lost to follow-up who did not have the event of interest were censored at the date of the last follow-up. Pre-specified subgroup analysis involved subgroups dichotomized by median age (67.6 years), sex, presence of diabetes, median creatinine value (0.9 mg/dL), and clinical presentation (stable vs. unstable angina) at the index PCI. Heterogeneity in treatment outcomes across subgroups was checked by assessing the interaction between the assigned treatment and the baseline variable defining the subgroup with respect to the primary outcome. This was done by entering the interaction term into the respective Cox proportional model.

All analyses were performed using S-PLUS statistical package (Version 4.5, Insightful Corporation, Seattle, WA, USA). A two-sided
Results

Baseline characteristics of the patients have been reported in the primary publication.7 None of the characteristics differed significantly among patients treated with bivalirudin or unfractionated heparin.

Clinical outcomes at 1 year

At 1 year, follow-up was complete in all but 48 patients (1.1%), 24 patients in each group. The median length of follow-up among patients in each group was 80 days (range: 1–299 days).

One-year clinical outcomes are shown in Table 1. There were no significant differences between the two groups in the 1-year composite endpoint or any of its individual endpoints. The 1-year incidence of the primary outcome—death, myocardial infarction, or TVR—was 17.1% (n = 389) in the bivalirudin group vs. 17.5% (n = 396) in the heparin group (HR, 0.98, 95% CI 0.86–1.13, P = 0.816; Figure 1). The frequency of death or myocardial infarction was 7.7% (n = 175) among patients treated with bivalirudin vs. 6.7% (n = 152) among patients treated with heparin (HR, 1.15, 95% CI 0.93–1.43, P = 0.200; Figure 2). By 1 year, 43 patients (1.9%) in the bivalirudin vs. 39 patients (1.7%) in the heparin group had died (HR, 1.10, 95% CI 0.71–1.70, P = 0.667). Myocardial infarctions occurred in 137 patients (6.0%) assigned to bivalirudin and 121 patients (5.3%) assigned to heparin (HR, 1.13, 95% CI 0.89–1.44, P = 0.320). Target vessel revascularization was performed in 252 patients (11.2%) in the bivalirudin group vs. 281 patients (12.5%) in the heparin group (HR, 0.89, 95% CI 0.75–1.06, P = 0.184).

The 1-year incidence of the primary outcome and the HR related to bivalirudin vs. unfractionated heparin therapy in the entire group of patients and the pre-specified subgroups are shown in Figure 3. There was no significant interaction between the treatment group and subgroups regarding the primary outcome.

Table 1  One-year clinical outcomes in the bivalirudin and heparin group

<table>
<thead>
<tr>
<th>One-year clinical outcome</th>
<th>Bivalirudin (n = 2289)</th>
<th>Heparin (n = 2281)</th>
<th>Hazard ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death, myocardial infarction, or target vessel revascularization</td>
<td>389 (17.1)</td>
<td>396 (17.5)</td>
<td>0.98 (0.86–1.13)</td>
<td>0.816</td>
</tr>
<tr>
<td>Death or myocardial infarction</td>
<td>175 (7.7)</td>
<td>152 (6.7)</td>
<td>1.15 (0.93–1.43)</td>
<td>0.200</td>
</tr>
<tr>
<td>Death</td>
<td>43 (1.9)</td>
<td>39 (1.7)</td>
<td>1.10 (0.71–1.70)</td>
<td>0.667</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>137 (6.0)</td>
<td>121 (5.3)</td>
<td>1.13 (0.89–1.44)</td>
<td>0.320</td>
</tr>
<tr>
<td>Target vessel revascularization</td>
<td>252 (11.2)</td>
<td>281 (12.5)</td>
<td>0.89 (0.75–1.06)</td>
<td>0.184</td>
</tr>
<tr>
<td>Percutaneous coronary intervention</td>
<td>234 (10.4)</td>
<td>268 (11.9)</td>
<td>0.87 (0.73–1.03)</td>
<td>0.113</td>
</tr>
<tr>
<td>Coronary artery bypass grafting</td>
<td>21 (0.9)</td>
<td>15 (0.7)</td>
<td>1.40 (0.72–2.71)</td>
<td>0.321</td>
</tr>
<tr>
<td>Definite stent thrombosis</td>
<td>16 (0.7)</td>
<td>16 (0.7)</td>
<td>1.00 (0.50–2.00)</td>
<td>0.996</td>
</tr>
</tbody>
</table>

Data are numbers of patients (%). Percentages are the Kaplan–Meier estimates.

Relationship between 30-day bleeding and 1-year overall mortality

At 30 days, 174 patients incurred a major bleeding according to the REPLACE 2 definition, 70 patients (3.1%) in the bivalirudin, and 104 patients (4.6%) in the heparin group (P = 0.008).7 In patients with REPLACE 2 major bleeding at 30 days, 1-year mortality was 7.5% (n = 13) compared with 1.6% (n = 69) in patients without such an event (HR 4.9, 95% CI 2.7–8.9).

Major bleeding based on TIMI criteria was observed in 36 patients, with 12 events (0.5%) in the bivalirudin and 24 events (1.1%) in the heparin group (P = 0.044).7 One-year mortality was 11.1% (n = 4) among patients with TIMI major bleeding and 1.7% (n = 78) in patients who had not bled at 30 days (HR 7.0, 95% CI 2.6–19.1).

Relationship between 30-day myocardial infarction and 1-year overall mortality

Within 30 days after randomization, 128 patients (5.6%) assigned to bivalirudin and 110 patients (4.8%) assigned to heparin suffered from myocardial infarction (P = 0.245).7 In patients with myocardial infarction at 30 days, 1-year mortality was 4.6% (n = 11) compared with 1.7% (n = 71) in patients without myocardial infarction at 30 days (HR 2.9, 95% CI 1.5–5.5).

Discussion

The main finding of the current analysis is that 1 year following enrolment in ISAR-REACT 3, neither the primary outcome (composite endpoint of death, myocardial infarction, or TVR) nor its individual components differed significantly among biomarker negative patients undergoing PCI with adjunct treatment with bivalirudin or unfractionated heparin.

This finding is in line with the 1 year results of the Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events (REPLACE) 2 trial12 and the Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial13 which did not demonstrate superiority of bivalirudin either alone or in combination with glycoprotein IIb/IIIa inhibitors in terms of a reduction in death, myocardial infarction, or TVR.
of ischaemic complications compared with unfractionated heparin plus a glycoprotein IIb/IIIa inhibitor. In distinction with these trials, the ISAR-REACT 3 trial was a head-to-head comparison of bivalirudin alone vs. unfractionated heparin alone, without the use of glycoprotein IIb/IIIa inhibitors. At 30 days, both these trials and the ISAR-REACT 3 trial demonstrated a significant reduction of in-hospital bleeding with bivalirudin when compared with unfractionated heparin. In ISAR-REACT 3, major bleeding events according to REPLACE 2 definition occurred in 70 of 2289 patients (3.1%) in the bivalirudin group vs. 104 of 2281 patients (4.6%) in the heparin group (RR 0.66, 95% CI 0.49–0.90).

Peri-PCI bleeding complications have recently been identified as a major predictor for short- and long-term prognosis of patients following PCI procedures. In the current study, it seems that the stricter TIMI definition of bleeding had an even higher impact on mortality compared with the more liberal REPLACE 2 criteria. However, specifically designed studies evaluating the relative prognostic value of different bleeding definitions are badly needed. In the past, bleeding was often considered an inevitable side effect of antithrombotic therapy. However, the use of ticlopidine plus aspirin was associated with lower rates of both thrombotic and bleeding events compared with anticoagulant therapy plus aspirin, indicating that increased antithrombotic efficacy may not necessarily occur at the expense of increased risk of bleeding.

The direct thrombin inhibitor bivalirudin was introduced as an alternative to unfractionated heparin plus glycoprotein IIb/IIIa inhibitors during PCI mainly because of its antithrombotic efficacy and its ability to reduce bleeding. Indeed, a reduction in haemorrhagic complications with bivalirudin was consistently found in clinical trials across a wide variety of clinical scenarios. Although bleeding strongly correlates with long-term mortality, reductions of bleeding with bivalirudin did not translate into a measurable clinical benefit at 1 year in this and a previous trial of bivalirudin. Several reasons may explain this. Mortality was very infrequent in ISAR-REACT 3, and differed little among patients in the two treatment groups. The present study was enormously underpowered to detect a difference in mortality between the two antithrombotic regimens; the assessment of mortality would have required a much larger sample size. However, the trial provides 81% power to detect a 17.5% relative reduction of the primary 1-year outcome. Despite this limitation, there is evidence that the advantage of bivalirudin in reducing bleeding might be offset by a greater risk of myocardial infarction in such patients. Myocardial infarction, such as bleeding, is a strong correlate of mortality.

Furthermore, a recent study dealing with the detailed profiles of peri-PCI bleeding complications with bivalirudin and unfractionated heparin demonstrated that the reduction of bleeding with bivalirudin occurred mostly in low risk patients. Since such patients are (by definition) at very low risk for mortality, the mortality reduction attributable to a reduction in bleeding might be numerically undetectable. And there is some experimental evidence that extracorplant properties of bivalirudin, particularly its ability to reduce nitric oxide bioavailability in the endothelial cells by trapping myeloperoxidase in the vascular wall, may favour endothelial dysfunction and predispose for thrombotic events. The clinical significance of this finding, if any, is unknown.

Although bleeding events were more frequently observed in heparin-treated patients, blood transfusions were not statistically different between the two groups. Twenty-five patients (1.1%) in the bivalirudin group and 32 patients (1.4%) in the heparin group received two or more units of packed red cells or whole blood according to REPLACE 2 criteria of major bleeding (P = 0.344). This restrictive approach to transfusion might have mitigated the adverse effects of more bleeding complications in the heparin group on long-term outcome.

The finding that the incidence of stent thrombosis did not differ between the two groups with numerically identical events at 1 year may have important clinical implications. In the recently published Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial, an increase in the risk of stent thrombosis within the first 24 h, but not beyond this time point in the bivalirudin-treated patients was observed. In view of the high morbidity and mortality associated with stent thrombosis, the finding of an identical incidence of stent thrombosis at 1
year in the bivalirudin and unfractionated heparin groups of ISAR-REACT 3 supports the excellent safety profile of bivalirudin after pre-treatment with clopidogrel and confirms previous findings of the ACUITY trial in the subset of patients with thienopyridine pre-treatment. However, all this considerations about stent thrombosis should be interpreted with caution due to the insufficient sample size of the study with respect to rare events.

The HORIZONS-AMI trial, which involved patients with acute myocardial infarction undergoing primary PCI, demonstrated for the first time that therapy with bivalirudin reduced not only bleeding but 1-year all-cause and cardiac mortality compared with unfractionated heparin with a glycoprotein IIb/IIIa inhibitor. This suggests that the impact of bleeding on ischaemic complications and mortality may depend on the clinical situation. Although at present it remains hypothetical, it may be that a reduction in bleeding complications with bivalirudin may be more strongly associated with an improvement in clinical outcome and a reduction in mortality in patients with acute myocardial infarction than in lower risk groups. Whether a reduction in bleeding will reduce mortality as observed in the HORIZONS-AMI trial in patients with acute coronary syndromes and an elevated troponin level (biomarker positive) remains to be determined.

Although bivalirudin was not associated with any significant advantage in any of the pre-specified subgroups, larger cohorts are needed to evaluate the tendencies observed for some of the interactions (age and sex).

The results of the current study should be interpreted in the context of the special conditions under which the trial was performed. The optimal regimen of heparin during PCI is currently unknown. A single bolus of 140 units per kilogram of heparin without monitoring of activated clotting time has been our long institutional practice. Whether and to what extent a lower dose of heparin than that used in ISAR-REACT 3 would have influenced clinical outcomes is speculative. This question is subject of the ongoing ISAR-REACT 3A study, a non-randomized, open-label, single-group assignment trial, aimed to evaluate the value of a reduced dose of 100 units per kilogram heparin compared with the historical ISAR-REACT 3 control population. Moreover, a 600 mg loading dose of clopidogrel administered to all patients at least 2 h prior to the intervention is higher than in previous trials of bivalirudin. Although definitive randomized clinical trials are pending, there is evidence for a faster and more potent inhibition of platelet aggregation with the higher 600 mg loading dose.

In conclusion, the current study reveals that both bivalirudin and unfractionated heparin, when administered during PCI in biomarker negative patients with stable and unstable coronary artery disease pre-treated with clopidogrel, provide comparable clinical outcomes at 1 year after randomization in terms of death, myocardial infarction, and repeat revascularization, despite the fact that bivalirudin reduces postprocedural bleeding in such patients.

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Conflict of interest: P.B.B. has served as a consultant to Accumetrics, The Medicines Company, Eli Lilly/Daiichi-Sankyo, Novartis' Portola, and Guerbet. A.K. has received lecture fees from Bristol-Meyers Squibb, Cordis, Lilly, Medtronic and Sanofi-Aventis. The other co-authors have no conflicts of interest.

References


