ISAR-REACT 3A: a study of reduced dose of unfractionated heparin in biomarker negative patients undergoing percutaneous coronary intervention

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Aims

Although a 140 U/kg dose of unfractionated heparin (UFH) was comparable with bivalirudin in terms of net clinical outcome in the Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment (ISAR-REACT) 3 trial, it was associated with a higher risk of bleeding. We designed this study to assess whether a reduction in the UFH dose from 140 to 100 U/kg is associated with improved net clinical outcome.

Methods and results

A total of 2505 biomarker negative patients undergoing percutaneous coronary intervention (PCI) after clopidogrel pre-treatment received a single bolus of 100 U/kg UFH. The primary endpoint was net clinical outcome—a quadruple endpoint of death, myocardial infarction, urgent target-vessel revascularization within 30 days, or in-hospital REPLACE 2 defined major bleeding. The primary comparison was with the historical UFH group of ISAR-REACT 3 (2281 patients). In a second analysis, we checked for non-inferiority against the historical bivalirudin arm of ISAR-REACT 3 (2289 patients). The incidence of the primary endpoint was 7.3% in the lower UFH dose group compared with 8.7% in the higher UFH dose group [hazard ratio (HR) 0.81; 95% confidence interval (CI) 0.67–1.00; P = 0.045]. The incidence of major bleeding was 3.6% in the lower UFH dose group and 4.6% in the higher UFH dose group (HR 0.79; 95% CI 0.59–1.05; P = 0.11). The lower UFH dose met the criterion of non-inferiority compared with bivalirudin (P < 0.001).

Conclusion

In biomarker negative patients undergoing PCI after clopidogrel loading, a reduced dose of 100 U/kg UFH provided net clinical benefit compared with the historical control of 140 U/kg UFH in the ISAR-REACT 3 trial. The benefit was mostly driven by reduction in bleeding.

Clinical trial registration information

URL www.clinicaltrials.gov; Unique identifier NCT00735280.

Keywords

Heparin, Bivalirudin, Clopidogrel, Stent

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Since the first percutaneous coronary intervention (PCI) was performed in 1977, unfractionated heparin (UFH) has been the standard antithrombin agent in interventional cardiology and the reference against which new antithrombotic agents have been tested. Two UFH dosing regimens are currently recommended for PCI: an initial UFH bolus dose of 70–100 units (U)/kg followed by additional boluses if required under activated clotting time (ACT) guidance and the other consisting of a single bolus dose of 100 U/kg of UFH without ACT monitoring. The first UFH regimen is more common in the USA and the second is typically employed in Europe.

In fact, recommendations regarding UFH dose to use during PCI are based on evidence level C that reflects the lack of sufficient data from randomized trials. Vainer et al. found no significant difference in outcomes among 404 patients randomly assigned to either 5000 or 20 000 U of UFH during PCI. Boccara et al. also found no difference in outcomes among 400 patients randomly assigned to either 100 U/kg or 15 000 U of UFH. In a British survey in 2001, 53% of practitioners used UFH doses of 10 000 U or higher during PCI. In an analysis of four randomized clinical trials on adjunct antithrombotic treatment where UFH dosing was done under ACT guidance, total UFH dose during PCI ranged on average between 67 and 89 U/kg. However, 43–100% of the patients included in these trials also received glycoprotein IIb/IIIa inhibitors, a situation which requires halving of the dose of UFH.

A single bolus dose of 140 U/kg of UFH led to net clinical outcome comparable with that achieved with bivalirudin—a direct thrombin inhibitor—in the Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment (ISAR-REACT) 3 trial, but it was associated with a higher risk of bleeding.

The aim of the prospective, multicentre, single-arm, open-label ISAR-REACT 3A trial was to evaluate whether a reduction in the UFH dose from 140 to 100 U/kg is associated with better net clinical outcome in biomarker negative patients undergoing PCI after pre-treatment with 600 mg clopidogrel. Results were to be primarily compared with those achieved in the higher (140 U/kg) UFH dose arm of the ISAR-REACT 3 trial (historical control).

Methods

Study population

Patients were enrolled in three German centres—the Deutsches Herzcentrum, Munich, the 1. Medizinische Klinik, Klinikum rechts der Isar, Munich, and the Herz-Zentrum Bad Krozingen—from August 2008 until February 2010. The eligibility, inclusion, and exclusion criteria were the same as that used for the ISAR-REACT 3 trial. Briefly, biomarker negative patients with stable and unstable angina undergoing PCI after pre-treatment with 600 mg clopidogrel for at least 2 h before the intervention were enrolled.

Data collection was performed by the ISAResearch Center in Munich. There was no industry involvement in the design, conduct, analysis, or interpretation of the data. Ethics committee approval was obtained and informed consent received from the subjects (or their guardians).

Study protocol

Eligible patients were included consecutively after establishing the indication for PCI. All patients enrolled in ISAR-REACT 3A received one open label bolus of 100 U/kg bodyweight UFH before the guide wire had crossed the lesion. Monitoring of ACT was not required and no additional boluses of UFH were administered. As in ISAR-REACT 3 trial, patients received 325–500 mg aspirin as well as 600 mg clopidogrel prior to PCI, the latter within a time interval of at least 2 h before the intervention. Sheath was removed and manual compression applied as soon as the aPTT was < 50 s. Post-interventional antithrombotic therapy consisted of aspirin 80–325 mg indefinitely and clopidogrel 75–150 mg 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. More details of the study protocol were reported in the primary publication.

Follow-up

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 interviewed by phone at 30 days. 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.

Study endpoints and definitions

In ISAR-REACT 3A, identical endpoints and definitions as used in ISAR-REACT 3 were applied. The primary net clinical outcome endpoint was the combined incidence of death from any cause, myocardial infarction (MI), urgent target vessel revascularization (TVR; coronary bypass surgery or PCI) at 30 days after inclusion, or major bleeding during the index hospitalization. Myocardial infarction was defined as the development of pathologic Q waves (≥ 30 ms in duration and ≥ 0.1 mV in depth) in two or more contiguous precordial or adjacent limb leads, or an elevation of CK-MB isoenzyme levels (or total CK if measures of CK-MB were not available) to at least two times the upper limit of the normal. Major bleeding was defined according to Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events (REPLACE-2) trial criteria: intracranial, intraocular, or retroperitoneal haemorrhage; clinically overt blood loss resulting in a decrease in haemoglobin of more than 3 g per decilitre; any decrease in haemoglobin of more than 4 g per decilitre; or transfusion of two or more units of packed red cells or whole blood. The secondary ‘ischaemic’ endpoint was a combined incidence of death from any cause, MI, or urgent TVR at 30 days after inclusion. In addition, major and minor bleeding were assessed according to the Thrombolysis in Myocardial Infarction criteria. Stent thrombosis was considered to have occurred when the Academic Research Consortium criteria for definite stent thrombosis were met. All events were adjudicated and classified by the event-adjudication committee.

Statistical analysis

The hypothesis to be tested was that the reduced dose of 100 U/kg UFH provides net clinical benefit compared with the higher heparin dose of 140 U/kg used in the ISAR-REACT 3 trial (historical control). In ISAR-REACT 3, the incidence of the primary quadruple endpoint
was 8.7% in the UFH arm and 8.3% in the bivalirudin arm. Assumptions of a 25% relative reduction (2.2% in absolute) in the incidence of the primary endpoint with the lower vs. the higher UFH dose, a power of 80%, and a two-sided α-level of 0.05 required the inclusion of 2367 patients. To account for possible losses to follow-up it was planned to enrol a total number of 2500 patients. This number of patients also provides the trial with 74% power for checking the non-inferiority of treatment with lower dose UFH vs. treatment with bivalirudin in the ISAR-REACT 3 trial with a margin of non-inferiority of 1.8% and a one-sided α-value of 0.05. The margin of non-inferiority aimed at preserving 80% of the superiority assumption of bivalirudin over UFH 140 U/kg of 2.2% in ISAR-REACT 3. Sample size calculation was performed with nQuery Advisor (version 4.0, Statistical Solutions).

Categorical data are presented as counts (%) and compared with the use of a chi-square test and Fisher’s exact test when expected cell values were less than 5. Continuous data were presented as median (25th and 75th percentiles) and compared by means of the Wilcoxon’s test, because they were not normally distributed (Kolmogorov–Smirnov’s test).

Because part of the patients received interventional treatment in multiple lesions, generalized estimation equation (GEE) models were employed to consider for repeated measurements (lesions) per subject within the analysis of group differences. The GEE approach properly reflects the structure of clustered data and takes within-subject dependencies (autocorrelation) into account.

Cumulative incidences of events were estimated by the Kaplan–Meier method. The hazard ratios (HRs) with 95% confidence intervals (CIs) associated with treatment assignment were calculated with the use of Cox proportional hazards models. The proportional hazards assumption was checked by the method of Grambsch and Therneau and was fulfilled in all cases in which the Cox proportional hazards model was used.

In order to balance covariates and thus reduce bias, we used propensity score methodology. The propensity score is the probability that a patient would have been treated with UFH 100 U/kg vs. UFH 140 U/kg and UFH 100 U/kg vs. bivalirudin, respectively, given the patient’s observed pre-treatment characteristics. The propensity score was estimated using a logistic regression model including baseline clinical and angiographic characteristics as predictor variables and treatment category as an outcome variable. The obtained propensity scores were used in two subsequent types of analysis. First, we created samples of patients matched for propensity scores within a caliper of ± 0.002. Matching was performed with the use of an internet-based software based on a Euclidean nearest neighbour metric method. In patients with multilesion interventions, only one lesion at random was selected for matching. Comparison of the parameters in the matched groups was done with the use of Wilcoxon’s (continuous variables) and McNemar’s (discrete variables) tests for paired samples. The risk for adverse outcomes was assessed by calculating the odds ratio (OR) with the McNemar’s test. Second, the individual propensity scores were entered into all multivariable models used for assessment of outcomes.

Pre-specified subgroups were defined by median age, sex, the presence or absence of diabetes, the median baseline serum creatinine value, and stable or unstable angina. No formal adjustment for multiple testing was performed. Heterogeneity of treatment differences across the levels of a baseline variable were checked by assessing the interaction between the assigned treatment and the baseline variable with respect to the primary endpoint. This was done by entering the interaction term into the respective Cox proportional hazards model with adjustment for propensity score.

For non-inferiority testing, a one-sided P-value < 0.05 was considered significant; otherwise, a two-sided P-value < 0.05 was considered to indicate statistical significance. The program EquivTest (Statistical Solutions) was used for non-inferiority testing (according to the method of Chow and Liu). In all other cases, S-PLUS software, version 4.5 (Insightful) was used.

**Results**

A total of 2505 eligible patients (1052 patients in the Deutsches Herzzentrum Munich; 1004 in the Herz-Zentrum Bad Krozingen, and 449 in the 1. Medizinische Klinik, Klinikum rechts der Isar, Munich) were consecutively included in this study and received a reduced single bolus dose of 100 U/kg UFH. These three centres had provided 93% of the patients enrolled in the previous ISAR-REACT 3 trial. None of the patients required administration of glycoprotein IIb/IIIa inhibitors. Thirty-day follow-up was complete in all but 21 patients, whose data were censored at the last available contact date (range 2–8 days after enrolment).

Baseline characteristics of the patients that received the lower heparin dose are shown in Tables 1 and 2 and compared with the higher heparin dose group and the bivalirudin group of ISAR-REACT 3. The analysis revealed significant differences in baseline variables.

**Thirty-day clinical outcomes**

Table 3 shows the cumulative incidences of ischaemic and bleeding events in the lower heparin dose group. Results were compared with outcomes of the higher heparin dose group of the ISAR-REACT 3 trial.

The primary endpoint of the study—the composite of death, MI, urgent TVR, or major bleeding—occurred in 183 patients in the lower dose heparin group (7.3%) and 199 patients in the higher heparin dose group (8.7%) (HR 0.81; 95% CI 0.67–1.00; P = 0.045) (Figure 1).

There was no significant interaction between any of the variables defining the pre-specified subgroups of interest and treatment effect on the primary endpoint (Figure 2).

The secondary, ischaemic endpoint of the study—the composite of death, MI, or urgent TVR—was reached in 111 patients in the lower heparin dose group (4.4%) and 115 patients in the higher heparin dose group (5.0%; HR 0.87; 95% CI 0.67–1.13; P = 0.29) (Figure 3).

After entering the propensity score in the multivariable Cox proportional hazards model, the HR associated with the use of the lower heparin dose was 0.75 (95% CI 0.60–0.92; P = 0.007) for the primary endpoint and 0.82 (95% CI 0.62–1.08; P = 0.15) for the secondary endpoint.

Definite stent thrombosis was observed in nine patients (0.4%) in either heparin group.

Major bleeding was observed in 91 patients in the lower heparin dose group (3.6%) and 104 patients (4.6%) in the higher heparin dose group (unadjusted HR 0.79; 95% CI 0.59–1.05; P = 0.11; adjusted HR 0.71; 95% CI 0.53–0.97; P = 0.03; Figure 3). According to TIMI criteria, major bleeding occurred in 16 patients (0.6%) in the lower heparin dose group and 24 patients (1.1%) in the higher heparin dose group; minor bleeding occurred in 27 patients (1.1%) in the lower heparin dose group and 51 patients (2.2%) in the higher heparin dose group.
When the ISAR-REACT 3A study period was divided in tertiles containing similar numbers of patients, there was no significant difference regarding the primary quadruple endpoint, the secondary triple endpoint, and the REPLACE-2 major bleeding within the lower heparin dose group across the tertiles.

As part of the secondary analysis, Table 4 tabulates ischaemic and bleeding events in the lower heparin dose group of the present study and in the bivalirudin group of the ISAR-REACT 3 trial. The difference regarding the primary quadruple endpoint between the lower heparin dose group and the bivalirudin group was 1% (upper one-sided 95% CI: 0.3%). This difference was significantly within the pre-specified non-inferiority margin of 1.8% (P < 0.001). The non-inferiority of the lower heparin dose compared with bivalirudin regarding the primary endpoint was also confirmed by the Cox proportional hazards model including the individual propensity scores. A HR of 0.78 (90% CI 0.65–0.93) was calculated. The upper limit of the 90% CI (one-sided test) did not exceed the threshold value of 1.21 (translated from the predefined non-inferiority margin for the difference in incidences of 1.8%).

It was not intended to test differences in other events for statistical significance; thus no non-inferiority margins were pre-specified for them.

### Table 1 Baseline characteristics of the patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>UFH 100 U/kg</th>
<th>UFH 140 U/kg</th>
<th>Bivalirudin</th>
<th>P-value*</th>
<th>P-value**</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>2505</td>
<td>2281</td>
<td>2289</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (year)</td>
<td>67.9 (60.0–74.4)</td>
<td>67.5 (60.2–74.2)</td>
<td>67.8 (60.4–73.8)</td>
<td>0.55</td>
<td>0.45</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>554 (22.1)</td>
<td>530 (23.2)</td>
<td>545 (23.8)</td>
<td>0.36</td>
<td>0.16</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>758 (30.3)</td>
<td>636 (27.9)</td>
<td>618 (27.0)</td>
<td>0.07</td>
<td>0.013</td>
</tr>
<tr>
<td>Insulin-treated, n (%)</td>
<td>247 (9.9)</td>
<td>191 (8.4)</td>
<td>176 (7.7)</td>
<td>0.07</td>
<td>0.008</td>
</tr>
<tr>
<td>Current smoker, n (%)</td>
<td>374 (14.9)</td>
<td>337 (14.8)</td>
<td>328 (14.3)</td>
<td>0.88</td>
<td>0.56</td>
</tr>
<tr>
<td>Arterial hypertension, n (%)</td>
<td>2283 (91.1)</td>
<td>2044 (89.6)</td>
<td>2034 (88.9)</td>
<td>0.07</td>
<td>0.008</td>
</tr>
<tr>
<td>Hypercholesterolaemia, n (%)</td>
<td>1791 (71.5)</td>
<td>1795 (78.7)</td>
<td>1850 (80.8)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Angina, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Unstable</td>
<td>566 (22.6)</td>
<td>415 (18.2)</td>
<td>421 (18.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stable</td>
<td>1939 (77.4)</td>
<td>1866 (81.8)</td>
<td>1868 (81.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of diseased coronary vessels, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>One vessel</td>
<td>339 (13.5)</td>
<td>459 (20.1)</td>
<td>452 (19.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Two vessels</td>
<td>617 (24.6)</td>
<td>658 (28.8)</td>
<td>633 (27.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Three vessels</td>
<td>1549 (61.8)</td>
<td>1164 (51.0)</td>
<td>1204 (52.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior myocardial infarction, n (%)</td>
<td>858 (34.3)</td>
<td>689 (30.2)</td>
<td>734 (32.1)</td>
<td>0.003</td>
<td>0.11</td>
</tr>
<tr>
<td>Prior aortocoronary bypass surgery, n (%)</td>
<td>346 (13.8)</td>
<td>248 (10.9)</td>
<td>286 (12.5)</td>
<td>0.002</td>
<td>0.18</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>81 (73–91)</td>
<td>81 (72–90)</td>
<td>80 (72–90)</td>
<td>0.32</td>
<td>0.005</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>27.4 (24.9–30.1)</td>
<td>27.2 (24.9–29.8)</td>
<td>27.1 (24.8–29.8)</td>
<td>0.43</td>
<td>0.049</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>1.0 (0.8–1.1)</td>
<td>0.9 (0.8–1.1)</td>
<td>0.9 (0.8–1.1)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Left ventricular ejection fraction (%)</td>
<td>58 (50–62)</td>
<td>60 (52–65)</td>
<td>60 (52–65)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

UFH, unfractionated heparin.

*Data are presented as n (%) or median (25–75th percentile).

*P for the comparison of the lower dose UFH group (100 U/kg) with the higher dose UFH group of ISAR-REACT 3 (140 U/kg).

**P for the comparison of the lower dose UFH group (100 U/kg) with the bivalirudin group of ISAR-REACT 3.

### Propensity score-matched cohorts

Propensity score matching algorithm identified 1000 closely matched patients for the comparisons between the 100 and 140 U/kg UFH groups as well as the 100 U/kg UFH and bivalirudin groups (Table 5).

The primary quadruple endpoint occurred in 6.1% of patients in the lower heparin dose group compared with 8.8% of patients in the higher heparin dose group (OR 0.69; 0.51–0.94; P = 0.02). The secondary endpoint was encountered in 3.5% of patients in the lower heparin dose group compared with 5.2% of patients in the higher heparin dose group (OR 0.67; 0.45–1.02; P = 0.06).

Major bleeding was observed in 3.5% of patients in the lower and 4.4% of patients in the higher heparin dose groups, respectively (OR, 0.80; 0.52–1.23; P = 0.30).

The primary quadruple endpoint occurred in 6.1% of patients in the lower heparin dose group compared with 8.5% of patients in the bivalirudin group. The non-inferiority of the lower heparin dose compared with bivalirudin regarding the primary endpoint was established by an estimated HR of 0.70 (90% CI 0.53–0.93). This conclusion is justified by the result that the upper limit of the 90% CI (one-sided test) did not exceed the threshold value of 1.21 (see above).
Table 2  Lesion and procedural characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>UFH 100 U/kg</th>
<th>UFH 140 U/kg</th>
<th>Bivalirudin</th>
<th>P-value*</th>
<th>P-value**</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of lesions</td>
<td>4252</td>
<td>3886</td>
<td>3869</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Target vessel, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.19</td>
<td>0.25</td>
</tr>
<tr>
<td>- Left main coronary artery</td>
<td>172 (4.0)</td>
<td>134 (3.4)</td>
<td>159 (4.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Left anterior descending coronary artery</td>
<td>1629 (38.3)</td>
<td>1507 (38.8)</td>
<td>1568 (40.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Left circumflex coronary artery</td>
<td>1158 (27.2)</td>
<td>1004 (25.8)</td>
<td>986 (25.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Right coronary artery</td>
<td>1208 (28.4)</td>
<td>1172 (30.2)</td>
<td>1086 (28.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Venous bypass graft</td>
<td>85 (2.0)</td>
<td>69 (1.8)</td>
<td>70 (1.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complex (type B2 or C) lesions, n (%)</td>
<td>3031 (71.3)</td>
<td>2636 (67.8)</td>
<td>2610 (67.5)</td>
<td>0.003</td>
<td>0.001</td>
</tr>
<tr>
<td>Chronic total occlusions, n (%)</td>
<td>364 (8.6)</td>
<td>266 (6.8)</td>
<td>268 (6.9)</td>
<td>0.004</td>
<td>0.006</td>
</tr>
<tr>
<td>Lesion length (mm)</td>
<td>13.4 (8.7–20.6)</td>
<td>11.9 (7.9–18.1)</td>
<td>12.0 (8.1–18.0)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Vessel size (mm)</td>
<td>2.8 (2.4–3.2)</td>
<td>2.8 (2.4–3.2)</td>
<td>2.8 (2.4–3.2)</td>
<td>0.70</td>
<td>0.76</td>
</tr>
<tr>
<td>Diameter stenosis prior to procedure (%)</td>
<td>66.4 (56.3–76.5)</td>
<td>61.3 (53.6–71.3)</td>
<td>61.6 (53.8–71.4)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Maximal balloon pressure (atm)</td>
<td>16 (13–18)</td>
<td>15 (12–18)</td>
<td>15 (12–18)</td>
<td>&lt;0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>Balloon-to-vessel ratio</td>
<td>1.09 (1.04–1.17)</td>
<td>1.09 (1.04–1.15)</td>
<td>1.09 (1.04–1.15)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Type of intervention, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>- Drug-eluting stent</td>
<td>3865 (90.9)</td>
<td>3383 (87.1)</td>
<td>3416 (88.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Bare-metal stent</td>
<td>68 (1.6)</td>
<td>238 (6.1)</td>
<td>198 (5.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Balloon angioplasty</td>
<td>319 (7.5)</td>
<td>265 (6.8)</td>
<td>255 (6.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Length of stented segment (mm)</td>
<td>24 (18–30)</td>
<td>20 (16–28)</td>
<td>20 (16–28)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diameter stenosis after procedure (%)</td>
<td>11.3 (7.8–16.0)</td>
<td>10.8 (7.3–14.9)</td>
<td>10.9 (7.3–14.9)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

UFH, unfractionated heparin.
aData are presented as n (%) or median (25th–75th percentile).
*P for the comparison of the lower dose UFH group (100 U/kg) with the higher dose UFH group of ISAR-REACT 3 (140 U/kg).
**P for the comparison of the lower dose UFH group (100 U/kg) with the bivalirudin group of ISAR-REACT 3.

Table 3  Primary quadruple endpoint, secondary triple endpoint, and their components in the two unfractionated heparin groups

<table>
<thead>
<tr>
<th>Event</th>
<th>UFH 100 U/kg (n = 2505)</th>
<th>UFH, 140 U/kg (n = 2281)</th>
<th>Unadjusted HR (95% CI)</th>
<th>Adjusted HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quadruple endpoint of death, myocardial infarction, urgent target vessel revascularization, or major bleeding</td>
<td>183 (7.3)</td>
<td>199 (8.7)</td>
<td>0.81 (0.67–1.00)</td>
<td>0.75 (0.60–0.92)</td>
</tr>
<tr>
<td>Triple endpoint of death, myocardial infarction, urgent target vessel revascularization</td>
<td>111 (4.4)</td>
<td>115 (5.0)</td>
<td>0.87 (0.67–1.13)</td>
<td>0.82 (0.62–1.08)</td>
</tr>
<tr>
<td>Death</td>
<td>5 (0.2)</td>
<td>4 (0.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>99 (4.0)</td>
<td>110 (4.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Q wave myocardial infarction</td>
<td>8 (0.3)</td>
<td>9 (0.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urgent target vessel revascularization</td>
<td>22 (0.9)</td>
<td>17 (0.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major bleeding</td>
<td>91 (3.6)</td>
<td>104 (4.6)</td>
<td>0.79 (0.59–1.05)</td>
<td>0.71 (0.53–0.97)</td>
</tr>
<tr>
<td>Bleeding according to TIMI definition</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Major</td>
<td>16 (0.6)</td>
<td>24 (1.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Minor</td>
<td>27 (1.1)</td>
<td>51 (2.2)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Hazard ratios were adjusted for the propensity scores.
HR, hazard ratio; TIMI, thrombolysis in myocardial infarction; UFH, unfractionated heparin.
aData are presented as n (%).
Figure 1 Cumulative incidence of the primary endpoint in the lower (100 U/kg) unfractionated heparin dose group of the ISAR-REACT 3A trial and in the higher (140 U/kg) unfractionated heparin dose group as well as in the bivalirudin group of the ISAR-REACT 3 trial (historical control). The primary, quadruple endpoint of the study was the 30-day composite of death, myocardial infarction, urgent target-vessel revascularization, or in hospital major bleeding. UFH denotes unfractionated heparin.

Figure 2 Incidences and adjusted hazard ratios of the primary endpoint (30-day composite of death, myocardial infarction, urgent target-vessel revascularization, or in hospital major bleeding) in pre-specified subgroups. Hazard ratios associated with the use of the lower unfractionated heparin dose (100 U/kg) are shown with their 95% confidence intervals. All hazard ratios were adjusted for the propensity scores. UFH indicates unfractionated heparin.
This prospective, multicentre, open-label, single-group assignment trial of biomarker negative patients undergoing PCI after clopidogrel pre-treatment suggests that a single bolus dose of 100 U/kg UFH may provide net clinical benefit compared with the higher (140 U/kg) unfractionated heparin dose group as well as in the bivalirudin group of the ISAR-REACT 3 trial (historical control). The secondary endpoint (30-day composite of death, myocardial infarction, urgent target-vessel revascularization) is shown on the left side of the graph; in-hospital major bleeding is shown on the right side of the graph.

**Figure 3** Incidence of events in the lower (100 U/kg) unfractionated heparin dose group of the ISAR-REACT 3A trial and in the higher (140 U/kg) unfractionated heparin dose group as well as in the bivalirudin group of the ISAR-REACT 3 trial (historical control). The secondary endpoint (30-day composite of death, myocardial infarction, urgent target-vessel revascularization) is shown on the left side of the graph; in-hospital major bleeding is shown on the right side of the graph.

**Table 4** Primary quadruple endpoint, secondary triple endpoint, and their components in the 100 U/kg unfractionated heparin and in the bivalirudin group

<table>
<thead>
<tr>
<th>Event</th>
<th>UFH 100 U/kg (n = 2505)</th>
<th>Bivalirudin (n = 2289)</th>
<th>(P_{\text{non-inferiority}})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quadruple endpoint of death, myocardial infarction, urgent target vessel revascularization or major bleeding</td>
<td>183 (7.3)</td>
<td>190 (8.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Triple endpoint of death, myocardial infarction, urgent target vessel revascularization</td>
<td>111 (4.4)</td>
<td>134 (5.9)</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>5 (0.2)</td>
<td>3 (0.1)</td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>99 (4.0)</td>
<td>128 (5.6)</td>
<td></td>
</tr>
<tr>
<td>Q-wave myocardial infarction</td>
<td>8 (0.3)</td>
<td>14 (0.6)</td>
<td></td>
</tr>
<tr>
<td>Urgent target vessel revascularization</td>
<td>22 (0.9)</td>
<td>19 (0.8)</td>
<td></td>
</tr>
<tr>
<td>Major bleeding</td>
<td>91 (3.6)</td>
<td>70 (3.1)</td>
<td></td>
</tr>
<tr>
<td>Bleeding according to TIMI definition</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major</td>
<td>16 (0.6)</td>
<td>12 (0.5)</td>
<td></td>
</tr>
<tr>
<td>Minor</td>
<td>27 (1.1)</td>
<td>29 (1.3)</td>
<td></td>
</tr>
</tbody>
</table>

TIMI, thrombolysis in myocardial infarction; UFH, unfractionated heparin.

aData are presented as n (%).

bNon-inferiority testing was performed for the primary quadruple endpoint only. Differences in other events were not tested for statistical significance.

**Discussion**

This prospective, multicentre, open-label, single-group assignment trial of biomarker negative patients undergoing PCI after clopidogrel pre-treatment suggests that a single bolus dose of 100 U/kg UFH may provide net clinical benefit compared with the higher bolus dose of 140 U/kg UFH used in the ISAR-REACT 3 trial (historical control). The lower UFH dose was associated with a significant reduction in the combined quadruple endpoint of 30-day ischaemic events (death, MI, and urgent TVR) and in-hospital major bleeding complications.

The design of the ISAR-REACT 3A trial bears several limitations. Although we applied the same eligibility criteria and protocol procedures as those used in the ISAR-REACT 3 trial, due to different recruitment periods temporal changes in the patients’ risk profile and their management may have occurred and considerably influenced the outcomes observed. The patients enrolled in ISAR-REACT 3A trial were clearly sicker patients with more complex lesions and interventions. This shows how important the parallel random assignment design is in eliminating an uneven distribution of entry characteristics and related bias in the observed outcomes.
### Table 5  Baseline characteristics in the matched cohorts

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>UFH 100 U/kg</th>
<th>UFH 140 U/kg</th>
<th>P-value</th>
<th>UFH 100 U/kg</th>
<th>Bivalirudin</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>1000</td>
<td>1000</td>
<td></td>
<td>1000</td>
<td>1000</td>
<td></td>
</tr>
<tr>
<td>Age (year)</td>
<td>67.5 (59.7–73.6)</td>
<td>67.4 (59.6–74.7)</td>
<td>0.42</td>
<td>67.9 (60.5–74.2)</td>
<td>67.8 (60.2–74.3)</td>
<td>0.54</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>226 (22.6)</td>
<td>222 (22.2)</td>
<td>0.83</td>
<td>224 (22.4)</td>
<td>230 (23.0)</td>
<td>0.75</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>295 (29.5)</td>
<td>305 (30.5)</td>
<td>0.62</td>
<td>284 (28.4)</td>
<td>280 (28.0)</td>
<td>0.84</td>
</tr>
<tr>
<td>Insulin-treated, n (%)</td>
<td>91 (9.1)</td>
<td>102 (10.2)</td>
<td>0.40</td>
<td>89 (8.9)</td>
<td>82 (8.2)</td>
<td>0.58</td>
</tr>
<tr>
<td>Arterial hypertension, n (%)</td>
<td>913 (91.3)</td>
<td>910 (91.0)</td>
<td>0.81</td>
<td>899 (89.9)</td>
<td>906 (90.6)</td>
<td>0.61</td>
</tr>
<tr>
<td>Hypercholesterolaemia, n (%)</td>
<td>745 (74.5)</td>
<td>746 (74.6)</td>
<td>0.96</td>
<td>755 (75.5)</td>
<td>735 (73.5)</td>
<td>0.29</td>
</tr>
<tr>
<td>Angina, n (%)</td>
<td>0.36</td>
<td></td>
<td></td>
<td></td>
<td>0.26</td>
<td></td>
</tr>
<tr>
<td>Unstable</td>
<td>222 (22.2)</td>
<td>205 (20.5)</td>
<td></td>
<td>215 (21.5)</td>
<td>195 (19.5)</td>
<td></td>
</tr>
<tr>
<td>Stable</td>
<td>778 (77.8)</td>
<td>795 (79.5)</td>
<td></td>
<td>785 (78.5)</td>
<td>805 (80.5)</td>
<td></td>
</tr>
<tr>
<td>No of diseased coronary vessels, n (%)</td>
<td></td>
<td></td>
<td>0.74</td>
<td></td>
<td>0.86</td>
<td></td>
</tr>
<tr>
<td>One vessel</td>
<td>153 (15.3)</td>
<td>143 (14.3)</td>
<td></td>
<td>150 (15.0)</td>
<td>142 (14.2)</td>
<td></td>
</tr>
<tr>
<td>Two vessels</td>
<td>266 (26.6)</td>
<td>278 (27.8)</td>
<td></td>
<td>254 (25.4)</td>
<td>252 (25.2)</td>
<td></td>
</tr>
<tr>
<td>Three vessels</td>
<td>581 (58.5)</td>
<td>579 (57.9)</td>
<td></td>
<td>596 (59.6)</td>
<td>606 (60.6)</td>
<td></td>
</tr>
<tr>
<td>Prior myocardial infarction, n (%)</td>
<td>324 (32.4)</td>
<td>335 (33.5)</td>
<td>0.60</td>
<td>332 (33.2)</td>
<td>363 (36.3)</td>
<td>0.16</td>
</tr>
<tr>
<td>Prior aortocoronary bypass surgery, n (%)</td>
<td>136 (13.6)</td>
<td>137 (13.7)</td>
<td>0.95</td>
<td>130 (13.0)</td>
<td>138 (13.8)</td>
<td>0.60</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>27.2 (24.8–30.1)</td>
<td>27.1 (24.9–29.8)</td>
<td>0.76</td>
<td>27.2 (24.7–29.7)</td>
<td>27.2 (24.8–30.0)</td>
<td>0.49</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>0.9 (0.8–1.1)</td>
<td>0.9 (0.8–1.1)</td>
<td>0.42</td>
<td>0.9 (0.8–1.1)</td>
<td>0.9 (0.8–1.1)</td>
<td>0.96</td>
</tr>
<tr>
<td>Left ventricular ejection fraction (%)</td>
<td>58 (52–62)</td>
<td>58 (49–64)</td>
<td>0.19</td>
<td>58 (52–62)</td>
<td>57 (48–63)</td>
<td>0.04</td>
</tr>
<tr>
<td>Target vessel, n (%)</td>
<td></td>
<td></td>
<td>0.90</td>
<td></td>
<td>0.91</td>
<td></td>
</tr>
<tr>
<td>Left main coronary artery</td>
<td>28 (2.8)</td>
<td>29 (2.9)</td>
<td></td>
<td>26 (2.6)</td>
<td>30 (3.0)</td>
<td></td>
</tr>
<tr>
<td>Left anterior descending coronary artery</td>
<td>369 (36.9)</td>
<td>382 (38.2)</td>
<td></td>
<td>390 (39)</td>
<td>374 (37.4)</td>
<td></td>
</tr>
<tr>
<td>Left circumflex coronary artery</td>
<td>274 (27.4)</td>
<td>261 (26.1)</td>
<td></td>
<td>265 (26.5)</td>
<td>265 (26.5)</td>
<td></td>
</tr>
<tr>
<td>Right coronary artery</td>
<td>303 (30.3)</td>
<td>297 (29.7)</td>
<td></td>
<td>288 (28.8)</td>
<td>302 (30.2)</td>
<td></td>
</tr>
<tr>
<td>Venous bypass graft</td>
<td>26 (2.6)</td>
<td>31 (3.1)</td>
<td></td>
<td>31 (3.1)</td>
<td>29 (2.9)</td>
<td></td>
</tr>
<tr>
<td>Complex (type B2 or C) lesions, n (%)</td>
<td>684 (68.4)</td>
<td>682 (68.2)</td>
<td>0.92</td>
<td>651 (65.1)</td>
<td>683 (68.3)</td>
<td>0.13</td>
</tr>
<tr>
<td>Chronic total occlusions, n (%)</td>
<td>80 (8.0)</td>
<td>89 (8.9)</td>
<td>0.47</td>
<td>98 (9.8)</td>
<td>84 (8.4)</td>
<td>0.27</td>
</tr>
<tr>
<td>Lesion length (mm)</td>
<td>12.7 (8.4–19.2)</td>
<td>13.2 (8.6–19.4)</td>
<td>0.29</td>
<td>12.8 (8.5–19.5)</td>
<td>13.1 (9.0–19.5)</td>
<td>0.19</td>
</tr>
<tr>
<td>Vessel size (mm)</td>
<td>2.8 (2.4–3.1)</td>
<td>2.8 (2.5–3.2)</td>
<td>0.08</td>
<td>2.8 (2.4–3.1)</td>
<td>2.8 (2.5–3.2)</td>
<td>0.09</td>
</tr>
<tr>
<td>Diameter stenosis prior to procedure (%)</td>
<td>65.6 (56.8–75.4)</td>
<td>63.5 (55.4–73.7)</td>
<td>0.07</td>
<td>66.4 (56.7–75.7)</td>
<td>63.8 (55.8–71.9)</td>
<td>0.02</td>
</tr>
<tr>
<td>Type of intervention, n (%)</td>
<td></td>
<td></td>
<td>0.14</td>
<td></td>
<td>0.55</td>
<td></td>
</tr>
<tr>
<td>Drug-eluting stent</td>
<td>904 (90.4)</td>
<td>916 (91.6)</td>
<td></td>
<td>892 (89.2)</td>
<td>890 (89.0)</td>
<td></td>
</tr>
<tr>
<td>Bare-metal stent</td>
<td>8 (0.8)</td>
<td>2 (0.2)</td>
<td></td>
<td>10 (1.0)</td>
<td>6 (0.6)</td>
<td></td>
</tr>
<tr>
<td>Balloon angioplasty</td>
<td>88 (8.8)</td>
<td>82 (8.2)</td>
<td></td>
<td>98 (9.8)</td>
<td>104 (10.4)</td>
<td></td>
</tr>
</tbody>
</table>

aData are presented as n (%) or median (25–75th percentile).
The degree of this potential bias might be difficult to quantify and fully eliminate by multivariable modelling and propensity score matching methods. Another limitation of the ISAR-REACT 3A trial design when compared with the predecessor ISAR-REACT 3 trial is its open-label nature of treatment assignment. In view of these limitations, the results of the present trial should be seen as hypothesis generating regarding the clinical value of a reduced UFH dose. Definition of the optimal UFH dose still awaits the conduct of large randomized clinical trials. In addition, the applicability of the results of the ISAR-REACT 3A trial should be confined to the setting of the predominant use of the femoral access approach with manual compression after sheath removal. Finally, the comparison between the lower UFH dose and bivalirudin was only done as a secondary exploratory analysis, acknowledging that the trial lacked sufficient power for this aspect.

Although heparin has been the standard antithrombin since the inception of PCI, there is currently no solid evidence to guide its dosing during contemporary PCI. During the history of PCI, the dosing regimen of UFH has undergone significant evolution. Initially, dosing regimens for PCI were adopted from experiences gained from cardiopulmonary bypass circuitry.\(^1\) With improved results of PCI over time, concerns about haemorrhagic complications led to an empirical reduction in the strength of anticoagulation,\(^4,5,20–22\) especially in the setting of adequate platelet inhibition. These efforts recently culminated in the hypothesis that in a very low-risk setting, the omission of any antithrombin agent could be safely performed against the background of aggressive platelet inhibition, achieved either by the use of glycoprotein IIB/IIa inhibitors\(^21,24\) or thienopyridines in addition to aspirin.\(^25\) In the randomized, double-blind Coronary Interventions Antiplatelet-based Only (CIAO) trial of 700 selected patients undergoing very low-risk procedures, the additional use of anticoagulant therapy with heparin was not found to be required in patients on dual antiplatelet therapy with aspirin and clopidogrel.\(^25\) Even if these results can be confirmed by adequately powered trials in the future, there is less doubt concerning the need for combined antiplatelet and antithrombolytic therapy in more complex patients and/or procedures. The lowest heparin dose required, however, has not yet been determined.

There are currently two dosing regimens in use: one that uses a weight adjusted bolus of 100 U/kg without monitoring of ACT (most common in Europe) and one that uses ACT guidance to maintain an ACT level of 250–350 s (most common in the USA).\(^2,3\)

At first glance, the use of a single bolus dose of 140 U/kg UFH as used in the ISAR-REACT 3 trial as part of our long institutional practice seems to be higher than the currently recommended dosing regimens with ACT measurement. However, in a pooled analysis of more than 6000 patients undergoing PCI with ACT guidance, the mean total dose of heparin administered was >14 000 U, which is higher than the total dose administered in the ISAR-REACT 3 trial.\(^26\)

Numerous analyses of the impact of different levels of anticoagulation measured by ACT on the ensuing haemorrhagic and ischaemic outcomes have been performed but yielded mostly conflicting results. Since none of them used a prospective randomized design, the optimal level of anticoagulation to achieve remains unclear. Although several trials found a correlation of higher ACT levels with increased bleeding rates,\(^2,7,26,27\) others failed to find any association.\(^2,27\) Current evidence for the impact of ACT levels on ischaemic outcomes is even more confusing, with several trials suggesting reduced ischaemic events with higher levels of ACT,\(^28–30\) and several others finding no association.\(^2,22\) A plateau at higher ACT levels has also been described\(^27\) as well as a U-shaped correlation, with more ischaemic events at very high ACT levels.\(^26\) Uncertainties about the optimal time point of ACT measurement, device-dependent variability in ACT levels, the low predictability of ACT after fixed UFH doses, and the fact that advised levels are achieved only in a minority of patients\(^27\) make current recommendations even more complicated.

New anti-IIa and anti-Xa agents with the advantage of a more homogeneous dose response are currently undergoing testing in clinical trials.\(^31,32\) The ISAR-REACT 3A study adds valuable information to the existing evidence. It shows that a simple reduction in the heparin dose from a single bolus of 140 U/kg to a single bolus of 100 U/kg without ACT monitoring or additional boluses may provide net clinical benefit in biomarker negative patients undergoing PCI after clopidogrel pre-treatment. The results with this approach also appeared to be non-inferior to those achieved with bivalirudin in the ISAR-REACT 3 trial.

Additional analysis revealed that the net clinical benefit of the lower UFH dose was achieved by a non-significant reduction in both bleeding and ischaemic events. This is important, since it shows that the reduction in bleeding is not achieved at the expense of an increased risk of thrombotic events. Both of these events are of important prognostic value.\(^1,2,13\) Although low doses of heparin are more apt to reduce platelet aggregation, and high doses are more likely to increase it \(\text{in vitro}\),\(^34\) it is not known whether this mechanism might have had an impact on the numerically lower ischaemic complication rate in the 100 U/kg UFH dose group of the ISAR-REACT 3A trial. Moreover, it has been shown that bleeding also influences the occurrence of ischaemic events.\(^35\)

In conclusion, the present trial shows that in biomarker negative patients, a reduced dose of UFH may represent a simple and safe method of lowering the bleeding risk after PCI without compromising the risk of ischaemic complications.

**Acknowledgements**

We gratefully acknowledge the precious contribution of Maria de Fátima Maimer Rodrigues da Cunha, Martina Schulz, Heike Paul, and Christine Peteler to patient event monitoring.

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**Conflict of interest:** None declared.
References


