Suboptimal anticoagulation with pre-hospital heparin in ST-elevation myocardial infarction

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Summary
This is a prospective, observational study performed in all consecutive ST-elevation myocardial infarction (STEMI) patients who had activated clotting time (ACT) measurement on arrival in the cathlab before coronary angiography. We studied the therapeutic effects of a pre-hospital fixed heparin bolus dose in consecutive patients with STEMI. A total of 1,533 patients received pre-hospital administration of aspirin, high dose clopidogrel (600 mg) and a fixed bolus dose of 5,000 IU unfractionated heparin (UFH), according to the national ambulance protocols. Some patients were also treated with glycoprotein IIb/IIIa inhibitors (GPI) in the ambulance. A therapeutic ACT range was defined according to the ESC guidelines as 200–250 seconds when patients had GPI pre-treatment and 250–350 seconds when no GPI pre-treatment. Of the 1,533 patients, 216 patients (14.1%) had an ACT within the therapeutic range, 82.3% of the patients had a too low ACT, whereas 3.5% of the patients had a too high ACT. After multivariable analysis, the only independent predictor of a too low ACT was increasing weight (odds ratio 1.02/kg, 95% confidence interval 1.01–1.03, p=0.001). Patients with a too low ACT had less often an open infarct related vessel (initial TIMI flow 2,3) as compared to patients with an ACT in range (36.5% vs. 45.9%, p=0.013). In only a minority of patients with STEMI, pre-hospital treatment with a fixed bolus dose UFH is within the therapeutic ACT range. Increased weight is an independent determinant of a too low ACT. We strongly recommend weight adjusted administration of UFH in the ambulance.

Keywords
Activated clotting time, fixed bolus dose, unfractionated heparin, ST-elevation myocardial infarction, primary percutaneous coronary intervention

Introduction
Since the first primary percutaneous coronary intervention (PCI), intravenous unfractionated heparin (UFH) has been the cornerstone of antithrombotic therapy during primary PCI for ST-elevation myocardial infarction (STEMI) to prevent acute vessel closure due to thrombus (1). It is recommended to perform the procedure under an activated clotting time (ACT) of 250–350 seconds (s) (200–250 s if glycoprotein IIb/IIIa inhibitors (GPI) are used) (2). Inadequate heparin dosing has been associated with an increased risk of re-infarction (3). UFH overdose is related with bleeding (4), and bleeding is strongly associated with poor prognosis (5, 6). Many trials and registries suggested to use a weight-adjusted UFH protocol in the ambulance (2, 7–10). We evaluated this in several local ambulance protocols of the Netherlands, Belgium, Germany and United Kingdom and found however, that all give a fixed bolus dose of 5,000 IU UFH in the ambulance in STEMI patients in daily clinical practice, possibly resulting in under- or over-treatment. Therefore, the aim of this study was to investigate the effects of a pre-hospital fixed heparin bolus dose on therapeutic ACT range in consecutive patients with ST-elevation myocardial infarction.

Material and methods
Population
From January 2006 to December 2009, individual patient data from all patients with diagnosis of STEMI admitted for primary PCI at the Isala klinieken (Zwolle, the Netherlands) and had ACT measurement were prospectively recorded. To avoid double inclusion of patients, only the first recorded admission for STEMI during the study period was used. Patients were diagnosed with STEMI if they had chest pain of >30 minutes (min) duration and electrocardiographic (ECG) changes with ST segment elevation >2 mm in at least 2 precordials and >1 mm in the limb leads. In ad-
dition, we did not restrict our population to those presenting within 12 hr of symptom onset but included those presenting at any time with ongoing symptoms or clinical instability and an indication for primary PCI.

**Procedure details and adjunctive medical therapy**

According to protocol all patients received 500 mg of aspirin intravenously (i.v.), high loading dose of clopidogrel (600 mg orally) and a fixed bolus dose of 5,000 IU UFH i.v. After bolus initiation in the ambulance or referral centre, ACT was measured on arrival in the cathlab before device activation, and this measurement was defined as the index ACT.

According to institutional guidelines additional UFH was administered only in cases were the ACT was less than 200 s, if the procedure lasted more than 1 hour or at the discretion of the operator if complications appeared. All ACT’s were measured locally by using a Hemochrom device (International Technidyne, Edison, NJ, USA) (11–15).

In some patients additional treatment with GPI’s (25 μg/kg bolus tirofiban) was given in the ambulance or referral centre. Primary PCI was routinely performed by femoral access using 6 French sheaths with selective thrombus aspiration and stent implantation where appropriate.

**Endpoint**

The primary endpoint of this study was the effect of a fixed bolus dose of UFH on therapeutic ACT range in consecutive STEMI patients. A therapeutic ACT range was defined according to the ESC guidelines as 200–250 s when patients had GPI pre-treatment and 250–350 s when no GPI pre-treatment (2).

**Data collection and follow-up**

Baseline clinical characteristics, laboratory measurements, angiographic characteristics, and procedural details were collected in a case record form. Follow-up information was obtained from the patient’s general physician or by direct telephone interview with the patient.

**Ethics**

The investigation conforms to the principles outlined in the Declaration of Helsinki. The study was approved by the Committee on Research Ethics of our hospital.

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**Statistical analysis**

Statistical analysis was performed with the Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA) version 16.0.1. Continuous data were expressed as mean ± standard deviation and categorical data as percentage, unless otherwise denoted. Differences between continuous data were performed by Student’s t-test or Mann-Whitney test and the chi-square or Fisher’s exact test or Kruskal Wallis test was used as appropriate for dichotomous data. Multivariable logistic regression analysis was performed to test the independent predictors of a too low ACT, selecting baseline variables with entry/stay criteria of p<0.10. Variables entered into the model for a too low ACT included age (per year increment), gender, length (per cm increase), weight (per kg increase), and time from UFH administration to ACT measurement. Significant vari-

**Table 1: General characteristics.**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Too low ACT N=1,261</th>
<th>ACT in range N=216</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>62.4 ± 12.2</td>
<td>64.6 ± 12.8</td>
<td>0.010</td>
</tr>
<tr>
<td>Male gender</td>
<td>75.8</td>
<td>71.8</td>
<td>0.200</td>
</tr>
<tr>
<td>BMI</td>
<td>26.9 ± 4.1</td>
<td>26.4 ± 3.7</td>
<td>0.156</td>
</tr>
<tr>
<td>Weight</td>
<td>83.1 ± 14.7</td>
<td>78.5 ± 13.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>33.5</td>
<td>35.8</td>
<td>0.516</td>
</tr>
<tr>
<td>Smoking</td>
<td>41.2</td>
<td>38.0</td>
<td>0.374</td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>20.5</td>
<td>26.1</td>
<td>0.068</td>
</tr>
<tr>
<td>Family history</td>
<td>39.8</td>
<td>42.1</td>
<td>0.515</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>10.6</td>
<td>7.4</td>
<td>0.146</td>
</tr>
<tr>
<td>Previous MI</td>
<td>9.2</td>
<td>10.2</td>
<td>0.658</td>
</tr>
<tr>
<td>Previous PCI</td>
<td>9.1</td>
<td>11.1</td>
<td>0.341</td>
</tr>
<tr>
<td>Previous CVA</td>
<td>3.4</td>
<td>4.2</td>
<td>0.580</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>12.2</td>
<td>18.7</td>
<td>0.012</td>
</tr>
<tr>
<td>Killip &gt; 1</td>
<td>5.3</td>
<td>6.0</td>
<td>0.672</td>
</tr>
<tr>
<td>Time from UFH administration to ACT measurement (min)</td>
<td>82 (63 – 109)</td>
<td>74 (60 – 91)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Ischemic time (min)</td>
<td>200 (145 – 320)</td>
<td>197 (139 – 291)</td>
<td>0.322</td>
</tr>
<tr>
<td>Aspirin pre-treatment</td>
<td>92.8</td>
<td>94.4</td>
<td>0.383</td>
</tr>
<tr>
<td>Clopidogrel pre-treatment</td>
<td>88.5</td>
<td>87.0</td>
<td>0.512</td>
</tr>
<tr>
<td>Tirofiban pre-treatment</td>
<td>34.0</td>
<td>67.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median ACT</td>
<td>178 (159 – 195)</td>
<td>223 (209 – 259)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Initial TIMI 2,3 flow</td>
<td>36.5</td>
<td>45.9</td>
<td>0.013</td>
</tr>
<tr>
<td>Final TIMI 3 flow</td>
<td>92.4</td>
<td>89.7</td>
<td>0.208</td>
</tr>
<tr>
<td>Non CABG-related bleeding 30 days</td>
<td>3.4</td>
<td>3.3</td>
<td>0.942</td>
</tr>
</tbody>
</table>

Data are n/N (%) or mean (SD), or median (IQR). BMI=body mass index. MI=myocardial infarction. PCI=percutaneous coronary intervention. CABG=coronary artery bypass grafting. CVA=cerebrovascular accident. UFH=unfractionated heparin. ACT=activated clotting time. TIMI=thrombolysis in myocardial infarction. Renal insufficiency=GFR (glomerular filtration rate) <60 (according MDRD).
ables analysed are reported with their respective odd ratios (OR) and 95% confidence intervals (CI). For all analyses, statistical significance was assumed when the two-tailed probability value was <0.05.

Results

Baseline characteristics

During the study period ACT was measured in 1,533 STEMI patients, mean age was 62.9 ± 12.4 years, weight was 82.3 ± 14.5 kg, 13.2% had a GFR <60 ml/min and 25.5% were females. The median ACT was 185 seconds (interquartile range [IQR] 163 – 207), whereas the mean was 191 ± 47 s.

Patients with a too low ACT as compared to patients with an ACT in range had a higher bodyweight and a longer time between UFH administration to ACT measurement (see Table 1).

A total of 14.1% of the patients had an ACT within the therapeutic range, 82.3% of the patients had a too low ACT, whereas 3.5% of the patients had a too high ACT. Of the 608 patients (39.7%) who had GPI pre-treatment, 23.8% had an ACT within the therapeutic range, 70.6% of the patients had a too low ACT, whereas 5.6% of the patients had a too high ACT. Of the 925 patients without GPI pre-treatment, 7.7% of the patients had an ACT within the therapeutic range, whereas 92.3% had a too low ACT, whereas 2.4% had a too high ACT.

Patients with a too low ACT had less often an open infarct related vessel (initial TIMI flow 2,3) as compared to patients with an ACT in range (36.5% vs 45.9%, p=0.013).

Predictors of a too low ACT (<200 s for GPI pre-treatment and <250 s for no GPI pre-treatment)

After multivariable analyses, adjusting for all variables that were statistically significant in univariate analyses, only weight (per kg increase) (OR 1.02, 95% CI 1.01 – 1.03, p=0.001) remained an independent predictor of a too low ACT. Furthermore, the finding that weight was an important predictor of a too low ACT was supported after stratifying weight into quartiles (p<0.001, Fig. 1). There were no independent predictors of a too high ACT.

Discussion

To our knowledge, this is the first large study in non-selected primary PCI patients which determines the effects of a fixed bolus dose of UFH in the ambulance or referral center on therapeutic ACT range. The major finding of the present study is that only 14.1% of the STEMI patients had an ACT within the therapeutic range.

Of those who had GPI pre-treatment, 23.8% had an ACT within the therapeutic range. Of the patients with no GPI pre-treatment only 7.7% had an ACT within the therapeutic range. Furthermore, increased weight is an independent determinant of a too low index ACT.

In univariate analyses there were significantly more patients in the ACT-in-range-population who had pre-hospital administration of high-dose tirofiban. Possibly this is in part an effect of tirofiban since it has been demonstrated that GPI use on top of heparin leads to a prolongation of the ACT (16, 17).
Therapeutic efficacy of heparin

Despite the fact that evidence for supporting UFH in primary PCI is limited, use of UFH for primary PCI in STEMI is widely supported (18). However, heparin has a number of limitations, including a narrow therapeutic window of adequate anticoagulation without bleeding, heparin induced thrombocytopenia, reduced ability to inactivate thrombin bound to fibrin as well as factor Xa bound to activated platelets within a thrombus, and a highly variable dose-response relation requiring laboratory monitoring. According to the European Society of Cardiology (ESC) guidelines, UFH should be given at a dose able to maintain an ACT of 250–350 s (200–250 s if GPIs are used) (2).

Greater peak ACT values have been associated with a greater incidence of bleeding and vascular complications (19–21). Four randomised trials of heparin dosing in patients undergoing PCI, consistently found that lowering the dose of heparin reduced minor, but not major, bleeding rates (22–25), which is in accordance with the results of the recently published FUTURA/OASIS-8 trial (26). With the introduction of GPIs, stenting, and clopidogrel treatment, post-hoc analyses of large clinical trials have suggested that a reduction of the UFH dose would reduce the risks of bleeding without compromising the ischaemic risks (27, 28). However, pooled data suggested a U-shaped curve for ischaemic and bleeding complications after PCI and UFH-only therapy, whereas with abciximab, the U-shape relation was no longer present (17).

In a more recent post hoc analysis of four PCI trials with UFH doses of 65 to 90 IU/kg, the previously described U-shaped curve for ischemic events could not be reproduced; however, a modest association was still found between greater ACT values and bleeding complications (27). This was confirmed by a sub-analysis of the ESPRIT trial (28).

Our analysis revealed that patients with a too low ACT had less often an open infarct related vessel, as compared with patients with an ACT within the range, but we can not prove a causal relationship with UFH.

Recommendations for improvement

Optimising heparin dose

The current ESC guidelines recommend for STEMI patients who are candidates for primary PCI an i.v. UFH bolus with a starting dose of 100 IU/kg weight (60 IU/kg if GPIs are used) (2). However, we observed after reviewing ambulance protocols from different countries, including the Netherlands, Belgium, Germany and UK, that in daily clinical practice a fixed bolus dose of UFH in the pre-hospital setting is used, probably due to practical reasons. Our results confirm that a weight adjusted dosing of UFH may improve anticoagulation level. However, because of the individual variation, also after weight adjusted administration of UFH, ACT on admission should be measured in every patient. Furthermore, in the ESC guidelines there are no references for the optimal therapeutic ACT range. Therefore, further analyses are warranted to determine the optimal therapeutic ACT range when using UFH weight adjusted.

Alternatives for UFH

Use of LMWH in patients with STEMI may result in a higher frequency of anticoagulation within the therapeutic range, possibly resulting in a reduction of ischaemic events (7, 29).

The HORIZONS-AMI trial showed beneficial clinical effects with bivalirudin and provisional GPI as compared to UFH and GPI (8). Because of a low variable dose response relation, there is no therapeutic range required for bivalirudin. Whether pre-hospital treatment with bivalirudin will further improve net clinical benefit, should be awaited from the ongoing EUROMAX trial (9). We have summarised our recommendations in Table 2.

Study strengths and limitations

This is a prospective observational study with known limitations. This study has only focussed on the effects of a fixed bolus dose of UFH given in the ambulance or referral centre on the index ACT. To demonstrate a potential association between suboptimal ACT and clinical outcome is more difficult in an observational study, particularly because ACT measurements influence administration of additional heparin. Because of inherent differences in the measurement of ACT by different ACT devices and to be consistent, we used only one point-of-care assay ACT device (13, 14). However, it should be noted that biological factors can influence the response to UFH in STEMI patients. Furthermore, the ACT at the end of the PCI procedure, before sheath removal, was not measured.

Conclusion

In only a minority of patients with ST-elevation myocardial infarction, pre-hospital treatment with a fixed bolus dose UFH is within the therapeutic ACT range. Increased weight is an important independent predictor of a too low ACT. We strongly recommend weight adjusted administration of UFH in the ambulance.

Table 2. Recommendations for treatment of STEMI patients, based on the study findings. UFH=unfractionated heparin. ACT=activated clotting time.

| Recommendation                                                                 |
|                                                                               |
| 1. Adjust UFH according to weight in the pre-hospital setting, as recommended in the European guidelines |
| 2. Record the time of administration of UFH in the ambulance or referral center |
| 3. Measure the ACT on arrival in the cath lab, administer additional heparin if necessary, and repeat ACT measurement at the end of the procedure |
| 4. Re-define therapeutic ACT range                                             |
| 5. Renew European guidelines regarding newer antithrombotic agents for use in the pre-hospital setting |


What is known about this topic?
- Despite the fact that evidence for supporting unfractionated heparin (UFH) in primary percutaneous coronary intervention (PCI) is limited, use of UFH for PCI in STEMI or ST-segment elevation myocardial infarction (STEMI) is widely supported.
- The current ESC guidelines recommend for STEMI patients who are candidates for primary PCI an i.v. UFH bolus with a starting dose of 100 IU/kg weight (60 IU/kg if glycoprotein IIb/IIIa inhibitors are used).
- It is recommended to perform the procedure under an activated clotting time of 250–350 seconds (200–250 seconds if glycoprotein IIb/IIIa inhibitors are used).

What does this paper add?
- Although the ESC guidelines recommend to use UFH weight adjusted in the pre-hospital setting, in daily clinical practice, several local ambulance protocols of many countries still give a fixed bolus dose of 5,000 IU UFH in the ambulance in STEMI patients.
- In only a minority of patients with STEMI, pre-hospital treatment with a fixed bolus dose UFH is within the therapeutic activated clotting time range.
- Increased weight is an independent determinant of a too low activated clotting time.

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Conflict of interest
None declared.

References