CLINICAL RESEARCH

Prehospital high-dose tirofiban in patients undergoing primary percutaneous intervention. The AGIR-2 study

Angioplastie primaire et administration préhospitalière de tirofiban. Étude AGIR2

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KEYWORDS
Acute myocardial infarction; Tirofiban; Glycoprotein IIb/IIIa

Summary
Background. — Compared with administration in the catheterization laboratory, early treatment with glycoprotein IIb/IIIa inhibitors provides benefits to patients with ST-segment elevation myocardial infarction who undergo primary percutaneous intervention. Whether this benefit is maintained on top of a 600 mg loading dose of clopidogrel is unknown.

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1 A complete list of AGIR-2 investigators and personnel can be found in the appendix.

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Methods. — In a multicentre, controlled, randomized study, 320 patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention received a high-dose bolus of tirofiban given either in the ambulance (prehospital group) or in the catheterization laboratory. The primary endpoint was a TIMI flow grade 2–3 of the infarct-related vessel at initial angiography. Secondary endpoints included ST-segment resolution 1 h after percutaneous coronary intervention and peak serum troponin I concentration.

Results. — Tirofiban was administered 48 (95% confidence interval 21.4–75.0) min earlier in the prehospital group. At initial angiography, the combined incidence of TIMI 2–3 flow was 39.7% in the catheterization-laboratory group and 44.2% in the prehospital group (p = 0.45). No difference was found on postpercutaneous intervention angiography or peak troponin concentration. Complete ST-segment resolution 60 min after the start of intervention was 55.4% in the catheterization-laboratory group and 52.6% in the prehospital group (p = 0.32).

Conclusion. — Prehospital initiation of high-dose bolus tirofiban did not improve significantly initial TIMI 2 or 3 flow of the infarct-related artery or complete ST-segment resolution after coronary intervention compared with initiation of tirofiban in the catheterization laboratory (NCT00538317).

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Abbreviations

STEMI   ST-segment elevation myocardial infarction
AMI     acute myocardial infarction
PCI     percutaneous coronary intervention
GP IIb/IIIa glycoprotein IIb/IIIa
TIMI    thrombolysis in myocardial infarction
IRA     infarct-related artery
On-TIME2 Ongoing tirofiban in myocardial infarction evaluation2
BRAVE 3 Bavarian reperfusion alternatives evaluation-3

Introduction

In patients undergoing primary percutaneous intervention (PCI), glycoprotein (GP) IIb/IIIa inhibitors improve angiographic and clinical outcome [1] and are a class IIa recommendation [2]. Compared with administration in the catheterization laboratory (cath lab), early initiation of GP IIb/IIIa inhibitors in the emergency department or the ambulance had been associated with a better recanalization rate [3].

Most studies comparing early and late administration of GP IIb/IIIa inhibitors were performed before the generalization of adjuvant antiplatelet aggregation with high
loading-dose clopidogrel. Loading with 600 mg of clopidogrel provides a high degree of platelet-aggregation inhibition within a short time [4]. With a 600 mg clopidogrel regimen, prehospital administration of high-dose tirofiban was associated with an improved ST-segment resolution compared with placebo [5].

However, prehospital tirofiban has not been compared with tirofiban given in the cath lab in the modern era of adjuvant antiplatelet therapy in patients undergoing primary PCI. It is not only a clinical question but also an organizational problem. If applied widely, the systematic prehospital administration of GP IIb/IIIa inhibitors would raise the cost and complexity of prehospital protocols for the management of ST-segment elevation myocardial infarction (STEMI). We therefore performed a multicentre, prospective randomized trial to evaluate the extent of the benefit of prehospital tirofiban compared with cath-lab tirofiban on top of a high loading-dose of clopidogrel in patients undergoing primary PCI.

Methods

Study patients

The study recruited out-of-hospital patients managed by mobile intensive care units (MICU) staffed by a physician. The study was conducted within the organization of the RESCUe and RESURCOR networks that associate 12 tertiary cardiology centres with a round-the-clock catheterization laboratory, six medical dispatching centres and 20 MICU services. Patients were eligible for inclusion if they presented within 12 h after the onset of symptoms of myocardial infarction, i.e., characteristic pain lasting for at least 30 min and not responsive to nitrates, and electrocardiographic ST-segment elevation ≥ 0.2 mV in two or more contiguous precordial leads or 0.1 mV for limb leads. Patients were excluded if they were known to have haemorrhagic diathesis; were pregnant; had any allergy or contraindication to heparin, aspirin or tirofiban; suffered from severe renal or hepatic insufficiency; had had major surgery within the past month; had any sign of cerebral ischaemic disease for < 1 month or non-ischaemic disease whatever its date; had received oral anticoagulant treatment, a fibrinolytic or a GP IIb/IIIa antagonist within the past 7 days; had uncontrolled hypertension, severe conduction disorder or cardiogenic shock; or if duration of transfer to the hospital (entrance to the cath lab) was to exceed 1 h.

The study protocol was approved by the hospital and regional ethics committees. Oral informed consent was required in the ambulance and written consent was obtained from all patients no later than the time of catheterization.

Randomisation and treatment strategies

After initial screening and patient consent, open-label randomisation was conferred at the site of initial management (usually at home or at the patient’s workplace) to high-dose tirofiban in the ambulance (prehospital group) or in the catheterization laboratory (cath-lab group). Randomisation was done in dispatching medical centres according to a computer-generated random sequence enclosed in scratch cards.

All patients received, in the prehospital setting, a loading dose of 600 mg of clopidogrel, a 60 IU/kg intravenous (IV) heparin bolus (maximum dose 5000 IU) and 250–500 mg aspirin (oral or IV). Patients were transported immediately to the hospital for coronary angiography and angioplasty whenever possible.

Open-label tirofiban was administered as soon as possible at the site of initial management in patients assigned to the prehospital group, and at the admission to the cath lab before vascular access in those assigned to the cath-lab group. A loading dose of 25 μg/kg was administered in 3 min followed by an infusion of 0.15 μg/kg per min for 18–24 h.

Angioplasty was performed according to local standards with the intention of re-establishing blood flow in the infarct-related artery as soon as possible.

Electrocardiograms, biological data and procedural reports were collected and analysed centrally. Data on coronary angiograms were reported by the investigators. If discrepancies appeared between the case-report form and the procedural report, a request was sent to the investigator for further details. Electrocardiograms were recorded at presentation, on admission to the cath-lab and 1 h after PCI or angiography if no PCI was performed. They were collected and analysed centrally according to the same protocol by two trained research monitors unaware of the therapeutic strategy. ST-segment elevation was measured in all leads to the nearest 0.5 mm at 60 ms after the J point with hand-held callipers. ST-segment resolution was defined as the ratio between cath-lab or 60 min post-PCI values and the initial sum of ST-segment elevation.

Creatine kinase and troponin I concentrations were measured on admission, after the procedure, and every 6 h for 24 h, then every day until discharge.

Endpoints

The primary endpoint was the presence of TIMI 2 or 3 flow in the culprit artery during the first injection in coronary angiography. Secondary endpoints were sum residual ST-segment deviation and the frequency of ST-segment resolution 60 min after the angioplasty, creatine kinase and troponin peak serum concentrations. ST-segment resolution was considered complete when > 70% from baseline. To allow comparison with previous studies [5], residual ST-segment deviation was stratified as 0 mm, 1–3 mm, 4–6 mm and > 6 mm. Peak creatine kinase and peak troponin I serum concentrations were defined as the highest creatine kinase and troponin I serum concentrations within the first 48 h. Clinical and safety endpoints were in-hospital death, reinfarction, acute stent thrombosis or major bleeding. Major bleeding was defined as signs of haemorrhage associated with a drop in haemoglobin > 50 g/L, excluding patients who underwent coronary artery bypass graft surgery.

Statistical analysis

Continuous data are presented as mean with standard deviation or median with 25th and 75th quartiles unless otherwise stated. Comparisons were made with Student’s t-test or the Mann-Whitney U test. Discrete data are summarized as
frequencies and comparisons were made with Pearson’s $c^2$ test or Fisher’s exact test. The $c^2$ test was also used to test for trends in various grades of TIMI flow, ST-segment resolution and residual ST-segment elevation. A subgroup analysis was performed in patients managed early (before the median time from symptom onset to arrival in the MICU) or later (after the median time). Statistical analysis was performed on the basis of intention-to-treat. A $p$-value of < 0.05 was considered statistically significant.

Based on the results of a previous meta-analysis [6], the initial sample size calculation was 300 patients with a 5% alpha risk and an 80% power to detect a 16% difference in the primary endpoint. The study population was set to 320 patients. Since some patients were wrongly randomised due to errors in the dispatching centre or withdrew their informed consent before angiography, the recruitment was increased to 337 patients to reach at least 155 patients in each group. Incorrectly randomised patients were excluded from all analyses. The SAS software (Windows V 9.1) was used for all analyses.

The study is registered, number NCT00538317.

**Results**

**Clinical data**

From July 2007 to July 2008, 320 patients with an out-of-hospital diagnosis of STEMI and planned primary PCI were included and assigned randomly to prehospital tirofiban ($n = 164$) or cath-lab tirofiban ($n = 156$) (Fig. 1).

The baseline characteristics of the study population according to treatment strategy are presented in Table 1. No statistically significant difference was found in baseline distribution of demographic, clinical and procedural characteristics except for previous PCI, which was more frequent in the cath-lab group.

Delays in patient management are shown in Table 1. Tirofiban administration increased the transport time in the prehospital group and the preangiographic time in the cath-lab group. Tirofiban was administered 48 (95% confidence interval 21.4—75.0) min earlier in the prehospital initiation group.

**Angiographic and interventional results**

One patient in the prehospital group did not undergo angiography because of changes in symptoms during transport related the evolving STEMI to an acute aortic dissection. The rate of the primary endpoint — TIMI grade 2—3 flow in the culprit artery — was 39.7% (62 patients) in the cath-lab group and 44.2% (72 patients) in the prehospital group ($p = 0.42$).

After initial angiography, 118 patients underwent thrombus aspiration (51 patients [32.9%] in the cath-lab group; 67 patients [41.1%] in the prehospital group). Stents were placed in 225 patients (113 [72.4%] and 112 [69.1%], respectively). No PCI was performed in 50 (15.6%) patients, 24 of whom had normal angiograms, 10 had unsuitable lesions, seven underwent coronary artery bypass graft surgery, five had delayed angioplasty and four for unknown reasons.

Slow-flow occurred in 9.0% ($n = 14$) of patients in the cath-lab group and in 9.1% ($n = 15$) in the prehospital group ($p = 0.95$). No differences in various grades of TIMI flow post-PCI between the cath-lab and prehospital groups were observed on first angiography and at the end of the procedure (Fig. 2).
Table 1  Baseline clinical characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Cath-lab initiation of tirofiban (n = 156)</th>
<th>Prehospital initiation of tirofiban (n = 164)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>124 (79.5)</td>
<td>123 (75.0)</td>
<td>0.34</td>
</tr>
<tr>
<td>Diabetes</td>
<td>17 (10.9)</td>
<td>18 (11.0)</td>
<td>0.98</td>
</tr>
<tr>
<td>Hypertension</td>
<td>62 (39.7)</td>
<td>74 (45.1)</td>
<td>0.33</td>
</tr>
<tr>
<td>Current smoker</td>
<td>56 (35.9)</td>
<td>61 (37.2)</td>
<td>0.81</td>
</tr>
<tr>
<td>Dyslipidaemia</td>
<td>67 (43.0)</td>
<td>55 (33.5)</td>
<td>0.08</td>
</tr>
<tr>
<td>Anterior myocardial infarction</td>
<td>68 (43.6)</td>
<td>84 (51.2)</td>
<td>0.17</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>24 (15.4)</td>
<td>15 (9.1)</td>
<td>0.09</td>
</tr>
<tr>
<td>Previous coronary artery bypass</td>
<td>6 (3.8)</td>
<td>2 (1.2)</td>
<td>0.13</td>
</tr>
<tr>
<td>Killip class ≥ 2</td>
<td>13 (8.3)</td>
<td>19 (11.6)</td>
<td>0.33</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>75.4 ± 16.2</td>
<td>77.2 ± 22.2</td>
<td>0.42</td>
</tr>
<tr>
<td>Systolic arterial pressure (mmHg)</td>
<td>139 ± 28</td>
<td>141 ± 25</td>
<td>0.80</td>
</tr>
<tr>
<td>Cumulative ST-deviation on</td>
<td>12 ± 9</td>
<td>13 ± 8</td>
<td>0.25</td>
</tr>
<tr>
<td>diagnostic electrocardiogram (mm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment delay, median [25—75%]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Onset of chest pain to MICU</td>
<td>98 [50—200]</td>
<td>104 [56—233]</td>
<td>0.30</td>
</tr>
<tr>
<td>MICU to cath lab</td>
<td>54 [45—69]</td>
<td>61 [54—74]</td>
<td>0.0002</td>
</tr>
<tr>
<td>Cath lab to first angiography</td>
<td>26 [15—35]</td>
<td>21 [13—30]</td>
<td>0.007</td>
</tr>
<tr>
<td>MICU to first angiography</td>
<td>83 [70—96]</td>
<td>85 [72—100]</td>
<td>0.46</td>
</tr>
</tbody>
</table>

Data presented as mean ± SD or number (%) of patients unless otherwise stated. MICU: mobile intensive care unit arrival on site of intervention; Cath lab: admission in the catheterization laboratory.

ST-segment analysis

Owing to insufficient quality or for reasons relating to timing, an electrocardiogram was evaluated on admission to the cath-lab in 74.6% of patients (n = 239; 127 patients in the cath-lab group and 112 in the prehospital group) and 60 min after the procedure in 93.7% (n = 300; 148 patients and 152 patients, respectively).

On admission to the cath lab, there was a non-statistically significant trend toward a higher rate of complete ST-segment resolution in the prehospital group (8.7% [11/127] vs 15.2% [17/112]; p = 0.11). After the procedure, no such trend was apparent. Complete ST-segment resolution was observed in 55.4% (82/148) of patients in the cath-lab group and in 52.6% (80/152) in the prehospital group (p = 0.32). Various grades of ST-segment resolution were similar in both groups (Table 2).

An additional subgroup analysis compared the two treatment strategies in patients who were managed very early, within 100 min of symptom onset, and those managed later (Fig. 3). In the early patients, there was a trend toward a lower rate of TIMI grade 2–3 flow in the cath-lab group (39.7% [31/78] vs 51.2% [41/80]; p = 0.15). No such trend was apparent for the complete ST-segment resolution endpoints. For patients managed later, no differences were observed for either endpoint in both groups.

Laboratory results

Peak and 24 h serum concentrations of creatine kinase and troponin I did not show a favourable trend in the prehospital group (Table 2).
Table 2  Electrocardiogram and biological parameters.

<table>
<thead>
<tr>
<th></th>
<th>Cath-lab initiation of tirofiban</th>
<th>Prehospital initiation of tirofiban</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ST-segment resolution</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In the cath lab</td>
<td>n = 127</td>
<td>n = 112</td>
<td></td>
</tr>
<tr>
<td>&gt; 70%</td>
<td>11 (8.7)</td>
<td>17 (15.2)</td>
<td>0.11</td>
</tr>
<tr>
<td>60 min after angiography/PCI</td>
<td>n = 148</td>
<td>n = 152</td>
<td></td>
</tr>
<tr>
<td>&gt; 70%</td>
<td>82 (55.4)</td>
<td>80 (52.6)</td>
<td>0.32</td>
</tr>
<tr>
<td>&gt; 50%</td>
<td>113 (76.3)</td>
<td>104 (68.4)</td>
<td>0.12</td>
</tr>
<tr>
<td><strong>Residual ST-segment elevation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60 min after angiography/PCI</td>
<td>n = 148</td>
<td>n = 152</td>
<td></td>
</tr>
<tr>
<td>4—6 mm</td>
<td>33 (22.3)</td>
<td>31 (20.4)</td>
<td></td>
</tr>
<tr>
<td>&gt; 6 mm</td>
<td>20 (13.5)</td>
<td>38 (25.0)</td>
<td>0.07</td>
</tr>
<tr>
<td><strong>Biological variables</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak creatine kinase (IU/L)</td>
<td>1860 ± 1568</td>
<td>2220 ± 2202</td>
<td>0.10</td>
</tr>
<tr>
<td>Creatine kinase (at 24 h) (IU/L)</td>
<td>1047 ± 907</td>
<td>1057 ± 928</td>
<td>0.90</td>
</tr>
<tr>
<td>Peak troponin I (ng/mL)</td>
<td>41.8 ± 68.7</td>
<td>57.9 ± 132.0</td>
<td>0.18</td>
</tr>
<tr>
<td>Troponin I (at 24 h) (ng/mL)</td>
<td>23.6 ± 34.3</td>
<td>30.6 ± 87.3</td>
<td>0.36</td>
</tr>
</tbody>
</table>

Data presented as mean ± SD or number (%) of patients. PCI: percutaneous coronary intervention; TIMI: thrombolysis in myocardial infarction.

Figure 3. Prepercutaneous coronary intervention (PCI) epicardial flow and 60 min post-PCI complete ST-segment resolution with catheterization laboratory (cath lab) versus prehospital tirofiban administration. TIMI grade 2–3 flow at first angiography and complete ST-segment resolution 1 h after PCI in patients who were managed within 100 min of symptom onset (left part) and later (right part) according to cath-lab (yellow) or prehospital (orange) tirofiban administration. TIMI: thrombolysis in myocardial infarction.

Safety and in-hospital outcomes

Few adverse events occurred in the study. Overall in-hospital mortality was 4.4% (14 patients); 3.2% (five patients) in the cath-lab group and 5.5% (nine patients) in the prehospital group (p = 0.26). All but two deaths were cardiovascular. Major bleeding complications occurred in eight (2.5%) patients, two (1.3%) in the cath-lab group and six (3.7%) in the prehospital group (p = 0.28). In-stent thrombosis occurred in three (1.9%) patients in the cath-lab group and in one patient (0.6%) in the prehospital group (p = 0.36). One ischaemic stroke occurred in the cath-lab group and two haemorrhagic strokes in the prehospital group.

Discussion

The main result of this trial is that in patients with STEMI treated in the prehospital setting with a high loading-dose of clopidogrel and who were eligible to undergo primary PCI, prehospital administration of tirofiban was not associated with an increase in the initial patency rate of the culprit artery or a difference in complete ST-segment resolution 1 h after the procedure compared with administration of tirofiban in the cath lab.

In patients undergoing primary PCI, normal (TIMI 3) flow [7] or coronary patency (TIMI 2–3 flow) [8] before PCI have been associated with smaller myocardial infarctions and improved early and late survival. Most studies on early administration of GP IIb/IIIa inhibitors in patients undergoing primary PCI have shown benefits in terms of patency rates [9] compared with later administration. However, all these studies were performed before the widespread use of a high loading-dose of clopidogrel early in the management of these patients. Compared with older studies [3], the blunted difference in patency rate between the early and late groups in our study appears related to a higher patency rate in the late group, reflecting the efficacy on this endpoint of an early high loading-dose of clopidogrel. Similar results were observed in the On-TIME2 and BRAVE-3 studies [5,10].

Resolution of ST-segment elevation after fibrinolytic therapy has been considered a marker of epicardial, microvascular and tissue-level reperfusion. In AGIR2, 1 h after the procedure, rates of complete ST-segment resolution on the electrocardiogram were similar in both groups. These results contrast with those of the On-TIME2 study that had shown improved ST-segment resolution in the early
tirofiban group [5]. In On-TIME2, one-third of patients in the control group received tirofiban and it was administered after angiography. In AGIR2, all patients in the cath-lab group had high-bolus tirofiban administered before vascular access. Time from angiography to PCI was not registered in our study, but we know from the ongoing registry in the RESCUe network, which is recruiting the same population, that this delay is 15 min (median, unpublished data). Therefore, most patients in AGIR2 had GP IIb/IIIa inhibitors on board at least 20 min before PCI. This delay is enough to allow adequate platelet inhibition by high bolus-dose tirofiban and might explain the similar rates in complete ST-segment resolution [11—13].

The systematic use of GP IIb/IIIa inhibitors in STEMI had been questioned by the negative results of the BRAVE-3 [10] and FINESSE [14] studies and the ambivalent results of the On-TIME2 study [5]. However, a subpopulation (those managed very early) could benefit from the early initiation strategy. In AGIR2, shorter delays from onset of chest pain to tirofiban initiation and longer duration of treatment seem to improve pre-PCI rates of ST-segment resolution and coronary patency. Delays to diagnosis have also been found to influence outcomes with eptifibatide [15] and abciximab [10]. In patients pretreated with a 600 mg loading dose of clopidogrel, timing of the initiation of the GP IIb/IIIa inhibitor in relation to symptom onset might be critical for preprocedural endpoints, but its significance on postprocedural outcome is uncertain.

Our study has several limitations. It was open-label and data on angiograms were investigator-reported. To compensate for these limitations, we restricted our analysis to the patency rate (TIMI 2—3 flow), which is a more robust endpoint regarding interobserver variability. The initial sample size calculation rested on data that were available in 2006 when the study was designed. Results of the BRAVE-3 [10] and On-TIME2 [5] studies were not available at that time. The higher than expected rate of patency in the late tirofiban group, similar to the one observed in the OnTime-2 study, lowered the power of the study to detect a difference.

Conclusions and clinical implications

In patients with acute myocardial infarction managed in the prehospital setting with a 600 mg loading dose of clopidogrel, immediate initiation of tirofiban did not improve significantly preprocedural or postprocedural patency and ST-segment resolution. These results do not support the need to initiate GP IIb/IIIa inhibitor therapy in all patients in the prehospital setting. Further studies could help to clarify the benefit of GP IIb/IIIa initiation in patients managed very early in the prehospital setting.

Conflict of interest statement

The authors have no conflict of interest to declare.

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Appendix A.

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