Efficacy and Safety of Glycoprotein IIb/IIIa Inhibitors on Top of Ticagrelor in STEMI: A Subanalysis of the ATLANTIC Trial


1 Department of Cardiology, Isala, Zwolle, The Netherlands
2 Cardiovascular Department, University of Trieste, Trieste, Italy
3 SAMU 93, Hôpital Avicenne, Bobigny, France
4 ACTION Study Group, Pitié-Salpêtrière Hospital (AP-HP), Sorbonne University, Paris, France
5 Department of Cardiology, St. Antonius Hospital, Nieuwegein, The Netherlands
6 Department of Cardiology, Odense University Hospital, Odense, Denmark
7 Cardiovascular Department, Azienda Ospedaliera, Toscana Sudest, Arezzo, Italy
8 Division of Cardiology, Southlake Regional Health Centre, University of Toronto, Toronto, Canada
9 Heart Disease Institute, Bellvitge University Hospital, IDIBELL, University of Barcelona, Barcelona, Spain
10 Centre Hospitalier Universitaire Frantz Fanon, Bli, Algeria
11 Terrence Donnelly Heart Centre, St. Michael’s Hospital, University of Toronto, Toronto, Canada
12 Department of Cardiology, Royal Brisbane and Women’s Hospital, Brisbane, QLD, Australia
13 3rd Department of Medicine, Cardiology and Intensive Care Medicine, Wilhelmenspital , Medical School, Sigmund Freud University, Vienna, Austria

Address for correspondence Renicus S. Hermanides, MD, PhD, Dr. van Heesweg 2, 8025 AB Zwolle, Postbus 10400, 8000 GK Zwolle, The Netherlands (e-mail: r.s.hermanides@isala.nl).

14 Department of Cardiology, Linköping University, Linköping, Sweden
15 Department of Medical and Health Sciences, Linköping University, Linköping, Sweden
16 Heart and Vascular Center, Semmelweis University, Budapest, Hungary
17 Department of Infection, Immunity and Cardiovascular Disease, University of Sheffield, Sheffield, United Kingdom
18 Klinikum Ludwigshafen und Institut für Herzinfarktforschung, Ludwigshafen, Germany
19 Rijnstate Hospital, Arnhem, The Netherlands
20 ACTION Study Group, Statistical Unit, Lariboisière Hospital (AP-HP), Paris VII University, Paris, France
21 Kerckhoff Campus, University of Giessen, Bad Nauheim, Germany
22 Department of Cardiology, Zuyderland Medical Center, Heerlen, The Netherlands
23 Department of Cardiology, Maastricht University Medical Center, Maastricht, The Netherlands

Abstract

Keywords

► glycoprotein IIb/IIIa inhibitors
► primary percutaneous coronary intervention
► STEMI
► ticagrelor
► bailout
► tirofiban
► epitifibatide
► abciximab

Background Glycoprotein IIb/IIIa inhibitors (GPIs) in combination with clopidogrel improve clinical outcome in ST-elevation myocardial infarction (STEMI); however, finding a balance that minimizes both thrombotic and bleeding risk remains fundamental. The efficacy and safety of GPI in addition to ticagrelor, a more potent P2Y12-inhibitor, have not been fully investigated.

Methods 1,630 STEMI patients who underwent primary percutaneous coronary intervention (PCI) were analyzed in this subanalysis of the ATLANTIC trial. Patients were divided in three groups: no GPI, GPI administration routinely before primary PCI, and GPI administration in bailout situations. The primary efficacy outcome was a composite of death, myocardial infarction, urgent target revascularization, and definite stent thrombosis at 30 days. The safety outcome was non-coronary artery bypass graft (CABG)-related PLATO major bleeding at 30 days.

Accepted after revision September 7, 2019
Results  Compared with no GPI ($n = 930$), routine GPI ($n = 525$) or bailout GPI ($n = 175$) was not associated with an improved primary efficacy outcome ($4.2\%$ no GPI vs. $4.0\%$ routine GPI vs. $6.9\%$ bailout GPI; $p = 0.58$). After multivariate analysis, the use of GPI in bailout situations was associated with a higher incidence of non-CABG-related bleeding compared with no GPI (odds ratio [OR] $2.96$, $95\%$ confidence interval [CI] $1.32–6.64$; $p = 0.03$). However, routine GPI use compared with no GPI was not associated with a significant increase in bleeding (OR $1.78$, $95\%$ CI $0.88–3.61$; $p = 0.92$).

Conclusion  Use of GPIs in addition to ticagrelor in STEMI patients was not associated with an improvement in 30-day ischemic outcome. A significant increase in 30-day non-CABG-related PLATO major bleeding was seen in patients who received GPIs in a bailout situation.

Introduction

Fast and adequate platelet inhibition is an important therapeutic goal in the treatment of patients with ST-elevation myocardial infarction (STEMI). Glycoprotein IIb/IIIa inhibitors (GPIs) are used in addition to P2Y12 inhibitors to inhibit platelet aggregation in STEMI, but their role in contemporary practice is uncertain.

Previous trials studied the influence of GPI in STEMI patients receiving clopidogrel or ticlopidine. A meta-analysis of abciximab use in STEMI (ISAR-2, ADMIRAL, ACE trial) with a follow-up of 3 years showed an association with a significant and persistent reduction on hard clinical endpoints (in the composite of mortality and reinfarction) without an increase in major bleeding.

In another trial, abciximab added to ticlopidine reduced 30-day major adverse cardiac events, but did not reduce target vessel revascularization or angiographic restenosis after 1-year of follow-up in STEMI. Trials which included the more potent P2Y12 inhibitors in acute coronary syndrome (ACS) patients, also showed no significant benefits of GPI use on ischemic endpoints.

GPI in addition to heparin have also been studied in comparison to bivalirudin. A pooled analysis of the EURO- MAX and HORIZONS-AMI trials showed a lower rate of stent thrombosis but higher rates of mortality and bleeding in STEMI patients treated with heparin and GPI compared with patients who received bivalirudin. In a post hoc analysis of the MATRIX trial of patients with ACS, GPI in addition to heparin showed no significant differences on hard ischemic endpoints and stent thrombosis but an increase in nonaccess site-related bleedings compared with bivalirudin alone or heparin alone.

Timing of GPI administration is important and has been subject of research. Early administration of GPI tends to improve coronary patency with improved myocardial tissue perfusion, and lower incidences of early stent thrombosis and mortality. A subanalysis of the ON-TIME 2 trial showed that routine prehospital treatment with tirofiban was less likely to result in a bailout situation.

Although some trials suggest beneficial effects of GPI in STEMI, routine use of GPI is no longer recommended in European and American guidelines with the newer P2Y12 inhibitors available. This may be partly due to the assumption that ticagrelor and prasugrel yield rapid onset of potent P2Y12 inhibition, but it is now recognized that their onset of action may be delayed in STEMI patients partly as a consequence of opiate administration. Moreover, the efficacy and safety of GPI on top of more potent P2Y12 inhibitors, like ticagrelor, have not fully been investigated yet. This subanalysis of the ATLANTIC trial aims to evaluate GPI use in ticagrelor-treated STEMI patients.

Methods

Study Design

The ATLANTIC trial was an international, randomized, double-blind study (NCT01347580). Patients diagnosed with STEMI in the ambulance were randomized to receive either prehospital (in the ambulance) or inhospital (at the catheterization laboratory) treatment with $180\,\text{mg}$ loading dose of ticagrelor, in addition to aspirin and unfractionated heparin or enoxaparin. The trial design and main results have been published.

In this subgroup analysis, only STEMI patients who underwent primary percutaneous coronary intervention (PCI) were selected to evaluate the association of GPI use on clinical outcome.

Study Procedures

Patients in the prehospital group received $180\,\text{mg}$ ticagrelor before transfer in the ambulance followed by matching placebo at the time of arrival in the catheterization laboratory. Patients in the inhospital group received placebo before transfer in the ambulance followed by $180\,\text{mg}$ ticagrelor in the catheterization laboratory. Following primary PCI, all patients received ticagrelor $90\,\text{mg}$ twice daily for at least 30 days, up to a maximum of 12 months. Use of GPI at arrival in the absence or in the catheterization laboratory was at the discretion of the physician and had to be identified as a routine GPI strategy (GPI start before primary PCI) or as bailout GPI (use during or after primary PCI). Bailout GPI use could be given for the following predefined indications: decrease in Thrombolyis In Myocardial Infarction (TIMI) flow grade (TIMI flow grades of 0–2 or...
slow reflow), dissection with decreased flow, distal embolization, side branch closure, abrupt closure of the culprit vessel, clinical instability, and prolonged ischemia. By study protocol, use of GPI during transfer was discouraged.

All patients in this subanalysis underwent coronary angiography and primary PCI. Patient outcomes were stratified into three GPI categories: no GPI, routine GPI, and bailout GPI.

Study Endpoints
The primary efficacy endpoint of this subanalysis of the ATLANTIC trial was the composite of major adverse cardiovascular clinical events defined as death, myocardial infarction, stroke, urgent revascularization, or acute definite stent thrombosis at 30 days.

The primary safety endpoint was 30-day non-coronary artery bypass graft (CABG)-related PLATO major bleeding.

Centralized, blinded reviews of angiographic and electrocardiogram recordings were conducted by Cardialysis Core Laboratory services (Rotterdam, the Netherlands) and eResearch Technology (Peterborough, United Kingdom) respectively. An independent adjudication committee, whose members were unaware of the treatment assignments, reviewed the clinical endpoints, except deaths and minimal bleeding events.

Statistical Analysis
Patients were analyzed in the following subgroups: no GPI use, routine GPI use before start of primary PCI, or bailout GPI use. Continuous variables are presented as mean and standard deviation or median and interquartile range, and compared using Kruskal-Wallis test. Categorical variables are presented as numbers and percentages and compared using Fisher’s exact test or Pearson’s chi-square test. Efficacy and safety endpoints were analyzed using Fisher’s exact test or Pearson’s chi-square test. Univariate and multivariate analyses were performed for the composite endpoint of death, myocardial infarction, stroke, urgent target vessel revascularization and stent thrombosis, and non-CABG-related major PLATO bleeding.

In a multivariate logistic regression model for testing the association between GPI use and efficacy endpoints, age group (< 75, ≥ 75 years), sex, arterial access, thrombus aspiration, myocardial infarction, PCI with stent, drug-eluting stent, bare metal stent, and intravenous anticoagulant during primary PCI were forced into the model. The 95% confidence interval (CI) for the odds ratio (OR) was calculated.

The significance level was set at p-value of < 0.05. All tests were performed with SAS version 9.4 (SAS Institute Inc, Cary, North Carolina, United States).

Results
No GPI versus Routine GPI versus Bailout GPI
Patient Characteristics
Of 1,630 STEMI patients who underwent primary PCI, 525 patients (32.2%) received routine GPI, 175 patients (10.7%) received bailout GPI, and 930 patients (57.1%) did not receive GPI (Fig. 1). Of patients who received GPI, 53% received abciximab, 26% received eptifibatide, and 21% tirofiban. The descriptive analysis of patients with routine GPI, bailout GPI, or without GPI is shown in Tables 1 and 2. Patients treated with routine GPI had more frequently radial access (65.5% for no GPI vs. 73.9% for routine GPI vs. 60.6% for bailout GPI, p < 0.01), and more frequently use of enoxaparin (25.2% vs. 32.6% vs. 22.9%, p < 0.01). In the bailout GPI patients, less stenting occurred (95.4% vs. 93.5% vs. 90.3%, p = 0.02), but thrombus aspiration was more often performed (50.3% vs. 66.7% vs. 70.3%, p < 0.01). Intravenous anticoagulant during hospitalization (90.6% vs. 91.0% vs. 81.7%, p < 0.01) was less often administered in patients receiving bailout GPI. Morphine use was similar in all subgroups (50.2% vs. 52.9% vs. 56.7%, p = 0.30).

Angiographic and Electrocardiographic Outcome
Bailout GPI patients more often had an occluded infarct-related vessel (TIMI 0–2) before PCI (19.3% vs. 11.2% vs. 8.9%, p < 0.01) and less often had TIMI 3 flow postprimary PCI (16.8% vs. 19.5% vs. 26.6%; p = 0.01).

Before PCI, the bailout GPI group showed more frequently absence of ST-segment resolution (85.3% vs. 87.8% vs. 93.3%; p = 0.02). After primary PCI, no significant difference in ST-segment resolution was seen (44.8% vs. 43.9% vs. 50.0%; p = 0.40 in univariate analysis and p = 0.32 in multivariate analysis).

In patients with TIMI flow grade 0 before PCI, routine GPI was not associated with TIMI 3 flow grade post-PCI (OR 1.20 [95% CI 0.84–1.71], p = 0.32) or ST-resolution (OR 1.00 [95% CI 0.74–1.34], p = 0.99). Bailout GPI was associated with TIMI 3 flow after PCI (OR 1.78 [95% CI 1.11–2.86], p = 0.02), but not with ST-resolution (OR 0.98 [95% CI 0.65–1.49], p = 0.93) in this subgroup.

Efficacy and Safety of GPI

Thrombotic Events
Univariate (4.2% vs. 4.0% vs. 6.9%; p = 0.26) and multivariate analysis (p = 0.58) showed no association between no GPI, routine GPI, and bailout GPI, and the primary endpoint, the composite of death, myocardial infarction, stroke, urgent revascularization, and definite stent thrombosis at 30 days (Table 3). Kaplan–Meier curves are shown in Fig. 2. A lower percentage of stent thrombosis was observed in patients with bailout GPI than in those with no GPI (5.4% vs. 7.4% vs. 11.5%, respectively) in patients with TIMI 3 flow (p = 0.01).
## Table 1 Baseline characteristics of patients receiving no GPI versus routine GPI versus bailout GPI

<table>
<thead>
<tr>
<th></th>
<th>No GPI  \ N = 930</th>
<th>Routine GPI  \ N = 525</th>
<th>Bailout GPI  \ N = 175</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median, Q1–Q3)</td>
<td>61.0 (52.0–69.0)</td>
<td>59.0 (52.0–69.0)</td>
<td>59.0 (52.0–69.0)</td>
<td>0.14</td>
</tr>
<tr>
<td>Sex, male</td>
<td>733 (78.8%)</td>
<td>447 (85.1%)</td>
<td>141 (80.6%)</td>
<td>0.01</td>
</tr>
<tr>
<td>BMI ≥30 kg/m²</td>
<td>191 (20.5%)</td>
<td>92 (17.5%)</td>
<td>40 (22.9%)</td>
<td>0.22</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>130 (14.0%)</td>
<td>64 (12.2%)</td>
<td>20 (11.4%)</td>
<td>0.49</td>
</tr>
<tr>
<td>Hypertension</td>
<td>403 (43.3%)</td>
<td>205 (39.0%)</td>
<td>69 (39.4%)</td>
<td>0.24</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>334 (35.9%)</td>
<td>189 (36.0%)</td>
<td>52 (29.7%)</td>
<td>0.26</td>
</tr>
<tr>
<td>History</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>88 (9.5%)</td>
<td>28 (5.3%)</td>
<td>12 (6.9%)</td>
<td>0.02</td>
</tr>
<tr>
<td>PCI</td>
<td>72 (7.7%)</td>
<td>34 (6.5%)</td>
<td>10 (5.7%)</td>
<td>0.50</td>
</tr>
<tr>
<td>CABG</td>
<td>6 (0.6%)</td>
<td>3 (0.6%)</td>
<td>0 (0.0%)</td>
<td>0.79</td>
</tr>
<tr>
<td>Chronic renal disease</td>
<td>12 (1.3%)</td>
<td>11 (2.1%)</td>
<td>1 (0.6%)</td>
<td>0.33</td>
</tr>
<tr>
<td>COPD</td>
<td>37 (4.0%)</td>
<td>22 (4.2%)</td>
<td>6 (3.4%)</td>
<td>0.91</td>
</tr>
<tr>
<td>TIA</td>
<td>10 (1.1%)</td>
<td>3 (0.6%)</td>
<td>1 (0.6%)</td>
<td>0.67</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>11 (1.2%)</td>
<td>5 (1.0%)</td>
<td>0 (0.0%)</td>
<td>0.43</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>3 (0.3%)</td>
<td>0 (0.0%)</td>
<td>1 (0.6%)</td>
<td>0.32</td>
</tr>
<tr>
<td>TIMI risk score</td>
<td></td>
<td></td>
<td></td>
<td>0.24</td>
</tr>
<tr>
<td>0–2</td>
<td>551 (59.2%)</td>
<td>340 (64.8%)</td>
<td>110 (62.9%)</td>
<td></td>
</tr>
<tr>
<td>3–6</td>
<td>364 (39.1%)</td>
<td>178 (33.9%)</td>
<td>61 (34.9%)</td>
<td></td>
</tr>
<tr>
<td>&gt; 6</td>
<td>15 (1.6%)</td>
<td>7 (1.3%)</td>
<td>4 (2.3%)</td>
<td></td>
</tr>
<tr>
<td>Killip class I</td>
<td>855 (91.9%)</td>
<td>479 (91.2%)</td>
<td>155 (93.3%)</td>
<td></td>
</tr>
<tr>
<td>Aspirin use</td>
<td>926 (99.6%)</td>
<td>524 (99.8%)</td>
<td>174 (99.4%)</td>
<td>0.47</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; GPI, glycoprotein IIb/IIIa inhibitor; TIMI, Thrombolysis In Myocardial Infarction; PCI, percutaneous coronary intervention; TIA, transient ischemic event.

## Table 2 Angiographic characteristics and concomitant use of medication of patients receiving no GPI versus routine GPI versus bailout GPI

<table>
<thead>
<tr>
<th></th>
<th>No GPI  \ N = 930</th>
<th>Routine GPI  \ N = 525</th>
<th>Bailout GPI  \ N = 175</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial access</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Femoral</td>
<td>315 (33.9%)</td>
<td>136 (25.9%)</td>
<td>68 (38.9%)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Radial</td>
<td>609 (65.5%)</td>
<td>388 (73.9%)</td>
<td>106 (60.6%)</td>
<td></td>
</tr>
<tr>
<td>PCI with stenting</td>
<td>887 (95.4%)</td>
<td>491 (93.5%)</td>
<td>158 (90.3%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Drug-eluting stent</td>
<td>571 (61.4%)</td>
<td>284 (54.1%)</td>
<td>91 (52.0%)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Bare metal stent</td>
<td>330 (35.5%)</td>
<td>218 (41.5%)</td>
<td>69 (39.4%)</td>
<td>0.07</td>
</tr>
<tr>
<td>Thrombus aspiration</td>
<td>468 (50.3%)</td>
<td>350 (66.7%)</td>
<td>123 (70.3%)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Absence of TIMI flow grade 3 at angiography</td>
<td>734 (80.7%)</td>
<td>454 (88.8%)</td>
<td>159 (91.9%)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Absence of ST-segment elevation resolution</td>
<td>689 (85.3%)</td>
<td>410 (87.8%)</td>
<td>140 (93.3%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Intravenous anticoagulant</td>
<td>843 (90.6%)</td>
<td>478 (91.0%)</td>
<td>143 (81.7%)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Heparin</td>
<td>632 (68.0%)</td>
<td>385 (73.3%)</td>
<td>118 (67.4%)</td>
<td>0.08</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>234 (25.2%)</td>
<td>171 (32.6%)</td>
<td>40 (22.9%)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Bivalirudin</td>
<td>328 (35.3%)</td>
<td>4 (0.8%)</td>
<td>24 (13.7%)</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

Abbreviations: GPI, glycoprotein IIb/IIIa inhibitor; TIMI, Thrombolysis In Myocardial Infarction; PCI, percutaneous coronary intervention.
### Table 3 Efficacy and safety endpoints for no GPI versus routine GPI versus bailout GPI

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>No GPI N = 930</th>
<th>Routine GPI N = 525</th>
<th>Bailout GPI N = 175</th>
<th>p-Value&lt;sup&gt;a&lt;/sup&gt;</th>
<th>p-Value&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite of mortality, myocardial infarction, stroke, urgent revascularization, stent thrombosis</td>
<td>39 (4.2%)</td>
<td>21 (4.0%)</td>
<td>12 (6.9%)</td>
<td>0.26</td>
<td>0.58</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>22 (2.4%)</td>
<td>9 (1.7%)</td>
<td>7 (4.0%)</td>
<td>0.20</td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>9 (1.0%)</td>
<td>6 (1.1%)</td>
<td>2 (1.1%)</td>
<td>0.82</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>2 (0.2%)</td>
<td>1 (0.2%)</td>
<td>2 (1.1%)</td>
<td>0.13</td>
<td></td>
</tr>
<tr>
<td>Urgent revascularization</td>
<td>7 (0.8%)</td>
<td>4 (0.8%)</td>
<td>2 (1.1%)</td>
<td>0.77</td>
<td></td>
</tr>
<tr>
<td>Stent thrombosis</td>
<td>10 (1.1%)</td>
<td>1 (0.2%)</td>
<td>2 (1.1%)</td>
<td>0.13</td>
<td></td>
</tr>
<tr>
<td>Non-CABG-related major PLATO bleeding</td>
<td>18 (1.9%)</td>
<td>16 (3.1%)</td>
<td>11 (6.3%)</td>
<td>&lt; 0.01</td>
<td>0.03</td>
</tr>
<tr>
<td>Absence of TIMI 3 flow post-PCI</td>
<td>147 (16.8%)</td>
<td>97 (19.5%)</td>
<td>45 (26.6%)</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>Absence of ST-segment elevation resolution ≥70% post-PCI</td>
<td>371 (44.8%)</td>
<td>205 (43.9%)</td>
<td>80 (50.0%)</td>
<td>0.40</td>
<td>0.32</td>
</tr>
</tbody>
</table>

Abbreviations: CABG, coronary artery bypass grafting; GPI, glycoprotein IIb/IIIa inhibitor; PCI, percutaneous coronary intervention; TIMI, Thrombolysis In Myocardial Infarction.

<sup>a</sup>Univariate analysis.

<sup>b</sup>Multivariate logistic regression with variables forced in the model: age group (< 75 years, ≥75 years), sex, arterial access, thrombus aspiration, myocardial infarction in history, PCI with stenting, drug-eluting stent, bare metal stent, median aspirin dose during maintenance period, and intravenous anticoagulant during hospitalization.

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**Fig. 2** Kaplan–Meier curve of the primary efficacy endpoint specified for no glycoprotein IIb/IIIa inhibitor (GPI), routine GPI, and bailout GPI.
when routine GPI was administered, although this finding was not statistically significant (10/930 [1.0%] vs. 1/525 [0.2%] vs. 2/175 [1.1%], \( p = 0.13 \)).

**Bleeding Events**

There was an association between no GPI, routine GPI, and bailout GPI, and non-CABG-related major PLATO bleeding events in univariate (1.9% vs. 3.1% vs. 6.3%, \( p < 0.01 \)) and multivariate analysis (\( p = 0.03 \)) (Table 3 and Fig. 3). Significant differences in minor PLATO bleeding events between no GPI, routine GPI, and bailout GPI were not observed (≤ 48 hours 1.0% vs. 1.3% vs. 0.6%, \( p = 0.72 \); > 48 hours 1.2% vs. 1.0% vs. 0.0%, \( p = 0.58 \)).

Bailout use of GPI was associated with a higher incidence of 30-day non-CABG-related major bleeding when compared with no GPI use in univariate analysis (OR 3.4 [95% CI 1.58–7.33], \( p < 0.01 \)) and multivariate analysis (OR 2.96 [95% CI 1.32–6.64], \( p = 0.03 \)).

Patients with femoral artery access reached the primary safety outcome of non-CABG-related major bleeding more often than patients with radial access (5.0% vs. 1.6%, \( p < 0.01 \), Fig. 4).

**Effect on TIMI Flow and ST-Resolution**

TIMI flow grade 0 before PCI was seen in 517 patients (56%) without GPI, in 344 patients (66%) with routine GPI, and in 127 patients (73%) with bailout GPI. In patients with TIMI 0 flow before PCI, routine GPI was not associated with the primary efficacy endpoint (OR 0.82 [95% CI 0.42–1.64], \( p = 0.58 \)) or major bleeding (OR 1.86 [95% CI 0.81–4.39], \( p = 0.15 \)). Bailout GPI was also not associated with the primary efficacy endpoint (OR 1.26 [95% CI 0.55–2.89], \( p = 0.58 \)), but was associated with major bleeding (OR 3.18 [95% CI 1.24–8.15]; \( p = 0.02 \)).

No interaction between the prehospital and inhospital administration of ticagrelor and GPI use on the primary efficacy and safety endpoints (respectively \( p = 0.09 \) and...
was observed. Also, the time from symptom onset to administration of ticagrelor was similar in the three subgroups (median [Q1-Q3]: 113 [75–180] vs. 103 [72–170] vs. 109.5 [77.5–170] minutes, \( p = 0.18 \)).

Analyses of patients with GPI versus without GPI can be found in the *Supplementary Tables S1–S3* (available in the online version).

**Discussion**

This subanalysis of the ATLANTIC trial describes the clinical outcomes associated with GPI use in the setting of the potent P2Y12 inhibitor ticagrelor in STEMI patients. Routine and bailout GPI use were not associated with an improvement in 30-day ischemic outcomes.

Furthermore, bailout GPI use was associated with a higher incidence of 30-day non-CABG-related major PLATO bleeding. These findings provide further insights into the optimization of antiplatelet therapy in STEMI.

Compared with the PLATO trial regarding STEMI patients, use of GPI in our study population was slightly higher (43% vs. 36%). The transition from the clopidogrel era to the potent P2Y12 inhibitor ticagrelor era questions the additional benefit of GPI in STEMI.

**Ischemic Endpoints**

Ticagrelor has a faster onset of action than clopidogrel and is a more potent P2Y12 inhibitor. Thus, early initiation of GPI in STEMI treated added to potent P2Y12 inhibition may offer less relative benefit on ischemic endpoints. Routine GPI use was also not associated with a reduction in ischemic outcomes in ACS patients who were treated with clopidogrel or ticagrelor in the TRANSLATE-ACS trial. Although routine GPI use was not associated with reduced ischemic outcomes in this subanalysis of the ATLANTIC trial, a lower percentage of stent thrombosis (statistically nonsignificant) was observed when routine GPI was administered. It might suggest that upfront GPI treatment may still have a role in the treatment of STEMI patients, as suggested in the ON-TIME 2 trial.

The EUROMAX trial did not find differences between bivalirudin versus heparin with/without GPI on mortality and acute stent thrombosis in STEMI patients treated with clopidogrel, ticagrelor, or prasugrel. This was contradictory to the results of the HORIZONS-AMI trial including a reduction in mortality for bivalirudin. This trial consisted of STEMI patients who were treated with ticlopidine or clopidogrel. However, a post hoc analysis showed that the novel P2Y12 inhibitors in the EUROMAX trial did not mitigate acute stent thrombosis. A post hoc analysis of the MATRIX trial also did not observe significant differences on ischemic endpoints of heparin with/without GPI versus bivalirudin.

**Bleeding**

In this subanalysis, a significant increase in non-CABG-related major bleeding was seen in patients receiving GPI in a bailout situation. Patients requiring bailout GPI are known to be a vulnerable population with worse prognosis compared with patients without a bailout situation. This group of patients often receives an aggressive antiplatelet strategy in response to a high thrombus burden. However, the addition of a GPI in this patient population has never been fully investigated. This ATLANTIC subanalysis found that GPI use, especially in bailout situations, was associated with an increased risk of bleeding. This was also illustrated in patients with TIMI flow grade 0 at angiography by the association of bailout GPI use and absence of TIMI 3 flow post-PCI and by the association of bailout GPI use and bleeding.

As exhibited in this subanalysis, use of radial artery access was associated with less bleeding complications than a femoral access site. Therefore, in agreement with existing literature, this suggests that the radial artery as access site should be preferred over the femoral artery to reduce bleeding complications.

**Early and Efficient Platelet Inhibition**

Time to adequate treatment including platelet inhibition is important and is inversely related to outcome. Effie cient platelet inhibition can be achieved by early administration of potent P2Y12 inhibitors or GPI, and crushing of oral P2Y12 receptor inhibitors further reduces the time to adequate platelet inhibition.

The PRIVATE-ATLANTIC trial, an ancillary study of the ATLANTIC trial, demonstrated that the level of P2Y12-mediated platelet inhibition was suboptimal on arrival in the cath laboratory and was only efficient 3 hours after the loading dose in the prehospital administration group and after 7 hours in the in-hospital administration group of the loading dose of ticagrelor, highlighting the need for a better platelet inhibition in the acute setting. Also, morphine use might reduce platelet inhibition. However, these effects were not observed in this analysis, since morphine use was similar in all three subgroups.

**GPI and Outcome**

Patients receiving bailout GPI were less likely to have TIMI 3 flow postprimary PCI and this was associated with an increase in the use of thrombus aspiration. The potential benefit of GPI may rely on the timing and route of administration. This substudy of the ATLANTIC trial did not investigate the effects of prehospital administration of GPI as studied in the ON-TIME 2 trial or intracoronary use of GPI like the INFUSE-AMI trial.

The need for bailout GPI already suggests a clinical situation in which the thrombotic state is higher and poorer outcomes are expected. Although conflicting evidence in literature, the ON-TIME 2 trial showed that routine GPI was less likely to result in a bailout situation and therefore its role should be further delineated.

The European Society of Cardiology guidelines recommend GPI in bailout situations (class of recommendation IIa, level of evidence C). A retrospective study using propensity score matching suggests beneficial effects of bailout GPI on long-term mortality. A trial randomizing GPI compared with no GPI in bailout situations may further improve our knowledge of the potential beneficial effects of bailout GPI, though this kind of trial design may raise ethical concerns.
Moreover, further research is warranted in our current era with availability of alternative intravenous platelet inhibitors, such as bivalirudin and cangrelor, to delineate the role of GPI and its timing of administration in STEMI patients.

Limitations
This was a post hoc analysis and therefore should be viewed as hypothesis generating. Furthermore, use of GPI was not randomized, which can introduce potential bias.

Although the indication for routine GPI was left to the discretion of the operator, and although the indication for using bailout GPI was predefined, the decision to use bailout GPI in this trial was still left to the discretion of the treating cardiologist. Moreover, routine use of GPI was discouraged in the ATLANTIC trial, since GPI could have impacted upon the outcomes evaluated in our comparison of early versus later administration of ticagrelor. Further, prehospital or intracoronary GPI were not studied in the ATLANTIC trial. Finally, the absolute numbers of ischemic and bleeding endpoints were small such that the robustness of our findings is limited.

Conclusion
GPIs in addition to the potent P2Y12 inhibitor ticagrelor in STEMI patients were not associated with an improvement of 30-day clinical outcome and an increase in 30-day non-CABG-related major bleeding was seen in patients who received GPIs in a bailout situation.

What is known about this topic?
• Fast and adequate platelet inhibition is an important therapeutic goal in the treatment of patients with ST-elevation myocardial infarction. Glycoprotein IIb/IIIa inhibitors (GPIs) are used in addition to P2Y12 inhibitors to inhibit platelet aggregation in STEMI, but their role in contemporary practice is uncertain.
• GPI in combination with clopidogrel improves clinical outcomes; however, finding a balance that minimizes both thrombotic and bleeding risk remains fundamental.
• Although some trials suggest beneficial effects of GPI in STEMI, routine use of GPI is no longer recommended in European and American guidelines with the newer P2Y12 inhibitors available.

What does this paper add?
• The efficacy and safety of GPI on top of more potent P2Y12 inhibitors, like ticagrelor, have not fully been investigated yet. This subanalysis of the ATLANTIC trial aims to evaluate GPI use in ticagrelor-treated STEMI patients.
• Use of routine and bailout GPI in ticagrelor-treated STEMI patients is not associated with an improvement in ischemic endpoints at 30 days of follow-up.
• Bailout GPI use is associated with an increase in non-CABG-related bleeding.

Conflict of Interest
A.W.J.v’t H. reports institutional fees and nonfinancial support from AstraZeneca and grants and Medtronic. C. W.H. reports institutional fees and personal fees from AstraZeneca. R.F.S. reports institutional research grants from AstraZeneca and PlaqueTec; consultancy fees from AstraZeneca, Avacta, Bayer, Bristol Myers Squibb/Pfizer, Haemonetics, Idorsia, Novartis, PlaqueTec, and Thromboserin; and honoraria from AstraZeneca and Bayer. J.F.L. reports unrestricted grants from Medtronic, Abbott, Boston Scientific, Biotronik, and Terumo. A.C. reports institutional research grants from Abbott Vascular, Boston Scientific, Cordis, Medtronic, and Orbus Neich, and consulting/lecture fees from Abbott Vascular, AstraZeneca, Biotronik, Ferrer International, Medtronic, and Terumo. U.Z. reports grants and personal fees from AstraZeneca during the conduct of the study, personal fees from Bayer, grants and personal fees from BMS, grants and personal fees from Daiichi Sankyo, personal fees from Boehringer Ingelheim, personal fees from Medicines Company, personal fees from Sanofi, grants and personal fees from Novartis, outside the submitted work. M.J. reports lecture fees from AstraZeneca and Pfizer. K.H. reports lecture fees from AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Daiichi Sankyo, Sanofi Aventis, and the Medicines Company. J.S. reports the following disclosures during the past two years: Consulting fees from AstraZeneca, Bayer, Boehringer Ingelheim, CSL Behring, Gilead Science, and Sanofi-Aventis; Speaker honorariums from AstraZeneca, Amgen, Bayer, Algorhythm, and Sanofi-Aventis; and travel supports from Amgen, AstraZeneca, Bayer, and Bristol-Meyer Squibb. S.G.G. has received research grant support and/or speaker/consulting honoraria from AstraZeneca, Bayer Bristol Myers Squibb, Daiichi Sankyo, Eli Lilly, Fenix Group Internation, and Sanofi. L.B. reports lecture fees from AstraZeneca, Bayer, Amgen, Daiichi Sankyo, and Sanofi Aventis.

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