Clinical cases of Zalunfiban use

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### Potential conflicts of interest

<table>
<thead>
<tr>
<th>Nature of Financial Relationship</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grant/Research Support</td>
<td>ZonMw, AstraZeneca, Daichi Sankyo</td>
</tr>
<tr>
<td>Consultant Fees/Honoraria</td>
<td>AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Pfizer, CeleCor</td>
</tr>
<tr>
<td>Individual Stock(s)/Stock Options</td>
<td>None</td>
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<tr>
<td>Royalties/Patent Beneficiary</td>
<td>None</td>
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<tr>
<td>Executive Role/Ownership Interest</td>
<td>None</td>
</tr>
<tr>
<td>Other Financial Benefit</td>
<td>None</td>
</tr>
</tbody>
</table>
In the Netherlands:

Most STEMI patients are pre-treated in the ambulance with:

- 500 mg acetylsalicylic acid i.v.
- 180 mg ticagrelor p.o.
- 5000 IU Unfractionated heparin i.v.

### Recommendations

<table>
<thead>
<tr>
<th>Antiplatelet therapy</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin is recommended for all patients without contraindications at an initial oral LD of 150–300 mg (or 75–250 mg i.v.) and an MD of 75–100 mg o.d. for long-term treatment.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Pre-treatment with a P2Y$_{12}$ receptor inhibitor may be considered in patients undergoing a primary PCI strategy.</td>
<td>IIb</td>
<td>B</td>
</tr>
<tr>
<td>Pre-treatment with a GP IIb/IIIa receptor antagonist is not recommended.</td>
<td>III</td>
<td>A</td>
</tr>
</tbody>
</table>

ATLANTIC trial: P2Y12 pre-treatment
Results: No better reperfusion

FABOLUS-FASTER Trial & ON-TIME 2 Trial

Primary Endpoint: IPA% at 30’ with LTA with ADP 20 umol/L

<table>
<thead>
<tr>
<th>Residual ST - deviation (mm)</th>
<th>Placebo</th>
<th>Tirofiban</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Readable ECG</td>
<td>94.1%</td>
<td>95.5%</td>
<td>0.358</td>
</tr>
<tr>
<td>Residual ST - deviation (mm)</td>
<td>4.8 ±6.3</td>
<td>3.3 ± 4.3</td>
<td>0.002</td>
</tr>
<tr>
<td>normal ECG</td>
<td>30.2%</td>
<td>37.3%</td>
<td>0.031</td>
</tr>
<tr>
<td>&gt; 3 mm ST-deviation</td>
<td>44.3%</td>
<td>36.6%</td>
<td>0.026</td>
</tr>
</tbody>
</table>

Gargiulo G et al. Circulation. 2020;142(5):441-454. doi: 10.1161/CIRCULATIONAHA.120.046928
Why routine GP IIb/IIIa antagonists are not recommended by the guidelines?

- All three IIb/IIIa antagonist (abciximab, eptifibatide, and tirofiban) require **intravenous administration**, followed by an ongoing intravenous infusion controlled by a pump, which can be difficult to achieve in the ambulance.
- Due to the **long half-life** they increase bleeding especially in those patients needing urgent CABG.
- Lead to **thrombocytopenia**.
There is a Need for a Better GP IIb/IIIa Antagonist in STEMI

- **As potent** as the IV GP IIb/IIIa antagonists
- **As rapid** as IV GP IIb/IIIa antagonist
- **Shorter duration of action** to limit risk of bleeding
- **Subcutaneous** route (soluble by auto-injector)
- **No thrombocytopenia**

- **SC Zalunfiban** potentially has all these characteristics is being evaluated in the CeleBrate Trial (NCT0825743)
# Two Cases of STEMI with Zalunfiban in the Phase 2 study

<table>
<thead>
<tr>
<th>Patient A</th>
<th>Patient B</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="female.png" alt="Gender" />, 58 y</td>
<td><img src="male.png" alt="Gender" />, 57 y</td>
</tr>
<tr>
<td>Symptom onset 1H 15MIN before presentation</td>
<td>Symptom onset 1H 30 MIN before presentation</td>
</tr>
<tr>
<td>Heavy chest pain, radiation, transpiration</td>
<td>Heavy chest pain, radiation, transpiration, pale, nauseous</td>
</tr>
<tr>
<td>Active smoker</td>
<td>Hypertension, hypercholesterolemia</td>
</tr>
<tr>
<td>BP 113/77, HR, 89/min</td>
<td>BP 161/96, HR 75/min</td>
</tr>
<tr>
<td>In ambulance: ASA, ticagrelor 180 mg oral, UFH 5000 IU</td>
<td>In ambulance: ASA, ticagrelor 180 mg oral, UFH 5000 IU</td>
</tr>
</tbody>
</table>
Diagnostic ECG in the ambulance: patiënt A
Diagnostic ECG in the ambulance: patiënt B
Cath lab: SC administration Zalunfiban in left upper arm ~15 min before CAG

Low dose* (0.75 mg/kg)

High dose (0.110 mg/kg)
# Angiographic assessment*

<table>
<thead>
<tr>
<th></th>
<th>Pre-TIMI flow grade</th>
<th>Pre-TIMI blush grade</th>
<th>Thrombus grade</th>
<th>% platelet inhibition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Case A</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low dose Zalunfiban</td>
<td>0</td>
<td>0</td>
<td>5</td>
<td>76%</td>
</tr>
<tr>
<td><strong>Case B</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High dose Zalunfiban</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>90%</td>
</tr>
</tbody>
</table>

*Angiographic analysis was performed by an independent, blinded, core laboratory*
ECG 30 minutes after PCI: case A (Low dose zalunfiban)

Residual ST-elevation
ECG 30 minutes after PCI: case B (High dose zalunfiban)

No residual ST-elevation
3 cohorts of STEMI patients

**Single subcutaneous injection of RUC-4**

0.075 mg/kg  
* n=8

**Safety review**

0.090 mg/kg  
* n=8

**Safety review**

0.110 mg/kg  
* n=8

**Pharmacodynamic assessment**  
(VerifyNow iso-TRAP)

**Pharmacokinetic assessment**

**Safety outcomes**

- No thrombocytopenia
- Injection site bruises (41%)
- Mild access-site bleeding (22%)
- Severe access-site bleeding (7%)

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Objective
To determine a dose-dependent relationship between zalunfiban given in the cath lab ~15 min before initial angiogram and angiographic indices of reperfusion

Population
Patients in the phase 2 study with definite Type 1 MI (24/27)

Methods
Cochran-Armittage tests were used to assess dose-related trends

Analysis
Angiograms were analyzed by a blinded, independent core laboratory
Phase 2 study: Reperfusion indices pre-PCI

Phase 2 study – PD/PK correlation

Graph A: Cohort 0.075 mg/kg, 0.090 mg/kg, 0.110 mg/kg
- % platelet inhibition vs. Pre-PCI TIMI Flow grade
- R = 0.5, p = 0.018

Graph B: Cohort 0.075 mg/kg, 0.090 mg/kg, 0.110 mg/kg
- Zaluranib concentration (ng/mL) vs. Pre-PCI TIMI Flow Grade
- R = 0.43, p = 0.048

Graph C: Cohort 0.075 mg/kg, 0.090 mg/kg, 0.110 mg/kg
- % platelet inhibition vs. Pre-PCI TIMI Myocardial Perfusion Grade
- R = 0.46, p = 0.024

Graph D: Cohort 0.075 mg/kg, 0.090 mg/kg, 0.110 mg/kg
- Zaluranib concentration (ng/mL) vs. Pre-PCI TIMI Myocardial Perfusion Grade
- R = 0.45, p = 0.037

Graph E: Cohort 0.075 mg/kg, 0.090 mg/kg, 0.110 mg/kg
- % platelet inhibition vs. Pre-PCI TIMI Thrombus Grade
- R = -0.31, p = 0.16

Graph F: Cohort 0.075 mg/kg, 0.090 mg/kg, 0.110 mg/kg
- Zaluranib concentration (ng/mL) vs. Pre-PCI TIMI Thrombus Grade
- R = -0.48, p = 0.022
Conclusion: pre-hospital antiplatelet therapy in STEMI

• Pre-hospital Oral P2Y12-inhibition failed to improve outcome
• Pre-hospital IV GP-IIb/IIIa inhibition improved reperfusion and outcome but has a long half life
• SC Zalunfiban administered in the Cath lab shortly before PCI in a phase 2 study showed promising results, now tested in a large, pre-hospital, phase 3 randomized clinical outcome trial (CELEBRATE\(^1\), NCT04825743)
