Supplementary Table S1  Impact of bivalirudin and UFH on peri-PCI platelet reactivity

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Methods</th>
<th>Outcome</th>
</tr>
</thead>
</table>
| Sibbing et al\(^1\)  
Double blind, randomized | 100 patients pre-treated with 600 mg clopidogrel undergoing elective PCI | Bivalirudin (bolus 0.75 mg/kg plus infusion 1.75 mg/kg/h) versus UFH 140 U/kg during PCI  
Blood was drawn -immediately before PCI -directly after PCI | ADP (5 \( \mu \)M)-induced platelet aggregation [median (IQR)]  
Before PCI:  
Bivalirudin 30.0% (22.8–46.5)  
UFH 32.5% (20.8–48.0), \( p = 0.99 \)  
Directly after PCI:  
Bivalirudin 24.0% (17.8–39.0)  
UFH 29.5% (20.0–49.3)  
Bivalirudin induced further inhibition in ADP-induced platelet inhibition, \( p = 0.012 \)  
No change with UFH  
Similar results were obtained with LTA |
| Schneider and Sobel\(^2\)  
Observational | 10 patients undergoing elective PCI | Pre-treatment with aspirin 325 mg, bivalirudin given during PCI (bolus 0.75 mg/kg plus infusion 1.75 mg/kg/h) and clopidogrel 600 mg immediately after PCI | Platelet function using flow cytometry in the absence of agonist and in the presence of thrombin, ADP, PAF, collagen mimetic convulxin, immediately before and 1 and 2 hours after PCI  
Platelet reactivity was lower after the PCI compared with that in blood taken before PCI |
| Saucedo et al\(^3\)  
Open-label, parallel-group | 28 patients scheduled for PCI | Pre-treatment with aspirin and clopidogrel  
Bivalirudin (bolus 0.75 mg/kg plus infusion 1.75 mg/kg/h) versus UFH 60–70 U/kg | LTA assays 20 \( \mu \)mol of ADP and 5 \( \mu \)mol of TRAP  
No difference in platelet-aggregation inhibition between bivalirudin and UFH in blood samples obtained at baseline and at 10 and 30 minutes, and at 2, 8 and 24 hours |
| Ray et al\(^4\)  
Randomized | 32 ACS patients undergoing PCI | Bivalirudin+ provisional GP IIb/IIIa versus UFH\(^+\) with mandatory GP IIb/IIIa | P-selectin: no change with bivalirudin, significant increase with UFH (\( p < 0.01 \))  
% of platelets binding fibrinogen: no change with bivalirudin, significant increase with UFH (\( p < 0.01 \)) |
| Busch et al\(^5\)  
Randomized | 46 patients undergoing elective PCI | Bivalirudin versus UFH | Bivalirudin compared with UFH reduced post-PCI P-selectin, PAC-1 and GP Ib alpha |
| Kimmelstiel et al\(^6\)  
Observational | 22 patients undergoing elective PCI | Patients pre-treated with aspirin  
At the end of PCI: 600 mg of clopidogrel  
All patients:  
bivalirudin 0.75 mg/kg bolus following infusion of 1.75 mg/kg/h | Blood samples at baseline and 30 minutes after initiation of bivalirudin infusion  
Bivalirudin inhibited thrombin-induced platelet aggregation (94 ± 8 vs. −10 ± 7, \( p < 0.0001 \)), cleavage of PAR-1, collagen-induced platelet pro-coagulant activity (61 ± 24 vs. 50 ± 19, \( p < 0.001 \)) and reduced thrombin levels in plasma by > 50% during PCI |
| Pepke et al\(^7\)  
58 stable CAD patients undergoing PCI | Patients pre-treated with aspirin plus clopidogrel  
Bivalirudin 0.75 mg/kg as bolus following infusion of 1.75 mg/kg/h versus UFH 60–70 U/kg | Bivalirudin:  
Thrombospondin expression ADP-induced:  
7.9 ± 0.7 AU pre- versus 6.2 ± 0.4 AU post-PCI, \( p < 0.01 \)  
TRAP-induced: 15.3 ± 1.1 AU pre- versus 11.8 ± 0.8 AU post-PCI, \( p < 0.01 \)  
No changes in platelet reactivity with UFH |

Abbreviations: ACS, acute coronary syndrome; ADP, adenosine diphosphate; AU, arbitrary units; CAD, coronary artery disease; GP, glycoprotein; LTA, light transmission aggregometry, PAC, anti-platelet antibody that binds to activated platelets; PAF, platelet activating factor; PAR-1, protease-activated receptor-1; PCI, percutaneous coronary intervention; TRAP, thrombin receptor-activating peptide, UFH, unfractionated heparin.
### Supplementary Table S2

Current practice guidelines recommendations on P2Y₁₂ receptor antagonist pre-treatment in ACS patients

<table>
<thead>
<tr>
<th>STEMI</th>
<th>Recommendations</th>
<th>Class</th>
<th>LoE</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction&lt;sup&gt;8&lt;/sup&gt;</td>
<td>A loading dose of a P2Y₁₂ receptor inhibitor should be given as early as possible or at time of primary PCI to patients with STEMI</td>
<td>I</td>
<td>B</td>
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<tr>
<td>2014 ESC/EACTS Guidelines on myocardial revascularization&lt;sup&gt;9&lt;/sup&gt;</td>
<td>It is recommended to give P2Y₁₂ inhibitors at the time of first medical contact</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation&lt;sup&gt;10&lt;/sup&gt;</td>
<td>A potent P2Y₁₂ inhibitor (prasugrel or ticagrelor) or clopidogrel if there are not available or contraindicated, is recommended before (or latest at the time of) PCI</td>
<td>I</td>
<td>A</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>NSTEMI</th>
<th>Recommendations</th>
<th>Class</th>
<th>LoE</th>
</tr>
</thead>
<tbody>
<tr>
<td>2014 ESC/EACTS Guidelines on myocardial revascularization&lt;sup&gt;9&lt;/sup&gt;</td>
<td>Pre-treatment with prasugrel in patients in whom coronary anatomy is not known, is contraindicated</td>
<td>III</td>
<td>B</td>
</tr>
<tr>
<td>2014 AHA/ACC Guideline for the management of patients with non-ST elevation ACS&lt;sup&gt;11&lt;/sup&gt;</td>
<td>A loading dose of a P2Y₁₂ receptor inhibitor should be given before the procedure in patients undergoing PCI with stenting</td>
<td>I</td>
<td>A</td>
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<tr>
<td>2015 ESC Guidelines for the management of ACS in patients w/o persistent ST-segment elevation&lt;sup&gt;12&lt;/sup&gt;</td>
<td>Optimal timing of ticagrelor or clopidogrel: no recommendation for or against pre-treatment with these agents can be formulated</td>
<td></td>
<td></td>
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<tr>
<td>2017 ESC focused update on dual antiplatelet therapy in coronary artery disease in collaboration with EACTS&lt;sup&gt;13&lt;/sup&gt;</td>
<td>Pre-treatment is generally recommended in patients in whom coronary anatomy is known and the decision to proceed to PCI is made</td>
<td>I</td>
<td>A</td>
</tr>
</tbody>
</table>

Abbreviations: ACCF, American College of Cardiology Foundation; ACS, acute coronary syndrome; AHA, American Heart Association; EACTS, European Association for Cardio-Thoracic Surgery; ESC, European Society of Cardiology; LoE, level of evidence; NSTEMI, non-ST segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST segment elevation myocardial infarction.

### References