Choice of Antiplatelets for Acute Coronary Syndromes in 2018
Do we need to individualize?

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Disclosures

SPEAKER: Adam Witkowski

Advisory Board honoraria: AstraZeneca
Speaker fees: AstraZeneca
ACS Pathophysiology
Plaque rupture, thrombosis and microembolisation

Plaque rupture

Thrombus

Inflammation, spasm, endothelial dysfunction

Cutoff

1st embolus

2nd embolus

3rd embolus

Microvascular Obstruction

CK-MB

TnT Curve
P2Y<sub>12</sub> Inhibitors

<table>
<thead>
<tr>
<th></th>
<th>Clopidogrel</th>
<th>Prasugrel</th>
<th>Ticagrelor</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Class</strong></td>
<td>Thienopyridine</td>
<td>Thienopyridine</td>
<td>Triazolopyrimidine</td>
</tr>
<tr>
<td><strong>Reversibility</strong></td>
<td>Irreversible</td>
<td>Irreversible</td>
<td>Reversible</td>
</tr>
<tr>
<td><strong>Activation</strong></td>
<td>Prodrug, limited by metabolism</td>
<td>Prodrug, not limited by metabolism</td>
<td>Active drug</td>
</tr>
<tr>
<td><strong>Onset of effect</strong></td>
<td>2-4 h</td>
<td>30 min</td>
<td>30 min</td>
</tr>
<tr>
<td><strong>Duration of effect</strong></td>
<td>3-10 days</td>
<td>5-10 days</td>
<td>3-4 days</td>
</tr>
<tr>
<td><strong>Withdrawal before major surgery</strong></td>
<td>5 days</td>
<td>7 days</td>
<td>5 days *</td>
</tr>
</tbody>
</table>

2011 ESC Guidelines on NSTE-ACS

* 7 days recommended in Europe
TRITON (2007) and PLATO (2009)

- STEMI and NSTE-ACS:
  - TRITON STEMI 26%
  - PLATO STEMI 37.5%
- Prasugrel in clopidogrel-naive patients, ticagrelor also after clopidogrel (46% of patients)
- Primary end point: cardiovascular death, MI, stroke – significantly reduced in TRITON and PLATO vs clopidogrel


STEMI

Periprocedural and postprocedural antithrombotic therapy in patients undergoing primary percutaneous coronary intervention

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiplatelet therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A potent P2Y_{12} inhibitor (prasugrel or ticagrelor), or clopidogrel if these are not available or are contra-indicated, is recommended before (or at latest at the time of) PCI and maintained over 12 months unless there are contra-indications such as excessive risk of bleeding.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Aspirin (oral or i.v, if unable to swallow) is recommended as soon as possible for all patients without contra-indications.</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>GP IIb/IIIa inhibitors should be considered for bailout if there is evidence of no-reflow or a thrombotic complication.</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>Cangrelor may be considered in patients who have not received P2Y_{12} receptor inhibitors.</td>
<td>IIb</td>
<td>A</td>
</tr>
</tbody>
</table>
Platelet inhibition in NSTE-ACS

**Recommendations**

<table>
<thead>
<tr>
<th>Oral antplatelet therapy</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aspirin</strong> is recommended for all patients without contraindications at an initial oral loading dose of 150–300 mg (in aspirin-naive patients) and a maintenance dose of 75–100 mg daily long-term regardless of treatment strategy.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>A P2Y₁₂ inhibitor is recommended, in addition to aspirin, for 12 months unless there are contraindications such as excessive risk of bleeds.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>• Ticagrelor (180 mg loading dose, 90 mg twice daily) is recommended, in the absence of contraindications, for all patients at moderate- to high risk of ischaemic events (e.g. elevated cardiac troponins), regardless of initial treatment strategy and including those pretreated with clopidogrel (which should be discontinued when ticagrelor is started).</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>• Prasugrel (60 mg loading dose, 10 mg daily dose) is recommended in patients who are proceeding to PCI if no contraindication.</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>• Clopidogrel (300–600 mg loading dose, 75 mg daily dose) is recommended for patients who cannot receive ticagrelor or prasugrel or who require oral anticoagulation.</td>
<td>I</td>
<td>B</td>
</tr>
</tbody>
</table>

P2Y₁₂ Inhibitor administration for a shorter duration of 3–6 months after DES implantation may be considered in patients deemed at high bleeding risk.

It is not recommended to administer prasugrel in patients in whom coronary anatomy is not known.

[www.escardio.org/guidelines](http://www.escardio.org/guidelines)

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Dual antiplatelet therapy duration in patients with acute coronary syndrome treated with percutaneous coronary intervention

**Recommendations**

<table>
<thead>
<tr>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>In patients with ACS treated with coronary stent implantation, DAPT with a P2Y₁₂ inhibitor on top of aspirin is recommended for 12 months unless there are contra-indications such as excessive risk of bleeding (e.g. PRECISE-DAPT ≥25).</strong></td>
<td>I</td>
</tr>
<tr>
<td><strong>In patients with ACS and stent implantation who are at high-risk of bleeding (e.g. PRECISE-DAPT ≥25), discontinuation of P2Y₁₂ inhibitor therapy after 6 months should be considered.</strong></td>
<td>IIA</td>
</tr>
<tr>
<td><strong>In patients with ACS treated with bioresorbable vascular scaffolds, DAPT for at least 12 months should be considered.</strong></td>
<td>IIA</td>
</tr>
</tbody>
</table>

[www.escardio.org/guidelines](http://www.escardio.org/guidelines)
Risk scores validated for dual antiplatelet therapy duration decision-making

<table>
<thead>
<tr>
<th>PRECISE-DAPT score</th>
<th>DAPT score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time of use</td>
<td></td>
</tr>
<tr>
<td>At the time of coronary stenting</td>
<td>After 12 months of uneventful DAPT</td>
</tr>
<tr>
<td>DAPT duration</td>
<td></td>
</tr>
<tr>
<td>strategies assessed</td>
<td>Short DAPT (3–6 months) vs. Standard/long DAPT (12–24 months)</td>
</tr>
<tr>
<td>Score calculation</td>
<td></td>
</tr>
<tr>
<td>HB</td>
<td>Age</td>
</tr>
<tr>
<td></td>
<td>≥75</td>
</tr>
<tr>
<td>WBC</td>
<td>65 to &lt;75</td>
</tr>
<tr>
<td></td>
<td>&lt;65</td>
</tr>
<tr>
<td></td>
<td>Cigarette smoking +1 pt</td>
</tr>
<tr>
<td></td>
<td>Diabetes mellitus +1 pt</td>
</tr>
<tr>
<td></td>
<td>MI at presentation +1 pt</td>
</tr>
<tr>
<td></td>
<td>Prior PCI or prior MI +1 pt</td>
</tr>
<tr>
<td></td>
<td>Paclitaxel-eluting stent +1 pt</td>
</tr>
<tr>
<td></td>
<td>Stent diameter &lt;3 mm +1 pt</td>
</tr>
<tr>
<td></td>
<td>LVEF &lt;30% +2 pt</td>
</tr>
<tr>
<td></td>
<td>Vein graft stent +2 pt</td>
</tr>
</tbody>
</table>

Score range = 0 to 100 points

Decision making cut-off suggested

Score ≥25 → Short DAPT
Score <25 → Standard/long DAPT

Score ≥2 → Long DAPT
Score <2 → Standard DAPT

Timing of P2Y₁₂ inhibitor initiation in patients scheduled for an invasive strategy (pretreatment)

- As the optimal timing of ticagrelor or clopidogrel administration in NSTE-ACS patients scheduled for an invasive strategy has not been adequately investigated, no recommendation for or against pretreatment with these agents can be formulated. Based on the ACCOAST* results, pretreatment with prasugrel is not recommended.

ACCOAST design

NSTEMI + troponin ≥1.5 times ULN local lab value

Prasugrel 30 mg

Placebo

Randomise 1:1

Double-blind

N ~4100 (event driven)

Prasugrel 10 mg or 5 mg (based on weight and age) for 30 days

PCI

Coronary angiography

CABG

or medical management
(no more prasugrel)

CABG

or medical management
(no prasugrel)

Prasugrel 30 mg

Coronary angiography

Prasugrel 30 mg

Prasugrel 60 mg

1° Endpoint: CV Death, MI, Stroke, Urg Revasc, GP IIb/IIIa bailout, at 7 days


1° Efficacy end point @ 7 + 30 days
(all patients)

CV Death, MI, Stroke, Ur, GP IIb/IIIa Bailout

Days From First Dose

No. at Risk, Primary Efficacy End Point:

No pre-treatment

Pre-treatment

1996 1788 1775 1769 1762 1752 1621

2037 1821 1809 1792 1797 1791 1616

End point (%)

Pre-treatment 10.0

No Pre-treatment 9.8

Hazard Ratio, 1.02

(95% 0.84, 1.25)

P=0.81

Hazard Ratio, 0.997

(95% 0.83, 1.20)

P=0.98

All TIMI (CABG or non-CABG) major bleeding
(all treated patients)

No. at Risk. All TIMI Major Bleeding:
No pre-treatment 1996 1947 1328 1297 1286 1284 1283
Pre-treatment 2037 1972 1339 1310 1299 1297 1290

Hazard Ratio, 1.90 (95% 1.19, 3.02)
P=0.006

Hazard Ratio, 1.97 (95% 1.26, 3.08)
P=0.002


Dual antiplatelet therapy duration in patients with acute coronary syndrome treated with percutaneous coronary intervention (continued)

Recommendations

In patients with ACS who have tolerated DAPT without a bleeding complication, continuation of DAPT for longer than 12 months may be considered.

In patients with MI and high ischaemic risk who have tolerated DAPT without a bleeding complication, ticagrelor 60 mg b.i.d. for longer than 12 months on top of aspirin may be preferred over clopidogrel or prasugrel.

www.auardin.org/guidelines
2017 ESC focused Update on DAPT in Coronary Artery Disease, developed in collaboration with EACTS
European Heart Journal 2017 - doi:10.3359/euhart/jh1059
**Algorithm for dual antiplatelet therapy (DAPT) in patients treated with percutaneous coronary intervention**

**DAPT Duration after PCI with DES: Meta-analysis of RCT**

<table>
<thead>
<tr>
<th>Study</th>
<th>No of events/total</th>
<th>Odds ratio (95% CI) M-H, fixed</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Major Bleeding</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short term</td>
<td>12 month</td>
<td>0.58 (0.36 to 0.92)</td>
</tr>
<tr>
<td>28/7975</td>
<td>49/8020</td>
<td></td>
</tr>
<tr>
<td>Extended</td>
<td>12 month</td>
<td>1.62 (1.26 to 2.09)</td>
</tr>
<tr>
<td>160/8196</td>
<td>98/8096</td>
<td></td>
</tr>
<tr>
<td><strong>Myocardial Infarction</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short term</td>
<td>12 month</td>
<td>1.11 (0.87 to 1.43)</td>
</tr>
<tr>
<td>132/7975</td>
<td>120/8020</td>
<td></td>
</tr>
<tr>
<td>Extended</td>
<td>12 month</td>
<td>0.53 (0.42 to 0.66)</td>
</tr>
<tr>
<td>127/8196</td>
<td>234/8096</td>
<td></td>
</tr>
<tr>
<td><strong>Cardiovascular Mortality</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short term</td>
<td>12 month</td>
<td>0.95 (0.68 to 1.33)</td>
</tr>
<tr>
<td>68/5977</td>
<td>72/6013</td>
<td></td>
</tr>
<tr>
<td>Extended</td>
<td>12 month</td>
<td>1.09 (0.79 to 1.50)</td>
</tr>
<tr>
<td>78/7551</td>
<td>71/7455</td>
<td></td>
</tr>
</tbody>
</table>
Switching between oral P2Y\textsubscript{12} inhibitors

### Recommendations

In patients with ACS who were previously exposed to clopidogrel, switching from clopidogrel to ticagrelor is recommended early after hospital admission at a loading dose of 180 mg irrespective of timing and loading dose of clopidogrel, unless contra-indications to ticagrelor exist.

Additional switching between oral P2Y\textsubscript{12} inhibitors may be considered in cases of side effects/drug intolerance according to the proposed algorithms.

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Algorithm for switching between oral P2Y\textsubscript{12} inhibitors in the acute setting

CLOPIDOGREL

A C U T E

Setting

ALWAYS RELOAD

PRASUGREL

TICAGRELOR

- Prasugrel LD (60 mg) 24h after last Prasugrel dose
- Clopidogrel LD (600 mg) 24h after last Prasugrel dose
- Ticagrelor LD (180 mg) 24h after last ticagrelor dose
- Ticagrelor LD (180 mg)

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Algorithm for switching between oral P2Y12 inhibitors in the chronic setting

CLOPIDOGREL

- Prasugrel MD (60 mg p.o.) and clopidogrel 24h after last clopidogrel dose
- Ticagrelor MD (90 mg b.i.d.) 24h after last clopidogrel dose

PRASUGREL

- Prasugrel LD (60 mg) 24h after last ticagrelor dose

CHRONIC SETTING

TICAGRELOR

- Ticagrelor MD (90 mg b.i.d.) 24h after last clopidogrel dose
- Clopidogrel MD (75 mg b.i.d.) 24h after last ticagrelor dose

Antiplatelet therapy in NSTE-ACS patients requiring CABG (2)

**Recommendations**

- Aspirin is recommended 6–24h post-CABG in the absence of ongoing bleeding events.  
  **Class:** I  
  **Level:** A

- It is recommended to continue low-dose aspirin until CABG.  
  **Class:** I  
  **Level:** B

- In stabilised patients requiring CABG who are on DAPT, discontinuation of ticagrelor and clopidogrel 5 days before and prasugrel 7 days prior to surgery should be considered.  
  **Class:** IIa  
  **Level:** B

- After CABG, resuming P2Y12 inhibitor therapy should be considered as soon as deemed safe.  
  **Class:** IIa  
  **Level:** C

- Platelet function testing may be considered in shortening the time window to CABG following P2Y12 inhibitor discontinuation.  
  **Class:** IIb  
  **Level:** B

**Notes:**

CABG = coronary artery bypass surgery; DAPT = dual (oral) antiplatelet therapy.
Anticoagulation during PCI in ACS patients on oral anticoagulation

- 6–8% of pts undergoing PCI have an indication for long-term oral anticoagulation with a VKA or NOAC, due to various conditions such as moderate-to-high embolic risk AF, mechanical heart valves, or venous thromboembolism

- Primary PCI in pts on therapeutic oral anticoagulation should be performed via a radial approach with use of additional parenteral anticoagulation, regardless of the timing of the last dose of oral anticoagulant

- Given its short-term action of 25 minutes and lower bleeding risk, bivalirudin—used during the procedure and discontinued immediately after primary PCI—may be preferred over UFH or enoxaparin, especially when patients are exposed to dabigatran

- Enoxaparin should be the preferred parenteral anticoagulant in cases of prior exposure to direct anti-Xa inhibitors (rivaroxaban or apixaban)

- Unless for bail-out situations, IIb/IIIa GPIs should generally be avoided

2014 ESC/EACTS Guidelines on MR
Combining antiplatelet agents and anticoagulants in NSTE-ACS patients requiring chronic oral anticoagulation and undergoing stenting (2)

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>If at low bleeding risk (HAS-BLED ≤2), triple therapy with OAC, aspirin (75–100 mg/day) and clopidogrel 75 mg/day should be considered for 6 months, followed by OAC and aspirin 75–100 mg/day or clopidogrel (75 mg/day) continued up to 12 months.</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>If at high bleeding risk (HAS-BLED ≥3), triple therapy with OAC, aspirin (75–100 mg/day) and clopidogrel 75 mg/day should be considered for a duration of 1 month, followed by OAC and aspirin 75–100 mg/day or clopidogrel (75 mg/day) continued up to 12 months irrespective of the stent type (BMS or new-generation DES).</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>Following coronary stenting, DAPT including new P2Y₁₂ inhibitors should be considered as an alternative to triple therapy for patients with NSTE-ACS and atrial fibrillation with a CHA₂DS₂-VASc score of 1 (in males) or 2 (in females).</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>Dual therapy with OAC and clopidogrel 75 mg/day may be considered as an alternative to triple antithrombotic therapy in selected patients (HAS-BLED ≥3 and low risk of stent thrombosis).</td>
<td>IIb</td>
<td>B</td>
</tr>
<tr>
<td>The use of ticagrelor or prasugrel as part of triple therapy is not recommended.</td>
<td>III</td>
<td>C</td>
</tr>
</tbody>
</table>

![Diagram](image-url)
### Conclusions

**Individualization of DAPT in ACS patients**

- Antithrombotics are a cornerstone of adjunctive pharmacological therapy to PCI in ACS patients
- New oral P2Y<sub>12</sub> platelet receptor blockers (prasugrel, ticagrelor) are preferred over clopidogrel
- In general, the preferred length of DAPT after ACS (STEMI or NSTE-ACS) treated by PCI or CABG is 12 months
- This length of DAPT should be individualized according to:
  - Bleeding risk
  - Thrombotic risk
  - The concomitant use of OAC/NOAC (AF, artificial heart valve)
  - Undergoing revascularization by means of CABG
  - Awaiting major non-cardiac surgery