Patients at high risk of thrombotic events: Duration of antiplatelet therapy

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2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
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<tbody>
<tr>
<td>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 contraindications such as excessive risk of bleeding (e.g. PRECISE-DAPT ≥25). ²⁰,²³,⁴⁰</td>
<td>I</td>
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Valgimigle M, et al. EHJ 2018
However

Is 12 months DAPT enough in all patients?
Case presentation

• 75 year old man admitted via ambulance with anterior STEMI
• Ex-smoker, history of treated hypertension, no DM or CKD
• Treated with aspirin 300mg po in ambulance and loaded with ticagrelor 180mg in cath lab
• Emergency coronary angiography performed via the right radial artery
Severe circumflex disease

Occluded LAD
Chronically-occluded right coronary artery
Successful PCI to LAD
Post-PCI progress

- No further chest pain after PCI, mobilising around ward
- Decision to treat residual disease conservatively
- Aspirin, ramipril, atorvastatin, bisoprolol long term
- Ticagrelor 90 mg BD for 12 months
Subsequently..

- Required implantable loop recorder 11 months later for investigation of pre-syncopal episodes
- Ticagrelor stopped after 1 year
- Readmitted 2 months later with further STEMIs
- Emergency coronary angiography performed via the right radial artery
Very-late stent thrombosis in LAD

Thrombus aspiration then predilated with 2.5x12mm balloon – loss of cardiac output – adrenaline, CPR, Autopulse – PTCA to LAD with 3x20mm balloon gave satisfactory result but failed to recover cardiac output with further inotrope and died
PEGASUS-TIMI 54 study design

Stable patients >50 years old with history of MI 1–3 years prior + ≥1 additional atherothrombotic risk factor*
N = 21,162

Ticagrelor 90 mg BD
Placebo BD

Follow-up visits: 4-monthly for first year, then 6-monthly
Duration: Minimum 12 months, up to ~44 months (median 30 months)
Event-driven trial: n ~ 1360 events

Primary efficacy endpoint: CV death, MI or stroke
Primary safety endpoint: TIMI major bleeding

Planned treatment with ASA 75–150 mg + standard background care

*Age ≥65 years, diabetes, second prior MI, multivessel CAD or chronic non-end-stage renal dysfunction

BD, twice daily; CAD, coronary artery disease; TIMI, thrombolysis in myocardial infarction
PEGASUS-TIMI 54: Primary endpoint

Event rate (%)

Placebo
Ticagrelor 90 mg bid
Ticagrelor 60 mg bid

9.04% Placebo
7.85% 90 mg bid
7.77% 60 mg bid

Ticagrelor 90 mg vs placebo
HR 0.85 (95% CI 0.75–0.96) p=0.008
Ticagrelor 60 mg vs placebo
HR 0.84 (95% CI 0.74–0.95) p=0.004

**PEGASUS-TIMI 54: Primary endpoint events and individual components of the primary endpoint**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>3-year KM event rates (%)</th>
<th></th>
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<tbody>
<tr>
<td><strong>Primary – CV death, MI or stroke</strong> (1558 events)</td>
<td>Ticagrelor 60mg bd</td>
<td>Placebo</td>
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<td></td>
<td>7.77</td>
<td>9.04</td>
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<thead>
<tr>
<th><strong>CV death</strong> (566 events)</th>
<th>Ticagrelor 60mg bd</th>
<th>Placebo</th>
<th>HR (95% CI)</th>
<th>P value</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>2.86</td>
<td>3.39</td>
<td>0.83 (0.68–1.01)</td>
<td>0.07</td>
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<thead>
<tr>
<th><strong>MI</strong> (898 events)</th>
<th>Ticagrelor 60mg bd</th>
<th>Placebo</th>
<th>HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4.53</td>
<td>5.25</td>
<td>0.84 (0.72–0.98)</td>
<td>0.03*</td>
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<tr>
<th><strong>Stroke</strong> (313 events)</th>
<th>Ticagrelor 60mg bd</th>
<th>Placebo</th>
<th>HR (95% CI)</th>
<th>P value</th>
</tr>
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<tr>
<td></td>
<td>1.47</td>
<td>1.94</td>
<td>0.75 (0.57–0.98)</td>
<td>0.03*</td>
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*Indicates nominal p-value; p<0.026 indicates statistical significance. ** indicates Secondary endpoint; † indicates exploratory endpoint

Discontinuation of treatment due to bleeding was more common with ticagrelor 60 mg compared to ASA therapy alone (6.2% and 1.5%, respectively; \(p<0.001\)). The majority of these bleeding events were of lesser severity (classified as TIMI requiring medical attention), e.g., epistaxis, bruising and haematomas.
PEGASUS-TIMI 54: Estimates of first efficacy and bleeding events prevented and caused Ticagrelor 60 mg bd

Rates are annualised from 3-year Kaplan-Meier event rates in the intention-to-treat population.
MACE at 3 years with ticagrelor in patients with P2Y$_{12}$ inhibitor withdrawal ≤30 days from randomization


*https://www.medicines.org.uk/emc/medicine/23935/SPC/Brilique+90+mg+film+coated+tablets/*
PEGASUS-TIMI 54 Sub-analysis: Effect of ticagrelor 60mg bd on STEMI

* Nominal P Value.

Bonaca MP et al. Presented at AHA Congress 2015 (Abstract 891)

**Ticagrelor 60 mg bd**

HR 0.62
(95% CI 0.45, 0.86)
P=0.0016*
### Adverse events leading to discontinuation

3 year KM rate (%) – p-value for 60 mg ticagrelor versus placebo <0.001

<table>
<thead>
<tr>
<th>Treatment arm</th>
<th>Any AE</th>
<th>Bleeding</th>
<th>Dyspnoea</th>
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<tbody>
<tr>
<td>Ticagrelor 60 mg bid</td>
<td>16.4%</td>
<td>6.2%</td>
<td>4.6%</td>
</tr>
<tr>
<td>Placebo</td>
<td>8.9%</td>
<td>1.5%</td>
<td>0.8%</td>
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Efficacy of ticagrelor 60mg + ASA vs ASA alone in patients with multivessel CAD

DEF.ST, definite stent thrombosis
Bansilal S et al. J Am Coll Cardiol 2018;71:489–496
PEGASUS TIMI-54: exclusion criteria related to bleeding risk

• Prior ischaemic stroke
• History of previous intracranial bleed at any time, gastrointestinal (GI) bleed within the past 6 months, or major surgery within 30 days
• Known bleeding diathesis/coagulation disorder
• Requirement for oral anticoagulation
• Severe liver disease
• End-stage renal disease requiring dialysis or likely requirement for dialysis during course of study
• Alcohol or drug abuse
Example of decision process for DAPT duration post MI

Admission with MI and treated with DAPT
- Coronary angiography
  - Up to 12 months DAPT
    - Yes: PCI
    - No: Multivessel/extensive CAD with DM, PAD, CKD or recurrent MIs OR very severe multivessel CAD
      - Yes: Intolerance to ticagrelor (not bleeding related)
      - No: History of ischaemic stroke
  - No: Conservative treatment

Indication for oral anticoagulation (e.g. atrial fibrillation) OR high-risk features for life-threatening bleeding: anaemia, history of spontaneous major bleed, bleeding diathesis or thrombocytopenia, severe liver disease, intracranial vascular abnormality or neoplasm, extreme old age or frailty

Prolonged DAPT with aspirin + ticagrelor (downtitrate from 90 mg to 60 mg BD from 1 year post MI)

Adapted from Sumaya W et al. Thromb Haemost 2019
Summary

• Ischaemic risk **DOES NOT** diminish after 12 months following ACS

• Long-term dual aspirin + ticagrelor reduces ischaemic events following MI in patients at high CV risk at the cost of more *non-fatal* bleeding

• Selecting patients with multivessel disease, either very severe or associated with diabetes, CKD, PAD or recurrent MIs is likely to reduce CV death amongst other ischaemic outcomes
DISCUSSION