Ticagrelor and NICE Technology Appraisal (TA) 420

Background

Lifelong combinations of drug treatments are recommended for secondary prevention after acute myocardial infarction.

In December 2016, NICE issued TA420 Ticagrelor for preventing atherothrombotic events after myocardial infarction. There is one recommendation:

1.1 Ticagrelor, in combination with aspirin, is recommended within its marketing authorisation as an option for preventing atherothrombotic events in adults who had a myocardial infarction and who are at high risk of a further event.

Treatment should be stopped when clinically indicated or at a maximum of 3 years.

Clinical Trial

The NICE recommendation is based on the evidence from the PEGASUS-TIMI 54 study that showed ticagrelor at doses of 60mg and 90mg twice daily (in conjunction with aspirin 75-150mg once daily and compared with aspirin monotherapy) reduces the risk of ischaemic events in patients who had already survived to the first anniversary of their heart attack. However, it increased the risk of major bleeding.

The inclusion criteria in the trial and therefore the definition patients at high-risk of a further event were:

A myocardial infarction in the 1-3 years prior to enrolment and least 50 years of age PLUS at least one of the following additional atherothrombosis risk factors:

- age >=65 years
- diabetes mellitus requiring medication
- a second prior spontaneous myocardial infarction
- multivessel coronary artery disease
- non end-stage chronic renal dysfunction, defined as an estimated creatinine clearance of less than 60 ml per minute

Exclusion criteria and therefore patients who are not indicated for an additional 3 years’ treatment with ticagrelor at 60mg twice daily are those:

- Taking clopidogrel, prasugrel, dipyridamole, cilostazol, or an anticoagulant or with:
  - bleeding disorder
  - history of ischemic stroke
  - intracranial bleeding
  - central nervous system tumour
  - intracranial vascular abnormality
- gastrointestinal bleeding within the previous 6 months
- major surgery within the previous 30 days

**Patient review**

Patients taking dual antiplatelet therapy comprising ticagrelor and aspirin for a year post STEMI or nSTEMI who are being considered for extended dual antiplatelet therapy in line with the above criteria at the time of their index event should be reviewed at 12 months post-event with a view to lowering the strength of ticagrelor from 90mg twice daily to 60mg twice daily. This decision would balance the risks of bleeding with the benefits of preventing further ischaemic episodes. Patients and clinicians may have different views about the relative importance of these events. If DAPT is prolonged, a plan should be made for regular review of therapy and a date indicated for cessation of ticagrelor. Multiple studies show that adherence to secondary prevention drugs declines steeply after the index event and is therefore likely to represent a more important target for improving outcomes than extended dual antiplatelet therapy.

From the trial, numbers needed to treat for 3 years to prevent one outcome event or cause one adverse event: (the trial had two treatment arms – ticagrelor 60mg and ticagrelor 90mg; only 60mg reported here as that is the dose to be used)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Ticagrelor 60 mg</th>
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<tbody>
<tr>
<td><strong>Numbers needed to treat (NNT)</strong></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular death, MI or stroke</td>
<td>79</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>189</td>
</tr>
<tr>
<td>MI</td>
<td>139</td>
</tr>
<tr>
<td>Stroke</td>
<td>213</td>
</tr>
<tr>
<td><strong>Numbers needed to harm (NNH)</strong></td>
<td></td>
</tr>
<tr>
<td>TIMI major bleeding*</td>
<td>81</td>
</tr>
<tr>
<td>TIMI minor bleeding*</td>
<td>122</td>
</tr>
<tr>
<td>Bleeding requiring transfusion</td>
<td>73</td>
</tr>
<tr>
<td>Bleeding leading to discontinuation</td>
<td>22</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>11</td>
</tr>
<tr>
<td>Dyspnoea leading to discontinuation</td>
<td>27</td>
</tr>
<tr>
<td>Serious dyspnoea</td>
<td>333</td>
</tr>
<tr>
<td>Gout</td>
<td>217</td>
</tr>
</tbody>
</table>

*TIMI Bleeding Classification:*

Major:
1) Any intracranial* bleeding, OR
2) Clinically overt signs of haemorrhage associated with a drop in haemoglobin (Hgb) of ≥5 g/dL (or, when haemoglobin is not available, a fall in hematocrit of ≥15%), OR
3) Fatal bleeding (a bleeding event that directly led to death within 7 days)

Minor:
Any clinically overt sign of haemorrhage (including imaging) that is associated with a fall in Hgb of 3 to < 5 g/dL (or, when haemoglobin is not available, a fall in hematocrit of 9 to < 15%).

**Consideration of risks and benefits:**

- The pivotal trial enrolled patients with a spontaneous myocardial infarction in the previous 1-3 years, plus an additional risk factor for cardiovascular disease.
- Patients who survive a year or more after acute myocardial infarction remain at substantial risk of further cardiovascular events.
• Ticagrelor at a dose of 60 mg (or 90 mg) twice daily reduced the risk of the composite outcome of cardiovascular death, MI or stroke compared to placebo. The reductions were small but statistically significant.

• Both doses of ticagrelor significantly increased the risk of major and minor bleeding. Commonly used drugs which increase the risk of bleeding when given in conjunction with ticagrelor include NSAIDs, systemic corticosteroids and SSRIs. Low dose aspirin should be continued. Ticagrelor was also associated with increased rates of dyspnoea and gout.

• The results of the pivotal trial suggest that for every cardiovascular death, MI or stroke prevented, ticagrelor 60 mg twice daily is likely to cause one major bleed, one bleed requiring a blood transfusion, three to four bleeds leading to discontinuation and seven new cases of dyspnoea.

FMESG
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