Extended dual antiplatelet therapy following myocardial infarction

The following recommendations are based on NICE TA420: Ticagrelor for preventing atherothrombotic events after myocardial infarction

In December 2016, NICE TA420 gave 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.

Evidence

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 one year after their initial heart attack. However, it increased the risk of major bleeding.

The inclusion criteria in the trial and therefore the defined 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 risk factors for atherothrombosis:

- 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:

- Patients taking clopidogrel, prasugrel, dipyridamole, cilostazol, or an anticoagulant
- Patients with any of:
    - 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

The study reported the following numbers needed to treat for 3 years to prevent one outcome event or cause one adverse event:

Outcome	Ticagrelor 60mg
Numbers needed to treat (NNT)	
Cardiovascular death, MI or stroke	79
Cardiovascular death	189
MI	139
Stroke	213
Numbers needed to harm (NNH)	
TIMI major bleeding*	81
TIMI minor bleeding*	122
Bleeding requiring transfusion	73
Bleeding leading to discontinuation	22
Dyspnoea	11
Dyspnoea leading to discontinuation	27
Serious dyspnoea	334
Gout	218

* TIMI Bleeding Classifications

TIMI major bleeding:

1. Any intracranial bleeding,
2. Clinically overt signs of haemorrhage associated with a drop in haemoglobin (Hb) of ≥5 g/dl (or when Hb not available a fall in haematocrit of ≥15%),
3. Fatal bleeding (a bleeding event that directly led to death within 7 days).

TIMI minor bleeding:

Any clinically overt sign of haemorrhage (including imaging) that is associated with a fall in Hb of 3 to <5g/dl (or when Hb not available a fall in haematocrit of 9 to <15%)

Evidence Summary

- The study 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 study 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 (see table above).

Recommendation

For patients taking dual antiplatelet therapy (DAPT) comprising ticagrelor and aspirin for one year post STEMI or nSTEMI, and who are being considered for extended DAPT, the following recommendations should be followed:

1. Ticagrelor 60mg twice daily should be prescribed, in addition to aspirin 75mg daily, for selected patients with history of myocardial infarction within two years who are at high risk of further events.
2. Extended duration ticagrelor therapy 60mg twice daily should be continued for three years. In most cases this will comprise down-titration from 90mg twice daily prescribed for twelve months following myocardial infarction.
3. Because protection from further cardiovascular events is offset by an increased risk of major bleeding, the decision to prescribe extended duration therapy should be made by a clinician familiar with assessing risk following acute coronary syndrome.
4. In most cases, patients who will benefit from extended duration therapy will be identified during their admission with index myocardial infarction, taking into account findings at angiography (where available), risk factors and consideration of bleeding risk.
5. Patients must meet the following criteria for extended DAPT;
   - myocardial infarction in the 1-3 years prior and at least 50 years of age PLUS at least one of the following additional atherothrombotic risk factors:
     - Age 65 years and over
     - Diabetes mellitus requiring medication
     - Previous myocardial infarction in addition to index event
     - Multivessel coronary artery disease
     - Chronic kidney disease (eGFR<60ml/min) not requiring dialysis
6. If DAPT is extended, a plan should be made for regular review at least annually to assess the risks of bleeding with the benefit of preventing further ischaemic events. In addition a date must be indicated for cessation of ticagrelor.
7. The recommendation for extended duration therapy may be made either on patient discharge or at the routine follow up cardiology outpatient / cardiac rehabilitation clinic appointment. The decision must be clearly documented in the case notes and communicated to the general practitioner:

> Please continue ticagrelor 90mg twice daily for 1 year until _____.Then down titrate to 60mg twice daily for a further 3 years until _____, if tolerated in view of extent of coronary artery disease and clinical risk factors. Please review bleeding risk every 12 months.
>
> Continue aspirin, statin and other secondary prevention medication indefinitely.

Ticagrelor is contraindicated in patients with active pathological bleeding, a history of intracranial haemorrhage, or moderate-to-severe hepatic impairment. Co-administration of ticagrelor with a strong CYP3A4 inhibitor (for example, ketoconazole, clarithromycin, nefazodone, ritonavir or atazanavir) is also contraindicated. For further prescribing information for ticagrelor please consult the SPC.

References

Bonaca MP et al; for the PEGASUS-TIMI 54 Steering Committee and Investigators. Long-term Use of Ticagrelor in Patients with Prior Myocardial Infarction N Engl J Med 2015;372:1791-800.

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