NHS
Pan Mersey
Area Prescribing Committee

TICAGRELOR tablets (Brilique®)

The Pan Mersey Area Prescribing Committee recommends the prescribing of TICAGRELOR tablets (Brilique®), following specialist initiation, for the management of acute coronary syndromes in adults in accordance with NICE TA236 and for preventing atherothrombotic events after myocardial infarction in accordance with NICE TA420.

AMBER following specialist initiation

Acute Coronary Syndrome (ACS) with 90mg twice daily (for up to 1 year)

The Pan Mersey Area Prescribing Committee (APC) recommends ticagrelor 90mg twice daily in combination with low-dose aspirin, for up to 12 months, as a treatment option in adults with ACS, in accordance with NICE TA236[1] (October 2011) i.e. patients with ST-segment-elevation myocardial infarction (STEMI), non-ST-segment-elevation myocardial infarction (NSTEMI) or unstable angina. Following admission to hospital, suitable patients will be commenced on ticagrelor 90mg twice daily for a period of up to one year (as determined by the hospital physician).

Extended treatment with 60mg twice daily (for up to a further 3 years)

The Pan Mersey Area Prescribing Committee recommends extended treatment with ticagrelor 60mg twice daily in accordance with NICE TA420[2] (December 2016). Ticagrelor, in combination with aspirin, is recommended within its marketing authorisation as an option for preventing atherothrombotic events in adults who have a history of myocardial infarction of at least 1 year and who are at high risk of a further event (have at least one of the following risk factors for atherothrombosis: age ≥65 years, diabetes mellitus requiring medication, a second prior MI, evidence of multivessel CAD, or chronic non-end-stage renal dysfunction). Treatment should be stopped when clinically indicated or at a maximum of 3 years of 60mg twice daily.

Treatment may be started without interruption (continuation therapy) after the initial 1-year treatment with ticagrelor 90 mg or other adenosine diphosphate (ADP) receptor inhibitor therapy in patients with acute coronary syndromes and with a high risk of an atherothrombotic event. Treatment can also be started up to 2 years from the myocardial infarction, or within 1 year after stopping previous ADP receptor inhibitor treatment.

Clear diagnosis and duration of treatment information for high dose and low dose ticagrelor will be relayed to GPs upon discharge.

Note: Patients who are not eligible for treatment under this statement may be considered on an individual basis where their GP or consultant believes exceptional circumstances exist that warrant deviation from the rule of this policy. In this situation, follow locally defined processes.

SUPPORTING INFORMATION

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Effectiveness

Ticagrelor is an oral antagonist at the P2Y12 adenosine diphosphate receptor, which inhibits platelet aggregation and thrombus formation in atherosclerotic disease.

90mg twice daily

18,624 patients in the PLATO study[3] were admitted to hospital with ACS and randomised to either ticagrelor or clopidogrel for one year, plus aspirin. At 12 months, the primary end point (a composite of death from vascular causes, MI, or stroke) occurred in 9.8% of patients receiving ticagrelor as compared with 11.7% of those taking clopidogrel (hazard ratio, 0.84; 95% CI 0.77-0.92; p<0.001). Absolute risk reduction was 1.9%. NNT to prevent one cardiovascular event is 53. NNT to prevent one death from any cause is 71.

60mg twice daily (extended treatment)

The PEGASUS TIMI-54[4] study was a 21,162 patient, randomised, double-blind study to assess the prevention of atherothrombotic events with ticagrelor given at 2 doses (either 90 mg twice daily or 60 mg twice daily) combined with low dose aspirin (75-150 mg), compared to aspirin therapy alone in patients with history of MI and additional risk factors for atherothrombosis.

Although the efficacy profiles of 90 mg and 60 mg were similar, there is evidence that the lower dose has a better tolerability and safety profile in relation to risk of bleeding and dyspnoea. Consequently, the 90mg dose is not licensed for use for extended treatment.

At 3 years, the primary composite end point of cardiovascular death, MI or stroke was 7.77% in the ticagrelor 60mg group and 9.04% in the placebo group (hazard ratio for 60 mg of ticagrelor vs. placebo, 0.84; 95% CI, 0.74 to 0.95; P=0.004). Absolute risk reduction of 1.27%. NNT to prevent one cardiovascular event is 79.

Safety

The primary safety endpoint in PLATO was the first occurrence of any major bleeding event.[3] There was no significant difference between ticagrelor and clopidogrel (11.6% and 11.2%, respectively; p=0.43). Fatal or life-threatening bleeding (5.8% in both groups, p=0.70) did not differ between the groups but there was a higher rate of non-CABG-related major bleeding with ticagrelor (4.5% vs. 3.8%, p=0.03). Although overall rates of stroke did not differ between the groups, ticagrelor compared to clopidogrel had more episodes of fatal intracranial bleeding (0.1% vs.0.01%, p=0.02). Note there were fewer episodes of other types of fatal bleeding in the ticagrelor group compared to the clopidogrel (0.1% vs. 0.3%, p=0.03).Ticagrelor had an increased incidence of dyspnoea compared to clopidogrel 13.8% vs. 7.8% (p<0.001) but rates of discontinuation due to dyspnoea were much smaller 0.9% vs. 0.1% (p<0.001). For those experiencing dyspnoea, about half had resolution of symptoms within one week.

The primary safety endpoint in PEGASUS was major bleeding[4]. Rates were higher with ticagrelor (2.3%) Vs placebo (1.06%) (P<0.001); the rates of intracranial haemorrhage were 0.61% Vs 0.47% (p=0.31) and for fatal bleeding were 0.25% Vs 0.26% (p=1.00) respectively. Dyspnoea was more frequent in the 60mg group than placebo (15.84% Vs 6.38% respectively) (P<0.001). The majority of episodes with ticagrelor were either mild (58.1%) or moderate (36.9%) in severity. The rates of dyspnoea leading to discontinuation of the study drug Vs placebo were 4.55% Vs 0.79% respectively (P<0.001). Adverse events of gout were significantly more frequent with ticagrelor than with placebo. Ticagrelor is contraindicated in patients with active pathological bleeding, a history of intracranial haemorrhage, severe hepatic impairment. Co-administration of ticagrelor with a strong CYP3A4 inhibitor (for example, ketoconazole, clarithromycin, nefazodone, ritonavir, or atazanavir) is also contraindicated. The most commonly reported adverse reactions include dyspnoea, epistaxis, gastrointestinal haemorrhage, subcutaneous or dermal bleeding, and bruising.[5]

Consult the SPC for further details.

Cost

Estimated cost across Pan Mersey Region

NICE estimates the annual cost of implementing NICE TA420 at £1,478 per 100,000 population in 2017/18, rising to £15,518 per 100,000 population in 2022/23.

Patient factors

Use with caution in patients with an increased risk of bradycardic events and those on medicinal products known to induce bradycardia. New, prolonged or worsened dyspnoea should be investigated fully and if not tolerated, treatment should be reviewed (liaise with cardiology team). Caution in patients with history of asthma, COPD, hyperuricaemia or gouty arthritis. Use in patients with uric acid nephropathy is discouraged. For potential drug interactions consult SPC

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Prescribing and implementation information

Following a loading dose, ticagrelor is continued at 90 mg twice a day for up to 12 months. Patients taking ticagrelor should also take low-dose aspirin daily, unless specifically contraindicated. After 12months, patients who were deemed suitable candidates at index ACS event for extended therapy should be reduced to 60mg twice daily.

Primary care prescribing systems should ensure GPs are alerted to the need to switch selected patients. At the point of switching, GPs may wish to use the accompanying support resource to assess appropriateness of on-going therapy.

The specialist/specialist team must provide clear communication to the GP. The discharge letter will clearly state the duration of treatment of 90mg twice daily and any subsequent 60mg twice daily treatment together with a switch date.

Renal function should be checked after one month treatment of 90mg and thereafter according to routine medical practice, paying special attention to patients ≥75 years, patients with moderate/severe renal impairment and those receiving concomitant treatment with an ACE or ARB.

Do not routinely offer warfarin or DOAC in combination with ticagrelor to people who need anticoagulation after an MI.[6] Following an individual clinical assessment of risk versus benefit, a specialist may wish to initiate such a combination.

For patients who are unable to swallow the tablet(s) whole, ticagrelor tablets can be crushed to a fine powder and mixed in half a glass of water and drunk immediately[5] (refer to SPC for more info).

References

1. National Institute for Health and Care Excellence. NICE Technology Appraisal 236: Ticagrelor for the treatment of acute coronary syndromes, October 2011.
2. National Institute for Health and Care Excellence. NICE Technology Appraisal 420: Ticagrelor for preventing atherothrombotic events after myocardial infarction, December 2016.
3. Wallentin L et al PLATO Investigators. Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndromes. New England Journal of Medicine 2009; 361:1045-57.
4. Bonaca M P et al PEGASUS Investigators. Long-Term Use of Ticagrelor in Patients with Prior Myocardial Infarction. New England Journal of Medicine 2015; 372:1791-1800.
5. AstraZeneca UK Limited. Summary of Product Characteristics: Brilique film-coated tablets. Last updated 15/11/18. Accessed 18/02/19.
6. National Institute for Health and Care Excellence. NICE Clinical Guideline 172: MI secondary prevention, November 2013.