NHS
Pan Mersey
Area Prescribing Committee

TICAGRELOR tablets (Brilique®) to prevent thrombotic events post intracranial stenting

The Pan Mersey Area Prescribing Committee recommends the prescribing of TICAGRELOR tablets (Brilique®), following specialist initiation, to prevent thrombotic events post intracranial stenting.

AMBER following specialist initiation

Ticagrelor is recommended as an alternative to clopidogrel in patients who have had intracranial stenting procedures and have insufficient platelet inhibition with clopidogrel. Clopidogrel is a prodrug, the active metabolite of which is formed by CYP450 enzymes, some of which are polymorphic. As such, not all patients will derive adequate platelet inhibition. The frequency of high platelet reactivity during clopidogrel therapy is predicted to be 30%[1].

These intracranial procedures are performed endovascularly and require the use of flow diverter stents. The flow diverter's high metal surface area carries a risk of thrombogenicity. Efficacious antithrombotic therapy is therefore essential to prevent peri-procedural and post-procedural thromboembolic complications. Treatment with ticagrelor is commenced as part of a dual-antiplatelet therapy (DAPT) alongside aspirin; it is continued for 6 months post stent insertion and then stopped, whereas aspirin is continued for up to 2 years as directed by the patients' consultant neurosurgeon.

Ticagrelor is a direct acting, reversible $P2Y_{12}$ receptor antagonist and does not require hepatic metabolism to exert its effects. High platelet reactivity during ticagrelor treatment is estimated to be 0-3%. This lower frequency is explained by the absence of a metabolic activation process and low inter-individual variability. Patients not suitable for clopidogrel will be identified peri-operatively using a platelet inhibition test following a 7 day course of aspirin 75mg OD and clopidogrel 75mg OD. The decision to initiate ticagrelor in patients who do not adequately respond to clopidogrel will be made by the patient's consultant. Once established on ticagrelor, platelet function will be checked by the initiating team using the VerifyNow-P2Y12 Assay, to ensure adequate response.

Clear diagnosis and duration of treatment will be communicated to the GP 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.

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Effectiveness

Ticagrelor is an oral antagonist at the $P2Y_{12}$ adenosine diphosphate receptor, which inhibits platelet aggregation and thrombus formation in atherosclerotic disease.

The clinical decision to use ticagrelor for the prevention of thrombotic events post intracranial stenting, as an alternative to clopidogrel in patients deemed non-responsive, is based on the outcome of a few studies outlined below [2, 1, 3].

The first study is a systematic review and meta-analysis of studies looking at the complications and mortality of flow diverting stenting procedures using acetyl salicylic acid + ticagrelor or acetyl salicylic acid + prasugrel and acetyl salicylic acid + clopidogrel. 54 studies (total of 3531 patients) were analysed and the evidence suggests that dual antiplatelet regimens including ticagrelor or prasugrel are safe for patients undergoing flow diversion procedures [2]. Regimens using ticagrelor were associated with better survival than those using clopidogrel in the included studies [2].

The second study used a small sample size (18 patients) and looked at the safety and efficacy of ticagrelor for neuroendovascular procedures. The patients were known clopidogrel non-responders ($P2Y_{12}$ levels below 20% after receiving at least 600mg of clopidogrel) and were loaded on 180mg ticagrelor [1]. All but one patient showed an initial $P2Y_{12}$ response above 60%. Ticagrelor is an effective alternative to clopidogrel non-responders [1].

The RESPOND study (Response to Ticagrelor in Clopidogrel Non-responders and Responders and the Effect of Switching Therapies) was conducted in patients with stable coronary artery disease. Ticagrelor therapy (180mg loading dose followed by 90mg twice daily maintenance dose) overcame non-responsiveness to clopidogrel, and its antiplatelet effect is the same in responders and non-responders [3]. Nearly all clopidogrel non-responders and responders treated with ticagrelor will have platelet reactivity below the cut points associated with ischaemic risk [3].

Several other studies exploring the pharmacodynamic profiles of switching from clopidogrel to ticagrelor have been conducted [4]. All studies have shown enhanced platelet inhibition when escalating from clopidogrel to either ticagrelor or prasugrel and a reduction in rates of high-on-treatment platelet reactivity – a well-defined marker of risk of ischaemic recurrences, including stent thrombosis [4]. The degree of $P2Y_{12}$ receptor blockade after ticagrelor administration is similar regardless of previous exposure to clopidogrel [4].

It is possible and likely that most of the benefits, efficacy, and safety of ticagrelor that are described in the cardiac literature can be extrapolated and applied to cerebrovascular endovascular interventions [1].

Safety

The primary safety endpoint in PLATO was the first occurrence of any major bleeding event.[5] 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 [6]. 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 [7].
Consult the SPC for further details.

Cost
Total cost of treatment excluding VAT is £350. This is based on twice daily dose of ticagrelor for 6 months plus once daily dose of aspirin for 2 years (may be less – see prescribing and implementation information).
It is estimated that 26 patients per annum in the Pan Mersey region may require treatment with ticagrelor.
For information, the cost of treatment excluding VAT for clopidogrel would be £9.70.

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

Prescribing and implementation information

A minimum of two weeks supply of ticagrelor will be issued on patient discharge by the hospital. Dosing will be 75mg of aspirin daily in combination with ticagrelor 90mg twice daily (ticagrelor 180mg STAT dose will be administered whilst patient is admitted in hospital). The treatment plan (including dosage and duration) will be detailed in the patient's discharge summary to GP.

The treatment duration is 6 months from the date of the patient's procedure, after which ticagrelor is to be stopped. N.B. Patients will also be discharged on aspirin for a specified duration which is decided by the consultant neurosurgeon; this can range from a total of 6 months to 2 years in total.

Renal function should be checked after one month treatment within the community 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 ACEi or ARB.

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[7] (refer to SPC for more information).

References

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