Ticagrelor (Brilinta®)

Thrombosis Canada
Thrombose Canada

Objective:

To provide practical information on the optimal utilization of ticagrelor in clinical practice.

Background:

Ticagrelor is a cyclo-pentyl-triazolo-pyrimidine (CPTP), a selective, reversibly bound P2Y12 receptor antagonist that prevents adenosine diphosphate (ADP)-mediated platelet activation and aggregation. It is characterized as a non-competitive antagonist since its binding site on the platelet P2Y12 receptor is different from that of ADP. Unlike prasugrel and clopidogrel, ticagrelor is active in its unchanged form, not requiring conversion to an active metabolite.

Indications:

Ticagrelor, when co-administered with acetylsalicylic acid (ASA), is indicated for the secondary prevention of atherothrombotic events in patients with an acute coronary syndrome (ACS) treated medically or with percutaneous coronary intervention (PCI) (with or without stent implantation), and/or coronary artery bypass graft (CABG) surgery. It is also indicated for patients with a history of myocardial infarction (MI) at least one year prior, who are at high risk of atherothrombotic events for a duration of up to 3 years.

When ticagrelor was compared with clopidogrel in a large phase 3 randomized clinical trial (PLATO), there was a significant 1.9% absolute risk reduction (ARR) in the combined rate of myocardial infarction (MI), cardiovascular death and stroke in patients presenting with ACS managed by PCI, CABG or medically (number needed to treat [NNT] = 52). The rates of MI (1.1% ARR, NNT = 91) and all-cause mortality (1.4% ARR, NNT = 71) were also significantly reduced with ticagrelor. However, the efficacy benefit of ticagrelor over clopidogrel may be lost when doses of ASA above 150 mg daily are used.

Ticagrelor (in doses of 90 mg twice daily or 60 mg twice daily) was also compared against placebo in ASA-treated patients who had suffered a MI 1 to 3 years earlier (PEGASUS-TIMI 54). There was a statistically significant reduction in the composite of cardiovascular death, MI, or stroke (ARR of 1.2% with 90 mg twice daily [NNT=84] and 1.3% with 60 mg twice daily [NNT=79]). There was no reduction in overall mortality.

Ticagrelor (180 mg loading dose, then 90 mg twice daily), when co-administered with acetylsalicylic acid (ASA) (300-325 mg loading dose, then 75-100 mg daily), also has an indication as part of dual-antiplatelet therapy (DAPT) for a total duration 30 days for preventing recurrent stroke. This indication is similar to the use of DAPT (e.g. Clopidogrel with ASA in the CHANCE and POINT Trials) for minor stroke and TIA (THALES). Ticagrelor and ASA in combination was shows to be slightly superior to ASA alone (5% vs 6.3%, p=0.004) but was also associated with a significantly increased risk of severe bleeding (0.5% vs 0.1%, p=0.001) [NNT=92]. There was a similar increased risk of intracerebral hemorrhage [NNH=263].

Ticagrelor was not found to be superior to ASA in reducing the rate of stroke, MI, or death at 90 days in patients with acute ischemic stroke or transient ischemic attack.

Dosing:

In patients with ACS, a loading dose of 180 mg should be administered followed by 90 mg twice daily for up to 1 year. For patients with a history of MI at least 1 year prior, the dose is 60 mg twice daily for a duration of up to 3 years. Absorption is not affected by food intake and no dosing adjustment is required in patients with chronic renal disease or in patients with mild hepatic impairment. Patients taking ticagrelor should also take ASA 81 mg daily, unless specifically contraindicated.

Strong CYP3A4 inhibitors (e.g. ketoconazole, clarithromycin, nefazodone, ritonavir, and atazanavir) and inducers (e.g. phenytoin, carbamazepine, rifampin) are expected to affect the pharmacokinetics of ticagrelor; patients on these agents were excluded from the ticagrelor trials and are contraindicated from taking ticagrelor.

Adverse Effects:

As with all antiplatelet agents, ticagrelor increases the risk of major bleeding, including intracerebral hemorrhage. In the large phase 3 randomized PLATO trial, major bleeding unrelated to CABG occurred in approximately 4.5% of subjects taking ticagrelor, an absolute risk increase (ARI) of 0.7% (number needed to harm [NNH] = 143) over clopidogrel. In the large phase 3 randomized PEGASUS-TIMI 54 trial, the ARI for TIMI major bleeding was 1.2% with ticagrelor 60 mg twice daily and ASA (NNH=81) compared to ASA alone. Bleeding risks increase with age and ticagrelor has been associated with more frequent bleeding events than clopidogrel among older patients. In the POPular AGE trial, in which 1002 patients 70 years of age and older with non ST-elevation ACS were randomized to clopidogrel or either ticagrelor or prasugrel (95% received ticagrelor), the primary bleeding outcome (composite of PLATO major or minor bleeding) occurred less frequently in the clopidogrel group (18% versus 24%, HR 0.71, 95% CI 0.54–0.94, P = 0.02) but with a similar net clinical benefit outcome between the two groups (28% versus 32%), suggesting that clopidogrel may be preferred for older patients at increased risk of bleeding. Ticagrelor is contraindicated in patients with a history of intracranial hemorrhage.

Dyspnea, not related to cardiac or pulmonary causes, was observed in 14% of subjects taking ticagrelor in PLATO and 16% of subjects in PEGASUS-TIMI 54. Dyspnea is usually mild to moderate in intensity and often resolves during continued treatment. The mechanism of dyspnea is thought to be due to ticagrelor-related increased circulating adenosine leading to increased stimulation of pulmonary vagal C fibers. With the observation of bradycardia and ventricular pauses, caution should be exercised in patients with baseline bradycardia and heart block who have been given ticagrelor. Bradycardia is usually seen early in treatment and has not been associated with syncope, heart block or need for pacemaker insertion. Small but statistically significant increases in serum creatinine, uric acid, and gout have been observed.

Periprocedural Management:

The periprocedural use of antiplatelet agents may increase the risk of bleeding and transfusion requirements associated with surgery and other invasive procedures. However, discontinuation of dual

antiplatelet therapy within 12 months of stent implantation is associated with an increased risk of major adverse cardiovascular events and stent thrombosis.

Following medically managed ACS, dual antiplatelet therapy should be continued for a minimum of 3 months and preferably 1 year. For this reason, procedures associated with significant bleeding risk should be delayed beyond these time frames, if possible, and if not possible, done with consideration of the patient remaining on therapy. When appropriate, ticagrelor should be stopped 5 days prior to surgery. In general, consultation with a specialist is advised before discontinuing ticagrelor in patients with a coronary stent. In patients undergoing a minor procedure (e.g. dental, skin, cataract, arthrocentesis), discontinuation is not necessary. See **Clinical Guide Perioperative Management of Antiplatelet Therapy.**

Special Considerations:

Unlike clopidogrel and prasugrel, ticagrelor does not require conversion to an active metabolite; therefore, activity is not affected by proton pump inhibitors or in individuals with CYP2C19 loss of function alleles. The safety of ticagrelor in pregnancy has not been established. It is not known if ticagrelor is excreted in human milk; however, the use of this drug while breastfeeding is not recommended as studies in rats have shown that ticagrelor and its metabolites are excreted in breast milk.

Other Relevant Thrombosis Canada Clinical Guides:

- Acetylsalicylic Acid (ASA)
- Clopidogrel (Plavix®)
- Perioperative Management of Antiplatelet Therapy
- Prasugrel (Effient®)

References:

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