



**TARGET AUDIENCE:** All Canadian health care professionals.

## **OBJECTIVE:**

To provide practical point of care knowledge on the optimal utilization of ticagrelor in clinical practice.

## **ABBREVIATIONS:**

<b>ACS</b>	acute coronary syndrome
<b>ADP</b>	adenosine diphosphate
<b>ASA</b>	acetyl salicylic acid
<b>cAMP</b>	cyclic adenosine monophosphate
<b>CABG</b>	coronary artery bypass graft
<b>CPTP</b>	cyclo-pentyl-triazolo-pyrimidine
<b>MI</b>	myocardial infarction
<b>NNH</b>	number needed to harm
<b>NNT</b>	number needed to treat
<b>PCI</b>	percutaneous coronary intervention
<b>VASP</b>	vasodilator-stimulated phosphoprotein

## **MECHANISM OF ACTION:**

Ticagrelor (Brilinta®) is a cyclo-pentyl-triazolo-pyrimidine (CPTP), a selective, reversibly bound P2Y<sub>12</sub> 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 P2Y<sub>12</sub> 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 to inhibit this process.

## **INDICATION:**

Ticagrelor, when co-administered with acetyl salicylic acid (ASA), is indicated for the acute management and 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.

Use of ticagrelor should be considered because:

- The PLATO trial demonstrated a significant 1.9% absolute reduction with ticagrelor in the combined rate of myocardial infarction (MI), cardiovascular death and stroke, compared with

clopidogrel, in patients presenting with an ACS managed by PCI, CABG or medically (number needed to treat [NNT] = 52). The rate of MI (1.1% ARR, NNT = 91) and all-cause mortality (1.4% ARR, NNT = 71) were also significantly reduced.

- b) The efficacy benefit of ticagrelor over clopidogrel may be lost when doses of ASA above 150 mg daily are used.

## **DOSING:**

In patients with an ACS, a loading dose of 180 mg of should be administered. Following hospital discharge, ticagrelor should be administered at a dose of 90 mg twice daily. 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, unless specifically contraindicated. The dose of ASA is uncertain; however, for Canadian practice 81 mg daily is suggested.

## **MONITORING:**

No monitoring of ticagrelor is required.

## **ADVERSE EFFECTS:**

As with all antiplatelet agents, ticagrelor increases the risk of major bleeding, including intra-cerebral hemorrhage. In PLATO, a large phase 3 randomized trial, non-CABG-related major bleeding occurred in approximately 4.5% of subjects taking ticagrelor, an absolute increase of 0.7% (number needed to harm [NNH] = 143) over clopidogrel. Dyspnea, not related to cardiac or pulmonary causes, was observed in 14% of subjects taking ticagrelor in the same study. The dyspnea is usually mild to moderate in intensity and often resolves during continued treatment. The mechanism has not yet been elucidated but is felt to be due to adenosine effects and not related to pulmonary or cardiac dysfunction. Due to the observation of atrioventricular block, caution should be exercised in patients with bradycardia and heart block who have been given ticagrelor. Bradycardia is usually seen early in treatment and has not been associated with bradycardic events such as syncope, pacemaker insertion or heart block. Small, but statistically significant increases in serum creatinine and uric acid have been observed.

## **PERI-PROCEDURAL MANAGEMENT:**

The peri-procedural 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 drug-eluting stent implantation or within 6 weeks of bare-metal stent implantation is associated with a large increased risk of major adverse cardiovascular events and of stent thrombosis. Consultation with a specialist is advised before discontinuation of ticagrelor in patients with a coronary stent. 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 the patient remaining on therapy. When appropriate, ticagrelor should be stopped 5 days prior to surgery.

### **SPECIAL CONSIDERATIONS:**

Unlike clopidogrel and prasugrel, ticagrelor does not require conversion to an active metabolite; therefore, activity is not affected by the use of proton pump inhibitors or in individuals with loss of function of CYP2C19 alleles.

### **PEDIATRICS:**

There are no studies evaluating the use of ticagrelor in children. The use of ticagrelor in children is not recommended until dosing, safety and efficacy are confirmed.

### **REFERENCES:**

Bell AD, Roussin A, Cartier R, et al. The use of antiplatelet therapy in the outpatient setting: Canadian Cardiovascular Society Guidelines. Can J Cardiol 2011;27(Suppl A):S1-S59.

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*Please note that the information contained herein is not to be interpreted as an alternative to medical advice from your doctor or other professional healthcare provider. If you have any specific questions about any medical matter, you should consult your doctor or other professional healthcare providers, and as such you should never delay seeking medical advice, disregard medical advice or discontinue medical treatment because of the information contained herein.*