Te Awakairangi Health NETWORK

Medicines Update September 2013

# Ticagrelor (Brilinta®)

Ticagrelor is an **oral antiplatelet agent** that is indicated (in combination with aspirin) for the prevention of atherothrombotic events in adults with acute coronary syndromes (ACS).[1]

From July it became fully funded under Special Authority criteria. However, patients supplied ticagrelor via the manufacturer's special access programme (prior to July) will continue to receive supplies this way for the 12 month course.

## Key Messages:

- Mechanism of action is similar to clopidogrel and prasugrel.
- Provides **greater inhibition of platelet function** compared to clopidogrel and has a **faster onset of effect**. The reason for this is that clopidogrel (unlike ticagrelor) is a prodrug and requires activation in the liver first.[2]
- Ticagrelor has a faster **offset of effect** than clopidogrel as it is a **reversible antagonist** (clopidogrel is an *irreversible* agonist)[2], therefore patient adherence particularly important.
- One third of all major non-procedure-related bleeds were gastro-intestinal[4] so **gastroprotection should be strongly considered** (especially as patients are usually also on aspirin).
- Ticagrelor can cause a transient increase in creatinine levels. Check renal function at baseline, **one month** after initiating treatment and thereafter according to routine medical practice, particularly in patients ≥ 75 years, those with moderate/severe renal impairment and those receiving concomitant treatment with angiotensin receptor blockers (ARBs).[1]

## Efficacy of ticagrelor compared to clopidogrel

The clinical efficacy of oral ticagrelor in adults with ACS was evaluated in the PLATO (PLATelet inhibition and Outcomes) trial (n=18,624).[3] In this trial ticagrelor plus aspirin was compared to clopidogrel plus aspirin. Ticagrelor was shown to be more effective than clopidogrel in preventing ischaemic events over 12 months, providing a significantly lower risk of primary composite endpoint for myocardial infarction, stroke or death from vascular causes (9.8% vs 11.7% at 12 months). There was however no significant difference in the risk of stroke between the two treatment groups.

## Bleeding risk

Ticagrelor did not significantly differ from clopidogrel with regard to the incidence of major bleeding overall. However, the risk of non-coronary artery bypass graft-related bleeds was higher with ticagrelor than with clopidogrel (4.5% vs 3.8%)[3]; non-procedure related major bleeding was also more common with ticagrelor.[4] Ticagrelor had a higher incidence of intracranial bleeding and fatal intracranial bleeding (0.1% vs 0.01%) but lower incidence of fatal bleeding of other types than clopidogrel (0.1% vs 0.3%). A total of 224 (2.4%) patients in the ticagrelor group permanently discontinued it because of bleeding, compared with 95 (1%) of patients in the clopidogrel group (P<0.001).[4] Ticagrelor is a more potent platelet inhibitor than clopidogrel so it could be expected to comparatively cause more bleeding.

## Contraindications[1]

| | |
|---|---|
| • Hypersensitivity to ticagrelor or any of the excipients | • Active pathological bleeding |
| • History of intracranial haemorrhage | • Moderate to severe hepatic impairment |
| • Co-administration with strong CYP3A4 inhibitors (see Interactions) | |

## Precautions[1]

- The use of ticagrelor in patients at increased risk of bleeding should be balanced against the benefit in terms of prevention of atherothrombotic events.
- Use with **caution** in patients at risk of **bradycardia, history of asthma/COPD, hyperuricaemia, gout or uric acid nephropathy**[1].

## Dosage

180mg loading dose (usually administered in hospital), then 90mg twice daily for 12 months.[1] Patients should be taking low dose aspirin unless contraindicated.

## Common Adverse Reactions

The rate of treatment discontinuation because of an adverse event was significantly higher with ticagrelor than clopidogrel.[3] Epistaxis was also commonly reported.

The most common non-haemorrhagic adverse events that occurred were[2]:

| | |
|---|---|
| • dyspnoea (13.8%) – use with caution in asthma/COPD | • headache (6.5%) |
| • cough (4.9%) | • dizziness (4.5%) |
| • nausea | • atrial fibrillation (4.2%) |

## Drug Interactions

Ticagrelor's drug interaction profile is different to clopidogrel. It is a weak CYP3A4 and p-glycoprotein inhibitor. It is expected that risk of bleeding will increase with **antiplatelets, anticoagulants, NSAIDs and SSRIs.** Examples of drug interactions are listed below[1,2,5].

| Interacting medication | Comment | Recommendation |
|---|---|---|
| **Strong** CYP3A4 **inhibitors** | Expected to ↑ bleeding risk<br>Includes ketaconazole, clarithromycin, nefazodone, itraconazole, antiretroviral protease inhibitors | Concurrent use contraindicated[1] |
| **Moderate** CYP3A4 **inhibitors** | May ↑ risk of bleeding & ticagrelor-related ADRs.<br>Includes verapamil, diltiazem, erythromycin | Use cautiously. Monitor for ticagrelor-related ADRs[1,5]<br>Theoretical risk of bradycardia[5] with diltiazem, verapamil - monitor |
| **Strong** CYP3A4 **inducers** | Efficacy of ticagrelor could be reduced, especially with rifampicin (effect may occur with other inducers e.g. phenytoin, carbamazepine) | Avoid concurrent use if possible - could lead to failure of ticagrelor therapy[5] |
| **Simvastatin**<br>**Atorvastatin**<br>**Digoxin**<br>**Dabigatran** | Levels of these medications may be increased by ticagrelor | Simvastatin – max dose 40mg daily[5]<br>Atorvastatin – monitor for ADRs<br>Digoxin – monitor for ADRs & do digoxin serum levels if necessary[5]<br>Dabigatran – monitor for bleeding[5] |

**This list is not exhaustive, check references such as Brilinta ® datasheet[1] or New Zealand Formulary (NZF) Interaction Checker[5] before prescribing new medicines with ticagrelor.**

**Please refer to datasheet[1] for more detailed information on this medication or contact TeAHN Clinical Pharmacist**

## References


1. Brilinta ®datasheet, AstraZeneca Ltd, prepared on 14/06/12. Available on http://www.medsafe.govt.nz/ (accessed 17/01/2013)
2. Scott LJ, Deeks ED. Ticagrelor: a guide to its use in the management of acute coronary syndromes. Drugs Ther Perspect 2012; 28(1): 1-5
3. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor vs clopidogrel in patients with acute coronary syndromes. NEJM 2009;361:1045-57
4. Becker R, et al. Bleeding complications with the $P2Y_{12}$ receptor agonists clopidogrel and ticagrelor in the PLATelet inhibition and patient Outcomes (PLATO) trial. Eur Heart J (2011) 32(23):2933-2944
5. New Zealand Formulary Interaction Checker accessed via http://www.nzf.org.nz/interactions (10/8/13)


With thanks to Medwise, Tauranga for permitting access to their Ticagrelor bulletin