TICAGRELOR (BRILINTA) – NEW ANTIPLATELET AGENT

On 1st July ticagrelor became available fully subsidised on special authority for the treatment of acute coronary syndrome (ACS). Up until this time it has been available from the manufacturer on a special access programme - these patients will continue to have their supplies provided on the same programme for the duration of the 12 month treatment course.

Ticagrelor is an antiplatelet agent indicated in ACS with or without coronary stenting[1]. It works on the same $P2Y_{12}$ platelet receptor as clopidogrel but differs in that it is reversible, has a faster onset of effect and is active without needing biotransformation and therefore less likely than clopidogrel to be affected by genetic polymorphisms of cytochrome P450 enzymes[2]. The pivotal registration study was PLATO[3] (PLATelet Inhibition and Patient Outcomes), comparing aspirin plus either ticagrelor or clopidogrel in 18,624 patients admitted to hospital with an ACS (+/- ST elevation). The primary efficacy composite endpoint of vascular death, MI and stroke occurred less frequently in the ticagrelor group than the clopidogrel group (9.8% vs 11.7% at 12 months, RRR 16%, ARR 1.9%, HR 0.84, P<0.001). There was no difference in the primary safety endpoint of overall major bleeding with ticagrelor vs clopidogrel (11.6% vs 11.2%) but there was more non-procedure-related bleeding with ticagrelor[4] (major + minor: 5.9% vs 4.3% P<0.0001, major: 3.1% vs 2.3% P=0.01), more intracranial bleeding (total and fatal) and more major (209 vs 178 events) but fewer fatal (0 vs 5) GI bleeds. A total of 224 (2.4%) patients in the ticagrelor group permanently discontinued it because of bleeding, compared with 95 (1%) patients in the clopidogrel group[5] (P<0.001). Ticagrelor is a more potent platelet inhibitor than clopidogrel so it is perhaps to be expected that it would cause more bleeding overall. One-third of all major non-procedure-related bleeds were gastro-intestinal[5] so gastroprotection should be strongly considered, as patients are usually also on aspirin and there is a higher risk of bleeding with dual antiplatelet therapy.

Of note was a higher incidence of dyspnoea with ticagrelor (13.8% vs 7.8%, HR 1.84, P<0.001), requiring discontinuation in 6% of the ticagrelor patients who developed it[3]. The dyspnoea did not appear to be cardiac- or respiratory-related[3]. The cause of dyspnoea was thought to be medication-related in 15% of the ticagrelor group and 7% of the clopidogrel group[6]. Patients with dyspnoea on ticagrelor were more likely to have an earlier onset than clopidogrel patients with dyspnoea; median time to onset 23 vs. 43 days[6]. The dyspnoea with ticagrelor usually lasted less than a week[6], most patients had only one episode and it did not appear to cause any clinically relevant changes to lung function[7]. Patients reporting dyspnoea with ticagrelor were more likely to be older and have had dyspnoea prior to or at enrolment, CHF, COPD, asthma or a history of smoking[6]. The mechanism is unknown but theories include potentiation of adenosine[2], inhibition of P2Y12 on sensory neurons[8] and, controversially, a TRALI-like reaction[9] (transfusion-related acute lung injury). If a patient reports new, prolonged or worsened dyspnoea this should be investigated for cardiac or respiratory causes.

- Contraindicated in patients with active bleeding or a history of intracranial haemorrhage[1].
- Contraindicated in moderate to severe hepatic impairment[1] (increased incidence of adverse effects in this patient group in PLATO).
- The most common adverse effects with ticagrelor (in descending order) were dyspnoea, headache, epistaxis, cough, dizziness and nausea[7].
- Maintenance dose is 90mg bd; antiplatelet activity is maintained if one dose is missed but persistent erratic adherence could affect the efficacy of ticagrelor.

- May cause transient increase in creatinine levels (not associated with renal damage), recommend check renal function at baseline and after one month (paying special attention to patients 75 years, patients with moderate/severe renal impairment and those receiving concomitant treatment with an ARB).
- No dose adjustment is required in renal impairment but caution is advised with Clcr<30ml/min.
- Drug Interactions:
  - Contraindicated with strong CYP450 3A4 inhibitors (e.g. clarithromycin, ketoconazole, itraconazole, voriconazole, antiretroviral protease inhibitors) as they can increase ticagrelor exposure and therefore risk of bleeding.
  - Moderate inhibitors of CYP450 3A4 (e.g. diltiazem, verapamil, erythromycin) can also increase ticagrelor exposure ï not contraindicated but caution advised.
  - Caution with strong CYP450 3A4 inducers, especially rifampicin (other inducers include dexamethasone, phenytoin, carbamazepine, and phenobarbitone) as they can reduce ticagrelor exposure and risk treatment failure.
  - Ticagrelor can increase digoxin levels via effects on P-glycoprotein (monitor) and can increase exposure to simvastatin (ensure simvastatin dose is no higher than 40mg) and atorvastatin (no dose change recommended but caution advised with high doses).
- Aspirin dose should be 100mg/day or less.
- Ticagrelor should be stopped at least 5 days before surgical procedures.
- Food has no appreciable effect on ticagrelor absorption.
- Increased risk of bleeding with other medications which affect haemostasis e.g. anticoagulants; also manufacturer advises caution with SSRIs due to increased risk of bleeding via antiplatelet effects of SSRIs.
- Ticagrelor should usually be stopped after 12 months unless advised otherwise by a cardiologist.
- If ticagrelor is stopped within 12 months due to intolerance, clopidogrel should usually be prescribed as a replacement. In patients with recent PCI and coronary stent insertion, premature discontinuation of ticagrelor may result in stent thrombosis with associated mortality and morbidity if it is not substituted with an alternative antiplatelet agent (in combination with aspirin).

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References

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