Clinical guideline

Ticagrelor for patients with acute coronary syndrome

Ticagrelor is a potent antiplatelet agent licensed for use in combination with aspirin to reduce the risk of further cardiovascular events in patients presenting with acute coronary syndrome (ACS).

NICE TA 236 October 2011 recommends ticagrelor in combination with low-dose aspirin for up to 12 months as a treatment option in adults with acute coronary syndromes (ACS). That is, people:

with ST-segment-elevation myocardial infarction (STEMI) – defined as ST elevation or new left bundle branch block on electrocardiogram – that cardiologists intend to treat with primary percutaneous coronary intervention (PCI) **or**

with non-ST-segment-elevation myocardial infarction (NSTEMI) **or**

admitted to hospital with unstable angina – defined as ST or T wave changes on electrocardiogram suggestive of ischaemia plus ONE of the characteristics listed below:

- age 60 years or older
- previous MI or CABG
- coronary artery disease with stenosis of 50% or more in at least two vessels
- previous ischaemic stroke or TIA
- carotid stenosis of at least 50%, or cerebral revascularisation
- diabetes mellitus
- peripheral arterial disease
- chronic renal dysfunction, defined as a creatinine clearance of less than 60 ml/ min

Before ticagrelor is continued beyond the initial treatment, the diagnosis of unstable angina should first be confirmed, ideally by a cardiologist.

The **Chest pain pathway** should be followed to guide prescribing of ticagrelor.

Ticagrelor is not licensed for primary prevention or secondary prevention of stable cardiovascular (CV) disease and there is no evidence to support its use as monotherapy. Ticagrelor should not be initiated by primary care.

1. **Dosing**

There is no dose adjustment of **ticagrelor** based on weight or age.

• **Loading dose:** Give 180mg as early as possible after ACS presentation

• **Maintenance dose:** Ticagrelor should be continued at a dose of 90mg twice daily for a period of 12 months. Patients prescribed ticagrelor should also be taking aspirin at a dose of 75mg daily which should continue lifelong (higher aspirin doses are not recommended due to increased risk of bleeding) Durations of therapy should be clearly documented on discharge.

Clopidogrel or prasugrel should be stopped on starting ticagrelor. Patients treated with clopidogrel can be directly switched to ticagrelor if needed. Switching from prasugrel to ticagrelor has not been investigated.

2. Contra-indications and cautions

Contra-indications	Cautions
▪ Hypersensitivity to the active substance or to any of the excipients ▪ Active pathological bleeding ▪ History of intracranial haemorrhage ▪ Moderate to severe hepatic impairment ▪ Co-administration of ticagrelor with strong CYP3A4 inhibitors (e.g. ketoconazole, clarithromycin, nefazodone, ritonavir, and atazanavir) ▪ Pregnancy and breast-feeding	▪ Patients with a propensity to bleed (e.g. due to recent trauma, recent surgery, coagulation disorders, active or recent gastrointestinal bleeding) ▪ Concomitant administration of medicinal products that may increase the risk of bleeding (e.g. NSAIDs, oral anticoagulants and/or fibrinolytics) ▪ Patients with or at risk of bradycardia (see side effects) ▪ Patients with asthma or COPD (see side effects) ▪ Patients on renal dialysis ▪ Use in patients with uric acid nephropathy is discouraged ▪ Women of child-bearing age should use appropriate contraceptive measures whilst taking ticagrelor

3. Monitoring

3.1. Renal function - Creatinine levels may increase after initiation of ticagrelor (mechanism unknown)**.** Secondary care must ensure a baseline creatinine is communicated on the discharge summary to facilitate on-going monitoring. Renal function should be checked by the patients own GP after one month and thereafter according to routine medical practice. If there is a greater than 20% increase in serum creatinine (or 15% decline in eGFR) over pre-procedural baseline – seek advice from the initiating team (if urgent - via the on-call cardiology registrar).

Ticagrelor is a black triangle drug. ANY adverse effects must be reported to the Committee on Safety of Medicines (CSM). http://yellowcard.mhra.gov.uk/

4. Problem solving

Side effects - The most commonly reported adverse reactions are dyspnoea, subcutaneous or dermal bleeding and epistaxis. Procedural site haemorrhage is also reported commonly. In the PLATO study the following bleeding episodes were seen uncommonly: intracranial haemorrhage, GI bleeding, haemoptysis and haematemesis, urinary and vaginal bleeding. GI side effects also included nausea, vomiting, diarrhoea and abdominal pain.

Dyspnoea: in the PLATO study, 11.8% of patients reported dyspnoea with ticagrelor, and approximately 1% withdrew from ticagrelor as a result. Most reported symptoms of dyspnoea were mild to moderate, and most were reported as a single episode early after starting treatment. Dyspnoea usually resolves within 7 days. Patients with asthma or COPD may be at increased risk.

Do not stop ticagrelor prematurely without discussion with a cardiologist (if urgent - via the on-call cardiology registrar). Premature discontinuation is associated with a very high risk of cardiovascular events. If the patient is experiencing significant adverse effects, seek advice from the initiating team to discuss suitable alternatives

Surgery
Consider stopping ticagrelor 5-7 days before CABG in patients with low risk. For patients at intermediate or higher risk, discuss continuing ticagrelor or clopidogrel before CABG with the cardiac surgeon. Base the decision on the balance of ischaemic and bleeding risk.

5. Drug interactions

Selected interactions: (Refer to BNF/SPC for a full up-to-date list)

Drug Interactions	
Strong CYP3A4 inhibitors: Ketoconazole, Clarithromycin, Atazanavir, Ritonavir	Contra-indicated – significant increase in ticagrelor levels
Moderate CYP3A4 inhibitors: Erythromycin, Diltiazem and Fluconazole	Caution – increase or possible increase in ticagrelor levels
NSAIDs, SSRIs and SNRIs.	Increased risk of GI bleeding. Consider risk vs benefit and indications for treatment with both.
CYP3A4 inducers: Rifampicin, carbamazepine, Phenytoin, phenobarbital, dexamethasone	Discouraged may lead to a decrease in exposure and efficacy of ticagrelor.
Drugs metabolised by CYP3A4: Simvastatin Lovastatin	 Do not exceed 40mg Do not exceed 40mg
P-glycoprotein substrates Digoxin Cyclosporin	 Increased levels of digoxin and ciclosporin Monitor plasma levels
CYP3A4 substrates with narrow therapeutic index e.g. ergot alkaloids	Not recommended – ticagrelor may increase the plasma levels of ergot alkaloids
Warfarin and new oral anticoagulant drugs e.g. dabigatran	Increased risk of bleeding co-prescribing should be avoided.
Clopidogrel or prasugrel	Co-prescribing has not been studied therefore should be avoided.

6. Patient information

- All patients should be given the antiplatelet alert card and counselled on the details.
- Common side effects such as dyspnoea should be discussed with patients
- Ticagrelor has no specific storage requirements therefore is likely to be suitable for compliance aids
- Patients should be advised to inform physicians and dentists that they are taking ticagrelor before any surgery is scheduled and before any new medicinal product is taken
- All patients should be counselled on the duration of treatment.
- Avoid NSAIDs as increased bleeding risk

7. References

1. NICE guidance TA236 Acute Coronary Syndromes – Ticagrelor: guidance. Oct 2011
2. Brilique (ticagrelor) SPC 2011; Astra-Zeneca. Accessed at www.medicines.org.uk/emc/medicine/23935/SPC/brilique%2090%20mg%20film%20coated%20tablets/ 13th August 2012.
3. Wallentin L et al (2009) Ticagrelor versus Clopidogrel in Patients with Acute Coronary syndrome. NEJM 2009: 361:1045-1057
4. Acknowledgments to South London Cardiac and Stroke Network