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Oxford University Hospitals NHS
NHS Trust

Prescribing ticagrelor in acute coronary syndromes

Background
Ticagrelor is a potent antiplatelet agent, licensed for use in combination with aspirin to prevent atherothrombotic events in adult patients with acute coronary syndromes (unstable angina [UA], non ST-elevation myocardial infarction [NSTEMI] or ST-elevation myocardial infarction [STEMI])
Ticagrelor has been approved for the treatment of ACS by NICE: TAG 236 (October 2011).

Selection of Patients:
A t OUH ticagrelor is recommended for:
- Patients presenting with a STEMI undergoing primary percutaneous coronary intervention (pPCI)
- Patients presenting with a confirmed diagnosis of NSTEMI

Ticagrelor should only be initiated in secondary care, usually by a cardiac registrar or consultant. Ticagrelor may also be considered for certain high risk UA patients on the advice of a consultant cardiologist only.

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.

Dose
Initiation: A ticagrelor loading dose of 180mg should be given once diagnosis of STEMI OR NSTEMI is confirmed (this includes patients that may have already been loaded with clopidogrel)
Maintenance dose: Ticagrelor should be continued at a dose of 90mg twice daily for 12 months. Patients prescribed ticagrelor should also be taking aspirin at a maintenance dose of 75mg daily, following an initial loading dose of 300mg, which should continue lifelong (higher doses of aspirin are not recommended due to increased risk of bleeding).

Current practice of loading patients with possible ACS with 300mg of aspirin and 300mg or 600mg of clopidogrel (higher dose is used if coronary angioplasty likely) is to continue at present. In the future, if ambulance crews have access to ticagrelor, STEMI patients undergoing pPCI will be loaded with ticagrelor by ambulance crews pre-pPCI.

Ticagrelor therapy should not be discontinued prematurely without cardiology advice

Contra-indications
Ticagrelor is contra-indicated in the following situations:
- 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)
- Hypersensitivity to the active substance or to any of the excipients

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Ticagrelor should be used with caution in the following patient groups:

- Patients with an increased bleeding risk e.g. clinically important thrombocytopenia or anaemia or other coagulation disorders, active or recent gastrointestinal bleeding, recent trauma or major surgery.
- Patients with concomitant administration of medicinal products that may increase the risk of bleeding e.g. non-steroidal anti-inflammatory drugs (NSAIDs), oral anticoagulants, or fibrinolytics within 24 hours of ticagrelor dosing
- Patients with or at risk of bradycardia
- Patients with asthma or COPD (see under advice for GP)
- Patients on renal dialysis and patients with moderate to severe renal impairment (see under monitoring below).
- Patients with a history of hyperuricaemia or gouty arthritis
- Women of childbearing age (use of appropriate contraception is recommended)

Monitoring

Renal Function: Creatinine levels may increase after initiation of ticagrelor therapy. Renal function should be checked in secondary care upon initiation of therapy and by the patient's GP one month after starting treatment. Thereafter renal function should be checked according to routine medical practice, paying particular attention to patients over 75 years of age, patients with moderate to severe renal impairment and those receiving concomitant treatment with angiotensin receptor blockers (ARBs) e.g. losartan, candesartan.

Side effects (for full details see the BNF or Summary of product characteristics (SPC)
http://www.medicines.org.uk/EMC/medicine/23935/SPC/Brilique+90+mg+film+coated+tablets/
The most commonly reported side effects are dyspnoea, subcutaneous or dermal bleeding and epistaxis

Dyspnoea: In the PLATO study 11.8% of patients reported dyspnoea and approximately 1% withdrew from ticagrelor as a result. Most reported symptoms of dyspnoea were mild to moderate, and were reported as a single early episode after staring treatment. Dyspnoea usually resolves within 7 days. Ticagrelor does not affect pulmonary function tests. Patients with asthma or COPD may be at an increased risk of reporting dyspnoea.

Drug interactions

Commonly Used Interacting Drugs (See SPC and BNF for a full list of drug interactions)

- Clarithromycin - contraindicated. Consider using erythromycin as an alternative.
- Ketoconazole - contraindicated.
- Nefazodone - contraindicated
- Ritonavir and atazinavir - contraindicated
- Dexamethasone, phenytoin, carbamazepine and phenobarbital can reduce the efficacy of ticagrelor. Consider clopidogrel or prasugrel as an alternative.
- Ciclosporin – ticagrelor may increase ciclosporin levels
- Digoxin - ticagrelor may increase digoxin plasma levels
- Simvastatin - ticagrelor increases simvastatin levels, avoid simvastatin doses above 40mg due to risk of toxicity
- Diltiazem may increase ticagrelor levels
- Antidepressants – possible increased risk of bleeding when ticagrelor given with citalopram, paroxetine or sertraline

Advice for GPs:

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

- Check renal function one month after starting therapy. If there is a greater than 20% increase in serum creatinine seek advice from the intiating team (if urgent via the on-call cardiac registrar)

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- Ensure aspirin is continued for life and ticagrelor is discontinued after 1 year. It is recommended that a stop date for ticagrelor is entered into the practice computer system.

- When prescribing new drugs for patients on ticagrelor therapy consider potential drug interactions (see BNF / SPC for full information). Concomitant use of NSAIDS and / or SSRIs will increase bleeding risk

- Mild to moderate dyspnoea can occur, particularly in the first 7 days of treatment. Dypsnoea is usually transient, but if it is persistent or severe, seek advice from the initiating team. Patients with asthma or COPD are at increased risk of dyspnoea.

- Ticagrelor is a black triangle drug and therefore all adverse events should be reported to the MHRA using the yellow card system, even if the side effect is well documented.

References

1. NICE guidance TA236 Acute coronary syndromes - Ticagrelor: guidance. Oct 2011
2. Brilique (ticagrelor) SPC 2011; Astra Zeneca. Accessed at http://www.medicines.org.uk/EMC/medicine/23935/SPC/Brilique+90+mg+film+coated+tablets/ 17th October 2012
3. Wallentin et al (2009) Ticagrelor versus clopidogrel in patients with acute coronary syndrome. NEJM 2009: 361: 1045-1057