Oxford University Hospitals NHS
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Extended ticagrelor therapy for the prevention of atherothrombotic events after myocardial infarction

Amber Continuation Guideline

For patients initiated on Ticagrelor 90mg twice daily following MI between March 2016 and October 2017:

GPs are asked to identify and risk assess patients according to the criteria from the PEGASUS-TIMI54 study (see High Risk criteria table below). Resources are available; an Emis search to produce a list of patients for review and a patient letter to advise of Ticagrelor continuation following their first year. It is suggested that a clinical note or screen message is added to patient records of identified high risk patients, to commence 60mg continuation treatment following completion of one year on 90mg, and that start and stop dates are added to prescription direction information to ensure patient and pharmacist are aware.
The Medicines Optimisation Team is available to assist with patient identification for review.

This guideline provides prescribing and monitoring guidance for ticagrelor therapy in the prevention of atherothrombotic events in adults who have had a myocardial infarction (MI) and who are at risk of a further event. It should be read in conjunction with the Summary of Product Characteristics (SPC) available on www.medicines.org.uk/emc and the BNF.

Specialist responsibilities prior to transfer of prescribing

- Complete pre-treatment assessment
- Give recommendations for initiating / extending ticagrelor therapy in high risk patients in the community following completion of initial 1-year treatment with dual antiplatelet therapy (DAPT) which usually consists of aspirin and ticagrelor (treatment dose 90mg twice daily) or other adenosine diphosphate receptor inhibitor therapy, e.g. clopidogrel.
- Ensure patients understand the nature and complications of drug therapy and their role in reporting adverse effects promptly
- Provide copy of patient information leaflet and drug monitoring card where appropriate
- Be available to give advice to GP and patient during treatment.

GP responsibilities summary

- Prescribe medication as recommended below, at appropriate time.
- Ensure all monitoring is completed in accordance with ‘on-going monitoring’ section.
- Monitor patient for adverse effects, contraindications and precautions as listed below.
- Take subsequent recommended actions as outlined below, including referral back to specialist if appropriate.

Patient responsibilities

- Attend GP practice for monitoring tests as requested by the GP
- Report any side effects to the GP

Background for Use

NICE TA 420 recommends the use of ticagrelor 60mg twice a day in combination with aspirin 75mg to 150mg daily as an option for preventing atherothrombotic events in adults with a history of myocardial infarction (of at least 1 year) who are at risk of developing further atherothrombotic events (see table below).[1] Treatment may be started without interruption after the initial 1-year treatment with DAPT (which includes ticagrelor or other adenosine diphosphate receptor inhibitor e.g. clopidogrel) or started up to 2 years after the myocardial infarction e.g. within 1 year after stopping DAPT. The maximum recommended duration of therapy with extended ticagrelor treatment is 3 years.

High risk criteria: 1 or more of the following high risk features:	
• Aged 65 years or older	• Diabetes requiring medication
• Multi-vessel coronary artery disease	• Chronic non-end stage kidney disease (Creatinine clearance less than 60ml/min)
• More than one previous MI	

The NICE recommendation is based on the PEGASUS-TIMI 54 trial which compared two ticagrelor doses (60mg twice daily and 90mg twice daily) with placebo.[2] The primary composite end-point was cardiovascular death, myocardial infarction or stroke. Ticagrelor significantly reduced the rate of the primary composite end-point compared to placebo at 3 years: Kaplan-Meier rates were 7.85% in the 90mg ticagrelor group, 7.77% in the ticagrelor 60mg group and 9.04% in the placebo group. The trial estimated that for every 10,000 patients who began treatment 42 primary end-point events per year would be prevented with ticagrelor 60mg twice daily, compared to 40 primary end-point events per year with ticagrelor 90mg twice daily.

Ticagrelor significantly increased the rate of bleeding, including TIMI major bleeding, bleeding leading to transfusion and bleeding leading to discontinuation of the drug. Dyspnea was also more frequent with ticagrelor which occurred early after initiation. The trial concluded that the 60mg dose may offer a more attractive benefit-risk profile as there was a trend towards lower rates of bleeding and dyspnea. Discontinuation rates within the study were approximately 32% for the ticagrelor 90mg group, 28.7% for the ticagrelor 60mg group and 21.4% for the placebo group. Discontinuation in the ticagrelor group was largely due to adverse events.

Supporting Information

- **Summary of Product Characteristics**

Ticagrelor 60mg and 90mg tablets
Patient information leaflet ticagrelor 60mg tablets

- **NICE Technology Appraisal 420**

Ticagrelor for prevention atherothrombotic events after myocardial infarction

Contraindications and Precautions

Note: Most patients that are eligible for extended ticagrelor treatment will have already tolerated ticagrelor therapy as part of their initial year of DAPT. During extended treatment ongoing awareness of contra-indications and precautions are applicable in case of any changes in the patient's clinical status.

Contraindications Action: stop treatment	Precautions Action: advice is given below where applicable, contact cardiologist for further advice if needed
• Hypersensitivity to ticagrelor or other substances within tablets • Severe bleeding • History of intracranial haemorrhage • Severe hepatic impairment • Concomitant administration with strong CYP3A4 inhibitors (see under drug interactions)	• Increased risk of bleeding e.g. recent gastro-intestinal bleeding, recent trauma or surgery, clinically important thrombocytopenia, anaemia or other coagulation disorders. Continued treatment should be balanced against risk - stop treatment if bleeding severe. • Concomitant medication that may increase risk of bleeding e.g. non-steroidal anti-inflammatory drugs (NSAIDs), oral anticoagulants, SSRIs. • Prior ischaemic stroke – extended ticagrelor maintenance therapy beyond 1 year of DAPT is not recommended in these patients due to lack of data. • Moderate hepatic impairment. • Patients at risk of bradycardia or concomitant medication known to induce bradycardia. • Planned surgery – ticagrelor should be stopped 7 days prior to elective surgery if antiplatelet effect is not desired. • Asthma / COPD - increased risk of dyspnoea, which usually occurs at start of treatment. Stop treatment if dyspnoea severe or prolonged. • Patients with a history of hyperuricaemia or gouty arthritis • Patients on renal dialysis

Dosage

Indication	Dose
Prevention of atherothrombotic events after MI- extended ticagrelor treatment	60mg twice daily for up to a maximum of 3 years

Time to Response

Extended ticagrelor maintenance therapy is a long term therapy for prevention of atherosclerotic events. The beneficial effect of ticagrelor was observed early in the PEGASUS TIMI 54 trial compared to placebo.

Pre-Treatment Assessment

As extended ticagrelor therapy will be initiated in community 1 year after the cardiologist's recommendation for therapy, the GP should review the contra-indications and precautions before prescribing extended ticagrelor maintenance therapy in case of any change in patient's clinical status or concomitant medication which may affect prescribing of ticagrelor.

- **Patients previously on ticagrelor as part of initial DAPT following MI**

If extended ticagrelor treatment is to be initiated without interruption following completion of the initial 1-year treatment of DAPT which includes aspirin and ticagrelor, the patient must have one or more high risk features to meet criteria for therapy, as directed by a cardiologist (see supporting information). The decision to continue ticagrelor treatment must be agreed between the GP and the patient.

- **Patients not previously taking ticagrelor as part of initial DAPT**

Some patients may complete an initial 1-year of DAPT which includes aspirin and clopidogrel or other ADP receptor inhibitor. The cardiologist may recommend that the patient

is switched to extended treatment which involves ticagrelor, providing the patient meets criteria for therapy and has 1 or more high risk features. This scenario is unlikely to occur frequently but may occur if there has been a change in the patient's clinical status or concomitant therapy. In this situation, in addition to reviewing contra-indications and precautions (see above) the patient's renal function should be checked before initiating therapy, if not checked recently (within last month). The decision to start extended ticagrelor therapy must be agreed between the GP and the patient.

Ongoing Monitoring

Renal Function: Creatinine levels may increase after initiation of ticagrelor therapy. For those patients that have not received ticagrelor previously (see above) the GP should check renal function before starting therapy and then one month after starting treatment. Thereafter for all patients receiving extended ticagrelor therapy 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 converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARBs or sacubitril /valsartan therapy. There is no specific ongoing monitoring needed for maintenance ticagrelor therapy.

Actions to be taken

For advice contact the relevant cardiologist who initiated/ recommended extended ticagrelor therapy, alternatively, if urgent, contact the cardiology SpR on call on 0300 304 7777 bleep 4205.

Side Effects	Action
Thrombocytopenia	Review patient's clinical status for other causes. Repeat test, if trending downward contact cardiologist for advice, if less than 50 x 10^9/L consider stopping treatment.
Bleeding	If severe bleeding stop treatment and contact cardiologist for advice' If ongoing minor bleeding episodes e.g. frequent nose bleeds check haemoglobin, platelets and If anaemic / thrombocytopenic contact cardiologist for advice.
Dyspnoea	Mild to moderate dyspnoea can occur, particularly in the first 7 days of treatment. Dyspnoea is usually transient, but if it is persistent or severe, contact cardiologist for advice. Patients with asthma or COPD are at increased risk of dyspnoea.
Bradycardia	Review concomitant medication; if bradycardia is ongoing consider reducing dose of other heart rate lowering drugs. Contact cardiologist for advice if persistent.
Increased creatinine	Check renal function one month after starting therapy (if new to ticagrelor therapy). If there is a greater than 20% increase in serum creatinine contact cardiologist for advice.
Hyperuricaemic	Consider starting xanthine-oxidase inhibitor if symptomatic (do not start during acute attack).

Notable Drug Interactions (Refer to BNF and SPC)

The effects of drug interactions, especially those which result in increased exposure to ticagrelor might be less significant with the lower 60mg twice daily dose of ticagrelor used in

extended treatment. However data provided by the manufacturer does not differentiate between different doses of ticagrelor.

- Avoid concomitant use with strong CYP3A4 inhibitors e.g. clarithromycin, ketoconazole, nefazodone , ritonavir and atazanavir
- Other drugs may increase levels of ticagrelor e.g. cyclosporine, verapamil, quinidine, erythromycin, fluconazole, erythromycin, amprenavir, aprepitant: use with caution.
- Dexamethasone, phenytoin, carbamazepine and phenobarbital can reduce the efficacy of ticagrelor, consider changing to another antiplatelet/discuss with cardiologists.
- Digoxin - ticagrelor may increase digoxin plasma levels, monitor digoxin levels if appropriate.
- Aspirin – avoid use of high dose aspirin (above 300mg) in combination with ticagrelor.
- Simvastatin - ticagrelor increases simvastatin levels, avoid simvastatin doses above 40mg due to risk of toxicity.
- Antidepressants – possible increased risk of bleeding when ticagrelor given with SSRIs e.g. citalopram, paroxetine or sertraline, use with caution.
- Avoid use, or minimize use of NSAIDs with ticagrelor due to risks of bleeding.
- Anticoagulants – use of ticagrelor with anticoagulants should be avoided. Contact cardiologist for advice if initiation of an anticoagulant is indicated whilst patient is on extended ticagrelor therapy.
- Use of ticagrelor with other drugs known to cause bradycardia e.g. beta blockers, digoxin, calcium channel blockers may increase risk of bradycardia, see under ongoing monitoring.

Back-up Information and Advice

Contact the relevant consultant cardiologist for further advice, usually one of the interventional cardiologists responsible for the patient's care following MI. Alternatively contact the cardiology SpR on call via OUH switchboard on 0300 304 7777 bleep 4205.

References

1. NICE Technology Appraisal Guidance: Ticagrelor for preventing atherothrombotic events after myocardial infarction. December 2016.
2. Bonaca et al. Long-term use of ticagrelor in patients with prior myocardial infarction. NEJM 2015; 372: m1791-1800) PEGASUS-TIMI 54 trial.