Guidance for prescribing Ticagrelor to treat Acute Coronary Syndromes (ACS)

1. BACKGROUND

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 clinical guideline 172 (November 2013) recommends ticagrelor in combination with low-dose aspirin for up to 12 months as a treatment option in adults with acute coronary syndrome (ACS).

2. INDICATIONS

Ticagrelor should be considered for patients with:
- A new STEMI treated with primary PCI or thrombolytic therapy
- A confirmed diagnosis of NSTEMI irrespective of any revascularisation strategy.

3. DOSE

- STEMI: loading dose of ticagrelor 180mg STAT followed by - Ticagrelor 90mg TWICE a DAY for up to 12 months in combination with aspirin 75mg once a day lifelong
- ACS (except STEMI): load with clopidogrel 300mg STAT followed by 75mg once a day, plus aspirin 75mg once a day. When diagnosis of NSTEMI has been confirmed with a positive troponin result, load with ticagrelor 180mg STAT followed by Ticagrelor 90mg TWICE a DAY for up to 12 months in combination with aspirin 75mg once a day lifelong

Ticagrelor 90mg twice a day should be stopped when clinically indicated or at 12 months.

(Ticagrelor 90mg orodispersible tablets are now available)

4. DRUG INTERACTIONS

Ticagrelor is primarily a CYP3A4 substrate and a mild inhibitor of CYP4A4, also a P-glycoprotein (P-gp) substrate and a weak P-glycoprotein inhibitor and may increase the exposure of P-glycoprotein substrates.

Selected drug interactions (See BNF/SPC for a full up to date list)

<table>
<thead>
<tr>
<th>Drug Interactions</th>
<th>Interaction</th>
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<tbody>
<tr>
<td>Strong CYP3A4 inhibitors: Ketoconazole, clarithromycin, nefazodone, ritonavir and atazanavir</td>
<td>Contra-indicated – significant increase in ticagrelor levels</td>
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<tr>
<td>Moderate CYP3A4 inhibitors: Erythromycin, fluconazole, diltiazem</td>
<td>Caution – increase or possible increase in ticagrelor levels</td>
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<tr>
<td>NSAID’s and SSRI’s</td>
<td>Caution - may increase the risk of bleeding</td>
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<tr>
<td>CYP3A inducers: Rifampicin, phenytoin, carbamazepine and phenytoin</td>
<td>Discourage – may lead to a decrease in exposure and efficacy of ticagrelor</td>
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<tr>
<td>P-glycoprotein and CYP3A inhibitors: Cyclosporin, verapamil and quinidine</td>
<td>May increase ticagrelor exposure</td>
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<tr>
<td>P-glycoprotein substrates: Digoxin</td>
<td>Levels maybe increased – monitor plasma levels advised</td>
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<tr>
<td>CYP3A4 substrates with narrow therapeutic index: i.e. ergot alkaloids</td>
<td>Not recommended – ticagrelor may increase the levels of ergot alkaloids</td>
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<tr>
<td>Drugs metabolised by CYP3A4: Simvastatin</td>
<td>Greater than 40mg is not recommended</td>
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<tr>
<td>Warfarin and new oral anticoagulant agents</td>
<td>Co-prescribing with ticagrelor increases the risk of bleeding – use with caution or avoid</td>
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</tbody>
</table>
5. CONTRAINDICATIONS AND CAUTIONS

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), as co-administration may lead to a substantial increase in exposure to ticagrelor.
- Hypersensitivity to the active substance or to any of the excipients

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

- Increased risk of bleeding
- Patients with a tendency to bleed (e.g. due to trauma, recent surgery, coagulation disorders, active or recent GI bleeding)
- Patients on concomitant administration of medications that may increase the risk of bleeding (e.g. non-steroidal anti-inflammatory drugs (NSAIDs), oral anticoagulants,
- Antifibrinolytic therapy (tranexamic acid) and/or recombinant factor VIIa therapy may increase haemostasis. Ticagrelor may be resumed after the cause of bleeding has been identified and controlled.
- Elective surgery – discontinue ticagrelor 7 days prior to surgery
- Prior ischaemic stroke – ACS patients can be treated for up to 12 months (can use clopidogrel monotherapy after 12 months rather than aspirin monotherapy)
- Patients at risk of bradycardia
- Asthma/COPD: If a patient, particularly those with pre-existing asthma/COPD reports new, prolonged or worsened dyspnoea this should be investigated fully and if not tolerated, treatment with ticagrelor should be stopped and replaced with an alternative agent (clopidogrel, prasugrel).
- Renal impairment: Creatinine levels may increase during treatment with ticagrelor. Renal function should be checked at baseline, after one month and then as clinically indicated, paying special attention to patients ≥ 75 years, patients with moderate/severe renal impairment and those receiving concomitant treatment with an ACEI or ARB
- Ticagrelor may increase the risk of hyperuricaemia. Caution is advised in patients with history of hyperuricaemia or gouty arthritis. Ticagrelor is not recommended in patients with uric acid nephropathy.
- Co-administration of ticagrelor with high maintenance dose aspirin >300mg is not recommended
- Premature discontinuation should be avoided could result in an increased risk of cardiovascular death or MI
- Pregnancy and breastfeeding

6. ADVERSE EFFECTS

The most commonly reported adverse reactions (≥ 1/10) are blood disorder bleedings, hyperuricaemia, and dyspnoea

7. INFORMATION TO PATIENT

Patients should be advised on common side-effects

- Bruising
- Dyspnoea
All patients should be counselled on the duration of treatment: Avoid NSAIDs as increased bleeding risk.

Patients should be advised to inform physician and dentists that they are taking ticagrelor before any surgery is scheduled and before any new medications is taken.

Ticagrelor has no specific storage requirements and is suitable for compliance aids.

Details of contraindications, cautions, drug interactions and adverse effects listed above are not exhaustive. For further information always check with BNF www.bnf.org.uk or SPC (www.medicines.org.uk).

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**APPROVAL PROCESS**

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<tr>
<th>Written by:</th>
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<td>Approved by:</td>
<td>MMIG, HERPC Nov 2014</td>
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<tr>
<td>Updated by:</td>
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<td>Review date:</td>
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Use of Ticagrelor in patients with ST Elevation MI (STEMI)

Patient admitted with STEMI

Primary PCI as revascularisation strategy

Load with Ticagrelor 180mg and maintain with 90mg bd. Stop Clopidogrel if already on it.

Discharge with a maintenance dose of Ticagrelor 90mg bd for 12 months

Thrombolytic therapy as revascularisation strategy

Load with Ticagrelor 180mg and maintain with 90mg bd. Stop Clopidogrel if already on it.

Discharge with a maintenance dose of Ticagrelor 90mg bd for 12 months

NB Ticagrelor should be given to this patient group regardless of any revascularisation strategy. The usual strategy of ceasing anti-platelet therapy 7 days prior to CABG still applies. Ticagrelor should be given for 12 months post CABG.

For patients who are intolerant of Ticagrelor, Clopidogrel or prasugrel should be considered. Ticagrelor is available as an orodispersible preparation.

This flowchart should be used alongside the product prescribing information.

Use of Ticagrelor in patients with possible Acute Coronary Syndrome (ACS)

Patient admitted with possible ACS (Not STEMI)

All patients receive Clopidogrel including a loading dose (300mg loading, 75mg daily maintenance) whilst awaiting Troponin and cardiologist review

Confirmed diagnosis following troponin results and Cardiology review

Confirmed diagnosis of NSTEMI

Switch to Ticagrelor (Load with 180 mg then 90mg bd maintenance dose)

Discharge with a maintenance dose of Ticagrelor 90mg bd for 12 months

Confirmed diagnosis of Unstable Angina

Continue with Clopidogrel 75mg daily

Discharge with a maintenance dose of Clopidogrel for 12 months

NB
- All patients with a confirmed diagnosis of NSTEMI should receive Ticagrelor, unless contra-indicated.
- The initiation of Ticagrelor for NSTEMI patients should be restricted to Cardiologists therefore cardiologist review should be facilitated.
- Ticagrelor should be given to this patient group regardless of any revascularisation strategy. The usual strategy of ceasing anti-platelet therapy 7 days prior to CABG still applies.
- Ticagrelor should be given for 12 months post CABG.
- For patients who are intolerant of Ticagrelor, Clopidogrel should be considered.

This flowchart should be used alongside the product prescribing information.