NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Review of TA236; Ticagrelor for the treatment of acute coronary syndromes

This guidance was issued in October 2011.

The review date for this guidance is March 2013.

1. Recommendation

The guidance should be transferred to the 'static guidance list' and incorporated into the forthcoming NICE clinical guideline on the management of myocardial infarction with ST-segment elevation. That we consult on this proposal.

2. Original remit(s)

To appraise the clinical and cost effectiveness of ticagrelor, within its licensed indication, for the treatment of acute coronary syndromes.

3. Current guidance

1.1 Ticagrelor in combination with low-dose aspirin is recommended 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 defined in section 1.2. Before ticagrelor is continued beyond the initial treatment, the diagnosis of unstable angina should first be confirmed, ideally by a cardiologist.

1.2 For the purposes of this guidance, characteristics to be used in defining treatment with ticagrelor for unstable angina are: age 60 years or older; previous myocardial infarction or previous coronary artery bypass grafting (CABG); coronary artery disease with stenosis of 50% or more in at least two vessels; previous ischaemic stroke; previous transient ischaemic attack, carotid stenosis of at least 50%, or cerebral revascularisation; diabetes mellitus; peripheral arterial disease; or chronic renal dysfunction, defined as a creatinine clearance of less than 60 ml per minute per 1.73 m^2 of body-surface area.

4. Rationale[1]

The evidence base for ticagrelor has not changed significantly since publication of TA 236. The price of the comparator, clopidogrel, is now 25% lower than it was in TA236. However, because the ICERs in TA236 were at the lower end of what is normally considered cost effective (£7897 per QALY gained for all ACS, £8872 per QALY gained for STEMI, £7215 per QALY gained for NSTEMI and £9131 per QALY gained for unstable angina), it is not expected that the slightly lower comparator price would lead to the need to change the recommendations. The update of TA182 (prasugrel for ACS) are not expected to affect the recommendation for ticagrelor, as the latter did not depend on a comparison with prasugrel.

5. Implications for other guidance producing programmes

The TA overlaps with two guidelines currently in development. 1) ST-segment-elevation myocardial infarction (STEMI) and 2) The update of CG48 MI – secondary prevention: secondary prevention in primary and secondary care for patients following a myocardial infarction. CCP supports this proposal. The STEMI guideline will continue to incorporate the appropriate recommendations. CG48 will continue to cross refer to the existing TA.

6. New evidence

The search strategy from the original assessment report was re-run on the Cochrane Library, Medline, Medline In-Process and Embase. References from April, 2010 onwards were reviewed. Additional searches of clinical trials registries and other sources were also carried out. The results of the literature search are discussed in the 'Summary of evidence and implications for review' section below. See Appendix 2 for further details of ongoing and unpublished studies.

7. Summary of evidence and implications for review

The marketing authorisation for ticagrelor has not changed since the publication of TA 236. NICE's recommendation for ticagrelor in TA236 as a treatment option in adults with acute coronary syndromes (ACS) is in line with its marketing authorisation.

[redacted]

In TA 236, ticagrelor plus aspirin was compared with clopidogrel plus aspirin in all ACS patients. For people who are to be managed with PCI, ticagrelor plus aspirin was also compared with prasugrel plus aspirin via indirect comparison, but this was not used for the decision making because the indirect comparison was not considered to be robust. There have been no amendments to the marketing authorisations for the comparators included in the guidance. An update of TA 182

[1] A list of the options for consideration, and the consequences of each option is provided in Appendix 1 at the end of this paper

recommending another treatment for ACS, prasugrel, is in development (anticipated date of publication August 2014).

Other technologies are being studied in on-going clinical trials and include otamixaban and cangrelor. [redacted] At the present time it is unclear as to whether these technologies could be considered in the future as comparators to ticagrelor.

The clinical evidence in TA 236 came from the PLATO randomised controlled trial. Eighteen of the identified publications in the literature search were related to the PLATO trial. Five of them were published before TA 236 and therefore, they were incorporated into the guidance. The remaining 13 publications generally support the PLATO findings focusing on specific subgroups or outcomes.

One economic analysis was identified. The study by Nikolic et al, published after TA 236 was issued, assesses the long-term cost-effectiveness of treating ACS patients for 12 months with ticagrelor compared with generic clopidogrel from a Swedish perspective, and it is based on results from the PLATO trial. This study concludes that treating acute coronary syndrome patients with ticagrelor for 12 months is associated with a cost per QALY gained below generally accepted thresholds for cost-effectiveness.

TA 236 recommends that future research be undertaken comparing ticagrelor with prasugrel in people with ACS and into whether ticagrelor is particularly beneficial in any clinical or biological subgroups. Twelve trials have studied ticagrelor since the publication of TA 236, 10 of which are still ongoing. One of the completed trials compares ticagrelor with prasugrel, assessing adenosine-induced coronary vasodilatory responses in 38 patients with ACS undergoing PCI, but no results from the trial are available yet, or any information about the timing of the release of the results. The other completed trial investigates standard versus double loading dose of ticagrelor in patients with STEMI undergoing PCI. One of the ongoing trial (PEGASUS) compares ticagrelor with placebo for up to 38 months for the prevention of cardiovascular events in patients with a prior myocardial infarction (estimated study completion date February 2014). Of the remaining 9 ongoing relevant trials, none are relevant to this appraisal and none address the research recommendations in TA 236.

There has been no change to the acquisition cost of ticagrelor since the publication of TA 236. The price of prasugrel has not changed, however, the price of clopidogrel has dropped by approximately 26.5% (30 tablets pack) (BNF 63) since publication of TA 236.

8. Implementation

A submission from Implementation is included in Appendix 3.

Based on the implementation advice received, there has been an increase in prescribing costs and volume for ticagrelor in both primary care and hospitals

following the publication of NICE technology appraisal 236. Therefore, the increase on prescribing practices of ticagrelor seems to adhere to NICE guidance.

9. Equality issues

No equality issues were identified during the scoping process or the appraisal of ticagrelor. The Committee concluded that there were no equality issues that needed addressing.

GE paper sign off: Elisabeth George 25 02 13

Contributors to this paper:

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Appendix 1 – explanation of options

When considering whether to review one of its Technology Appraisals NICE must select one of the options in the table below:

Options	**Consequence**	**Selected – 'Yes/No'**
A review of the guidance should be planned into the appraisal work programme.	A review of the appraisal will be planned into the NICE's work programme.	No
The decision to review the guidance should be deferred to [specify date or trial].	NICE will reconsider whether a review is necessary at the specified date.	No
A review of the guidance should be combined with a review of a related technology appraisal.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the specified related technology.	No
A review of the guidance should be combined with a new technology appraisal that has recently been referred to NICE.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the newly referred technology.	No
The guidance should be incorporated into an on-going clinical guideline.	The on-going guideline will include the recommendations of the technology appraisal. The technology appraisal will remain extant alongside the guideline. Normally it will also be recommended that the technology appraisal guidance is moved to the static list until such time as the clinical guideline is considered for review. This option has the effect of preserving the funding direction associated with a positive recommendation in a NICE technology appraisal.	Yes

Options	Consequence	Selected – 'Yes/No'
The guidance should be updated in an on-going clinical guideline.	Responsibility for the updating the technology appraisal passes to the NICE Clinical Guidelines programme. Once the guideline is published the technology appraisal will be withdrawn. Note that this option does not preserve the funding direction associated with a positive recommendation in a NICE Technology Appraisal. However, if the recommendations are unchanged from the technology appraisal, the technology appraisal can be left in place (effectively the same as incorporation).	No
The guidance should be transferred to the 'static guidance list'.	The guidance will remain in place, in its current form, unless NICE becomes aware of substantive information which would make it reconsider. Literature searches are carried out every 5 years to check whether any of the Appraisals on the static list should be flagged for review.	Yes

NICE would typically consider updating a technology appraisal in an ongoing guideline if the following criteria were met:

i. The technology falls within the scope of a clinical guideline (or public health guidance)

ii. There is no proposed change to an existing Patient Access Scheme or Flexible Pricing arrangement for the technology, or no new proposal(s) for such a scheme or arrangement

iii. There is no new evidence that is likely to lead to a significant change in the clinical and cost effectiveness of a treatment

iv. The treatment is well established and embedded in the NHS. Evidence that a treatment is not well established or embedded may include;

- Spending on a treatment for the indication which was the subject of the appraisal continues to rise
- There is evidence of unjustified variation across the country in access to a treatment
- There is plausible and verifiable information to suggest that the availability of the treatment is likely to suffer if the funding direction were removed

- The treatment is excluded from the Payment by Results tariff

v. Stakeholder opinion, expressed in response to review consultation, is broadly supportive of the proposal.

Appendix 2 – supporting information

Relevant Institute work

Published

Clinical guidelines CG48. MI – secondary prevention: Secondary prevention in primary and secondary care for patients following a myocardial infarction. Issued: May 2007. Reviewed: February 2011 (the review decision was to update this guideline).

Clinical guidelines CG94 Unstable angina and NSTEMI: the early management of unstable angina and non-ST-segment-elevation myocardial infarction. Issued: March 2010. Review date: March 2013

Clinical guidelines CG130 Management of hyperglycaemia in people with acute coronary syndromes. Issued: October 2011. Review date: October 2014

Technology appraisals TA47 Glycoprotein IIb/IIIa inhibitors in the treatment of acute coronary syndromes. Issued: September 2002. This guidance has been partially updated (recommendation 1.1-1.6) by CG94 Unstable angina and NSTEMI: the early management of unstable angina and non-ST-segment-elevation myocardial infarction. Recommendations 1.7 and 1.8 of TA47 were transferred to the static list.

Technology appraisal TA80 Clopidogrel in the treatment of non-ST-segment-elevation acute coronary syndrome (recommendation 1.3 only). Issued: July 2004. Recommendation 1.1 and 1.2 have been updated by CG94 Unstable angina and NSTEMI: the early management of unstable angina and non-ST-segment-elevation myocardial infarction. Recommendation 1.3 was incorporated into the same guideline but reviewed as an RPP in December 2012 (proposed that recommendation 1.3 should be updated into CG94)

Technology appraisals TA182 Prasugrel for the treatment of acute coronary syndromes with percutaneous coronary intervention. Issued: October 2009. Review decision: June 2012 - it was decided to review this guidance.

In progress

Technology appraisal. Prasugrel with percutaneous coronary intervention for the treatment of acute coronary syndrome (review of TA182). Expected date of publication: August 2014.

Technology appraisal. Rivaroxaban for the prevention of adverse outcomes in patients after the acute management of acute coronary syndrome. Expected date of publication: September 2013.

Referred - QSs and CGs

- Acute coronary syndromes (including myocardial infarction)
- Secondary prevention of myocardial infarction and cardiac rehabilitation

Details of changes to the indications of the technology

Indication considered in original appraisal	Proposed indication (for this appraisal)
Ticagrelor, co-administered with low-dose aspirin, is indicated for the prevention of atherothrombotic events in adult patients with ACS, defined as STEMI, NSTEMI or unstable angina. Patients with ACS who receive ticagrelor and aspirin may receive drugs only (medical management) or may also undergo revascularisation with PCI or CABG.	[redacted]

Details of new products

Drug (manufacturer)	Details (phase of development, expected launch date)
Rivaroxaban (Bayer) (TA in development)	N/A

Registered and unpublished trials

Trial name and registration number	Details
Prevention of Cardiovascular Events (eg, Death From Heart or Vascular Disease, Heart Attack, or Stroke) in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin (PEGASUS) (NCT01225562)	Estimated enrolment: 21000 Estimated study completion date: February 2014
Evaluation of Ticagrelor Anti Platelet and Pleiotropic Effects in Patients Undergoing Percutaneous Coronary Intervention for an Acute Coronary Syndrome (NCT01626534)	Estimated enrolment: 105 Estimated study completion date: September 2013
Differential Effect of Ticagrelor Versus Prasugrel on the Adenosine-induced Coronary Vasodilatory Responses in Patients With Acute Coronary Syndrome Undergoing Percutaneous Coronary Intervention (NCT01642966)	Estimated enrolment: 38 Estimated study completion date: September 2012. Results not yet published.

Trial name and registration number	Details
Comparison of Antiplatelet Effect of Ticagrelor vs Tirofiban in Patients With Non-ST Elevation Acute Coronary Syndrome (TE-CLOT) (NCT01660373)	Estimated enrolment: 100 Estimated study completion date: August 2013
Ad Hoc Percutaneous Coronary Intervention Study in Acute Coronary Syndrome Patients (NCT01603082)	The purpose of this study is to assess the pharmacodynamic effect of ticagrelor in ACS patients undergoing an Ad Hoc PCI. Estimated enrolment: 100 Estimated study completion date: June 2013
Study Comparing Ticagrelor With Aspirin for Prevention of Vascular Events in Patients Undergoing CABG (TiCAB) (NCT01755520)	Estimated enrolment: 4008 Estimated study completion date: December 2015
Antithrombotic Effects of Ticagrelor Versus Clopidogrel (NCT01642238)	The purpose of this study is to determine whether treatment with ticagrelor (plus aspirin and bivalirudin) is more effective than treatment with clopidogrel (plus aspirin and bivalirudin). Estimated enrolment: 15 Estimated study completion date: June 2013
Tailored Antiplatelet Initiation to Lesson Outcomes Due to Decreased Clopidogrel Response After Percutaneous Coronary Intervention (TAILOR-PCI) (NCT01742117)	The purpose of this study is to determine if by genetic testing the best anti-platelet therapy, for patients who undergo a coronary stent placement who do not activate clopidogrel very well, is identified. Estimated enrolment: 5945 Estimated study completion date: June 2016
Cost-effectiveness of Genotype Guided Treatment With Antiplatelet Drugs in STEMI Patients: Optimization of Treatment (POPGenetics) (NCT01761786)	Estimated enrolment: 2700 Estimated study completion date: October 2014
High Clopidogrel Dose Versus Prasugrel and Ticagrelor in High Reactive Stable Patients (TRIPLETE RESET) (NCT01543932)	Estimated enrolment: 30 Estimated study completion date: February 2013

Trial name and registration number	Details
Standard (180mg) Versus Double (360mg) Loading Dose of Ticagrelor in Patients With ST-elevation Myocardial Infarction (STEMI), Undergoing Primary Percutaneous Coronary Intervention (PCI): a Multi-center Randomized Parallel Pharmacodynamic Study (NCT01575795)	Estimated enrolment: 130 Estimated study completion date: September 2012
On-treatment PLAtelet Reactivity-guided Therapy Modification FOR ST-segment Elevation Myocardial Infarction (PLATFORM) (NCT01739556)	Estimated enrolment: 632 Estimated study completion date: October 2016

References

Nikolic E, Janzon M, Hauch O et al (2013) Cost-effectiveness of treating acute coronary syndrome patients with ticagrelor for 12 months: results from the PLATO study. *European Heart Journal* 34 (3): 220-228.

Appendix 3 – Implementation submission

Implementation feedback: review of NICE technology appraisal guidance 236

NICE Technology Appraisal 236; Acute coronary syndromes - ticagrelor
Implementation input required by 17/12/2012
Please contact Rebecca Lea regarding any queries rebecca.lea@nice.org.uk

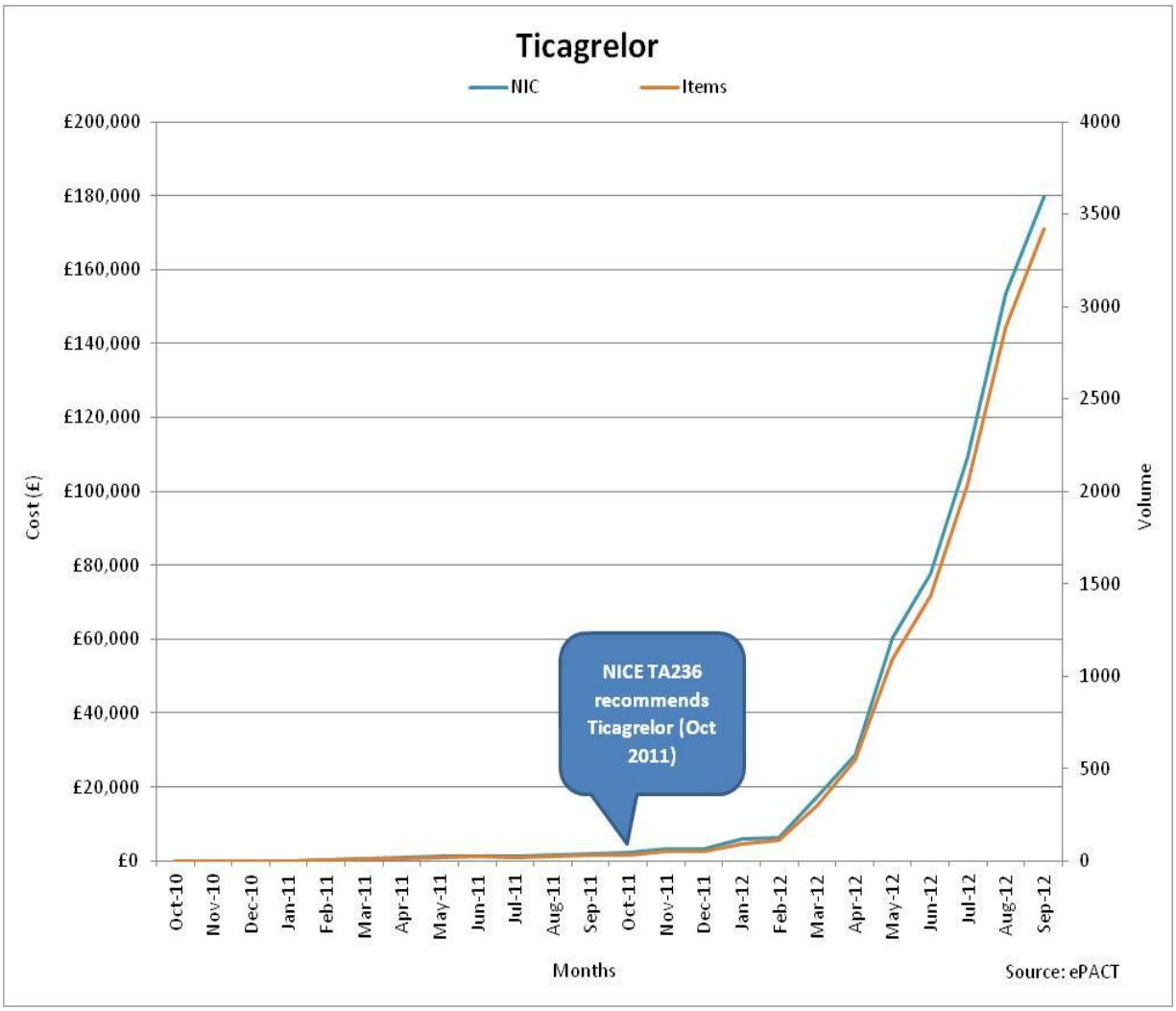
Contents

1 Routine healthcare activity data

1.1 ePACT and hospital ePACT

This section presents electronic prescribing analysis and cost tool (ePACT) data on the net ingredient cost (NIC) and volume of Ticagrelor, prescribed in primary care and in hospitals that has been dispensed in the community in England between October 2010 and September 2012.

Figure 1 Net ingredient cost and volume of Ticagrelor prescribed in primary care and in hospitals that has been dispensed in the community



2 Implementation studies from published literature

Information is taken from the uptake database (ERNIE) website.

Nothing to add at this time.

3 Qualitative input from the field team

The implementation field team have recorded the following feedback in relation to this guidance:

Nothing to add at this time.

Appendix A: Healthcare activity data definitions

Prescribing analysis and cost tool system

This information comes from the electronic prescribing analysis and cost tool (ePACT) system, which covers prescriptions by GPs and non-medical prescribers in England and dispensed in the community in the UK. The Prescription Services Division of the NHS Business Services Authority maintains the system. PACT data are used widely in the NHS to monitor prescribing at a local and national level. Prescriptions dispensed in hospitals or mental health units, and private prescriptions, are not included in PACT data.

Measures of prescribing

Prescription Items: Prescriptions are written on a prescription form. Each single item written on the form is counted as a prescription item. The number of items is a measure of how many times the drug has been prescribed.

Cost: The net ingredient cost (NIC) is the basic price of a drug listed in the drug tariff, or if not in the drug tariff, the manufacturer's list price.

Data limitations (national prescriptions)

PACT data do not link to demographic data or information on patient diagnosis. Therefore the data cannot be used to provide prescribing information by age and sex or prescribing for specific conditions where the same drug is licensed for more than one indication.