NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Technology Appraisal Review Proposal paper

Review of TA317; Prasugrel with percutaneous coronary intervention for treating acute coronary syndrome

Original publication date:	July 2014
Review date	June 2017
Existing recommendations:	Recommended To see the complete existing recommendations and the original remit for TA317, see Appendix A.

1. Proposal

The guidance should be transferred to the 'static guidance list'. That we consult on this proposal.

2. Rationale

Limited new evidence has been published since NICE technology appraisal guidance 317 and no evidence has been identified that suggests a review of this guidance is necessary. Therefore it is proposed that TA317 is moved to the static list.

3. Summary of new evidence and implications for review

Has there been any change to the price of the technology(ies) since the guidance was published?
The net price for a 28-tablet pack has not changed since the guidance was published.
Are there any existing or proposed changes to the marketing authorisation that would affect the existing guidance?
There are no changes or proposed changes to the marketing authorisation.
Were any uncertainties identified in the original guidance? Is there any new evidence that might address this?
The original guidance compared prasugrel in combination with aspirin with clopidogrel in combination with low-dose aspirin and ticagrelor in combination with

low-dose aspirin. The evidence for the comparison with clopidogrel in combination with low-dose aspirin came from 1 randomised controlled trial (TRITON-TIMI 38, Wiviott et al 2007), which compared prasugrel with clopidogrel in patients with moderate- to high-risk acute coronary syndromes (ACS; unstable angina, non-ST-segment-elevation myocardial infarction [NSTEMI] or ST-segment-elevation myocardial infarction [STEMI]) who were scheduled to have percutaneous coronary intervention (PCI). No evidence was presented for the comparison with ticagrelor as there were no trials directly comparing the 2 technologies and an indirect comparison was considered inappropriate because the trials for prasugrel and ticagrelor were not comparable.

In the original guidance the committee concluded that there was uncertainty about:

1. whether the 10mg dose of prasugrel was clinically superior to clopidogrel in patients with unstable angina or NSTEMI because of the lack of generalisability of the results from TRITON-TIMI 38 trial to clinical practice in England.
2. the efficacy and safety of the 5mg dose of prasugrel that is recommended in the summary of product characteristics for patients at increased risk of bleeding because no evidence was presented during the appraisal. The summary of product characteristics states that the use of prasugrel for people aged 75 years or over is not recommended but for people in this group where treatment is deemed necessary, a maintenance dose of 5 mg of prasugrel should be given.
3. the relative effectiveness of prasugrel and ticagrelor for people with STEMI, unstable angina, or NSTEMI (although there was some support for the possibility of clinical equivalence in the case of STEMI only) as there was a lack of evidence that directly compared the 2 technologies and an indirect comparison was not presented.

Since the original guidance was published, no new published trials and no ongoing trials have been identified that compare the 10mg dose of prasugrel with clopidogrel for people with ACS having PCI and therefore it is not possible to address the uncertainty resulting from the generalisability of the results from TRITON-TIMI 38 trial to clinical practice in England.

Since the original guidance was published, no published trials have been identified that compare the use of the 5mg dose of prasugrel with clopidogrel for people with ACS undergoing PCI. There are 2 ongoing trials that compare the reduced dose of prasugrel with clopidogrel for people older than 74 years with ACS; POPular AGE has an estimated completion date of January 2019 and Elderly ACS II has an estimated completion date of December 2017. These trials may address some of the uncertainty around the efficacy and safety of the 5mg dose of prasugrel. However, it is difficult to determine with the currently available information on the trials, whether these trials would lead to a change in the existing recommendations.

Since the original guidance was published, 3 published indirect comparisons and 1 published direct comparison have been identified (Rafique et al. 2016, Westman et al. 2017, Ye et al. 2014), which compare prasugrel with ticagrelor. Rafique et al. (2016) indirectly compared prasugrel and ticagrelor in people with STEMI only and found that prasugrel may be more effective than ticagrelor in some circumstances. Westman et al. (2017) indirectly compared prasugrel with ticagrelor in all people

with acute coronary syndromes and found comparable clinical outcomes. Ye et al. (2014) indirectly compared prasugrel with ticagrelor in all people with acute coronary syndromes and found that ticagrelor may be more clinically beneficial. Motovska et al. (2016) directly compared the effects of prasugrel with ticagrelor only in people with STEMI or very high risk NSTEMI. The study was randomised but not blinded, and was did not recruit enough participants to be able to conclude about the difference in efficacy and safety of prasugrel and ticagrelor. It was terminated early because of futility and did not find that prasugrel or ticagrelor was more effective or safer than the other. There are 2 ongoing studies; ISAR-REACT 5 directly compares prasugrel with ticagrelor and the expected completion date is January 2021. This is a large trial that will allow a formal comparison once completed. DUBIUS compares prasugrel with ticagrelor in NSTEMI and unstable angina and the expected completion date is November 2018. There is not enough information available to estimate the impact the DUBIUS trial would have on this appraisal. Since the original guidance was published, ticagrelor has received an extension to its marketing authorisation for the prevention of atherothrombotic events in adult patients with a history of myocardial infarction (MI) and a high risk of developing an atherothrombotic event. NICE has published guidance for this extension to the marketing authorisation (see NICE technology appraisal guidance 420). This does not have an impact on this appraisal.
Are there any related pieces of NICE guidance relevant to this appraisal? If so, what implications might this have for the existing guidance?
See Appendix C for a list of related NICE guidance.
Additional comments
None.

The search strategy from the original ERG report was re-run on the Cochrane Library, Medline, Medline In-Process and Embase. References from June 2013 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 C for further details of ongoing and unpublished studies.

4. Equalities issues

No equality issues relevant to the committee's recommendations were raised in the original guidance.

GE paper sign off: **Meindert Boysen, 9 June 2017**

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Appendix A – Information from existing guidance

5. Original remit

To appraise the clinical and cost effectiveness of prasugrel in combination with aspirin within its licensed indication for the treatment of acute coronary artery syndromes (review of TA182).

6. Current guidance

1.1 Prasugrel 10 mg in combination with aspirin is recommended as an option within its marketing authorisation, that is, for preventing atherothrombotic events in adults with acute coronary syndrome (unstable angina [UA], non-ST segment elevation myocardial infarction [NSTEMI] or ST segment elevation myocardial infarction [STEMI]) having primary or delayed percutaneous coronary intervention.

7. Research recommendations from original guidance

N/A

8. Cost information from original guidance

3.5 The price of prasugrel is £47.56 per 28-tab pack (excluding VAT, British National Formulary [BNF] edition 67). The cost of treatment for 12 months is £628.47 (excluding VAT). Costs may vary in different settings because of negotiated procurement discounts.

Appendix B – 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. The review will be conducted through the specify STA or MTA process.	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. The review will be conducted through the MTA process.	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. The review will be conducted through the MTA process.	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.	No

Appendix B

Options	Consequence	Selected – 'Yes/No'
The guidance should be updated in an on-going clinical guideline[1].	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
The guidance should be withdrawn	The guidance is no longer relevant and an update of the existing recommendations would not add value to the NHS. The guidance will be stood down and any funding direction associated with a positive recommendation will not be preserved.	No

[1] Information on the criteria for NICE allowing a technology appraisal in an ongoing clinical guideline can be found in section 6.20 of the guide to the processes of technology appraisal.

Appendix C – other relevant information

1. Relevant Institute work

Published

Acute coronary syndromes in adults (2014) NICE quality standard 68

Hyperglycaemia in acute coronary syndromes (2016) NICE pathway

Myocardial infarction: secondary prevention (2016) NICE pathway

Myocardial infarction with ST-segment elevation (2015) NICE pathway

Myocardial infarction: cardiac rehabilitation and prevention of further cardiovascular disease (2013) NICE guideline CG172

Myocardial infarction with ST-segment elevation: acute management (2013) NICE guideline CG167

Hyperglycaemia in acute coronary syndromes: management (2011) NICE guideline CG130
Review: Evidence Update (February 2013); 4-year surveillance report recommended remaining on the static list (May 2016)

Unstable angina and NSTEMI: early management (2010) NICE guideline CG94

Ticagrelor for preventing atherothrombotic events after myocardial infarction (2016) NICE technology appraisal guidance 420
Review date: December 2019

Rivaroxaban for preventing adverse outcomes after acute management of acute coronary syndrome (2015) NICE technology appraisal guidance 335
Review date: 3 years after publication (March 2018)

Ticagrelor for the treatment of acute coronary syndromes (2011) NICE technology appraisal guidance 236
Recommendations on STEMI are included in CG167. The guidance was reviewed in May 2013 and nothing new was found that would affect the recommendations.

Bivalirudin for the treatment of ST-segment-elevation myocardial infarction (2011) NICE technology appraisal guidance 230
Review date: July 2014. Review decision: static list and incorporate into clinical guideline (August 2012)

Clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events (2010) NICE technology appraisal guidance 210

Review date: July 2013. Review decision: static list (September 2013)

Guidance on the use of drugs for early thrombolysis in the treatment of acute myocardial infarction (2002) NICE technology appraisal guidance 52.
Review date: Review decision: static list and incorporate into clinical guideline (August 2012)

Guidance on the use of glycoprotein IIb/IIIa inhibitors in the treatment of acute coronary syndromes (2002) NICE technology appraisal guidance 47
Replaces TA12 (2000) Updated by CG94 (2010)

Coronary revascularisation: cangrelor (2015) NICE evidence summary of new medicines 63

In progress

None

Suspended/terminated

Vorapaxar for reducing atherothrombotic events after a myocardial infarction or in peripheral vascular disease. NICE technology appraisal guidance [ID616]. Publication expected November 2014

2. Details of new products

Drug (company)	Details (phase of development, expected launch date)
Anivamersen-pegnivacogin (Revolixys) Regado Biosciences - coronary artery disease requiring percutaneous coronary intervention (PCI) for non-ST segment elevation myocardial infarction, stable and unstable angina.	Marketing authorisation expected [redacted]
Ticagrelor (Brilique), AstraZeneca – new formulation orodispersible tablet for acute coronary syndrome	UK launch expected [redacted]

3. Details of changes to the indications of the technology

Indication and price considered in original appraisal	Proposed indication (for this appraisal) and current price
It has a marketing authorisation when co-administered with aspirin for the prevention of atherothrombotic events	Efient, co-administered with acetylsalicylic acid (ASA), is indicated for the prevention of atherothrombotic events in adult

Indication and price considered in original appraisal	Proposed indication (for this appraisal) and current price
in adults with acute coronary syndrome (that is, unstable angina or non-ST-segment-elevation myocardial infarction [NSTEMI] or ST-segment-elevation myocardial infarction [STEMI]) undergoing primary or delayed percutaneous coronary intervention.	patients with acute coronary syndrome (i.e. unstable angina, non-ST segment elevation myocardial infarction [UA/NSTEMI] or ST segment elevation myocardial infarction [STEMI]) undergoing primary or delayed percutaneous coronary intervention (PCI). Source: SPC (May 2016) At this current time no further extension on the marketing authorization for prasugrel with PCI for the treatment of acute coronary syndrome. Source: company email to NICE (30 March 2017) Note: Eli Lilly divested prasugrel to Daiichi Sankyo in 2015.
The price of prasugrel is £47.56 per 28-tab pack (excluding VAT, British National Formulary [BNF] edition 67). The cost of treatment for 12 months is £628.47 (excluding VAT). Costs may vary in different settings because of negotiated procurement discounts.	5mg tablets per 28 tablet pack = £47.56 10mg tablets per 28 tablet pack = £47.56 Source: BNF (March 2017)

4. Registered and unpublished trials

Phase 3

None.

Phase 4

Appendix C

Trial name and registration number	Details
Prospective, Randomized Trial of Ticagrelor Versus Prasugrel in Patients With Acute Coronary Syndrome - Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment ISAR-REACT 5 NCT01944800	Purpose: to assess whether ticagrelor is superior to prasugrel in patients with acute coronary syndrome and planned invasive strategy Design: randomized, open-label, multicenter Enrollment: 4000 Status: recruiting Start date: September 2013 Expected completion: January 2021
A Comparison of Reduced-dose Prasugrel and Clopidogrel in Elderly Patients With Acute Coronary Syndrome Undergoing Early Percutaneous Coronary Intervention Elderly ACS II NCT01777503	Purpose: to compare reduced-dose prasugrel (60mg loading dose followed by 5mg once daily) and standard dose clopidogrel in patients older than 74 years with ACS Design: Randomized, Parallel Assignment, Single Blind Enrollment: 2000 Status: recruiting Start date: November 2012 Expected completion: December 2017
Ticagrelor or Prasugrel Versus Clopidogrel in Elderly Patients With an Acute Coronary Syndrome and a High Bleeding Risk: Optimization of Antiplatelet Treatment in High-risk Elderly NCT02317198	Purpose: patients aged 70 years and older randomized to either clopidogrel or ticagrelor or prasugrel and followed for one year Design: randomized controlled, open label, multicenter Enrollment: 1000 Status: recruiting Start date: June 2013 Expected completion: January 2019

Trial name and registration number	Details
Downstream Versus Upstream Strategy for the Administration of P2Y12 Receptor Blockers In Non ST Elevated acUte Coronary Syndromes With Initial Invasive Indication DUBIUS NCT02618837	Purpose: To evaluate the impact on outcomes of the currently accepted antithrombotic strategies based on the administration of prasugrel and ticagrelor in a population of non ST elevated ACS (NSTEACS) patients with an initial invasive indication. Design: Randomized, Parallel Assignment, Open Label Enrollment: 2520 Status: recruiting Start date: December 2015 Expected completion: November 2018

5. Relevant services covered by NHS England specialised commissioning

NHS England (2016) Manual for prescribed specialised services 2016/17
Chapter 7 – Adult specialist cardiac services:

- Specialist centres provide primary angioplasty (PPCI) on a 24/7 basis.
- NHS England commissions adult specialist cardiac services from Adult Specialist Cardiac Centres including PPCI for ST-elevation myocardial infarction and provision of cardiac MRI
- CCGs commission other cardiological services, including PCI (angioplasty) for patients with stable angina and patients with non-ST elevation MI

NHS England (2013) 2013/14 NHS standard contract for cardiology: primary percutaneous coronary intervention (PPCI) (adult)

6. Additional information

British Cardiovascular Intervention Society (2014) National audit of percutaneous coronary interventional procedures (BCIS)

British Committee of Standards for Haematology (2016) Peri-operative management of anticoagulation and antiplatelet therapy

Department of Health (2013) Cardiovascular disease outcomes strategy.

European Society of Cardiology (2015) Acute Coronary Syndromes (ACS) in patients presenting without persistent ST-segment elevation (Management of). ESC Clinical Practice Guidelines

Appendix C

Myocardial Ischaemia National Audit Project (MINAP) (2017) Myocardial Ischaemia National Audit Project: 2014-2015

Scottish Intercollegiate Guidelines Network (2016) Acute coronary syndrome: SIGN 148

Appendix D – References

Motovska Z, Hlinomaz O, Miklik R et al (2016). Prasugrel Versus Ticagrelor in Patients With Acute Myocardial Infarction Treated With Primary Percutaneous Coronary Intervention: Multicenter Randomized PRAGUE-18 Study. *Circulation*. 134(21), pp.1603-1612.

Rafique A, Nayyar P, Wang T et al (2016) Optimal P2Y12 Inhibitor in Patients With ST-Segment Elevation Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention: A Network Meta-Analysis. *JACC. Cardiovascular interventions.* 9(10), 1036-46

Westman P, Lipinski M, Torguson R, and Waksman R (2017) A comparison of cangrelor, prasugrel, ticagrelor, and clopidogrel in patients undergoing percutaneous coronary intervention: A network meta-analysis. *Cardiovascular revascularization medicine : including molecular interventions.* 18(2), 79-85

Wiviott S, Braunwald E, McCabe C et al (2007) Prasugrel versus Clopidogrel in Patients with Acute Coronary Syndromes. *New England Journal of Medicine.* 357(20), 2001-2015

Ye Y, Xie H, Zeng Y et al (2014). Optimal oral antithrombotic regimes for patients with acute coronary syndrome: a network meta-analysis. *PloS one*. 9(3), pp.e90986.