NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Overview

Prasugrel with percutaneous coronary intervention for treating acute coronary syndrome (review of technology appraisal guidance 182)

This overview is a summary of:

- the evidence and views submitted by the manufacturers, the consultees and nominated clinical specialists and patient experts and
- the assessment report.

It highlights key issues for discussion at the first Appraisal Committee meeting should be read with the full supporting documents for this appraisal.

Please note that this document is a summary of the information available before comments on the assessment report have been received.

List of Abbreviations

ACE	Angiotensin-converting enzyme
ACS	Acute coronary syndrome
ARB	Angiotensin receptor blocker
ASA	Acetylsalicylic acid/Aspirin
CABG	Coronary artery bypass graft
CAPRIE	Clopidogrel versus aspirin in patients at risk of ischaemic events [clinical trial]
CCB	Calcium channel blocker
CI	Confidence interval
CV	Cardiovascular

ECG	Electrocardiogram
ERG	Evidence Review Group
HODaR	Health Outcomes Data Repository
HR	Hazard ratio
ICER	Incremental cost effectiveness ratio
ISAR-REACT 5	Intracoronary stenting and antithrombotic regimen: rapid early action for coronary treatment [clinical trial]
LCL	Lower confidence limit
MI	Myocardial infarction
MIMS	Monthly Index of Medical Specialities
MINAP	Myocardial Ischaemia National Audit Project
NSTEMI	Non-ST-segment elevation myocardial infarction
NV	Non vascular
OV	Other vascular
OXVASC	Oxford Vascular Study [cohort study]
PCI	Percutaneous coronary intervention
PLATO	Platelet inhibition and patient outcomes trial [clinical trial]
PROFESS	Prevention regimen for effectively avoiding second strokes [clinical trial]
QALY	Quality-adjusted life year
RCT	Randomised controlled trial

STEMI	ST-segment elevation myocardial infarction
TIA	Transient ischaemic attack
TIMI	Thrombolysis in myocardial infarction
TRITON-TIMI 38	Trial to assess improvement in therapeutic outcomes by optimizing platelet inhibition with prasugrel-thrombolysis in myocardial infarction [clinical trial]
UA	Unstable angina
UCL	Upper confidence limit
UTVR	Urgent target vessel revascularisation

Key issues for consideration

Clinical effectiveness

- The Assessment Group raised concerns regarding the generalisability of the TRITON-TIMI 38 trial results to patients in clinical practice in the UK. It highlighted that these concerns were also raised during the original appraisal of prasugrel (Technology appraisal guidance 182 [Acute coronary syndrome – prasugrel]). The Assessment Group is of the opinion that the clinical evidence for the equivalence of a 300 mg loading dose of clopidogrel (administered in TRITON-TIMI 38) with a 600 mg loading dose (often given in clinical practice in the UK) remains uncertain. Similarly, the importance of timing of the administration of the loading dose of clopidogrel on patient outcomes remains unresolved and differs between the TRITON-TIMI 38 trial and clinical practice in the NHS in England. Is TRITON-TIMI 38 generalisable to clinical practice in England?
- The definition of non-fatal MI in the TRITON-TIMI 38 study included non-clinical MI. Concerns were raised during the original appraisal of prasugrel (Technology appraisal guidance 182) that if the non-clinical MIs were excluded from the

analyses, the clinical difference in nonfatal MIs alone may not be statistically significant when comparing prasugrel with clopidogrel. The manufacturer has provided a re-analysis of the MIs from TRITON-TIMI 38 and stated that the re-analysis demonstrates that treatment with prasugrel significantly reduces the risk of all MIs when compared with clopidogrel. Is there sufficient evidence to demonstrate that prasugrel was more effective than clopidogrel at preventing occurrence of MIs?

- The Assessment Group focuses its clinical effectiveness review on the post hoc core clinical cohort population (patients who weigh more than 60 kg and are younger than 75 years of age) of the TRITON-TIMI 38 trial rather than the overall cohort. Is the core clinical cohort clinically meaningful and relevant?
- Is there sufficient evidence to demonstrate that prasugrel is effective in patients aged 75 years or older, weighing less than 60 kg or with a history of stroke or ischaemic attack and for whom a 5 mg maintenance dose of prasugrel should be used?
- Is there clinical rationale and evidence to demonstrate that prasugrel is particularly effective in certain subgroups? For example, the manufacturer presented efficacy data on people with STEMI, diabetes mellitus and stent thrombosis.
- The Assessment Group and the manufacturer considered it was inappropriate to undertake an indirect comparison between prasugrel and ticagrelor because of key differences between TRITON-TIMI 38 (comparing prasugrel with clopidogrel) and the PLATO study (comparing ticagrelor with clopidogrel). Can any conclusions be drawn regarding the comparative effectiveness of prasugrel and ticagrelor?

Cost effectiveness

- Both the Assessment Group's and manufacturer's decision economic model comprises two parts: a statistical model to represent the main clinical outcomes of the trial during the first 12 months of follow-up until the trial treatments clopidogrel or prasugrel have finished, and a long-term model extrapolating outcomes for up to an additional 39 years. The Assessment Group used the manufacturer's short-term statistical model in its own economic model but developed a different long-term model because it considered the manufacturer's long-term model to be

unsatisfactory. The Assessment Group's long-term model was based on the economic model developed by the Assessment Group for NICE technology appraisal guidance 210 (Clopidogrel and modified release dipyridamole for the prevention of occlusive vascular events). Which long-term model is the most appropriate?

- The main source of data used to populate the Assessment Group's long-term model was the CAPRIE clinical trial (the main source of evidence used in NICE technology appraisal guidance 210 (Clopidogrel and modified release dipyridamole for the prevention of occlusive vascular events). Only CAPRIE data from 5,741 MI patients without prior history of other vascular events were used. Is the CAPRIE data an appropriate source for extrapolating long-term events? In particular, are the patients with STEMI or UA/STEMI in the core clinical cohort (TRITON-TIMI 38) similar to those patients with MI in CAPRIE?
- The Assessment Group structured its economic model to accommodate 4 mutually exclusive subgroups of the core clinical cohort population (STEMI with diagnosed diabetes, STEMI without diagnosed diabetes, UA/NSTEMI with diagnosed diabetes and UA/NSTEMI without diabetes). It provided cost-effectiveness results only for these subgroups. Does the data presented in the assessment report support the efficacy and cost effectiveness of prasugrel in these subgroups?

1 Background: clinical need and practice

1.1 Acute coronary syndromes (ACS) refers to a group of symptoms associated with acute myocardial ischaemia. It encompasses a spectrum of disorders or syndromes including acute myocardial infarction (MI) and unstable angina pectoris. ACS is usually the result of an acute or sub-acute primary reduction of myocardial oxygen supply provoked by disruption of an atherosclerotic plaque (build-up of material within a heart vessel) associated with inflammation, thrombosis, vasoconstriction and microembolisation.

1.2 The presence of ST-segment elevation on an electrocardiogram usually indicates total occlusion of the affected artery, resulting in

necrosis of the tissue supplied by that artery or ST-segment elevation myocardial infarction (STEMI). This condition is treated immediately with reperfusion therapy (thrombolysis or percutaneous coronary intervention [PCI]). ACS without STEMI is classified as either unstable angina (UA) or non-ST-segment-elevation myocardial infarction (NSTEMI). NSTEMI differs from UA primarily in the severity of myocardial ischaemia. In NSTEMI, the ischaemia is severe enough to result in the release of biochemical markers of myocardial injury into the blood. Immediate treatment for these conditions aims to prevent progression to total occlusion of the artery and, for people at high risk of MI, may include coronary revascularisation, either by means of PCI or coronary artery bypass graft.

1.3 ACS becomes more prevalent with increasing age and incidence is higher in men than women. In England, there were approximately 54,000 finished consultant episodes and 32,000 hospital admissions for UA in 2012/13. In England it is estimated that there are approximately 82,000 MIs every year. Of the 80,974 hospital admissions with a final diagnosis of MI recorded in the Myocardial Ischaemia National Audit Project (MINAP), 40% were STEMIs and 60% were NSTEMIs. The average age of people with STEMI and NSTEMI was 65 years and 72 years respectively. Twice as many men had MIs as women.

1.4 Treatment with antiplatelet therapy is an established adjunct to PCI both before and for up to 12 months after the procedure (Myocardial infarction with ST-segment elevation [NICE clinical guideline 167] and Unstable angina and NSTEMI [NICE clinical guideline 94]). The purpose of antiplatelet treatment is to inhibit the aggregation of platelets that can lead to thrombus formation and further vascular events including stent thrombosis. Dual antiplatelet therapy, aspirin plus prasugrel, clopidogrel or

ticagrelor are the standard antiplatelet treatments in clinical practice in the England.

1.5 NICE has recommended prasugrel in combination with aspirin as an option for preventing atherothrombotic events in people with ACS having PCI, only when: immediate primary PCI for STEMI is necessary, stent thrombosis has occurred during clopidogrel treatment or the patient has diabetes mellitus (NICE technology appraisal guidance 182 [Acute coronary syndrome - prasugrel], published in October 2009). During the development of technology appraisal guidance 182, generic formulations of clopidogrel, the comparator to prasugrel, received European Medicines Agency positive opinion (May 2009). At that time no reduced national prices for the generic versions were available, but it was noted that a reduction in the price of clopidogrel was likely. On this basis the Committee recommended that a review be considered after issuing guidance because a reduction in the cost of the comparator could affect the cost effectiveness of prasugrel. NICE has also recommended ticagrelor in combination with low-dose aspirin for up to 12 months as an option for people with STEMI who are to be treated with PCI, NSTEMI or unstable angina (NICE technology appraisal guidance 236 [Acute coronary syndromes - ticagrelor], published in October 2011).

2 The technology

2.1 Prasugrel (Efient, Daiichi Sankyo/Eli Lilly and Company) is an oral inhibitor of platelet activation and aggregation through the irreversible binding of its active metabolite to the P2Y12 class of adenosine diphosphate receptors on platelets. It has a marketing authorisation when co-administered with aspirin for the prevention of atherothrombotic events in patients with ACS (that is UA or NSTEMI or STEMI) undergoing primary or delayed PCI.

2.2 The summary of product characteristics for prasugrel states that it should be initiated with a single 60 mg loading dose and then

continued at 10 mg once a day, and that patients taking prasugrel should also take 75 mg to 325 mg aspirin daily. Treatment duration of up to 12 months is recommended unless the discontinuation of prasugrel is clinically indicated.

2.3 According to the summary of product characteristics, the use of prasugrel in patients who are 75 years or older is generally not recommended, however, if treatment is deemed necessary a reduced maintenance dose of 5 mg should be prescribed. For people with a body weight less than 60 kg, the summary of product characteristics states that the 10 mg maintenance dose is not recommended and the 5 mg maintenance dose should be used. For people with UA or NSTEMI, where coronary angiography is performed within 48 hours after admission, the summary of product characteristics states that the loading dose should be given at the time of PCI .

2.4 The summary of product characteristics lists the following adverse reactions for prasugrel: increased bleeding risk, hypersensitivity reactions including angioedema, and thrombotic thrombocytopaenic purpura. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.5 The price of prasugrel is £47.56 per 28-tab pack (excluding VAT, ‘British national formulary’ [BNF] edition 66). The cost of treatment for 12 months is £628.48 (excluding VAT). Costs may vary in different settings because of negotiated procurement discounts.

3 Remit and decision problem(s)

3.1 The remit from the Department of Health for this appraisal is: 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 NICE technology appraisal guidance 182).

	Final scope issued by NICE
Population	Patients with acute coronary syndrome undergoing primary or delayed percutaneous coronary intervention
Intervention	Prasugrel in combination with aspirin
Comparators	• clopidogrel in combination with low-dose aspirin • ticagrelor in combination with low-dose aspirin
Outcomes	The outcome measures to be considered include: • nonfatal and fatal cardiovascular events • mortality (from any cause) • atherothrombotic events • incidence of revascularisation procedures • adverse effects of treatment (including bleeding events) • health-related quality of life.
Economic evaluation	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per QALY gained The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared Costs should be considered from an NHS and Personal Social Services perspective
Other considerations	If the evidence allows, the following subgroups will be considered: people with ST-segment elevation myocardial infarction (STEMI), unstable angina (UA)/non-ST-segment-elevation myocardial infarction (NSTEMI), people with diabetes mellitus Guidance will only be issued in accordance with the marketing authorisation The availability of any patient access schemes for the interventions and comparators should be taken into account in the analysis

3.2 The final scope issued by NICE (presented in the table above) identifies the relevant population as patients with ACS undergoing primary or delayed percutaneous coronary intervention. It further states that if the evidence allows, subgroups of patients will be considered, including people with STEMI, UA or NSTEMI and people with diabetes. The Assessment Group stated that no new randomised controlled trial (RCT) evidence for prasugrel has been

published and the evidence base for the effectiveness of prasugrel remains unchanged from that considered for Technology appraisal guidance 182 (Acute coronary syndrome – prasugrel). The Assessment Group therefore took its starting position for its review as a reassessment of the evidence from the original appraisal of prasugrel and focused on patients for whom the full 10 mg maintenance dose of prasugrel would be considered suitable, specifically patients younger than 75 years, weighing 60 kg or more, and with no history of stroke or transient ischaemic attack (TIA) (referred to as the 'core clinical cohort' in the TRITON-TIMI 38 study and the 'target population' in NICE technology appraisal guidance 182). The Assessment Group explained that during the development of NICE technology appraisal guidance 182, the Appraisal Committee agreed that the core clinical cohort population to be the most relevant as the excluded patients were either explicitly excluded from the marketing authorization or were not supported by trial evidence (since the trial was based on the full 10 mg dose). The Assessment Group's economic evaluation focused on 4 subgroups of this population (STEMI with diabetes, STEMI without diabetes, UA/NSTEMI with diabetes and UA/NSTEMI without diabetes) as these subgroups were considered in the original appraisal of prasugrel (see section 2, pages 4 -5 of Addendum 1 to the assessment report, for further explanation of the Assessment Group's choice of patient population and subgroups).

4 Clinical-effectiveness evidence

4.1 Manufacturer's submission

Prasugrel compared with clopidogrel

4.1.1 The manufacturer conducted a systematic search of the literature and identified 1 relevant RCT (TRITON-TIMI 38), 5 publications

and 1 abstract relating to TRITON-TIMI 38 for inclusion in its review. TRITON-TIMI 38 was considered for the original appraisal of prasugrel (NICE technology appraisal guidance 182 [Acute coronary syndrome – prasugrel]).

4.1.2 TRITON-TIMI 38 was a randomised double-blind trial that compared prasugrel with clopidogrel in 13,608 patients with moderate- to high-risk ACS (UA, STEMI or NSTEMI) who were scheduled to have PCI. Patients were given aspirin (at a recommended daily dose of between 75 and 162 mg) in combination with the drugs studied. Patients were randomised to receive a loading dose of 60 mg prasugrel followed by 10 mg prasugrel daily or a loading dose of 300 mg clopidogrel followed by 75 mg clopidogrel daily for up to 15 months (the median treatment period was 14.5 months). After PCI, patients received daily maintenance doses of placebo tablets matched to clopidogrel or prasugrel.

4.1.3 The primary efficacy endpoint was a composite of the rate of nonfatal myocardial infarction (MI), nonfatal stroke or death from cardiovascular causes, during the entire follow-up period. A range of secondary composite endpoints were also included. Major safety endpoints included thrombolysis in myocardial infarction (TIMI) major bleeding not related to coronary artery bypass graft (CABG), non-CABG-related TIMI life-threatening bleeding, and TIMI major bleeding (a fall in haemoglobin of 5 g/100 ml or more) or minor bleeding (a fall in haemoglobin of 3 to less than 5 g/100 ml).

4.1.4 The results for the efficacy endpoints for the overall cohort population (n= 13,608) enrolled in the TRITON-TIMI 38 are presented in table 1.

Table 1: TRITON –TIMI 38 efficacy results at 15 months (overall cohort population)

End point	Clopidogrel (n=6,795) n (%)	Prasugrel (n=6,813) n (%)	HR (95% CI)	P value
Primary efficacy endpoint of death from CV causes, nonfatal MI, or non fatal stroke	781 (12.1)	643 (9.9)	0.81 (0.73-0.90)	<0.001
Death from CV causes	150 (2.4)	133 (2.1)	0.89 (0.70-1.12)	0.31
Nonfatal MI	620 (9.5)	475 (7.3)	0.76 (0.67-0.85)	<0.001
Nonfatal stroke	60 (1.0)	61 (1.0)	1.02 (0.71-1.45)	0.93
Death from any cause	197 (3.2)	188 (3.0)	0.95 (0.78-1.16)	0.64
Death from CV causes, nonfatal MI or UTVR	798 (12.3)	652 (10.0)	0.81 (0.73-0.89)	<0.001
Stent thrombosis	142 (2.4)	68 (1.1)	0.48 (0.36-0.64)	<0.001
Death from CV causes, nonfatal MI, nonfatal stroke, or rehospitalisation for ischaemia	938 (14.6)	797 (12.3)	0.84 (0.76-0.92)	<0.001
HR hazard ratio, CI confidence interval, CV cardiovascular, MI myocardial infarction, UTVR urgent target vessel revascularisation				

4.1.5 The manufacturer stated that, with regard to the primary efficacy endpoint, the analysis of prespecified subgroups showed that there was no evidence to suggest that the overall treatment effect was different in the subgroups. The prespecified subgroups included STEMI, UA/NSTEMI, people with diabetes and types of stent placements.

4.1.6 In the overall cohort of patients, fewer patients in the clopidogrel group than in the prasugrel group met the primary safety endpoint

(non-CABG-related TIMI major bleeding) during the 15 month follow-up period. The rate of the primary safety endpoint at 15 months was 1.8% in the clopidogrel group, which was significantly lower than in the prasugrel group (2.4%, p=0.03). The net clinical benefit (composite of death from any cause, nonfatal MI, nonfatal stroke, and non-CABG-related nonfatal TIMI major bleed) significantly favoured prasugrel (13.9% of patients in the clopidogrel group compared with 12.2% in the prasugrel group, hazard ratio [HR] 0.87%, 95% confidence interval [CI] 0.79 to 0.95, p=0.004).

4.1.7 The manufacturer provided additional analyses from other publications from TRITON-TIMI 38. These were: Core clinical cohort (Wiviott et al. 2011, n=10,084), Spontaneous and procedural myocardial infarction using the Universal Definition of Myocardial Infarction (Morrow 2009), Landmark Analyses (Antman 2008), Recurrent Events (Murphy 2008), STEMI cohort sub-analysis (Montalescot et al., 2008 n=3,534), Diabetes Subpopulation (Wiviott 2008a, n=3,146) and Stent sub-analysis (Wiviott 2008b).

Core clinical cohort (Wiviott et al., 2011)

4.1.8 This subpopulation had been considered during the development of the original appraisal of prasugrel (NICE technology appraisal guidance 182 [Acute coronary syndrome – prasugrel]). In the core clinical cohort of patients (younger than 75 years, weighing 60 kg or more, and with no history of stroke or TIA, prasugrel showed a clinically significant and robust reduction in the primary endpoint (death from cardiovascular causes, nonfatal MI or nonfatal stroke) with a favourable net clinical outcome (composite of death from any cause, nonfatal MI, nonfatal stroke, and non-CABG-related nonfatal TIMI major bleed), compared with clopidogrel. Further details of the results are presented in table 2.

Table 2: TRITON-TIM 38 Efficacy and safety in the core clinical cohort

Endpoint	Clopidogrel n/N (%)	Prasugrel n/N (%)	HR for Prasugrel (95% CI)	P Value
Death from CV causes, nonfatal MI, or nonfatal stroke (primary efficacy endpoint)	569/5,383 (11.0)	433/5,421 (8.3)	0.74 (0.66 -0.84)	< 0.001
Non-CABG-related TIMI major bleeding	73/5,337 (1.5)	91/5,390 (1.9)	1.24 (0.91-1.69)	0.17
Death from any cause, nonfatal MI, nonfatal stroke, or non-CABG-related nonfatal TIMI major bleeding	641/5,383 (12.5)	522/5,421 (10.2)	0.80 (0.71-0.89)	< 0.001
HR hazard ratio, CI confidence interval, CV cardiovascular, MI myocardial infarction, CABG coronary artery bypass grafting, TIMI thrombolysis in myocardial infarction				

Spontaneous and procedural myocardial infarction using the Universal Definition of Myocardial Infarction (Morrow 2009)

4.1.9 In a post-hoc analysis, reviewers blinded to treatment allocation classified 1,218 MIs that occurred during the TRITON-TIMI 38 study based on the Universal Definition of Myocardial Infarction. The results of the analysis showed that there was a consistent reduction in the incidence of MIs with prasugrel compared with clopidogrel for MIs of every size as measured by biomarker elevation, with the greatest absolute reduction seen in those MIs associated with the greatest extent of myocardial necrosis.

Landmark Analyses (Antman 2008)

4.1.10 The objective of this study was to evaluate the relative contributions of the prasugrel loading dose and maintenance dose on events in TRITON-TIMI 38 in an analysis of efficacy, safety, and net clinical benefit from randomisation to Day 3 and from Day 3 to the end of the trial. The landmark analysis of TRITON-TIMI 38 found statistically significantly greater reductions in ischaemic events, including MI, stent thrombosis, and urgent

target vessel revascularisation (UTVR), in people treated with prasugrel-compared with clopidogrel from randomisation to Day 3 to the end of the trial, indicating that the benefit of treatment with prasugrel occurred early and was sustained, and therefore was not an artefact of the loading dose.

Recurrent Events (Murphy 2008)

4.1.11 The objective of this study was to evaluate whether first events (primary composite endpoint) and subsequent events (components of the primary composite endpoint) were reduced with prasugrel compared with clopidogrel. Efficacy results indicated that, in addition to the significantly greater number of first events with clopidogrel than with prasugrel, there also were significantly more subsequent events in the clopidogrel group (n = 115) than in the prasugrel group (n = 58, p <0.001). The analysis from the time of the first event to recurrent event or last follow-up (a secondary primary endpoint event) occurred in 10.8% of the prasugrel group and 15.4% of the clopidogrel group (HR= 0.65, 95% CI 0.46 to 0.92, p<0.001).

STEMI cohort sub-analysis (Montalescot et al., 2008; n=3,534)

4.1.12 This subgroup had been considered during the development of the original appraisal of prasugrel (NICE technology appraisal guidance 182 [Acute coronary syndrome – prasugrel]). Montalescot et al. reported outcomes in patients with STEMI enrolled into the TRITON-TIMI 38 study. Results showed that the primary endpoint (cardiovascular death, nonfatal MI or nonfatal stroke) was significantly reduced with prasugrel at 30 days (HR= 0.68, p=0.002) and 15 months (HR 0.79, 95% CI 0.65 to 0.97). The key secondary endpoint of cardiovascular death, MI or UTVR was also significantly reduced with prasugrel through 30 days (p=0.02) and 15 months (p=0.03). Efficacy was consistent among patients with a primary PCI and with secondary PCI. There was

no interaction between timing of PCI and randomised treatment with respect to outcome (p>0.05).

Diabetes Subpopulation (Wiviott 2008a, n=3,146)

4.1.13 This subgroup had been considered during the development of the original appraisal of prasugrel (NICE technology appraisal guidance 182 [Acute coronary syndrome – prasugrel]). The objective of this study was to compare treatment with prasugrel and clopidogrel among the subpopulation of patients with diabetes in the TRITON-TIMI 38 study. The results showed that patients with diabetes tended to have a greater reduction in ischaemic events without an observed increase in non-CABG TIMI major bleeding, and therefore a greater net treatment benefit with prasugrel compared with clopidogrel.

Stent sub-analysis (Wiviott 2008b)

4.1.14 The objective of the prespecified subgroup analysis was to assess the rate, outcomes and prevention of ischaemic events in patients treated with prasugrel or clopidogrel who received at least one coronary artery stent (bare metal or drug eluting) during the initial hospitalisation in TRITON-TIMI 38. The results showed treatment with prasugrel resulted in reduction in stent thrombosis. This result was also irrespective of stent type and this effect was consistent whether the stent thrombosis occurred early or late.

Health related quality of life

4.1.15 Health-related quality of life was assessed in a substudy of TRITION-TIMI 38 using the Angina Frequency and Physical Limitations Scores scales of the Seattle Angina Questionnaire; the London School of Hygiene Dyspnoea Questionnaire score; the EQ-5D self-report questionnaire and the EQ visual analogue scale. Quality of life was assessed at baseline, Day 30, Day 180, Day 360 and Day 450 or last visit. Improvements in quality of life

were observed early (between baseline and 30 days) and these improvements remained at 12 months. There were no significant differences between prasugrel and clopidogrel.

Manufacturer's additional comments

4.1.16 The manufacturer provided a commentary on the key points of discussion that occurred during the development of NICE technology appraisal guidance 182 (Acute coronary syndrome – prasugrel). The key points included interpretation of the definition of myocardial infarction, defining the risk factors for stent thrombosis (recommendation for further research), and the size and timing of the clopidogrel loading dose. The manufacturer highlighted that the additional analysis of TRITON-TIMI 38 using the Universal definition of MI showed that prasugrel significantly reduced spontaneous and procedural MI compared with clopidogrel and this was consistent across the spectrum of MIs of varying type, size and timing (Morrow 2209, see section 4.1.9 of the overview). The manufacturer also highlighted that robust research has identified risk factors for stent thrombosis which could be used as a guide for clinicians to judge risk and choose treatments accordingly (Gershlick et al; manuscript in preparation). The manufacturer commented that the clinical trial, CURRENT-OASIS 7, comparing standard and high loading doses of clopidogrel in patients with ACS did not meet its primary endpoint and several lines of evidence of TRITON-TIMI 38 suggested that the timing of clopidogrel loading did not substantially influence the overall efficacy of prasugrel.

4.1.17 The manufacturer provided a commentary on additional data which has become available since the publication of NICE technology appraisal guidance 182 (Acute coronary syndrome – prasugrel). The manufacturer commented that prasugerel has being investigated in a number of trials in patients with ACS, and

that these trials were outside the remit of this appraisal. The manufacturer stated that evidence from some of these trials had led regulators to change the summary of product characteristics. The following sections of the summary of product characteristics have been updated:

- Section 5.1 with new data on switching from clopidogrel to prasugrel (based on the study TABF, PRINCIPLE study and the ACAPULCO study).
- Sections 4.2, 4.8, 5.1 and 5.2 with new data regarding the reduced 5 mg maintenance dose of prasugrel in patients 75 years and older or weighing less than 60 kg (based on the FEATHER, GENERATION, and the TRILOGY-ACS [for further details of this study, see Addendum 3 to the assessment report] studies).
- Sections 4.2, 4.4, 4.8 and 5.1 up-dated in order to optimise the instructions regarding the timing of the loading dose of prasugrel in patients with NSTEMI undergoing PCI (based on the ACCOAST study [for further details of the study, see Addendum 3 to the assessment report]). Sections 4.2 and 4.4 of the summary of product characteristics state that in patients with UA or NSTEMI where coronary angiography is performed within 48 hours after admission, the loading dose should be given at the time of PCI.

Prasugrel compared with ticagrelor

4.1.18 The manufacturer stated that indirect comparisons have been attempted and published by independent researchers using different methodologies, however, no clear benefit of one treatment over the other has been demonstrated. As a result of key differences between the trials, the results were inconclusive. The manufacturer considered a formal indirect comparison to be inappropriate.

4.2 Assessment Group

Prasugrel compared with clopidogrel

4.2.1 The Assessment Group conducted a systematic search of the literature and identified 1 RCT (TRITON-TIMI 38) and 1 publication (Wiviott et al., 2011) related to TRITON-TIMI 38 for inclusion in its review. Both the RCT and the publication had also been identified by the manufacturer and were considered for the original appraisal of prasugrel (NICE technology appraisal guidance 182 [Acute coronary syndrome – prasugrel]). The Assessment Group commented that no new evidence had been identified since the publication of the original appraisal of prasugrel in 2009.

4.2.2 For conciseness the summary information for TRITON-TIMI 38 has not been reproduced in this section of the overview. For details of the TRITON-TIMI 38, see sections 4.1.1-4.1.7 of the overview (or Appendix 4 of the assessment report).

4.2.3 Overall, the Assessment Group considered that TRITON-TIMI 38 was robustly designed and of strong methodological quality. However, the Assessment Group raised concerns around the generalisability of the TRITON-TIMI 38 study results to patients in clinical practice in England and Wales. The Assessment Group commented that the loading dose of clopidogrel administered in the trial was 300 mg whereas a loading dose of 600 mg may be administered in clinical practice in England and Wales. It also commented that the majority (74%) of patients in the trial received the clopidogrel loading dose during the PCI procedure. In clinical practice in England and Wales, patients undergoing planned PCI receive the clopidogrel loading dose before the PCI procedure. The Assessment Group stated that the clinical efficacy in the trial was largely driven by statistically significant differences in nonfatal

MIs. Nonfatal MIs included both clinical MIs (symptoms) and non-clinical MIs (biomarkers and ECG readings). The Assessment Group noted that if the incidence of clinical MIs were compared between arms, there may be no differences in outcomes between the arms. The Assessment Group highlighted that theses issues were considered during the original appraisal of prasugrel (NICE technology appraisal guidance 182 [Acute coronary syndrome – prasugrel]).

4.2.4 The Assessment Group provided a critique of the manufacturer's commentary on the generalisability of the TRITON-TIMI 38 study (see section 4.1.16 of the overview). The Assessment Group considered that the size and timing of the loading dose of clopidogrel and the impact these have on the primary outcome of the TRITON-TIMI 38 study remain unclear. The Assessment Group commented that the re-analysis of the MIs by the manufacturer demonstrated that prasugrel was more effective than clopidogrel in preventing occurrence of MIs. For further details of the Assessment Group's critique, see section 5.5 (pages 36-43) of the assessment report.

4.2.5 The Assessment Group considered the publication by Wiviott et al. (2011) (see section 4.1.8 of the overview) to be the key publication relevant to this appraisal and focused its clinical effectiveness on the core clinical cohort described in the publication. The Assessment Group highlighted that the core clinical cohort was a subpopulation of patients for whom the full 10 mg maintenance dose of prasugrel would be considered suitable, specifically patients younger than 75 years, weighing 60 kg or more, and with no history of stroke or TIA. The Assessment Group explained that during the original appraisal of prasugrel, the Appraisal Committee agreed that the core clinical cohort population was the most relevant as the excluded patients

were either explicitly excluded from the marketing authorisation or were not supported by trial evidence (since the trial was based on the full 10 mg dose). This sub-population was described in NICE technology appraisal guidance 182 (Acute coronary syndrome – prasugrel) as the 'target population' or 'licensed population' for treatment with prasugrel. The Assessment Group noted that the authors of the publication had stated that the core clinical cohort was identified post hoc and defined by regulatory criteria and should be considered as hypothesis generating.

4.2.6 The Assessment Group stated that the patients in the overall trial population and the core clinical cohort appear to be similar in terms of baseline characteristics. The baseline characteristics of the patients in the core clinical cohort and the overall trial population are presented in table 3. The Assessment Group noted that the proportions of patients reported were not presented by treatment trial arm. However, it also noted that Wiviott et al. stated that patients in the core clinical cohort randomised to prasugrel and clopidogrel were well-matched and that 50% of the core clinical cohort was randomised to prasugrel.

Table 3: Summary of patient characteristics for TRITON-TIMI 38 study

Characteristic	Core clinical cohort (n=10,804)	Overall trial population (n=13,608)
Age (median)	not specified	61 years
UA/NSTEMI	73%	74%
Male	79%	74%
White	93%	93%
Region:		
North America	32%	32%
South America	4%	4%
Western Europe	25%	26%
Eastern Europe	25%	25%
Africa/Asia/Middle East	14%	14%
Hypertension	62%	64%
Hypercholesterolemia	56%	56%
Diabetes mellitus	22%	23%
Previous MI	17%	18%
Previous CABG	7%	8%
Creatinine clearance <60 ml/min	4%	12%
Multivessel coronary intervention	14%	14%
Glycoprotein IIb/IIIa inhibitor	56%	55%
ACE/ARB	75%	76%
Beta Blocker	89%	88%
Statin	93%	92%
CCB	16%	18%
ASA	100%	99%
ACE angiotensin-converting enzyme; ARB angiotensin receptor blocker; ASA aspirin; CABG coronary artery bypass grafting; CCB calcium channel blocker; MI myocardial infarction, NSTEMI non-ST-segment-elevation myocardial infarction, UA unstable angina		

4.2.7 For conciseness the results for the primary and secondary efficacy endpoints for the core clinical cohort have not been reproduced in this section of the overview. For the results, see table 2, section 4.1.8 of the overview (or table 8, page 31 of the assessment report). The Assessment Group commented that the

results for both composite outcomes appeared to be driven by the number of nonfatal MIs.

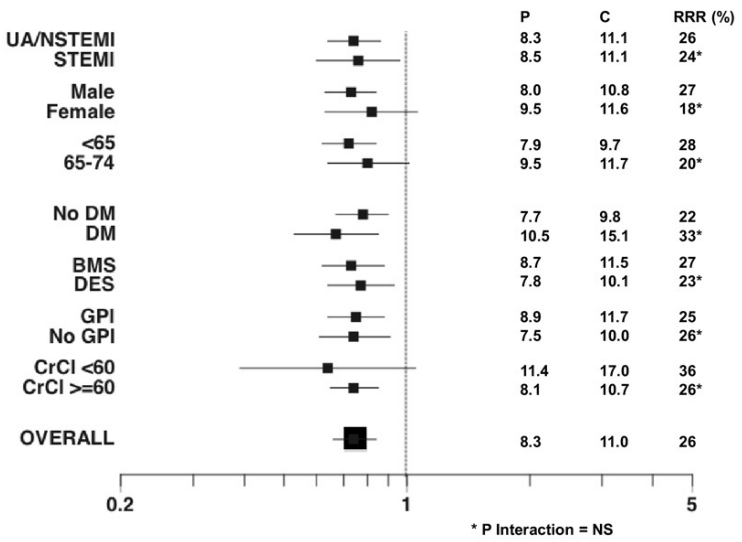
4.2.8 The Assessment Group stated that for the core clinical cohort, prasugrel was also more effective than clopidogrel for the primary endpoint at 30 days (7.0% in the clopidogrel group compared with 5.0% in the prasugrel group; HR=0.70, 95% CI 0.60 to 0.82; p<0.0001) as well as at the 15 month follow-up (4.5% in the clopidogrel group compared with 3.6% in the prasugrel group; HR=0.80, 95% CI 0.65 to 0.97; p=0.027).

4.2.9 The Assessment Group stated that no statistically significant difference in non-CABG-related TIMI major bleeding was noted in the core clinical cohort between patients in the prasugrel and clopidogrel treatment arms, however, there was a significant difference in favour of clopidogrel when major and minor bleeding events were combined (3.0% compared with 3.9%; HR=1.26, 95% CI 1.02 to1.57; p=0.03). The Assessment Group commented that analysis of the net clinical benefit outcome (death from any cause, nonfatal MI, nonfatal stroke, or non-CABG-related nonfatal TIMI major bleeding) favoured the use of prasugrel in the core clinical cohort (12.5% in the clopidogrel group compared with 10.2% in the prasugrel group; HR=0.80, 95% CI 0.71 to 0.89; p<0.001).

4.2.10 The Assessment Group stated that statistically significant differences in favour of prasugrel were reported for the outcomes of definite stent thrombosis (HR=0.41, 95% CI 0.29 to 0.60; p<0.001) and definite or probable stent thrombosis (HR=0.44, 95% CI 0.31 to 0.62 p<0.001) in the core clinical cohort. There were also statistically significantly fewer myocardial infarctions in the prasugrel group (6.7%) compared with the clopidogrel group (94%; HR=0.71, 95% CI 0.62 to 0.81; p<0.001).

4.2.11 The Assessment Group presented a Forest plot (**Error! Reference source not found. Error! Reference source not found.**) from the Wiviott et al publication that displays the relative effectiveness of prasugrel compared with clopidogrel across a range of subgroups within the core clinical cohort. The Assessment Group noted that the clinical effectiveness of prasugrel appeared to be consistent across the range of subgroups presented, including STEMI, UA/STEMI and patients with and without diabetes. It highlighted that no specific clinical effectiveness data were available for patients with STEMI and diabetes, STEMI without diabetes, UA/STEMI with diabetes and UA/STEMI without diabetes. The Assessment Group also highlighted that it was able to extract economic data pertaining to these subgroups from the manufacturer's economic model.

Figure 1 Forest plot of relative effectiveness of prasugrel compared with clopidogrel across a range of subgroups



4.2.12 In summary, the results for the core clinical cohort of the TRITON-TIMI 38 trial demonstrated statistically significant differences in favour of prasugrel compared with clopidogrel across a range of outcomes and clinical subgroups. In terms of safety (bleeding

events), one statistically significant difference between prasugrel and clopidogrel was noted. The exception was for the combined outcome of TIMI major and minor bleeding for which significantly more events occurred with prasugrel than with clopidogrel.

4.2.13 The Assessment Group reported the efficacy, bleeding and net clinical benefit for patients aged 75 years and older, weighing less than 60 kg or with a history of stroke or TIA (see appendix 4, page 142 of the assessment report). These outcomes are presented in table 4.

Table 4: TRITON-TIMI 38 efficacy, bleeding and net clinical benefit for patients aged 75 years or older, weighing less than 60 kg or with a history of stroke or ischaemic attack

Endpoint	Clopidogrel n/N (%)	Prasugrel n/N (%)	HR for Prasugrel (95% CI)	p-value
Death from CV causes, nonfatal MI, nonfatal stroke (primary efficacy endpoint	199/1,347 (16.0)	198/1,320 (16.1)	1.02 (0.84-1.24)	0.83
Non-CABG-related TIMI major bleeding	38/1328 (3.3)	52/1305 (4.3)	1.42 (0.93-2.15)	0.10
Death from any cause, nonfatal MI, nonfatal stroke, non-CABG-related nonfatal TIMI major bleeding	239/1347 (19.0)	249/1320 (20.2)	1.07 (0.90-1.28)	0.43
HR hazard ratio, CI confidence interval, CV cardiovascular, MI myocardial infarction, CABG coronary artery bypass grafting, TIMI thrombolysis in myocardial infarction				

Health related quality of life

4.2.14 The Assessment Group noted that health-related quality of life was assessed in a substudy of TRITION-TIMI 38 (see section 4.1.15 of the overview for further details of the substudy). It also

noted that the study had recruited fewer people than was initially planned (475 patients compared with 3000 patients). The Assessment Group highlighted that during the development of NICE technology appraisal guidance 182 (Acute coronary syndrome – prasugrel) concerns were raised regarding the representiveness of the substudy and the clinical utility of the results. The Assessment Group commented that it was unable to draw any conclusions as to the health-related quality of life of patients treated with prasugrel or clopidogrel in the TRITON-TIMI 38 trial.

Prasugrel compared with ticagrelor

4.2.15 The Assessment Group noted that there were no trials directly comparing prasugrel with ticagrelor. It considered performing an indirect comparison between prasugrel and ticagrelor using data from TRITON-TIMI 38 and the PLATO trial, with clopidogrel as the common comparator.

4.2.16 NICE technology appraisal guidance 236 (Acute coronary syndromes – ticagrelor) recommends ticagrelor as a treatment option (in combination with low-dose aspirin) for up to 12 months in adults ACS, including people with STEMI who are to be treated with PCI, people with NSTEMI or people with UA. The recommendations made in NICE technology appraisal 236 were based on a single RCT (PLATO). The PLATO trial was an international, multicentre, double-blind, double-dummy phase III trial comparing ticagrelor plus aspirin with clopidogrel plus aspirin in 18,624 patients admitted to hospital with ACS with or without STEMI. Patients were randomised to the trial irrespective of planned intervention and therefore the patient population included patients with ACS who were to be medically managed as well as those who were to undergo PCI. The trial follow-up was for 12 months, however the trial protocol stipulated that once the

requisite number of events (1780) had accrued, patients were required to leave the trial after their 6 month or 9 month visit. The key trial characteristics are presented in table 5.

4.2.17 In the overall trial population, a statistically significant benefit of ticagrelor was found for the primary composite endpoint (9.8% compared with 11.67% [HR= 0.84; 95% CI 0.77-0.92; p<0.001]). When the individual components of the composite endpoint were disaggregated, the reduction in the primary endpoint were driven by statistically significant reductions in death from vascular causes (HR= 0.79; 95% CI 0.69- 0.91; p=0.001) and MI (HR= 0.84; 95% CI 0.75- 0.95; p=0.005). There were no statistically significant differences between the two arms of the trial for the endpoints of PLATO major bleed (primary safety endpoint) and PLATO major fatal/life-threatening bleed; however, statistically significant differences in favour of clopidogrel were evident for the endpoints of PLATO total major + minor bleed, (HR=1.11; 95% CI 1.03-o 1.20; p=0.008) and PLATO non-CABG major bleed (HR= 1.19; 95% CI 1.02-1.38; p=0.03). Further details of the efficacy and safety results of the PLATO trial and PLATO defined bleeding events are provided on pages 6-8 of Addendum 2 to the assessment report.

4.2.18 The Assessment Group stated that the TITRON-TIMI 38 and PLATO trials were not comparable and, by inference, a comparison between prasugrel and ticagrelor based on these trials was inappropriate. It noted that TRITON-TIMI 38 and PLATO were similar in many ways as both trials were conducted in a population with ACS, use clopidogrel as a comparator and report the same primary composite efficacy endpoint (death from cardiovascular causes, nonfatal MIs, or nonfatal stroke during the follow-up period). However, there were significant differences in the target population, clopidogrel loading, myocardial infarction

assessment, study duration and primary analyses of the studies. The key features of the TRITON-TIMI 38 and PLATO trials are presented in table 5.

Table 5: Comparison of TRITON-TIMI 38 and PLATO studies

Characteristic	TRITON-TIMI 38	PLATO
Number patients	13,608	18,624
Patient population	Early invasively managed ACS scheduled for PCI (including STEMI and NSTEMI patients undergoing same admission PCI). Symptom onset within 72 hours	Broad ACS population (including STEMI). Symptom onset within 24 hours
Prior clopidogrel	Excluded	Allowed (including in-hospital prior to randomisation)
% STEMI	Capped at 26% (18% undergoing primary PCI)	40.5% (all intended for primary PCI)
Clopidogrel load	Only 300 mg allowed	300 mg or 600 mg
Timing of randomisation	Later After angiography After decision to perform PCI	Earlier Usually before angiography (if done)
Randomisation	Prasugrel 60 mg load 10 mg once daily Or Clopidogrel 300 mg load 75 mg once daily	Ticagrelor 180 mg load 90 mg twice daily Or Clopidogrel 300 mg to 600 mg load 75 mg once daily
Administration of study drug	Started in the time interval from randomisation up to 1 hour after PCI	Started immediately after randomisation
Primary efficacy endpoint	CV death/MI/stroke	CV death/MI/stroke
Primary safety endpoint	Non-CABG TIMI major bleeding	PLATO major bleeding
PCI	99% (all at randomisation)	61% (49% within 24 hours of randomisation)
CABG	3.2% (0.35% on primary admission)	10.2% (4.5% on primary admission)
Medical management only	1.1%	34%
Glycoprotein IIb/IIIa use	54%	27%
Follow-up	Up to 15 months	Up to 12 months
ACS acute coronary syndromes, PCI percutaneous coronary intervention, STEMI ST-elevation myocardial infarction, NSTEMI non-ST-elevation myocardial infarction, CV cardiovascular, MI myocardial infarction, CABG coronary artery bypass grafting, TIMI Thrombolysis in Myocardial Infarction		

4.2.19 The Assessment Group highlighted that the manufacturer of prasugrel had not provided an indirect comparison of prasugrel with ticagrelor in its submission for this appraisal and that during the appraisal of ticagrelor for acute coronary syndromes (NICE technology appraisal guidance 236), both the manufacturer of ticagrelor and the Appraisal Committee considered such an indirect comparison to be inappropriate.

4.2.20 Although the Assessment Group considered an indirect comparison to be inappropriate, it identified 4 publications reporting an indirect comparison of prasugrel with ticagrelor based on TRITON-TIMI 38 and the PLATO trials. These publications reported that there were no statistically significant differences in overall death, nonfatal MI, nonfatal stroke, or their composite. Prasugrel was associated with a significantly lower risk of stent thrombosis and ticagrelor was associated with a significantly lower risk of any major bleeding and major bleeding associated with cardiac surgery.

4.2.21 The Assessment Group identified an ongoing trial designed to assess whether ticagrelor is superior to prasugrel in patients with ACS and planned invasive strategy (ISAR-REACT 5). This study is due to complete in October 2018 (final data collection date for primary outcome measure is October 2016). The results of this study should allow a formal comparison of the efficacy of prasugrel compared with ticagrelor.

5 Comments from other consultees

5.1 A professional group commented that although data for the use of prasugrel in STEMI treated by primary percutaneous coronary intervention (PCI) are unclear, the data supporting the use of prasugrel for STEMI treated by a variety of means (as still occurs in the UK) remain strong and there are no robust new data to

challenge the original guidance defining the patient population for whom prasugrel may be prescribed. The benefit of prasugrel therapy is limited to patients without any of the following clinical criteria: older than 75 years, less than 60 kg and history of TIA or stroke. This professional group commented that data produced after NICE technology appraisal guidance 182 (Acute coronary syndrome – prasugrel) do not support extending the use of prasugrel to all patients with non-ST-elevation-ACS – whether treated medically or by urgent revascularization. There is evidence from subgroup analysis for efficacy of prasugrel over clopidogrel in the reduction of stent thrombosis in patients receiving an intracoronary stent for treatment of ACS.

5.2 The professional group commented that since the publication of NICE technology appraisal guidance 182 (Acute coronary syndrome – prasugrel), few further data have become available about prasugrel in the context of non-ST-elevation-ACS and that no important new data are available for STEMI. It stated that while prasugrel reduces major adverse cardiac events and stroke in high risk ACS patients receiving PCI with stents, there is no evidence that prasugrel reduces mortality. The professional group commented that prasugrel should not be recommended in patients older than 75 years old, weighing less than 60 kg or with a past history of TIA or stroke. However, prasugrel should remain a treatment option in patients with STEMI treated by primary PCI or by other means and in diabetic patients with ACS of any variety (STEMI, NSTEMI or UA).

6 Cost-effectiveness evidence

Table 5: Summary of the Assessment Group's and the manufacturer's mean deterministic ICERs at year 40 follow up

Subgroup	Total cost		Total QALYs		Incremental		ICER (£ per QALY)
	Clopidogrel	Prasugrel	Clopidogrel	Prasugrel	Cost	QALYs	
Assessment Group							
STEMI and diabetes[1]	£19,904	£20,351	10.054	10.326	+£447	+0.272	£1,640
STEMI without diabetes[1]	£21,167	£21,722	10.950	11.033	+£555	+0.084	£6,626
UA/NSTEMI with diabetes[1]	£19,015	£18,939	9.919	10.095	-£77	+0.176	Dominant
UA/NSTEMI without diabetes[1]	£20,328	£20,576	10.655	10.708	+£248	+0.053	£4,667
Manufacturer							
All ACS licensed population[2]	£5,469	£6,062	10.16	10.21	+£593	0.05	£11,660
ACS Core clinical cohort[3]	£5,867	£6,463	10.97	11.02	+£596	0.05	£11,796
UA/NSTEMI licensed population[2]	£5,480	£6,067	10.16	10.20	+£587	0.04	£15,452
STEMI: licensed population[2]	£5,437	£6,046	10.16	10.25	+£609	0.09	£6,987
ACS diabetes licensed population[2]	£5,209	£5,809	9.50	9.63	+£600	0.13	£4,675

QALYs quality-adjusted life years, ICER incremental cost effectiveness ratio, STEMI ST-elevation myocardial infarction, UA unstable angina, NSTEMI non-ST-elevation myocardial infarction, ACS acute coronary syndromes

[1]mutually exclusive subgroups of the core clinical cohort:(that is all patients with ACS excluding those with a history of stroke or transient ischaemic attack, those with a body weight less than 60 kg or 75 years or older).

[2] excluding prior stroke or transient ischaemic attack and including patients who are now recommended to be treated with a 5 mg dose

[3] excluding prior stroke or transient ischaemic attack and those with a body weight less than 60 kg or 75 years or older).

6.1 Manufacturer's economic model

6.1.1 The manufacturer submitted a similar economic model to that it previously presented during the original appraisal of prasugrel (NICE technology appraisal guidance 182). The economic model had a Markov model structure with two phases. The first phase spanned the duration of the TRITON-TIMI 38 trial and the second phase extrapolated outcomes and costs beyond the trial, up until death or lifetime horizon (40 years). Rather than using data from the trial directly in the model, separate risk equations for primary endpoint events were obtained from individual patient data from the TRITON-TIMI 38 trial. These risk equations were then used to model events and hospitalisation. Mortality was modelled based on adjustment of population life tables, to reflect the impact on mortality in the long term of the events modelled over the short term. Patients entered the model at the point of experiencing an ACS event, immediately before having PCI.

6.1.2 However, some aspects of the submitted economic model had been updated in light of feedback generated during the original appraisal of prasugrel. These revisions included:

- the use of sensitivity analysis encompassing the entire population as opposed to a 'typical' patient profile
- scenario analysis using the ERG's suggestions for utility values, amended long-term relative risk of mortality and reduced incidence of nonfatal MI
- the (reduced) price of generic clopidogrel
- updated costs.

6.1.3 Although the TRITON-TIMI 38 trial included a health-related quality of life sub-study, the manufacturer stated that it was not possible to provide robust health-related quality of life estimates as a result of the very small numbers of patients with events

included in the analysis. The manufacturer, therefore, conducted a systematic review of the literature to identify studies relevant to the modelled trial population. Mean utility decrements for ACS (0.049) and stroke/MI (0.052) were taken directly from a US study (Sullivan et al., 2006) which was designed to produce a specific list of preference weights for use in economic evaluations; the study used the US version of the EQ-5D. To calculate utility weights for use in the economic evaluation, background UK population norms (free of disease) which vary by age and sex, as described by Kind et al. (1999), were applied to all patients in the study. The utility decrements for ACS and stroke/MI were then used alongside these background utility estimates. Finally, the manufacturer assumed that for a major bleed a decrement of 25% of the population (utility) norm was applicable for a 14 day period.

6.1.4 The key categories of cost estimates in the manufacturer's submission were related to hospitalisations and drug costs. Only hospitalisations related to endpoints or to serious adverse events requiring re-hospitalisation and potentially related to the ACS condition or the PCI intervention were included in the manufacturer's cost analysis. Re-hospitalisations were valued at a weighted average unit cost per hospitalisation (using NHS reference costs) and differences in hospitalisation rates were applied by geographic location. The weighted average unit cost per hospitalisation used by the manufacturer in its submission was £3070 for clopidogrel and £3081 for prasugrel. Patients were assumed to be treated with either aspirin and clopidogrel or aspirin and prasugrel for 12 months. The acquisition costs of prasugrel, clopidogrel and aspirin are shown in table 6.

Table 6:drug costs used in the manufacturer's economic model

	Cost of loading dose (per day)	Cost of maintenance dose (per day)	Source
Prasugrel	£10.20	£1.70	MIMS August 13 (based upon £47.56 per pack of 28 tablets)
Clopidogrel	£0.24	£0.07	NHS Drug Tariff 75 mg (28 tab) £1.83
Aspirin		£0.01	

6.1.5 The manufacturer considered 5 subgroups in its cost effectiveness analysis: (i) all ACS licensed population (excluding prior stroke or TIA and including patients who are now recommended to be treated with a 5 mg maintenance dose); (ii) ACS Core (excluding prior stroke or TIA and those with a body weight less than 60 kg or 75 years or older); (iii) UA/ NSTEMI licensed population; (iv) STEMI licensed population and (v) ACS diabetes, licensed population (excluding prior stroke or TIA). The manufacturer's cost effectiveness results for prasugrel compared with clopidogrel for each of these groups over a lifetime horizon (40 years) are shown in table 5.

6.1.6 The manufacturer carried out a series of one-way deterministic sensitivity analyses on the ACS Core population (excluding prior stroke or TIA and those with a body weight less than 60 kg or 75 years or older).The following changes to the model resulted in incremental cost-effectiveness ratios (ICERs) of more than £13,000 per QALY gained (that is an increase of more than £1,000 from the base case ICER):

- discounting at 6% for both costs and effects (ICER £16,000 per QALY gained).
- relative risks for all-cause mortality associated with clinical events reduced by 50% (ICER £20,619 per QALY gained).

- clopidogrel pre-loading adjustment set at 70% (ICER £13,959 per QALY gained).

6.1.7 The manufacturer also carried out a series of scenario analysis for each of the subgroups described in section 6.1.5 of the overview.. The scenario analyses undertaken were: use of alternative values obtained from the Health Outcomes Data Repository (HODaR) database, amendment to the long term relative risks of mortality (by ignoring the initial impact of ACS prior to TRITON events) and a reduction in the incidence of nonfatal MIs such that the underlying rate of MIs was 50% of that of the trial. The results of the scenario analysis showed that using alternative utility values, relative risks for mortality and myocardial infarction, the ICER for prasugrel compared with clopidogrel remained below £20,000 per QALY gained.

6.1.8 Probabilistic sensitivity analysis was not undertaken.

Assessment Group's critique of the manufacturer's economic model

6.1.9 The Assessment Group provided a critique of the manufacturer's economic model. It stated that in the long-term component of the model there is an assumption that differences established between the prasugrel and clopidogrel treatment arms of the TRITON-TIMI 38 trial will be preserved indefinitely at the level observed at the end of the trial. However, the Assessment Group considered that there is no reason to believe that further serious nonfatal events will not continue to occur to patients in both cohorts. It stated that if events occurring during the trial are presumed to influence later survival, then it is also likely that any such events in subsequent periods will also have important effects. Since active treatment with clopidogrel or prasugrel will have ceased, it can be expected that event rates will be similar in both treatment arms. As a result of this process, it is likely that

over time the disease history of patients will converge, and therefore any initial advantage for either treatment will be progressively attenuated.

6.2 Assessment Group's economic model

6.2.1 The Assessment Group carried out a systematic review to identify existing economic evaluations of prasugrel. Of the 15 potentially eligible references identified by the Assessment Group, none of the papers met the full inclusion criteria that had been set. The review identified the 3 studies included in the manufacturer's review of cost-effectiveness evidence. Two of these studies were carried out from a US perspective, and the third study used employed the economic model originally submitted during technology appraisal guidance 182 (Acute coronary syndrome – prasugrel). These were excluded by the Assessment Group.

Model design and structure

6.2.2 The Assessment Group developed a 2 phase model economic model: a short-term statistical model of the data from the TRITON-TIMI 38 trial and a long-term model projecting outcomes and costs at the end of the first phase up to a maximum of 40 years. The model compared dual antiplatelet therapy for 12 months from time of PCI with either clopidogrel in combination with low-dose aspirin or prasugrel in combination with low-dose aspirin. As a result of the lack of clinical evidence available, the Assessment Group did not compare prasugrel with ticagrelor.

6.2.3 The Assessment Group accepted the manufacturer's statistical model for the initial phase (up to 12 months) but replaced the long-term projection with a more detailed structure that provided an improved representation of subsequent cardiovascular events, accumulating patient histories, alteration in health states and

associated care costs, as well as patient health-related quality of life.

6.2.4 The Assessment Group's decision model assessed four mutually exclusive subgroups of the core clinical cohort:(that is all patients with ACS excluding those with a history of stroke or TIA, those with a body weight less than 60 kg or those aged 75 years or older).

- ACS patients treated with PCI for STEMI and diagnosed with diabetes
- ACS patients treated with PCI for STEMI and without diagnosed diabetes
- ACS patients treated with PCI for UA or NSTEMI and with diagnosed diabetes
- ACS patients treated with PCI for UA or NSTEMI and without diagnosed diabetes

Specific clinical data relating to patients with STEMI, UA/NSTEMI or diabetes mellitus in the core clinical cohort were not available from the manufacturer's submission or the most recent publication. Therefore, the Assessment Group extracted the outcomes from the manufacturer's short-term model for the four mutually exclusive subgroups of the core clinical cohort and employed these as the initial conditions for surviving patients entering the Assessment Group's long-term state-transition model.

6.2.5 For the long term projection, the Assessment Group used a modified version of an economic model which it developed for NICE technology appraisal guidance 210 (Clopidogrel and modified release dipyridamole for the prevention of occlusive vascular events). The economic model developed for NICE technology appraisal guidance 210 used data provided by the manufacturer of clopidogrel from the CAPRIE clinical trial,

supplemented with data provided by the manufacturer of dipyridamole from the PROFESS clinical trial. The Assessment Group stated that the myocardial infarction subpopulation model submitted for NICE technology appraisal guidance 210, which was based largely on data from the MI subpopulation in the CAPRIE trial, addressed issues similar to those in this appraisal. In order to reduce the time in generating model results from an individual patient simulation approach, the Assessment Group re-structured the economic model submitted for NICE technology appraisal guidance 210 into a long-term Markov chain.

6.2.6 The possible inter-state transitions from year to year in the Assessment Group's long-term model are represented in detail in Table 27 of the assessment report. A graphic representation of the Assessment Group's long-term model is provided on page 7 of Addendum 1 to the assessment report.

6.2.7 The main source of data used to populate the Assessment Group's long-term model was the CAPRIE clinical trial. The Assessment Group stated that its clinical advisor had confirmed that CAPRIE data was an appropriate trial source for extrapolating long-term vascular events and that no better source had become available since 2010. The CAPRIE trial was a double-blind placebo comparison of clopidogrel with aspirin involving 19,185 patients with atherosclerotic vascular diseases manifested as either ischaemic stroke (IS), MI or symptomatic peripheral arterial disease. Only CAPRIE data from 5,741 patients with myocardial infarctions and without prior history of other vascular events were used to populate the Assessment Group's long-term model. The manufacturer of clopidogrel carried out extensive re-analyses of the CAPRIE trial data as requested by the Assessment Group in order to estimate independent event hazards adjusted to age, gender and event history. Full details of the estimated event rates

and event fatality rates are provided in the assessment report submitted for NICE technology appraisal guidance 210 (Clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events). For the parameter values used for event rates and event fatality rates, see tables 29 and 30, pages 81-82 of the assessment report. For the parameter sources and values used for the relative risk of key events for patients with and without diabetes, see table 31, page 82 of the assessment report.

Costs

6.2.8 The cost of prasugrel, clopidogrel and aspirin used in the Assessment Group's economic model are shown in table 8.

Table 8: Summary of drug costs used in the Assessment Group's economic model

Detail	Clopidogrel	Prasugrel	Low-dose aspirin
Pack price (28 tablets)	£1.71 (Drug Tariff November 2013)	£47.56 (BNF October 2013)	£0.82 (Drug Tariff November 2013)
Cost of loading dose	£0.24	£10.19	-
Cost of 12 months' supply (*adjusted for treatment duration)	£18.43*	£511.67*	£10.70
Total dual antiplatelet therapy cost (year 1)	£29.37	£532.56	-
Annual maintenance cost	-	-	£10.70

6.2.9 The Assessment Group used the same unit costs as used in NICE technology appraisal guidance 182 (Acute coronary syndrome – prasugrel) but updated to 2012 prices using the Hospital and Community Health Services inflation index. The unit costs used by the Assessment Group are shown in table 9.

Table 9 Unit costs for events and treatment used in the Assessment Group's model

	Mean	Standard error	LCL	UCL
Event				
Fatal MI	£2,373.68	£121.11	£2,136.31	£2,611.05
Nonfatal MI	£6,165.21	£314.55	£5,548.69	£6,781.73
Fatal stroke	£9,381.43	£478.64	£8,443.29	£10,319.57
Nonfatal non-disabling stroke	£6,858.64	£349.93	£6,172.77	£7,544.50
Nonfatal disabling stroke	£14,602.70	£754.04	£13,142.43	£16,062.97
OV death	£2,407.50	£122.83	£2,166.75	£2,648.25
NV death	£2,407.50	£122.83	£2,166.75	£2,648.25
Annual cost in health state				
Event free / MI only	£618.03	£31.53	£556.23	£679.84
Non-disabling stroke	£1,804.06	£92.04	£1,623.66	£1,984.47
Disabling stroke	£5,537.72	£282.54	£4,983.95	£6,091.50
MI myocardial infarction, OV other vascular, NV non vascular, LCL lower confidence limit, UCL upper confidence limit				

Health-related utility estimation

6.2.10 The Assessment Group obtained the continuing health-state EQ-5D utility value for patients who were event-free or suffered a nonfatal MI (but no strokes) and who were alive12 months after PCI from the economic sub-study of the PLATO clinical trial. The values were based on the weighted average of patients meeting those criteria. Utility parameters reflecting gender differences and mild versus severe strokes for patients suffering at least 1 stroke/TIA were obtained from a study of EQ-5D observations as part of the Oxford Vascular Study (OXVASC). The Assessment Group used an annual loss of utility estimated from the UK

population EQ-5D norms which was calculated by fitting a linear regression trend line to all people aged 35 years or over. The results were used to adjust the initial health state utilities of each subgroup for the differences in mean age between the TRITON-TIMI 38 cohort and OXVASC data. This decrement was also applied annually to the results of the model to reflect the average decline of utility score with increasing age.

6.2.11 The Assessment Group expected that 7 events in its model would be expected to result in additional utility decrement in the first year of follow-up during early recovery. The Assessment Group identified a specific value for nonfatal MI using an analysis of UK Prospective Diabetes Study trial results which compares utility values for events occurring within 12 months with those occurring earlier. Sources for nonfatal stroke parameters gave contradictory figures suggesting that there is no clear additional early disutility effect beyond the long-term continuing effect of a stroke. As a result, the Assessment Group set these parameters to zero and conducted one-way sensitivity analyses on these parameters instead. No sources were identified for utility values for fatal MI, fatal stroke, other vascular death or non-vascular death. The Assessment Group assigned these parameters a notional value of −0.1 and conducted sensitivity analyses.

6.2.12 The Assessment Group discounted costs and outcomes annually at 3.5% and carried out one-way sensitivity analyses using 0% and 6% discount rates for both costs and outcomes. The Assessment Group's model generates results at the end of every year from trial randomisation. However, deterministic results were reported at 1, 5, 10, 20 and 40 years, and probabilistic results at 5 and 40 years.

6.2.13 The Assessment Group assumed that follow-up secondary prophylaxis was limited to low-dose aspirin. The Assessment Group stated that it made this assumption for convenience and to avoid the possibility of obscuring the primary comparison between prasugrel and clopidogrel use. For the same reason, the Assessment Group did not incorporate other post-stroke and post-MI care including surgery and other medication options. The Assessment Group did not incorporate the adverse effects of aspirin therapy, the possibility that people discontinue aspirin treatment or the risk of bleeding events associated with long-term prophylaxis as all these issues would affect patients in both treatment arms and the incremental difference would be expected to be minimal.

Assessment group's cost-effectiveness results

6.2.14 Results from the Assessment Group's model were presented separately for each of the four patient subgroups described in section 6.2.4 of the overview. The Assessment Group considered that it was in appropriate to calculate an ICER for the overall core clinical cohort (see section 4, page 8 of Addendum 1 to the assessment report). For each subgroup, deterministic cost effectiveness results were presented across a range of time periods: 1, 15, 10, 20 and 40 years after the initial PCI. Probabilistic cost effectiveness results were presented for 5 and 40 years follow-up. A summary of the deterministic cost effectiveness results at 40 years are provided in table 5.

STEMI - diabetes subgroup

6.2.15 For people in the STEMI-diabetes subgroup, the ICER was high at the end of the first year because of the inclusion of the full additional cost of treatment. Over time, the estimated ICER decreased steadily, suggesting that incremental benefit continues to accrue over subsequent decades while the incremental cost

increases at a slower rate. The mean deterministic ICER for prasugrel compared with clopidogrel for people in the STEMI-diabetes subgroup was £31,915 per QALY gained at the end of year 1 of follow-up and decreased to £1,640 per QALY gained at year 40 of follow-up. The Assessment Group conducted one-way sensitivity analyses, the results of which indicated that uncertainty from individual model parameters had a minor effect on the magnitude of the ICER in this subgroup. Discount rates for costs and outcomes had the largest effect on the ICER, but it remained within the range of £1,000 to £2,500 per QALY gained. Probabilistic analysis at the 40 year follow-up horizon for this subgroup resulted in a higher estimated ICER of £1,732 per QALY gained (incremental cost £515 and incremental QALYs 0.297).

STEMI - no diabetes subgroup

6.2.16 The cost-effectiveness results for the STEMI-no diabetes subgroup was similar to the STEMI-diabetes subgroup, although in this subgroup the ICER was higher at the end of the first year (£224,302 per QALY gained) because of the inclusion of the full additional cost of treatment. At year 5 follow up, the ICER decreased to £29,607 per QALY gained and decreased to £6,626 per QALY gained at year 40. The Assessment Group conducted one-way sensitivity analyses, the results of which indicated that uncertainty from individual model parameters had a minor effect on the magnitude of the ICER in this subgroup. Discount rates for costs and outcomes had the largest effect on the ICER, but it remained within the range of £4,000 and £9,000 per QALY gained. Probabilistic analysis at the 40 year follow-up horizon for this subgroup resulted in a higher estimated ICER of £7,073 per QALY gained obtained from small incremental cost and QALY estimates (incremental cost £609 and incremental QALYs 0.086).

UA/NSTEMI - diabetes subgroup

6.2.17 The cost-effectiveness result for the UA/NSTEMI-diabetes subgroup is similar to the previously described subgroups. In this subgroup the ICER for prasugrel compared with clopidogrel was £76,856 per QALY gained at the end of the first year as a result of the inclusion of the full additional cost of treatment. At year 5 follow up, the ICER for prasugrel decreased to £2,846 per QALY gained and dominated (that is, was less costly and more effective than) clopidogrel from year 10 and beyond. The Assessment Group undertook one-way sensitivity analyses, which indicated that uncertainty from event incidence and fatality rates had the largest effect on the estimated ICER for this subgroup (ranging between -£1,000 and +£400 per QALY gained). Probabilistic analysis at the 40 year follow-up horizon for this subgroup confirmed that prasugrel dominated clopidogrel with a small net cost saving and positive incremental benefit (incremental cost -£120 and incremental QALYs 0.191 respectively).

UA/NSTEMI - no diabetes subgroup

6.2.18 The cost-effectiveness result for the UA/NSTEMI-no diabetes subgroup is similar to the previously described subgroups. In this subgroup the ICER for prasugrel compared with clopidogrel was £1,101,662 per QALY gained at the end of the first year as a result of the inclusion of the full additional cost of treatment. At year 5 follow up, the ICER for prasugrel decreased to £52,288 per QALY gained and decreased to £4,667 per QALY gained at year 40. The Assessment Group undertook one-way sensitivity analyses, which indicated that uncertainty from event incidence and fatality rates had the largest effect on the estimated ICER for this subgroup (ranging between £2,500 and £6,500 per QALY gained). Probabilistic analysis at the 40 year follow-up horizon for this subgroup resulted in a lower estimated ICER of £4,154 per

QALY gained (incremental cost £212 and incremental QALYs 0.051).

6.3 Comparison of the Assessment Group's model, the manufacturer's model and the model for NICE technology appraisal guidance 182

6.3.1 Table 10 illustrates the differences in the cost-effectiveness estimates for the 3 different models: the manufacturer's model; the ERG's adjusted results for NICE technology appraisal guidance 182 (referred to as TA182) and the Assessment Group's model for the current appraisal (referred to as the R182 model.

Table 10 Comparison of the deterministic base-case results for the Core clinical cohort at 40 years follow-up

	Incremental cost-effectiveness ratio (ICER, Cost per QALY gained)		
	Manufacturer	TA182	R182
Core clinical cohort[1]	£11,796	£20,247	-
STEMI with diabetes[2]	-	£1,805	£1,640
STEMI without diabetes[2]	-	£6,616	£6,626
UA/NSTEM with diabetes[2]	-	£3,005	Dominant
U/ANSTEMI without diabetes[2]	-	£136,888	£4,667

STEMI ST-elevation myocardial infarction, UA unstable angina, NSTEMI non-ST-elevation myocardial infarction,
[1] excluding prior stroke or transient ischaemic attack and those with a body weight less than 60 kg or 75 years or older
[2] mutually exclusive subgroups of the core clinical cohort:

7 Equality issues

7.1 No potential equalities issues were identified during the scoping process.

8 Innovation

8.1 The manufacturer did not address innovation with respect to prasugrel in its submission.

9 Authors

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Appendix A: Supporting evidence

Related NICE guidance

Published

Technology Appraisals

- Ticagrelor for the treatment of acute coronary syndromes (ACS). NICE technology appraisal guidance 236 (October 2011)

  Ticagrelor in combination with low-dose aspirin is recommended for up to 12 months as a treatment option in adults with acute coronary syndrome that is, people:

  - *with STEMI-defined as ST elevation or new left bundle branch block on electrocardiogram-that cardiologists intend to treat with percutaneous coronary intervention or*
  - *NSTEMI or*
  - *admitted to hospital with unstable angina. Before ticagrelor is continued beyond the initial treatment, the diagnosis of unstable angina should first be confirmed, ideally by a cardiologist*

- Prasugrel for the treatment of acute coronary syndromes with percutaneous coronary intervention. NICE technology appraisal guidance 182 (October 2009)

  Prasugrel in combination with aspirin is recommended as an option for preventing atherothrombotic events in people with acute coronary syndrome having percutaneous coronary intervention, only when:

  - *immediate primary percutaneous coronary intervention for STEMI is necessary or*
  - *stent thrombosis has occurred during clopidogrel treatment or*
  - *the patient has diabetes mellitus*

Clinical Guidelines

- Secondary prevention in primary and secondary care for patients following a myocardial infarction (replaces NICE clinical guideline 48). NICE clinical guideline 172 (November 2013)

Aspirin should be offered to all people after an MI and continued indefinitely, unless individuals are aspirin intolerant or have an indication for anticoagulation

For patients with aspirin hypersensitivity, clopidogrel monotherapy should be considered as an alternative treatment

Clopidogrel is a treatment option for up to 12 months for:

- *people who have had an NSTEMI, regardless of treatment*
- *people who have had a STEMI and received a bare-metal or drug-eluting stent*

Ticagrelor is also recommended as per NICE technology appraisal guideline 236 noted above

Prasugrel-prasugrel for the treatment of acute coronary syndrome has not been incorporated in this guidance because this technology appraisal is currently scheduled for update

There are special recommendations for antiplatelet therapy in people with an indication for anticoagulation

- Myocardial infarction with ST-segment elevation: The acute management of myocardial infarction with ST-segment elevation. NICE clinical guideline 167 (July 2013)

  *Following reperfusion therapy for STEMI, treatment with aspirin should be continued in line with clinical guideline 48 MI secondary prevention**

  The Guideline Development Group considered that treatment with clopidogrel is an established option in the pharmacological treatment of people with acute STEMI including people undergoing primary percutaneous coronary intervention. The Guideline Development Group were aware that a clopidogrel loading dose of 600mg is not licensed in the UK but is used widely in current practice, especially in people undergoing primary percutaneous coronary intervention

  Prasugrel was noted as a recommended treatment from NICE technology appraisal guideline 182 and is the subject of this current appraisal

  Ticagrelor is recommended as in NICE technology appraisal guideline 236

- Unstable angina and NSTEMI: the early management of unstable angina and non-ST-segment-elevation myocardial infarction. NICE clinical guideline 94 (March 2010)

Offer a 300mg loading dose of clopidogrel to all patients with no contraindications who may undergo percutaneous coronary intervention within 24 hours of admission to hospital

In line with 'Prasugrel for the treatment of acute coronary syndromes with percutaneous coronary intervention' (NICE technology appraisal 182), prasugrel in combination with aspirin is an option for patients undergoing percutaneous coronary intervention who have diabetes or have had stent thrombosis with clopidogrel treatment

It is recommended that treatment with clopidogrel in combination with low-dose aspirin should be continued for 12 months after the most recent acute episode of NSTEMI. Thereafter, standard care, including treatment with low-dose aspirin alone, is recommended.

- Secondary prevention in primary and secondary care for patients following a myocardial infarction'. NICE clinical guideline 48 (May 2007)

Medical Technology Guidance

- SeQuent Please balloon catheter for in-stent coronary restenosis. NICE medical technology guidance 1 (December 2010)

Under development

NICE is developing the following guidance (details available from www.nice.org.uk):

- Rivaroxaban for the prevention of adverse outcomes in patients after the acute management of acute coronary syndrome. NICE technology appraisal. (March 2015)
- Acute coronary syndrome (including myocardial infarction). NICE quality standard. (September 2014)

NICE pathways

- There is a NICE pathway on acute coronary syndromes, which is available from http://pathways.nice.org.uk/pathways/acute-coronary-syndromes.

Appendix B: Clinical efficacy section of the draft European public assessment report

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/000984/WC500021975.pdf