

Prasugrel with percutaneous coronary intervention for treating acute coronary syndromes

Technology appraisal guidance

Published: 23 July 2014

[nice.org.uk/guidance/ta317](https://www.nice.org.uk/guidance/ta317)

Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance are at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

1 Guidance	4
2 Clinical need and practice	5
3 The technology	7
4 Evidence and interpretation	8
4.1 Clinical effectiveness	8
4.2 Cost effectiveness	17
4.3 Consideration of the evidence	28
Summary of Appraisal Committee's key conclusions	38
5 Implementation	49
6 Review of guidance	50
7 Appraisal Committee members and NICE project team	51
7.1 Appraisal Committee members	51
7.2 NICE project team	53
8 Sources of evidence considered by the Committee	54
About this guidance	56

This guidance replaces TA182.

1 Guidance

This guidance replaces [NICE technology appraisal guidance 182](#) issued in October 2009.

The review of prasugrel for treatment of acute coronary syndromes has resulted in a change in the guidance. See [About this guidance](#) for more information.

- 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.

2 Clinical need and practice

- 2.1 Acute coronary syndromes refers to a group of symptoms associated with acute myocardial ischaemia with or without infarction. It encompasses a spectrum of disorders or syndromes including acute myocardial infarction and unstable angina pectoris. Acute coronary syndromes are 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 in a heart vessel) associated with inflammation, thrombosis, vasoconstriction and microembolisation.
- 2.2 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). Acute coronary syndrome without STEMI is classified as either unstable angina or non-ST-segment-elevation myocardial infarction (NSTEMI). NSTEMI differs from unstable angina 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 myocardial infarction, may include coronary revascularisation, either by means of percutaneous coronary intervention or coronary artery bypass graft.
- 2.3 Acute coronary syndromes become more prevalent with increasing age and incidence is higher in men than women. There were around 32,000 hospital admissions for unstable angina in England in 2012–13, and it is estimated that there are about 82,000 myocardial infarctions in the country every year. Of the 80,974 hospital admissions with a final diagnosis of myocardial infarction recorded between April 2012 and March 2013 in the Myocardial Ischaemia National Audit Project (MINAP), 40% were STEMI 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 myocardial infarctions as women.
- 2.4 Long-term management of acute coronary syndromes includes the use of aspirin in combination with a thienopyridine (clopidogrel, prasugrel) or acyclopentyl-triazolo-pyrimidine (ticagrelor). NICE has produced clinical

guidelines on [Myocardial infarction with ST-segment-elevation: The acute management of myocardial infarction with ST-segment-elevation](#) (NICE clinical guideline 167) and on [Unstable angina and NSTEMI: the early management of unstable angina and non-ST-segment-elevation myocardial infarction](#) (NICE clinical guideline 94). NICE's [myocardial infarction with ST-segment-elevation](#) guideline recommends that after STEMI, patients treated with clopidogrel in combination with low-dose aspirin during the first 24 hours after the myocardial infarction should continue with treatment for at least 4 weeks. Thereafter, standard treatment, including low-dose aspirin, should be given unless there are other indications to continue clopidogrel in combination with aspirin. In its [unstable angina and NSTEMI](#) guideline, NICE recommends that 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 unless there are other indications to continue clopidogrel in combination with aspirin.

2.5 NICE recommends prasugrel in combination with aspirin as an option for preventing atherothrombotic events in people with acute coronary syndromes having percutaneous coronary intervention, only when: immediate primary percutaneous intervention for STEMI is necessary; stent thrombosis has occurred during clopidogrel treatment; or the person has diabetes ([NICE technology appraisal guidance 182](#)). NICE also recommends 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 percutaneous coronary intervention, NSTEMI or unstable angina ([NICE technology appraisal guidance 236](#)).

2.6 Since the publication of the [original appraisal of prasugrel](#) (NICE technology appraisal guidance 182) in October 2009, generic formulations of clopidogrel have become available and NICE has published its appraisal of ticagrelor (2011; [NICE technology appraisal guidance 236](#)).

3 The technology

- 3.1 Prasugrel (Efient, Eli Lilly and Company/Daiichi-Sankyo) is an oral inhibitor of platelet activation and aggregation. It works by 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 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.
- 3.2 The summary of product characteristics for prasugrel states that it should be started with a single 60 mg loading dose and then continued at 10 mg once a day. People taking prasugrel should also take 75 mg to 325 mg aspirin daily. Treatment for up to 12 months is recommended unless stopping prasugrel is clinically indicated.
- 3.3 According to the summary of product characteristics, the use of prasugrel in people 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 who weigh 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 unstable angina or NSTEMI, if coronary angiography is performed within 48 hours after admission, the summary of product characteristics states that the loading dose should only be given at the time of percutaneous coronary intervention.
- 3.4 The summary of product characteristics lists the following adverse reactions for prasugrel: increased bleeding risk, hypersensitivity reactions including angioedema, and thrombotic thrombocytopenic purpura. For full details of adverse reactions and contraindications, see the summary of product characteristics.
- 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.

4 Evidence and interpretation

Details of membership of the Appraisal Committee are given in [section 7](#), and a list of the sources of evidence used in the preparation of this document is given in [section 8](#).

4.1 *Clinical effectiveness*

Prasugrel compared with clopidogrel

- 4.1.1 The manufacturer and the Assessment Group both identified 1 randomised controlled trial (TRITON-TIMI 38) and 1 publication related to the core clinical cohort from TRITON-TIMI 38 (Wiviott et al. 2011) from a systematic search of the literature. Both the randomised controlled trial and the publication were also considered for the original appraisal of prasugrel ([Prasugrel for the treatment of acute coronary syndromes with percutaneous coronary intervention](#), NICE technology appraisal guidance 182). The Assessment Group commented that no new evidence had been identified since the original appraisal was published.
- 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 acute coronary syndromes (unstable angina, non-ST-segment-elevation myocardial infarction [NSTEMI] or ST-segment-elevation myocardial infarction [STEMI]) who were scheduled to have percutaneous coronary intervention. Patients were given aspirin (at a recommended daily dose of between 75 mg 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).
- 4.1.3 The primary efficacy end point for TRITON-TIMI 38 was a composite of the rate of non-fatal myocardial infarction, non-fatal stroke, and death from cardiovascular causes during the entire follow-up period. A range of secondary composite end points were also included. Major safety end points 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 g to less than 5 g/100 ml).

- 4.1.4 Wiviott et al. (2011) reported the results for a core clinical cohort of the TRITON-TIMI 38 population (n=10,084). This cohort consisted of patients younger than 75 years, weighing 60 kg or more, and with no history of stroke or transient ischaemic attack. This subpopulation was described in NICE's [previous appraisal of prasugrel](#) (NICE technology appraisal guidance 182) as the 'target population' or 'licensed population' for treatment with prasugrel.

Manufacturer's submission

- 4.1.5 The manufacturer's submission focused on the results of the overall cohort population of TRITON-TIMI 38. At 15 months, the composite primary end point for the overall cohort population of TRITON-TIMI 38 (n= 13,608) occurred statistically significantly more frequently in the clopidogrel group than in the prasugrel group (clopidogrel 781 of 6795 patients [12.1%] and prasugrel 643 of 6813 patients [9.9%], hazard ratio 0.81 [95% confidence interval {CI} 0.73 to 0.90], p<0.001). In the clopidogrel group there were also statistically significantly more non-fatal myocardial infarctions (clopidogrel 620 of 6795 patients [9.5%] and prasugrel 475 of 6813 patients [7.3%], hazard ratio 0.76 [95% CI 0.67 to 0.85], p<0.001); deaths from cardiovascular causes, non-fatal myocardial infarctions or urgent target vessel revascularisation (clopidogrel 798 of 6795 patients [12.3%] and prasugrel 652 of 6813 patients [10.0%], hazard ratio 0.81 [95% CI 0.73 to 0.89], p<0.001); stent thromboses (clopidogrel 142 of 6795 patients [2.4%] and prasugrel 68 of 6813 patients [1.1%], hazard ratio 0.48 [95% CI 0.36 to 0.64], p<0.001); and deaths from cardiovascular causes, non-fatal myocardial infarctions, non-fatal stroke or rehospitalisations for ischaemia (clopidogrel 938 of 6795 patients [14.6%] and prasugrel 797 of 6813 patients [12.3%], hazard ratio 0.84 [95% CI 0.76 to 0.92], p<0.001) than in the prasugrel group. There were no statistically significant differences between the groups in the number of deaths from cardiovascular causes (clopidogrel 150 of 6795 patients [2.4%] and prasugrel 133 of 6813 patients [2.1%], hazard ratio 0.89 [95% CI 0.70 to 1.12], p=0.31); non-fatal strokes (clopidogrel 60 of 6795 patients [1.0%] and prasugrel 61 of 6813 patients [1.0%], hazard ratio 1.02 [95% CI 0.71 to 1.45], p= 0.93); or deaths from any cause (clopidogrel 197 of 6795 patients [3.2%] and prasugrel 188 of 6813 patients [3.0%], hazard ratio 0.95 [95% CI 0.78 to 1.16], p=0.64).
- 4.1.6 In the overall cohort, statistically significantly fewer patients in the clopidogrel group than in the prasugrel group met the primary safety end point

(non-CABG-related TIMI major bleeding) during the 15-month follow-up period (clopidogrel 1.8% and prasugrel 2.4%, hazard ratio 1.32 [95% CI 1.03 to 1.68], $p=0.03$). The net clinical benefit (composite of death from any cause, non-fatal myocardial infarction, non-fatal stroke and non-CABG-related non-fatal TIMI major bleed) statistically significantly favoured prasugrel (clopidogrel 13.9% and prasugrel 12.2%, hazard ratio 0.87 [95% CI 0.79 to 0.95, $p=0.004$]).

- 4.1.7 The manufacturer presented an analysis of pre-specified subgroups for the overall cohort in its submission. These subgroups included STEMI, unstable angina or NSTEMI, people with diabetes and types of stent placements. The analysis showed that there was no evidence to suggest that the overall treatment effect was different in the subgroups compared with the overall cohort.
- 4.1.8 The manufacturer also provided post-hoc subgroup analyses from other publications, which included the following:
- A subgroup analysis of the 1218 myocardial infarctions that occurred during TRITON-TIMI 38 based on a paper by Morrow et al. (2009) showed that there was a consistent reduction in the incidence of myocardial infarctions with prasugrel compared with clopidogrel for myocardial infarctions of every size as measured by biomarker elevation, with the greatest absolute reduction seen in those myocardial infarctions associated with the greatest extent of myocardial necrosis. The manufacturer highlighted that this analysis showed that prasugrel statistically significantly reduced spontaneous and procedural myocardial infarction compared with clopidogrel, and that this was consistent across myocardial infarctions of varying type, size and timing.
 - A subgroup analysis of the 3146 patients with diabetes in TRITON-TIMI 38 (Wiviott et al. 2008) showed that patients with diabetes tended to have a greater reduction in ischaemic events without an observed increase in non-CABG-related TIMI major bleeding, and therefore showed a greater net treatment benefit with prasugrel compared with clopidogrel.

Assessment Group's report

- 4.1.9 The Assessment Group's report focused on the results of the core clinical cohort population of TRITON-TIMI 38, as reported in Wiviott et al. (2011). The Assessment Group explained that during NICE's [original appraisal of prasugrel](#), the Appraisal Committee agreed that the core clinical cohort population was

the most relevant because the excluded patients were either explicitly excluded from the marketing authorisation or were not supported by trial evidence (because the trial was based on the full 10 mg dose). The Assessment Group noted that the authors of the Wiviott et al. study stated that the core clinical cohort was identified post hoc and defined by regulatory criteria, and that the study should therefore be considered as an exploratory analysis.

- 4.1.10 The Assessment Group stated that the patients in the overall trial population of TRITON-TIMI 38 and the core clinical cohort as reported in Wiviott et al. (2011) appeared to be similar in terms of baseline characteristics. These included the proportion of patients with unstable angina or NSTEMI (74% and 73% respectively), the proportion of males (74% and 79%), and the proportion of patients with diabetes (23% and 22%). 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.
- 4.1.11 For the patients in the core clinical cohort, prasugrel showed a clinically significant and robust reduction in the primary end point compared with clopidogrel (death from cardiovascular causes, non-fatal myocardial infarction or non-fatal stroke; clopidogrel 569 of 5383 patients [11.0%] and prasugrel 433 of 5421 patients [8.3%], hazard ratio 0.74 [95% CI 0.66 to 0.84], $p < 0.001$) with a favourable net clinical outcome (composite of death from any cause, non-fatal myocardial infarction, non-fatal stroke, and non-CABG-related non-fatal thrombolysis in myocardial infarction [TIMI] major bleed; clopidogrel 641 of 5383 patients [12.5%] and prasugrel 522 of 5421 patients [10.2%], hazard ratio 0.80 [95% CI 0.71 to 0.89], $p < 0.001$). There was no statistically significant difference between the 2 groups in terms of the number of patients with non-CABG-related TIMI major bleeding (clopidogrel 73 of 5337 patients [1.5%] and prasugrel 91 of 5390 patients [1.9%], hazard ratio 1.24 [95% CI 0.91 to 1.69], $p = 0.17$). The Assessment Group commented that the results for both composite outcomes appeared to be driven by the number of non-fatal myocardial infarctions.
- 4.1.12 The Assessment Group stated that for the core clinical cohort, prasugrel was more effective than clopidogrel on the primary end point at 30 days (clopidogrel 7.0% and prasugrel 5.0%, hazard ratio 0.70 [95% CI 0.60 to 0.82], $p < 0.0001$) as

well as at the 15-month follow up (clopidogrel 4.5% and prasugrel 3.6%, hazard ratio 0.80 [95% CI 0.65 to 0.97], $p=0.027$).

- 4.1.13 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 statistically significant difference in favour of clopidogrel when major and minor bleeding events were combined (clopidogrel 3.0% and prasugrel 3.9%, hazard ratio 1.26 [95% CI 1.02 to 1.57], $p=0.03$). The Assessment Group commented that analysis of the net clinical benefit outcome (death from any cause, non-fatal myocardial infarction, non-fatal stroke, or non-CABG-related non-fatal TIMI major bleeding) favoured the use of prasugrel in the core clinical cohort (clopidogrel 641 of 5383 patients [12.5%] and prasugrel 522 of 5421 patients [10.2%], hazard ratio 0.80 [95% CI 0.71 to 0.89], $p<0.001$).
- 4.1.14 The Assessment Group stated that statistically significant differences in favour of prasugrel were reported for the outcomes of definite stent thrombosis (hazard ratio 0.41 [95% CI 0.29 to 0.60], $p<0.001$) and definite or probable stent thrombosis (hazard ratio 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 compared with the clopidogrel group (clopidogrel 9.4% and prasugrel 6.7%, hazard ratio 0.71 [95% CI 0.62 to 0.81], $p<0.001$).
- 4.1.15 The Assessment Group reviewed a Forest plot from the Wiviott et al. publication that showed 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, unstable angina or NSTEMI 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, unstable angina or NSTEMI with diabetes, or unstable angina or NSTEMI without diabetes. The Assessment Group also highlighted that it was able to extract economic data about these subgroups from the manufacturer's economic model.
- 4.1.16 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), there was no statistically significant difference between the prasugrel and clopidogrel groups for non-CABG-related major bleeding. Only 1 statistically significant difference between prasugrel and clopidogrel was noted and this was for the combined outcome of TIMI major and minor bleeding, for which statistically significantly more events occurred with prasugrel than with clopidogrel.

- 4.1.17 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 transient ischaemic attack. There were no statistically significant differences between the 2 groups for the primary efficacy end point (death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke) or the primary safety end point (non-CABG-related TIMI major bleeding). The results for the primary efficacy end point were 16.0% in the clopidogrel group and 16.1% in the prasugrel group (hazard ratio 1.02 [95% CI 0.84 to 1.24], $p=0.83$). The results for the primary safety end point were 3.3% in the clopidogrel group and 4.3% in the prasugrel group (hazard ratio 1.42 [95% CI 0.93 to 2.15], $p=0.10$).
- 4.1.18 Overall, the Assessment Group considered that the TRITON-TIMI 38 trial was robustly designed and of strong methodological quality. The Assessment Group highlighted, that during the original appraisal of prasugrel, the Appraisal Committee identified 3 areas of uncertainty about the generalisability of the results from TRITON-TIMI 38 to people in England and Wales. These were:
- 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.
 - The majority (74%) of patients in the trial received the clopidogrel loading dose during the percutaneous coronary intervention procedure. In clinical practice in England and Wales, patients undergoing planned percutaneous coronary intervention receive the clopidogrel loading dose before the procedure.
 - The clinical efficacy in the trial was largely driven by statistically significant differences in non-fatal myocardial infarctions. Non-fatal myocardial infarctions included both clinical myocardial infarctions (symptomatic) and non-clinical myocardial infarctions (shown by biomarkers and electroencephalograph [ECG] readings).

The Assessment Group considered that the size and timing of the loading dose of clopidogrel and the impact these factors have on the primary outcome of the TRITON-TIMI 38 trial remain unclear. However, the manufacturer's re-analysis of myocardial infarctions (see section 4.1.8) provided a convincing case that prasugrel is effective across all types of myocardial infarction when compared with clopidogrel.

- 4.1.19 The Assessment Group noted that health-related quality of life was assessed in a sub-study of TRITON-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 and at days 30, 180, 360 and 450 after the baseline measurement was taken, or at the 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 statistically significant differences between prasugrel and clopidogrel. The Assessment Group also noted that the study had recruited fewer people than was initially planned (475 compared with 3000), and raised concerns about how representative the sub-study was of the TRITON TIMI 38 trial population. The Assessment Group was therefore unable to draw any conclusions about the health-related quality of life of patients treated with prasugrel or clopidogrel in the TRITON-TIMI 38 trial.

Prasugrel compared with ticagrelor

- 4.1.20 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.
- 4.1.21 [Ticagrelor for the treatment of acute coronary syndromes](#) (NICE technology appraisal guidance 236) recommends ticagrelor as a treatment option (in combination with low-dose aspirin) for up to 12 months in adults with acute coronary syndromes, including people with STEMI who are to be treated with percutaneous coronary intervention, people with NSTEMI or people with unstable angina. These recommendations were based on a single randomised controlled trial (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 acute coronary syndromes with or without STEMI. Patients were randomised to the

trial irrespective of planned intervention and therefore the patient population included patients with acute coronary syndromes who were to be medically managed as well as those who were to have percutaneous coronary intervention. The trial follow up was for 12 months, but the trial protocol stipulated that once the requisite number of events (1780) had accrued, patients had to leave the trial after their 6-month or 9-month visit.

- 4.1.22 In the overall trial population, a statistically significant benefit of ticagrelor was found for the primary composite end point (ticagrelor 9.8% and clopidogrel 11.67%, hazard ratio 0.84 [95% CI 0.77 to 0.92], $p < 0.001$). When the individual components of the composite end point were disaggregated, the reduction in the primary end point was driven by statistically significant reductions in death from vascular causes (hazard ratio 0.79 [95% CI 0.69 to 0.91], $p = 0.001$) and myocardial infarction (hazard ratio 0.84 [95% CI 0.75 to 0.95], $p = 0.005$). There were no statistically significant differences between the 2 arms of the trial for the end points of major bleed (primary safety end point) and major fatal or life-threatening bleed. However, statistically significant differences in favour of clopidogrel were evident for the end points of total major and minor bleed (hazard ratio 1.11 [95% CI 1.03 to 1.20], $p = 0.008$) and non-CABG-related major bleed (hazard ratio 1.19 [95% CI 1.02 to 1.38], $p = 0.03$).
- 4.1.23 The Assessment Group stated that the TITRON-TIMI 38 and PLATO trials were not comparable, and so 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: both trials were conducted in a population with acute coronary syndromes, used clopidogrel as a comparator and reported the same primary composite efficacy end point (death from cardiovascular causes, non-fatal myocardial infarctions, or non-fatal stroke during the follow-up period). However, there were substantial differences in several characteristics of the studies. TRITON-TIMI 38 included patients with acute coronary syndromes who were early invasively managed and scheduled for percutaneous coronary intervention within 72 hours of symptom onset, whereas PLATO included a broad acute coronary syndromes population with symptom onset within 24 hours. TRITON-TIMI 38 only allowed a 300 mg loading dose of clopidogrel whereas PLATO allowed a 300 mg or 600 mg loading dose. TRITON-TIMI 38 had a 15-month follow-up period, whereas PLATO had a 12-month follow-up period.

- 4.1.24 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. 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, non-fatal myocardial infarction, non-fatal stroke or their composite. Prasugrel was associated with a statistically significantly lower risk of stent thrombosis, and ticagrelor was associated with a statistically significantly lower risk of any major bleeding and major bleeding associated with cardiac surgery.
- 4.1.25 The Assessment Group identified an ongoing trial designed to assess whether ticagrelor is superior to prasugrel in patients with acute coronary syndromes and planned invasive strategy (ISAR-REACT 5). This study is due to complete in October 2018 (the 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.

Submission statements from other consultees

- 4.1.26 A professional group commented that although evidence supporting the use of prasugrel in STEMI treated by primary percutaneous coronary intervention is unclear, the data supporting the use of prasugrel for STEMI treated by a variety of means (as still occurs in the UK) remain strong. As such, there is no robust new evidence to challenge the original guidance defining the patient population for whom prasugrel should be a treatment option. The group stated that the benefit of prasugrel therapy is limited to patients younger than 75 years, weighing more than 60 kg and without a history of transient ischaemic attack or stroke. It commented that data produced after NICE's [previous appraisal](#) of prasugrel (NICE technology appraisal 182) do not support extending the use of prasugrel to all patients with non-ST-elevation acute coronary syndromes, whether treated medically or by urgent revascularisation. It noted evidence from subgroup analyses for efficacy of prasugrel over clopidogrel in the reduction of stent thrombosis in patients receiving an intracoronary stent for treatment of acute coronary syndromes.

4.1.27 The professional group commented that since the publication of NICE's [previous technology appraisal](#) of prasugrel (NICE technology appraisal 182), few further data have become available about prasugrel in the context of non-ST-elevation acute coronary syndromes and that no new data are available for STEMI. It stated that although prasugrel reduces major adverse cardiac events and stroke in patients with acute coronary syndromes at high risk of receiving percutaneous coronary intervention with stents, there is no evidence that prasugrel reduces mortality. The professional group commented that prasugrel should not be offered to people aged 75 years or older, weighing less than 60 kg or with a past history of transient ischaemic attack or stroke. However, it stated that prasugrel should remain a treatment option in patients with STEMI treated by primary percutaneous coronary intervention or by other means and in patients with diabetes and acute coronary syndromes of any variety (STEMI, NSTEMI or unstable angina).

4.2 *Cost effectiveness*

Manufacturer's economic model

4.2.1 The manufacturer submitted an economic model similar to the model described in [Prasugrel for the treatment of acute coronary syndromes with percutaneous coronary intervention](#) (NICE technology appraisal guidance 182). The economic model had a Markov model structure with 2 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 a time horizon of 40 years. Rather than using data from the trial directly in the model, separate risk equations for primary end point 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 longer-term mortality of the events modelled over the short term. Patients entered the model at the point of experiencing an acute coronary syndromes event, immediately before having percutaneous coronary intervention. Some aspects of the submitted economic model had been updated based on feedback during the original appraisal of prasugrel. These revisions included:

- the sensitivity analysis encompassing the entire population as opposed to a 'typical' patient profile

- scenario analysis using the Evidence Review Group's suggestions for utility values, amended long-term relative risk of mortality and reduced incidence of non-fatal myocardial infarction
- the (reduced) price of generic clopidogrel
- updated costs.

4.2.2 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 because of the very small numbers of patients with events included in the analysis. Therefore, the manufacturer conducted a systematic review of the literature to identify studies relevant to the modelled trial population. Mean utility decrements for acute coronary syndromes (0.041) and stroke or myocardial infarction (0.052) were taken directly from a US study (Sullivan et al., 2006) that 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) varied by age and sex, as described by Kind et al. (1999), were applied to all patients in the study. The utility decrements for acute coronary syndromes and stroke or myocardial infarction 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.

4.2.3 The key categories of cost estimates in the manufacturer's submission were related to hospitalisations and drug costs. Only hospitalisations related to end points or to serious adverse events needing re-hospitalisation and potentially related to the acute coronary syndrome condition or the percutaneous coronary 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 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 cost for prasugrel was calculated at £10.20 per day for the loading dose and £1.70 per day for the maintenance dose (MIMS August 13, based on £47.56 per pack of 28 tablets). The cost of clopidogrel was

calculated at £0.24 per day for the loading dose and £0.07 per day for the maintenance dose (NHS Drug Tariff, based on £1.83 per pack of 28 75 mg tablets). The cost of aspirin was calculated as £0.01 per day for the maintenance dose.

4.2.4 The manufacturer considered 5 subgroups in its cost-effectiveness analysis, resulting in the following incremental cost-effectiveness ratios (ICERs):

- For the all acute coronary syndromes licensed population (excluding prior stroke or transient ischaemic attack and including patients who are now recommended to be treated with a 5 mg maintenance dose), the ICER was £11,660 per quality-adjusted life year (QALY) gained.
- For the core clinical cohort (excluding prior stroke or transient ischaemic attack and those weighing less than 60 kg, or aged 75 years or older), the ICER was £11,796 per QALY gained.
- For the unstable angina or NSTEMI licensed population (excluding patients with prior stroke or transient ischaemic attack and including patients who are now recommended to be treated with a 5 mg dose), the ICER was £15,452 per QALY gained.
- For the STEMI licensed population (excluding patients with prior stroke or transient ischaemic attack and including patients who were recommended to be treated with a 5 mg dose), the ICER was £6987 per QALY gained.
- For the acute coronary syndromes licensed population with diabetes (excluding patients with prior stroke or transient ischaemic attack and including patients who were recommended to be treated with a 5 mg dose) the ICER was £4675 per QALY gained.

4.2.5 The manufacturer carried out a series of one-way deterministic sensitivity analyses on the core clinical cohort population (excluding prior stroke or transient ischaemic attack and those 75 years or older or weighing less than 60 kg). The following changes to the model resulted in ICERs of more than £13,000 per QALY gained (an increase of more than £1000 from the base-case ICER):

- discounting at 6% for both costs and effects (ICER £16,475 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).

4.2.6 The manufacturer did not carry out probabilistic sensitivity analysis.

4.2.7 The manufacturer also carried out a series of scenario analyses for each of the following:

- using alternative values obtained from the Health Outcomes Data Repository (HODaR) database
- amending the long-term relative risks of mortality (by ignoring the impact of acute coronary syndromes before events that occurred in the TRITON-TIMI 38 trial)
- reducing the incidence of non-fatal myocardial infarctions such that the underlying rate was 50% of that of the trial.

The results of the scenario analyses showed that when 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.

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

4.2.8 The Assessment Group provided a critique of the manufacturer's economic model. It stated that in the long-term component of the model, there was 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 non-fatal events will not continue to occur to patients in both cohorts. It stated that if events 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. Because active treatment with clopidogrel or prasugrel will have stopped, it can be expected that event rates will be similar in both treatment arms. The Assessment Group commented that as a result of this process, it is likely that over time the disease histories of patients will converge, and so any initial advantage for either treatment will progressively decrease.

Assessment Group's economic model

- 4.2.9 The Assessment Group carried out a systematic review to identify existing economic evaluations of prasugrel. Of the 15 potentially eligible references identified, 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 from a US perspective and one which used the economic model originally submitted during NICE's [previous appraisal of prasugrel](#) (NICE technology appraisal 182) - but these were excluded by the Assessment Group.
- 4.2.10 The Assessment Group developed a 2-phase 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 percutaneous coronary intervention 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.
- 4.2.11 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 representation of subsequent cardiovascular events, accumulating patient histories, alteration in health states and associated care costs, as well as health-related quality of life.
- 4.2.12 The Assessment Group's decision model assessed 4 mutually exclusive subgroups of the core clinical cohort (that is, all patients with acute coronary syndromes, treated with percutaneous coronary intervention, excluding those with a history of stroke or transient ischaemic attack, those aged 75 years or older or weighing less than 60 kg). The 4 subgroups were:
- treated for STEMI and with diagnosed diabetes
 - treated for STEMI and without diagnosed diabetes
 - treated for unstable angina or NSTEMI and with diagnosed diabetes

- treated for unstable angina or NSTEMI and without diagnosed diabetes.

Specific clinical data relating to patients with STEMI, unstable angina or NSTEMI or diabetes in the core clinical cohort were not available from the manufacturer's submission or the most recent publication. In place of these data, the Assessment Group extracted the outcomes from the manufacturer's short-term model for the 4 mutually exclusive subgroups of the core clinical cohort and used these as the initial conditions for surviving patients entering the Assessment Group's long-term state-transition model.

- 4.2.13 For the long-term projection, the Assessment Group used a modified version of the economic model described in [Clopidogrel and modified release dipyridamole for the prevention of occlusive vascular events](#) (NICE technology appraisal 210). This model used data provided by the manufacturer of clopidogrel from the CAPRIE clinical trial, supplemented by data provided by the manufacturer of dipyridamole from the PROFESS clinical trial. The Assessment Group stated that the myocardial infarction subpopulation analysis submitted for NICE's [clopidogrel and modified release dipyridamole guidance](#) addresses issues similar to those in this appraisal and was based largely on data from the myocardial infarction subpopulation in the CAPRIE trial. In order to reduce the time in generating model results from an individual patient simulation approach, the Assessment Group restructured the economic model submitted for [NICE technology appraisal 210](#) into a long-term Markov chain for the purpose of this appraisal.
- 4.2.14 In the Assessment Group's long-term model the initial health state was determined by the worst previous event (none, myocardial infarction or stroke), the number of prior events (none, 1, 2, or 3 or more) and whether the event was disabling or not. Moving into another health state was determined by whether the patient experienced non-fatal myocardial infarction, non-fatal haemorrhagic stroke (disabling or non-disabling), or ischaemic stroke or transient ischaemic attack (disabling or non-disabling). The patient may also have experienced no event during the year, and therefore stay in the same health state, or may have died if they experienced fatal myocardial infarction, fatal haemorrhagic stroke, fatal ischaemic stroke or transient ischaemic attack, other vascular death, or non-vascular death.
- 4.2.15 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 adviser 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, myocardial infarction or symptomatic peripheral arterial disease. Only CAPRIE data from 5741 patients with myocardial infarctions and without a 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, sex and event history.

- 4.2.16 The Assessment Group's economic model included costs calculated from the pack price for 28 tablets of clopidogrel, prasugrel and low-dose aspirin as stated in the NHS Drug Tariff (November 2013; clopidogrel and low-dose aspirin) and the BNF (October 2013, edition 66; prasugrel). Clopidogrel has a pack price of £1.71, giving a cost of £0.24 per loading dose, £18.43 for a 12-month supply (adjusted for treatment duration), and £29.37 for the total dual antiplatelet therapy cost in year 1. Prasugrel has a pack price of £47.56, giving a cost of £10.19 per loading dose, £511.67 for a 12-month supply (adjusted for treatment duration) and £532.56 for the total dual antiplatelet therapy cost in year 1. Low-dose aspirin has a pack price of £0.82, giving a cost of £10.70 for a 12-month supply and annual maintenance cost.
- 4.2.17 The Assessment Group used the same unit costs as used in NICE's [clopidogrel and modified release dipyridamole guidance](#), updated to 2012 prices using the Hospital and Community Health Services inflation index. The unit cost of a fatal myocardial infarction is £2373.68 (standard error £121.11, 95% CI £2136.31 to £2611.05), a non-fatal myocardial infarction is £6165.21 (standard error £314.55, 95% CI £5548.69 to £6781.73), a fatal stroke is £9381.43 (standard error £478.64, 95% CI £8443.29 to £10,319.57), a non-fatal non-disabling stroke is £6858.64 (standard error £349.93, 95% CI £6172.77 to £7544.50), a non-fatal disabling stroke is £14,602.70 (standard error £754.04, 95% CI £13,142.43 to £16,062.97), and a non-vascular or other vascular death is £2407.50 (standard error £122.83, 95% CI £2166.75 to £2648.25). The annual cost in the event-free or myocardial infarction-only health state is £618.03 (standard error £31.53, 95% CI £556.23 to £679.84). In the non-disabling stroke health state it is £1804.06

(standard error £92.04, 95% CI £1623.66 to £1984.47) and in the disabling stroke health state it is £5537.72 (standard error £282.54, 95% CI £4983.95 to £6091.50).

- 4.2.18 The Assessment Group obtained the continuing health-state EQ-5D utility value for patients who were event-free or suffered a non-fatal myocardial infarction (but no strokes) and who were alive 12 months after percutaneous coronary intervention 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 sex differences and mild versus severe strokes for patients suffering at least 1 stroke or transient ischaemic attack 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 older. 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.
- 4.2.19 The Assessment Group commented 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 non-fatal myocardial infarction using an analysis of UK Prospective Diabetes Study trial results which compared utility values for events occurring within 12 months against those occurring earlier. Sources for non-fatal 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 myocardial infarction, 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.
- 4.2.20 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 generated 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.

- 4.2.21 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-myocardial infarction care including surgery and other medication options. The Assessment Group did not incorporate the adverse effects of aspirin therapy, the possibility that people stop aspirin treatment or the risk of bleeding events associated with long-term prophylaxis, because all these issues would affect patients in both treatment arms and the incremental difference would be expected to be minimal.
- 4.2.22 The Assessment Group considered that it was inappropriate to calculate an ICER for the overall core clinical cohort. It reported separate results from the model for the 4 patient subgroups: STEMI with diabetes, STEMI without diabetes, unstable angina or NSTEMI with diabetes and unstable angina or NSTEMI without diabetes. For each subgroup, deterministic cost-effectiveness results were presented at 1, 15, 10, 20 and 40 years after the initial percutaneous coronary intervention. Probabilistic cost-effectiveness results were presented at 5-year and 40-year follow up.
- 4.2.23 For the STEMI with diabetes subgroup, the ICER was £31,915 per QALY gained at year 1 of follow up (incremental cost £230, incremental QALYs 0.007). The ICER decreased to £4603 per QALY gained at year 5 (incremental cost £269, incremental QALYs 0.059), £2139 per QALY gained at year 10 (incremental cost £275, incremental QALYs 0.129), and at year 40 it was £1640 per QALY gained (incremental cost £447, incremental QALYs 0.272). 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 ICER in this subgroup. Varying discount rates for costs and outcomes had the largest effect on the ICER, but it remained within the range of £1000 to £2500 per QALY gained. Probabilistic analysis at 40 years of follow up for this subgroup resulted in a higher estimated ICER of £1732 per QALY gained (incremental cost £515 and incremental QALYs 0.297).

- 4.2.24 For the STEMI without diabetes subgroup, the ICER at year 1 of follow up was £224,302 per QALY gained (incremental cost £422, incremental QALYs 0.002). The ICER decreased to £29,607 per QALY gained at year 5 of follow up (incremental cost £465, incremental QALYs 0.016), £13,370 per QALY gained at year 10 (incremental cost £482, incremental QALYs 0.036), and at year 40 the ICER had decreased to £6626 per QALY gained (incremental cost £555, incremental QALYs 0.084). 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 ICER in this subgroup. Varying discount rates for costs and outcomes had the largest effect on the ICER, but it remained within the range of £4000 to £9000 per QALY gained. Probabilistic analysis at 40 years of follow up resulted in a higher estimated ICER of £7073 per QALY gained obtained from small incremental cost and QALY estimates (incremental cost £609 and incremental QALYs 0.086).
- 4.2.25 For the unstable angina or NSTEMI with diabetes subgroup, the ICER at year 1 of follow up was £76,856 per QALY gained (incremental cost £259, incremental QALYs 0.003). At year 5 of follow up, the ICER for prasugrel decreased to £2846 per QALY gained (incremental cost £96, incremental QALYs 0.034). From year 10 and beyond prasugrel dominated (that is, was less costly and more effective than) clopidogrel (at year 40 of follow up: incremental cost -£77, incremental QALYs 0.176). 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 (ranging between -£1000 and £400 per QALY gained). Probabilistic analysis at 40 years of follow up confirmed that prasugrel dominated clopidogrel with a small net cost saving and positive incremental benefit (incremental cost -£120 and incremental QALYs 0.191).
- 4.2.26 For the unstable angina or NSTEMI without diabetes 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 (incremental cost £413, incremental QALYs 0.00037). The ICER for prasugrel decreased to £52,288 per QALY gained at year 5 of follow up (incremental cost £346, incremental QALYs 0.007), £14,276 per QALY gained at year 10 (incremental cost £280, incremental QALYs 0.020) and at year 40 the ICER decreased to £4667 per QALY gained (incremental cost £248, incremental QALYs 0.053). 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 (ranging between £2500 and £6500 per QALY gained). Probabilistic analysis at 40 years of follow up resulted in a lower estimated ICER of £4154 per QALY gained (incremental cost £212 and incremental QALYs 0.051).

Summary of the deterministic base-case results from the manufacturer and the Assessment Group

4.2.27 Table 1 illustrates the differences in the cost-effectiveness estimates for the 3 different models: the Evidence Review Group's exploratory analyses from the original appraisal of prasugrel ([NICE technology appraisal 182](#)), the manufacturer's model, and the Assessment Group's model for the current appraisal.

Table 1 Comparison of the deterministic base-case results for the core clinical cohort at 40 years follow up for the comparison of prasugrel with clopidogrel

Patient group	ICER (cost per QALY gained)		
	NICE technology appraisal guidance 182	Current appraisal	
	Evidence Review Group's exploratory analyses	Manufacturer's model	Assessment Group's model
Core clinical cohort*	£20,247	£11,796	-
STEMI with diabetes*	£1805	-	£1640
STEMI without diabetes*	£6616	-	£6626
Unstable angina or NSTEMI with diabetes*	£3005	-	Dominant
Unstable angina or NSTEMI without diabetes*	£136,888	-	£4667

Dominant, less costly and more effective; ICER, incremental cost-effectiveness ratio; NSTEMI, non-ST-segment-elevation myocardial infarction; STEMI, ST-segment-elevation myocardial infarction

* Excluding prior stroke or transient ischaemic attack, those aged 75 years or older and those weighing less than 60 kg

The differences between the cost-effectiveness results submitted during the original appraisal of prasugrel and those in the current appraisal (as shown in table 1) are a result of the different economic models used. In particular, in the current appraisal both the manufacturer and the Assessment Group used the whole licensed population in their models, rather than the typical/median patient profile used in the model for the original appraisal (see sections 4.2.1 and 4.2.11). Also, in the current appraisal the Assessment Group used data from the CAPRIE trial in its long-term model rather than data from TRITON-TIMI 38 (see section 4.2.15).

4.3 Consideration of the evidence

The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of prasugrel, having considered evidence on the nature of acute coronary syndromes and the value placed on the benefits of prasugrel by people with the condition, those who represent them, and clinical specialists. It also took into account the effective use of NHS resources.

Clinical effectiveness

4.3.1 The Committee discussed the clinical management of acute coronary syndromes. The Committee heard from the clinical specialists that current management is in line with NICE's [previous appraisal of prasugrel](#), (NICE technology appraisal 182) as well as [Ticagrelor for the treatment of acute coronary syndromes](#) (NICE technology appraisal guidance 236), [Myocardial infarction with ST-segment-elevation: The acute management of myocardial infarction with ST-segment-elevation](#) (NICE clinical guideline 167) and [Unstable angina and NSTEMI: the early management of unstable angina and non-ST-segment-elevation myocardial infarction](#) (NICE clinical guideline 94). The Committee understood that, in England, treatment options for people with STEMI are prasugrel in combination with aspirin, ticagrelor in combination with low-dose aspirin or clopidogrel in combination with low-dose aspirin, along with percutaneous coronary intervention followed by dual antiplatelet treatment. It also understood that people in England with NSTEMI are offered treatments depending on their Global Registry of Acute Coronary Events (GRACE) or TIMI

score. Medical management using aspirin is an option for people at the lowest risk of future adverse cardiovascular events, whereas people at higher risk are offered percutaneous coronary intervention along with either ticagrelor, or clopidogrel and subsequent dual antiplatelet therapy with clopidogrel and aspirin. In patients with NSTEMI and diabetes, prasugrel is an alternative to clopidogrel or ticagrelor. The Committee heard from patient experts and clinical specialists that, overall, prasugrel is a useful addition to the treatment options available. It has a potentially key advantage over clopidogrel because of its faster antiplatelet action. However, the Committee also noted that prasugrel increased the chance of (potentially fatal) bleeding compared with clopidogrel. The Committee also heard from the clinical specialists that there was variation in opinion among clinicians in England as to which of prasugrel, ticagrelor or clopidogrel should be considered the standard treatment for all patients with STEMI who have a percutaneous coronary intervention because of the chance of increased bleeding with these treatments. The Committee recognised that antiplatelet therapy such as prasugrel was a valued treatment option.

Prasugrel compared with clopidogrel

4.3.2 The Committee considered the evidence presented by the manufacturer and the Assessment Group on the clinical effectiveness of prasugrel compared with clopidogrel for the treatment of acute coronary syndromes in people having percutaneous coronary intervention. The Committee noted that both the manufacturer and the Assessment Group had identified 1 randomised controlled trial (TRITON-TIMI 38) and that this trial had been the main source of evidence for NICE's [previous appraisal of prasugrel](#). The Committee noted that both the manufacturer and the Assessment Group had stated that no significant new evidence had become available since the publication of the previous appraisal comparing prasugrel with clopidogrel. The Committee heard from one of the clinical specialists that although there were no new data comparing prasugrel with clopidogrel, new data had become available on prasugrel in patients with NSTEMI: specifically the ACCOAST and TRILOGY trials. The clinical specialist highlighted that the results from ACCOAST (designed to assess the effectiveness of pre-treatment with prasugrel in patients with NSTEMI prior to angiography and at time of percutaneous coronary intervention compared with no pre-treatment) indicated that pre-treatment with prasugrel did not reduce the rate of occurrence of the primary end point (composite of death from cardiovascular causes, myocardial

infarction, stroke, urgent revascularisation or glycoprotein IIb/IIIa inhibitor rescue therapy), but that the rate of major bleeding complications was statistically significantly increased. The Committee was aware that since the publication of the ACCOAST results, the summary of product characteristics for prasugrel had been updated to explicitly state that in patients with unstable angina or NSTEMI, if angiography is performed within 48 hours of admission, the loading dose should only be given at the time of percutaneous coronary intervention. The clinical specialist highlighted that the results from TRILOGY (designed to compare the effectiveness of prasugrel plus aspirin with clopidogrel plus aspirin in patients with NSTEMI who were treated with medical management) demonstrated that for the primary end point of the trial (composite of death from cardiovascular causes, myocardial infarction or stroke in patients under the age of 75 years) there was no statistically significant difference between the groups treated with prasugrel or clopidogrel and that similar frequencies of bleeding events were reported for both treatment groups. The Committee heard from the Assessment Group that because the patients recruited to TRILOGY were not treated with percutaneous coronary intervention, data from the trial was peripheral to this appraisal. Although the Committee accepted that new data on prasugrel had become available since the publication of NICE's [previous appraisal of prasugrel](#), it concluded that these new data were not particularly generalisable to the population being appraised (that is, people with acute coronary syndromes who are to be treated with percutaneous coronary intervention) and so could not be considered by Committee.

- 4.3.3 The Committee discussed the overall trial population and the subpopulation of the TRITON-TIMI 38 trial presented by both the manufacturer and the Assessment Group. It noted that the manufacturer and the Assessment Group had presented clinical-effectiveness results for the overall cohort of patients in the TRITON-TIMI 38 trial and also for the core clinical cohort (which excluded patients aged 75 years or older, those who weighed less than 60 kg, and those with a history of stroke and transient ischaemic attack). The Committee concluded that the core clinical cohort population was the most relevant for decision-making because it only included those people specified in the summary of product characteristics for prasugrel for whom the full 10 mg dose was considered appropriate, that is, those younger than 75 years and with a body weight of 60 kg or more.

4.3.4 The Committee identified 2 main areas of uncertainty in the evidence for the clinical effectiveness of prasugrel compared with clopidogrel in the TRITON-TIMI 38 trial. Firstly, the Committee heard from clinical specialists that, in clinical practice, clopidogrel is administered several hours before percutaneous coronary intervention (preloading) in most non-urgent procedures carried out in England. Additionally, the preloaded dose of clopidogrel is often 600 mg. This dose and timing of clopidogrel therefore differed from that used in TRITON-TIMI 38 in which 300 mg (as in the marketing authorisation for clopidogrel) was given without preloading (see section 4.1.2). The Committee discussed the dose of clopidogrel. It heard from the manufacturer of prasugrel that the CURRENT-OASIS 7 trial (published after the original appraisal of prasugrel (NICE technology appraisal 182) and designed to assess the effectiveness of a standard or double dose of clopidogrel in patients with acute coronary syndromes) showed that there was no statistically significant difference in the results for the primary composite outcome (death from cardiovascular causes, myocardial infarction or stroke) for those having a higher dose of clopidogrel (600 mg on day 1, 150 mg on days 2 to 7, and then 75 mg daily) compared with those having a lower dose (300 mg on day 1 then 75 mg daily). The Committee accepted that the results from the CURRENT-OASIS 7 trial suggested there was no clear benefit from the 600 mg dose of clopidogrel compared with the 300 mg dose and agreed that the efficacy results seen in TRITON-TIMI 38 with a 300 mg loading dose were unlikely to have differed materially from those seen if the 600 mg dose was used (although a higher rate of bleeding in the clopidogrel group may have been seen). The Committee then discussed the timing of the loading dose of clopidogrel. It heard from the manufacturer of prasugrel that the results of TRITON-TIMI 38 showed that the benefit seen with prasugrel was relatively consistent over time, as shown through the similarity of the hazard ratios for the primary efficacy end point in the prasugrel group throughout the TRITON-TIMI 38 trial. This implied a relative advantage for prasugrel could have arisen even after the pre-loading of clopidogrel. The Committee also heard from the manufacturer that the management of patients with NSTEMI in clinical practice has changed since the publication of the original appraisal of prasugrel (NICE technology appraisal 182) as the 'door-to-needle time' for patients in England decreases, so too does the time for pre-loading with clopidogrel. The Committee agreed that there is still limited evidence on the importance of the timing of the clopidogrel loading dose and so its effect on patient outcomes remains an issue. The Committee therefore considered that more cardiovascular events could have occurred in

the clopidogrel group in the trial than might be experienced in a similar cohort of patients having percutaneous coronary intervention in routine clinical practice in England. As a result, the advantages of prasugrel over clopidogrel in preventing cardiovascular events may have been overstated in the overall trial population and core clinical cohort population of the TRITON-TIMI 38 study.

4.3.5 A second source of uncertainty concerning the clinical data from TRITON-TIMI 38 was the use of a composite end point that included non-clinically detected myocardial infarctions (shown by biomarkers and ECG readings). The Committee noted that the main positive result in favour of prasugrel was a decrease in non-fatal myocardial infarctions including non-clinical myocardial infarctions, which would have increased composite end point event rates for clopidogrel reported in the trial. The Committee heard from the clinical specialists that non-clinical myocardial infarctions are often included in composite end points of cardiology studies to ensure that the trials are statistically powered to detect differences in outcomes. The Committee considered whether any statistically significant differences would remain between prasugrel and clopidogrel if only clinical myocardial infarctions (symptomatic) were included. The Committee noted the evidence submitted by the manufacturer on the definition of myocardial infarction and the Assessment Group's review of the evidence, which suggested that there was a significant reduction in myocardial infarctions with prasugrel compared with clopidogrel for myocardial infarctions of varying type, size and timing. However, the Committee heard differing opinions from the clinical specialists about whether non-clinical myocardial infarctions have a similar impact to clinical myocardial infarctions on clinical effectiveness and if they can therefore be considered equally. The Committee considered that the similarity of the clinical effectiveness between the treatments was unproven, and because of the difficulty in relating results of the TRITON-TIMI 38 trial to clinical practice in England, the relative effectiveness of prasugrel compared with clopidogrel was uncertain.

4.3.6 The Committee concluded that, despite being well conducted, the TRITON-TIMI 38 trial was not wholly applicable to current clinical practice in England. When considering the absence of preloading with clopidogrel, the limitations of the end points used, and the greater incidence of bleeding adverse events (when major and minor bleeding events were combined) with prasugrel, the Committee agreed that there was uncertainty about whether prasugrel was

clinically superior to clopidogrel in terms of net clinical benefit for either the overall trial population or the Committee's preferred population, the core clinical cohort (see section 4.3.3). The Committee therefore considered whether there were any identifiable subgroups of patients for whom prasugrel might show superiority over clopidogrel with less uncertainty.

- 4.3.7 The Committee considered the clinical evidence for prasugrel in the subgroup of patients with STEMI. In clinical practice, there is only a short time between diagnosis and primary percutaneous intervention in these patients. The Committee considered the subgroup results presented by the Assessment Group for the core clinical cohort which indicated a trend towards benefit for prasugrel compared to clopidogrel in patients with STEMI across end points. The Committee heard from the clinical specialists that the onset of antiplatelet activity was more consistent and faster with prasugrel than with clopidogrel. The delayed onset of antiplatelet activity with clopidogrel was of particular concern when immediate percutaneous coronary intervention was needed because there would be little or no time to give a preloading dose of clopidogrel. Having taken all the above factors into consideration, the Committee agreed that prasugrel could have an advantage over clopidogrel for patients with STEMI who need immediate primary percutaneous coronary intervention.
- 4.3.8 The Committee then considered the use of prasugrel compared with clopidogrel in patients with diabetes in the core clinical cohort who were having percutaneous coronary intervention. It noted that in these patients, prasugrel reduced the rate of non-fatal myocardial infarction, non-fatal stroke or death from cardiovascular causes compared with clopidogrel to a greater extent than for the licensed population of patients (including those without diabetes). The Committee, aware of the views expressed by the clinical specialists, considered that the lack of a preloading dose in the trial may have underestimated the effectiveness of clopidogrel in the population with diabetes. It agreed, however, that diabetes represented an important and definable risk factor for more severe cardiovascular disease and greater risk of cardiovascular events during and after percutaneous coronary intervention. The Committee therefore concluded that it would be appropriate to consider prasugrel for the treatment of people with diabetes having percutaneous coronary intervention in its decision-making.

- 4.3.9 The Committee then considered the use of prasugrel in patients who are clopidogrel-resistant (that is, patients whose platelet levels do not respond adequately to the dosage of clopidogrel with which they are treated). The Committee understood that these patients may be at risk of further events if their treatment is not adjusted adequately, but the Committee was aware that it was not routine clinical practice to test for platelet response to clopidogrel. The Committee heard from the clinical specialists that in around a quarter of patients having percutaneous coronary intervention, stent thrombosis can occur despite clopidogrel treatment. The Committee recognised that these patients could reasonably be considered to be at high risk of further cardiovascular events, are clearly identified and so could benefit from the option of treatment with prasugrel. Because of this, the Committee concluded it was appropriate to consider patients with clopidogrel resistance in its decision-making.
- 4.3.10 The Committee then considered the use of prasugrel compared with clopidogrel in the subgroup of patients with unstable angina or non-ST-segment-elevation myocardial infarction (NSTEMI). It noted that in the core clinical cohort, the clinical effectiveness of prasugrel in these patients appeared to be consistent with the effectiveness in patients with STEMI. The Committee, aware of the views expressed by the clinical specialists, considered that the lack of a preloading dose in the TRITON-TIMI 38 trial may have underestimated the effectiveness of clopidogrel in this subgroup. The Committee therefore concluded that there was uncertainty about whether prasugrel was clinically superior to clopidogrel in patients with unstable angina or NSTEMI. The Committee therefore concluded it was appropriate to consider patients with unstable angina or NSTEMI as a separate subgroup in its decision-making.
- 4.3.11 The Committee also discussed patients excluded from its preferred core clinical cohort population of TRITON-TIMI 38, that is, patients with a history of a stroke or transient ischaemic attack, patients aged 75 years or older and patients weighing less than 60 kg. The Committee noted that a history of stroke or transient ischaemic attack is listed as a contraindication in the summary of product characteristics for prasugrel and that the summary of product characteristics also recommends a lower maintenance dose of 5 mg prasugrel for patients aged 75 years or over and for patients weighing less than 60 kg. It heard from the clinical specialists that, in clinical practice, prasugrel is not used in these groups because of a higher bleeding risk. The Committee noted

comments received during consultation that new data had become available on the 5 mg dose since the publication of the original appraisal of prasugrel, which included data from the TRILOGY trial (see section 4.3.2). The Committee was aware that safety data for the 5 mg dose of prasugrel from the TRILOGY trial had led to an update of the information on the 5 mg dose in the drug's summary of product characteristics. However, the Committee noted that it had not been presented with any evidence for the efficacy of the lower dose of prasugrel and, therefore, agreed that it would be inappropriate to make a recommendation for prasugrel in patients aged 75 years or over and patients weighing less than 60 kg.

Prasugrel compared with ticagrelor

4.3.12 The Committee noted that there were no trials directly comparing prasugrel with ticagrelor and that neither the manufacturer nor the Assessment Group had presented an indirect comparison of the 2 treatments. The Committee was aware of the rationale provided by both the manufacturer and the Assessment Group for not undertaking the indirect comparison, specifically differences in the trial design, patient population, and outcome measures used in the prasugrel (TRITON-TIMI 38) and ticagrelor (PLATO) trials. However, given that ticagrelor is in established use in clinical practice, that it is recommended for the treatment of acute coronary syndromes in NICE technology appraisal 236, and that it was included as a comparator in the final scope issued by NICE, the Committee agreed that an indirect comparison should have been performed, recognising that it would have been imperfect. It noted that the clinical specialists stated that ticagrelor is used in clinical practice in England and that prasugrel and ticagrelor are considered similarly effective for treating patients with STEMI. However, the clinical specialists were unable to comment similarly on the comparative effectiveness of prasugrel with ticagrelor in patients with unstable angina or NSTEMI, because prasugrel is not often used in these groups. The Committee noted that the Assessment Group had highlighted several published indirect comparisons in its report and that the Assessment Group considered the results from these publications to be unreliable given the differences in the trials. Nonetheless, the Committee discussed the results of the published indirect comparisons of prasugrel and ticagrelor, which reported that there were no statistically significant differences in overall death, non-fatal myocardial infarction, non-fatal stroke or their composite. The publications also reported that although prasugrel was associated with a significantly lower risk

of stent thrombosis, ticagrelor was associated with a significantly lower risk of any major bleeding and major bleeding associated with cardiac surgery. The Committee concluded that, on balance, it was not able to distinguish the clinical effectiveness of prasugrel and ticagrelor in patients with STEMI, unstable angina, or NSTEMI. However, in the case of STEMI only, there was some support for the possibility of clinical equivalence.

Cost effectiveness

- 4.3.13 The Committee considered the economic models submitted by the manufacturer and the Assessment Group. The Committee considered the cost-effectiveness results for the comparison of prasugrel and clopidogrel. The Committee noted that the manufacturer and the Assessment Group had presented cost-effectiveness results (for the 10 mg dose of prasugrel only) for different populations and so the results could not be directly compared, although all of the results for prasugrel 10 mg compared with clopidogrel were below £20,000 per QALY gained at a time horizon of 40 years. The Committee then discussed which of the cost-effectiveness data it should consider in its decision making. Bearing in mind its considerations on clinical effectiveness (see sections 4.3.7, 4.3.8, 4.3.9, and 4.3.10), the Committee agreed that an advantage of prasugrel over clopidogrel was plausible in patients without an increased risk of bleeding (under the age of 75 and weighing more than 60 kg) if they had ST-segment-elevation or had diabetes (with STEMI or NSTEMI). However, in people with NSTEMI without diabetes, it was less certain whether there was an advantage of prasugrel over clopidogrel. The Committee noted that the Assessment Group had presented cost-effectiveness results for these subgroups and concluded that these results were the most appropriate for the cost-effectiveness decision-making.
- 4.3.14 The Committee considered the cost-effectiveness results from the Assessment Group's economic model. It noted that the Assessment Group had provided cost-effectiveness results for each of the subgroups at time horizons of 1, 5, 10 and 40 years. It noted that all of the ICERs at 10 or 40 years were below £20,000 per QALY gained (ranging from prasugrel dominating [that is, it was less costly and more effective than clopidogrel] to £14,276 per QALY gained at 10 years, and from prasugrel dominating to £6626 per QALY gained at 40 years), however, at 5 years the ICERs for people with STEMI without diabetes and NSTEMI without diabetes were over £20,000 per QALY gained

(£29,607 and £52,288 per QALY gained respectively). The Committee noted that the QALY gains for prasugrel over the 40-year time horizon for the STEMI without diabetes and the unstable angina or NSTEMI without diabetes subgroups were small (0.084 and 0.053 respectively), as was the difference in costs between prasugrel and clopidogrel treatment (STEMI without diabetes: clopidogrel total cost £21,167, prasugrel total cost £21,722, incremental cost £555; UA/NSTEMI without diabetes: clopidogrel total cost £20,328, prasugrel total cost £20,576, incremental cost £248). It accepted that, as a result, the cost effectiveness of prasugrel was highly sensitive to changes in key model assumptions. The Committee therefore considered which time horizon was the most appropriate for its decision-making. The Committee noted that the clinical data used in the second phase of the Assessment Group's economic data were obtained from the CAPRIE study, which had a maximum follow up of 3 years, and that these data were used to extrapolate results of the health economic analysis up to 40 years. The Committee agreed that, although the extrapolation of short-term clinical data over longer time horizons could only increase overall uncertainty, it is necessary in economic modelling and longer time horizons are generally preferable. The Committee noted that the time horizon within which the results would fall to within the range usually considered to be cost effective by NICE (£20,000 to £30,000 per QALY gained) is likely to be much less than 40 years. The Committee considered that despite uncertainty in the ICERs arising from this 40 year extrapolation, the results were sufficiently robust to permit their use, and concluded that the 40 year time horizon was the most appropriate for decision making.

- 4.3.15 The Committee considered the ICERs for a 10 mg dose of prasugrel compared with clopidogrel in patients with STEMI with and without diabetes. The Committee noted that, for patients with STEMI and diabetes, the 40-year ICER from the Assessment Group's model was £1600 per QALY gained. For patients with STEMI and without diabetes, the 40-year ICER from the Assessment Group's model was £6600 per QALY gained. The Committee concluded that prasugrel was a cost-effective use of NHS resources compared with clopidogrel for treating people with STEMI with and without diabetes.
- 4.3.16 The Committee considered the ICER for a 10 mg dose of prasugrel compared with clopidogrel in patients with unstable angina or NSTEMI with and without diabetes. The Committee noted that for patients with unstable angina or NSTEMI and diabetes, prasugrel dominated clopidogrel at the 40-year time

horizon. For patients with unstable angina or NSTEMI without diabetes, the 40-year ICER from the Assessment Group's model was £4700 per QALY gained. It accepted that the difference between the TRITON-TIMI 38 trial and clinical practice in the time delay between diagnosis and treatment meant that there is uncertainty about whether the results of the TRITON-TIMI 38 trial can be generalised to patients with unstable angina or NSTEMI in England. However, taking into account the slight advantage of prasugrel over clopidogrel beyond the period when preloading is relevant, and that the ICERs are well within the range usually considered to be cost effective by NICE (£20,000 to £30,000 per QALY gained), the Committee concluded that prasugrel can be considered a cost-effective use of NHS resources compared with clopidogrel for treating people with unstable angina or NSTEMI with and without diabetes.

- 4.3.17 Regarding the cost-effectiveness of prasugrel compared with ticagrelor, the Committee noted that neither the Assessment Group nor the manufacturer had included ticagrelor in their economic modelling. Given the lack of a cost-effectiveness analysis, the Committee concluded that it was unable to calculate a precise ICER for this comparison. It agreed, however, that given the similar cost-effectiveness of prasugrel compared with clopidogrel and that of ticagrelor compared with clopidogrel, and their similar treatment costs, it was reasonable to accept that prasugrel is similarly cost-effective to ticagrelor.

Summary of Appraisal Committee's key conclusions

TA317	Appraisal title: Prasugrel with percutaneous coronary intervention for treating acute coronary syndrome (review of technology appraisal guidance 182)	Section
Key conclusion		
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.		1.1

<p>The Committee agreed that there was considerable uncertainty about whether prasugrel was clinically superior to clopidogrel in terms of net clinical benefit for the Committee's preferred population, the core clinical cohort, because the TRITON-TIMI 38 trial was not wholly applicable to current clinical practice in England. The Committee agreed that prasugrel could have a valuable advantage over clopidogrel for patients with ST-segment-elevation myocardial infarction (STEMI), stent thrombosis, or diabetes regardless of whether they have STEMI, unstable angina or non-ST-segment-elevation myocardial infarction (NSTEMI). The Committee concluded that there was uncertainty about whether prasugrel was clinically superior to clopidogrel in patients with unstable angina or NSTEMI because of the lack of generalisability of the TRITON-TIMI 38 trial to clinical practice in England, and in patients at an increased risk of bleeding because of a lack of evidence on the efficacy and safety of the 5 mg dose of prasugrel recommended in the summary of product characteristics.</p>	4.3.6– 4.3.9
--	--------------

<p>The Committee noted that neither the manufacturer nor the Assessment Group had included ticagrelor in their respective economic models. Given the lack of a cost-effectiveness analysis, the Committee concluded that it was unable to make specific recommendations relating to the cost effectiveness of prasugrel compared with ticagrelor. It agreed, however, that given the clinical effectiveness of prasugrel in the Committee's 4 preferred subgroups (see sections 4.3.7 and 4.3.10), and recognising the clinical and cost effectiveness of ticagrelor (NICE technology appraisal 236, in which ticagrelor was compared with clopidogrel) in people with STEMI, NSTEMI or unstable angina, who are to be treated with percutaneous coronary intervention, it would be reasonable to consider the cost-effectiveness element of the appraisal of ticagrelor, focusing only on the comparison of prasugrel with clopidogrel.</p> <p>The Committee considered the cost-effectiveness estimates presented by the Assessment Group for the STEMI with diabetes, STEMI without diabetes, unstable angina or NSTEMI without diabetes, and unstable angina or NSTEMI with diabetes groups. The Committee agreed that the use of a 40-year time horizon was most appropriate for decision-making, while acknowledging that there will be some uncertainty as a result of the extrapolation of data over the longer time horizon. The Committee concluded that the most plausible incremental cost-effectiveness ratios (ICERs) for prasugrel compared with clopidogrel were as follows: £1600 per quality-adjusted life year (QALY) gained for the STEMI with diabetes group, £6600 per QALY gained for the STEMI without diabetes group, and £4700 per QALY gained for the unstable angina or NSTEMI without diabetes group. In the unstable angina with diabetes group, prasugrel dominated clopidogrel (that is, was more effective and less costly).</p>	<p>4.3.13– 4.3.17</p>
<p>Current practice</p>	

<p>Clinical need of patients, including the availability of alternative treatments</p>	<p>The Committee heard from the patient experts and clinical specialists that prasugrel is a useful addition to the treatment options available. It has a potentially important advantage over clopidogrel because of its faster antiplatelet action. However, the Committee also noted that prasugrel increased the chance of (potentially fatal) bleeding compared with clopidogrel. The Committee also heard from the clinical specialists that there was variation in opinion among clinicians in England as to which of prasugrel, ticagrelor or clopidogrel should be considered the standard treatment for all patients with STEMI who have a percutaneous coronary intervention, because of the chance of increased bleeding with these treatments.</p> <p>The Committee recognised that antiplatelet therapy such as prasugrel is a valued treatment option.</p>	<p>4.3.1</p>
<p>The technology</p>		
<p>Proposed benefits of the technology</p> <p>How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?</p>	<p>The Committee heard from clinical specialists that prasugrel has a potentially key advantage over clopidogrel because of its faster antiplatelet action and because it is absorbed more effectively.</p> <p>This appraisal is a review of NICE technology appraisal guidance 82 which was published in 2009.</p>	<p>4.3.1</p>

<p>What is the position of the treatment in the pathway of care for the condition?</p>	<p>The Committee understood that, in England, treatment options for people with STEMI are prasugrel in combination with aspirin, ticagrelor in combination with low-dose aspirin, or clopidogrel in combination with low-dose aspirin, along with percutaneous coronary intervention followed by dual antiplatelet treatment.</p> <p>It also understood that, in England, people with NSTEMI are offered treatments depending on their Global Registry of Acute Coronary Events (GRACE) or TIMI score. Medical management using aspirin is an option for people at the lowest risk of future adverse cardiovascular events, whereas people at higher risk are offered percutaneous coronary intervention along with either ticagrelor, or clopidogrel and subsequent dual antiplatelet therapy with clopidogrel and aspirin.</p> <p>In patients with NSTEMI and diabetes, prasugrel is an alternative to clopidogrel or ticagrelor.</p>	<p>4.3.1</p>
<p>Adverse reactions</p>	<p>The Committee was aware that prasugrel increased the chance of (potentially fatal) bleeding compared with clopidogrel.</p>	<p>4.3.1</p>
<p>Evidence for clinical effectiveness</p>		

Availability, nature and quality of evidence	<p>The Committee noted that both the manufacturer and the Assessment Group had identified 1 randomised controlled trial (TRITON-TIMI 38) and that this trial had been the main source of evidence for NICE technology appraisal guidance 182. The Committee also noted that both the manufacturer and the Assessment Group had stated that no significant new evidence had become available since the publication of NICE technology appraisal guidance 182 comparing prasugrel with clopidogrel.</p> <p>The Committee was aware of the rationale provided by both the manufacturer and the Assessment Group for not undertaking the indirect comparison – that is, differences between the design and populations included in the prasugrel (TRITON-TIMI 38) and ticagrelor (PLATO) trials. However, given that ticagrelor is in established use in clinical practice, that it is recommended for the treatment of acute coronary syndromes in NICE technology appraisal 236, and that it was included as a comparator in the final scope issued by NICE, the Committee agreed that an indirect comparison should have been performed, recognising that it would have been imperfect.</p>	4.3.2, 4.3.12
Relevance to general clinical practice in the NHS	The Committee concluded that, despite being well conducted, the TRITON-TIMI 38 trial was not wholly applicable to current clinical practice in England.	4.3.6

<p>Uncertainties generated by the evidence</p>	<p>The Committee agreed that there was considerable uncertainty about whether prasugrel was clinically superior to clopidogrel in terms of net clinical benefit for either the overall trial population or the Committee's preferred population, the core clinical cohort. This was because the trial was not wholly applicable to current clinical practice in England.</p> <p>The Committee concluded that, on balance, it was unable to distinguish the clinical effectiveness of prasugrel and ticagrelor in patients with STEMI, unstable angina, or NSTEMI. However, in the case of STEMI only, there was some support for the possibility of clinical equivalence.</p>	<p>4.3.6, 4.3.12</p>
<p>Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?</p>	<p>The Committee considered the use of prasugrel compared with clopidogrel in patients with diabetes in the core clinical cohort. It noted that in these patients, prasugrel reduced the rate of non-fatal myocardial infarction, non-fatal stroke or death from cardiovascular causes compared with clopidogrel to a greater extent than for the licensed population of patients with and without diabetes.</p> <p>The Committee concluded that it would be appropriate to consider prasugrel for the treatment of people with diabetes having percutaneous coronary intervention.</p> <p>The Committee, aware of the views expressed by the clinical specialists, considered that the lack of a preloading dose in the TRITON-TIMI 38 trial may have underestimated the effectiveness of clopidogrel in the unstable angina or NSTEMI subgroup. The Committee therefore concluded that there was uncertainty about whether prasugrel was clinically superior to clopidogrel in patients with unstable angina or NSTEMI.</p>	<p>4.3.8, 4.3.10</p>

<p>Estimate of the size of the clinical effectiveness including strength of supporting evidence</p>	<p>Prasugrel compared with clopidogrel</p> <p>The Committee agreed that prasugrel could have an advantage over clopidogrel for patients with STEMI who need immediate primary percutaneous coronary intervention.</p> <p>The Committee concluded that it would be appropriate to consider prasugrel for the treatment of people with diabetes having percutaneous coronary intervention.</p> <p>The Committee concluded that there was uncertainty about whether prasugrel was clinically superior to clopidogrel in patients with unstable angina or NSTEMI.</p>	<p>4.3.7, 4.3.8, 4.3.10</p>
	<p>Prasugrel compared with ticagrelor</p> <p>The Committee concluded that, on balance, it was not able to distinguish the clinical effectiveness of prasugrel and ticagrelor in patients with STEMI, unstable angina, or NSTEMI. However, in the case of STEMI only, there was some support for the possibility of clinical equivalence.</p>	<p>4.3.12</p>
<p>For reviews: How has the new clinical evidence that has emerged since the original appraisal (TA182) influenced the current (preliminary) recommendations?</p>	<p>No new data comparing prasugrel with clopidogrel have become available since the original appraisal of prasugrel, although new data have become available on prasugrel in patients with NSTEMI. The Committee was aware that the summary of product characteristics for prasugrel had been updated since the original appraisal of prasugrel to take into account the results of the ACCOAST and TRILOGY trials. The Committee considered that the new data in patients with NSTEMI was not particularly generalizable to the population being appraised and therefore the new evidence on prasugrel in patients with NSTEMI has not influenced the recommendations in section 1.</p>	<p>4.3.2, 4.3.11</p>
<p>Evidence for cost effectiveness</p>		

Availability and nature of evidence	<p>The manufacturer submitted an economic model similar to the model described in NICE technology appraisal guidance 182.</p> <p>The Assessment Group developed a 2-phase 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.</p>	4.2.1, 4.2.10
Uncertainties around and plausibility of assumptions and inputs in the economic model	<p>The Committee heard from the Assessment Group that extrapolating the data to 5 years would provide a much more certain estimate of the ICERs than extrapolating the data to 40 years. The Committee agreed that, although the extrapolation of short-term clinical data over longer time horizons could only increase overall uncertainty, it is necessary in economic modelling and that long time horizons are generally preferable. The Committee concluded that the 40-year time horizon was the most appropriate for decision-making while acknowledging that there will be some uncertainty as a result of the extrapolation of data over the longer time horizon.</p> <p>The Committee noted that neither the manufacturer nor the Assessment Group had included ticagrelor in their respective models.</p>	4.3.14, 4.3.17

<p>Incorporation of health-related quality-of-life benefits and utility values</p> <p>Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?</p>	<p>Not applicable as the Committee had no concerns about the health-related quality of life data used in either the manufacturer's or the Assessment Group's economic model.</p>	
<p>Are there specific groups of people for whom the technology is particularly cost effective?</p>	<p>The ICERs for all 4 of the subgroups (STEMI with diabetes, STEMI without diabetes, unstable angina or NSTEMI with diabetes, unstable angina and NSTEMI without diabetes) were lower than £20,000 per QALY gained. For patients with unstable angina or NSTEMI and diabetes, prasugrel dominated (that is, it was more effective and less costly than) clopidogrel.</p>	<p>4.3.15, 4.3.16</p>
<p>What are the key drivers of cost effectiveness?</p>	<p>The Committee noted that the estimated QALY gains for prasugrel over the 40-year time horizon for the STEMI without diabetes and the unstable angina or NSTEMI without diabetes subgroups were small (0.084 and 0.053 respectively) and that the difference in costs between prasugrel and clopidogrel treatment was also small (£555 and £248 respectively). It accepted that as a result, the cost effectiveness of prasugrel was highly sensitive to changes in key model assumptions. Therefore, the Committee considered the main driver of cost effectiveness was which time horizon was considered to be most appropriate for decision-making.</p>	<p>4.3.14</p>

Most likely cost-effectiveness estimate (given as an ICER)	The Committee concluded that the most plausible ICERs for 3 of the 4 subgroups were: £1600 per QALY gained for the STEMI with diabetes group, £6600 per QALY gained for the STEMI without diabetes group, and £4700 per QALY gained for the unstable angina or NSTEMI without diabetes group. In the 4 th subgroup (unstable angina or NSTEMI with diabetes), prasugrel dominated (that is, it was less costly and more effective than) clopidogrel.	4.3.15-4.3.16
For reviews: How has the new cost-effectiveness evidence that has emerged since the original appraisal (TA182) influenced the current recommendations?	The new cost-effectiveness evidence has not influenced the recommendations in section 1. There are differences in the cost-effectiveness results submitted during the original appraisal of prasugrel and in the current appraisal which are a result of the different economic models used. In particular, in the current appraisal both the manufacturer and the Assessment Group used the whole licensed population in their models, rather than the typical/median patient profile used in the model for the original appraisal. Also, in the current appraisal the Assessment Group used data from the CAPRIE trial in its long-term model rather than data from TRITON-TIMI 38.	4.2.1, 4.2.11, 4.2.15, 4.2.27
Additional factors taken into account		
Patient access schemes (PPRS)	Not applicable. No patient access schemes were submitted.	
End-of-life considerations	Not applicable to this appraisal.	
Equalities considerations and social value judgements	No equality issues relevant to the Committee's recommendations were raised.	

5 Implementation

- 5.1 Section 7(6) of the [National Institute for Health and Care Excellence \(Constitution and Functions\)](#) and the [Health and Social Care Information Centre \(Functions\) Regulations 2013](#) requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.
- 5.2 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraph above. This means that, if a person has acute coronary syndromes and the doctor responsible for their care thinks that prasugrel is the right treatment, it should be available for use, in line with NICE's recommendations.
- 5.3 NICE has developed a [costing statement](#) explaining the resource impact of this guidance, to help organisations put this guidance into practice.

6 Review of guidance

- 6.1 The guidance on this technology will be considered for review in June 2017. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Andrew Dillon
Chief Executive
July 2014

7 Appraisal Committee members and NICE project team

7.1 *Appraisal Committee members*

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are 4 Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Professor Andrew Stevens

Chair of Appraisal Committee C, Professor of Public Health, University of Birmingham

Professor Eugene Milne

Vice Chair of Appraisal Committee C, Director of Public Health, City of Newcastle upon Tyne

Professor Kathryn Abel

Director of Centre for Women's Mental Health, University of Manchester

Dr David Black

Medical Director, NHS South Yorkshire and Bassetlaw

David Chandler

Lay member

Gail Coster

Advanced Practice Sonographer, Mid Yorkshire Hospitals NHS Trust

Professor Peter Crome

Honorary Professor, Dept of Primary Care and Population Health, University College London

Professor Rachel A Elliott

Lord Trent Professor of Medicines and Health, University of Nottingham

Dr Greg Fell

Consultant in Public Health, Bradford Metropolitan Borough Council

Dr Alan Haycox

Reader in Health Economics, University of Liverpool Management School

Dr Janice Kohler

Formerly Senior lecturer and consultant in paediatric oncology, Southampton University Hospitals Trust

Emily Lam

Lay member

Dr Nigel Langford

Consultant in Clinical Pharmacology and Therapeutics and Acute Physician, Leicester Royal Infirmary

Dr Allyson Lipp

Principal Lecturer, University of South Wales

Dr Claire McKenna

Research Fellow in Health Economics, University of York

Professor Gary McVeigh

Professor of Cardiovascular Medicine, Queens University Belfast and Consultant Physician, Belfast City Hospital

Henry Marsh

Consultant Neurosurgeon, St George's Hospital, London

Professor Stephen O'Brien

Professor of Haematology, Newcastle University

Dr Anna O'Neill

Deputy Head of Nursing & Healthcare School / Senior Clinical University Teacher, University of Glasgow

Alan Rigby

Academic Reader, University of Hull

Professor Peter Selby

Consultant Physician, Central Manchester University Hospitals NHS Foundation Trust

Professor Matt Stevenson

Technical Director, School of Health and Related Research, University of Sheffield

Dr Paul Tappenden

Reader in Health Economic Modelling, School of Health and Related Research, University of Sheffield

Professor Robert Walton

Clinical Professor of Primary Medical Care, Barts and The London School of Medicine & Dentistry

Dr Judith Wardle

Lay member

7.2 NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Helen Tucker/ Ella Fields

Technical Leads

Nicola Hay

Technical Adviser

Nicole Fisher

Project Manager

8 Sources of evidence considered by the Committee

A. The assessment report for this appraisal was prepared by Liverpool Reviews and Implementation Group:

- Greenhalgh, J, et al. (2013) Prasugrel with percutaneous coronary intervention for treating acute coronary syndromes (review of TA182).

B. The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, assessment report and the appraisal consultation document (ACD). Organisations listed in I, II and III were also invited to make written submissions and have the opportunity to appeal against the final appraisal determination.

I. Manufacturers/sponsors:

- Eli Lilly and Company/Daiichi-Sankyo

II. Professional/specialist and patient/carer groups:

- Pumping Marvellous Foundation
- South Asian Health Foundation
- British Cardiovascular Intervention Society
- British Heart Foundation
- Royal College of Nursing
- Royal College of Physicians

III. Other consultees:

- Department of Health
- NHS Fylde & Wyre CCG
- Welsh Government

IV. Commentator organisations (without the right of appeal):

- Commissioning Support Appraisals Service

- Department of Health, Social Services and Public Safety- Northern Ireland
- Health Improvement Scotland
- Medicines and Healthcare products Regulatory Agency

C. The following individuals were selected from clinical specialist and patient expert nominations from the consultees and commentators. They participated in the Appraisal Committee discussions and provided evidence to inform the Appraisal Committee's deliberations. They gave their expert personal view on prasugrel with percutaneous coronary intervention for treating acute coronary syndrome by attending the initial Committee discussion and/or providing written evidence to the Committee. They were also invited to comment on the ACD.

- Professor Nick Curzen, Professor of Interventional Cardiology, nominated by British Cardiovascular Intervention Society – clinical specialist
- Dr Tim Kinnaird, Consultant Cardiologist, nominated by Eli Lilly and Company
- Nick Hartshorne- Evans, CEO, nominated by the Pumping Marvellous Foundation – patient expert

D. Representatives from the following manufacturers/sponsors attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- Eli Lilly and Company

About this guidance

NICE technology appraisal guidance is about the use of new and existing medicines and treatments in the NHS.

This guidance was developed using the NICE [multiple technology appraisal](#) process.

It updates and replaces NICE technology appraisal guidance 182 (published October 2009).

It has been incorporated into the following NICE pathways along with other related guidance and products: [acute coronary syndromes](#), [myocardial infarction with ST-segment elevation](#), and [myocardial infarction: secondary prevention](#).

We have produced a [summary of this guidance for patients and carers](#). Tools to help you put the guidance into practice and information about the evidence it is based on are also [available](#).

NICE produces guidance, standards and information on commissioning and providing high-quality healthcare, social care, and public health services. We have agreements to provide certain NICE services to Wales, Scotland and Northern Ireland. Decisions on how NICE guidance and other products apply in those countries are made by ministers in the Welsh government, Scottish government, and Northern Ireland Executive. NICE guidance or other products may include references to organisations or people responsible for commissioning or providing care that may be relevant only to England.

Your responsibility

This guidance represents the views of NICE and was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity and foster good relations. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties.

Copyright

© National Institute for Health and Care Excellence 2014. All rights reserved. NICE copyright material can be downloaded for private research and study, and may be reproduced for educational and not-for-profit purposes. No reproduction by or for commercial organisations, or for commercial purposes, is allowed without the written permission of NICE.

ISBN 978-1-4731-0658-1

Accreditation

