NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Premeeting briefing

Ticagrelor for the treatment of acute coronary syndromes

This briefing presents the key issues arising from the manufacturer's submission, Evidence Review Group (ERG) report and statements made by consultees and their nominated clinical specialists and patient experts. Please note that this briefing is a summary of the information available and should be read with the full supporting documents.

The manufacturer was asked to:

1) Provide Kaplan–Meier survival analysis results for primary and secondary end points in the form of numeric tables showing: the time from randomisation, the estimated event-free survival (with standard error), the number of patients remaining at risk of an event, the cumulative number of events and the cumulative number of censored observations.

2) Provide more detailed results of primary and secondary end points stratified by gender and age, preferably in 10 year bands (for the whole trial population).

3) Provide a table showing the following baseline characteristics for each treatment group by each modelled population and sub-population:

- age (mean, standard deviation, minimum, maximum)
- proportion with previous history of stroke or transient ischaemic attack (TIA)
- proportion with previous history of peripheral vascular disease
- proportion with substantial or severe disability (Rankin scale 3+ or equivalent) at baseline.

4) Provide separate analyses for each modelled subgroup stratified by:

- patients with a previous history of stroke or TIA and/or PAD and
- those with no such previous history (that is, those with history of previous cardiac events or diagnosis only).

5) Provide the rates of compliance for each arm for each period of the trial between assessments.

6) Carry out, for each modelled population and sub-population, Cox proportional hazards regression analyses of the following events (censored by the other two events and other withdrawals):

- acute myocardial infarction (MI) (fatal and non-fatal combined)
- acute stroke or TIA (fatal and non-fatal combined)
- other death (not MI or stroke).

7) Include the following factors as covariates in the analyses:

- age (in years) at baseline
- gender
- serious or severe disability (Rankin 3+ or equivalent) at baseline
- randomised treatment.

8) Report regression coefficients for each variable with standard errors and significance level (p value).

9) Provide outcomes, including safety end points, for the cohort of patients from Europe.

10) Provide results of any analyses that compare rates of bleeding between countries or regions.

11) Clarify the rationale for the chosen model structure and assumptions in light of the following:

- The ERG commented on the simplicity of the economic model and raised concerns, at the clarification stage, that this could hinder both the exploration of key issues and the provision of robust evidence of cost effectiveness.
- The ERG highlighted that, given the small outcome difference between the treatments, the incremental cost-effectiveness ratio (ICER) must be considered vulnerable to small alterations in projection methods, modelling assumptions and parameter values. It noted that the final estimated survival gain was 20 times the initial result reported in the PLATO trial. Since nearly 95% of the estimated benefit was generated by the post-trial Markov model, it is important that this model is robust and reflect current knowledge of the long-term experience of patients with chronic cardiovascular disease.
- The ERG commented that the Markov model was designed with a basic structure that assigns patients to health states on the basis of the occurrence of a first non-fatal MI or stroke event, which then governs their future care and morbidity until death. There were concerns that this model may not reflect the natural history of cardiovascular disease and does not allow for exploration of key assumptions, for example, whether early survival gain could be attenuated over time as accumulating patient histories converge.

The ERG suggested that a more detailed model reflecting the complex sequence of events experienced by patients with cardiovascular disease over their lifetime could be more appropriate. In particular, the ERG noted the following areas of concern:

- Long-term non-fatal event risks were fixed for life and did not reflect known alterations due to ageing, previous (and accumulating) event history, whether patients had single or multivascular disease, and disability status following a severe stroke.
- Long-term mortality rates were adjusted for age but not for event history or whether patients had single or multivascular disease.
- Only initial non-fatal MI and stroke events were projected, so that subsequent non-fatal events and all fatal events were not explicitly estimated and so no specific NHS costs were estimated.
- Implicitly, the fatality rates of subsequent events were assumed to be immaterial within the model, though the ERG has shown that fatality is influenced by age, gender, previous event history and whether patients had single or multivascular disease.

Licensed indication

Ticagrelor (Brilique, AstraZeneca) is a $P2Y_{12}$ inhibitor that is taken with aspirin. It is indicated for the prevention of atherothrombotic events in adult patients with acute coronary syndromes (ACS). This population consists of people with unstable angina, non-ST-segment-elevation MI (NSTEMI) or ST-segment-elevation MI (STEMI) including those managed medically, and those managed with percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). Ticagrelor was granted marketing authorisation in January 2011 by the European Medicines Agency. Ticagrelor is administered as 90 mg film-coated tablets. Treatment should be initiated with a single 180 mg loading dose and then continued at 90 mg twice daily.

Key issues for consideration

Clinical effectiveness

- How does the fact that not all patients were followed up for 12 months affect the robustness of the evidence from the direct comparison PLATO trial?
- Does the Committee consider that the population in the PLATO trial reflects the UK population with ACS?
- Does the Committee consider the comparator arm as representative of NICE guidance or clinical practice in England and Wales for the three subgroups of patients specified in the scope: those with unstable angina, STEMI, and NSTEMI?
- Does the Committee consider the overall composite end point appropriate?
- Does the Committee consider that potential for increased risk of haemorrhagic stroke was considered appropriately?
- What is the Committee's view on ticagrelor as an option for patients who have contraindications to clopidogrel, considering that patients were excluded from the PLATO trial if clopidogrel was contraindicated?
- Does the fact that ticagrelor is a twice-daily medication have an effect on adherence in clinical practice?
- What is the Committee's view on the indirect comparison of ticagrelor and prasugrel?

Cost effectiveness

- What is the Committee's view on how the model structure adopted in the manufacturer's submission represents real world clinical experience considering that it does not allow patients to have multiple cardiovascular events in their lifetime?
- How does the omission of the outcome 'need for revascularisation' affect the results?

- Does the Committee consider that the long-term experience of patients' future costs and utilities were modelled adequately?
- What is the Committee's view on how the manufacturer adjusted the age of the trial patients to ensure the economic evaluation would be generalisable to the UK population with ACS?
- What is the Committee's view on the ICER presented for STEMI considering that there are four potential STEMI subgroups: STEMI without stenting; STEMI with bare-metal stents; STEMI with drug-eluting stents and STEMI with other treatment (for example, CABG)?
- What is the Committee's view on the ICER presented for unstable angina considering that unstable angina may be further classified in clinical practice using the Global Registry of Acute Coronary Events (GRACE) classification to estimate risk of a future event?
- Does the Committee consider that there are any subgroups of patients for whom ticagrelor is more cost effective?

1 Decision problem

1.1 Decision problem approach in the manufacturer's submission

Population	Patients presenting with ACS irrespective of whether they have undergone revascularisation
Intervention	Ticagrelor plus aspirin
Comparators	For all ACS patients including those medically managed and those to be managed with PCI (as per the full PLATO population): • clopidogrel plus aspirin. Data on the following subgroups: STEMI, NSTEMI and unstable angina will also be presented. For people who are to be managed with PCI: • prasugrel plus aspirin.
Outcomes	Mortality (all cause) Thrombotic cardiovascular events Adverse effects of treatment Health-related quality of life Recurrent ischaemia
Economic evaluation	Cost effectiveness presented as incremental cost per quality-adjusted life year (QALY) The time horizon for the modelling is a lifetime which was assumed to be 40 years Costs evaluated from NHS and Personal Social Services perspectives

1.2 Evidence Review Group comments

1.2.1 Population

The ERG considered that the population described in the decision problem as patients presenting with ACS irrespective of whether they have undergone revascularisation was consistent with the population of the key trial cited by the manufacturer.

The ERG noted that the antiplatelet treatment recommendations for the three subgroups of patients (specified in the scope), those with STEMI, NSTEMI

and unstable angina, fall under the remit of different NICE guidance. 'MI: secondary prevention' (NICE clinical guideline 48) recommends that patients with NSTEMI should receive dual antiplatelet therapy (combination of aspirin and clopidogrel) for 12 months after the index event. For patients with STEMI who are treated with dual antiplatelet therapy during the first 24 hours after MI, NICE clinical guideline 48 recommends continuing with this treatment for at least 4 weeks. The subgroup of STEMI patients who are treated for 4 weeks with dual antiplatelet therapy is not represented in the manufacturer's key trial. The ERG noted that although the manufacturer's submission had acknowledged the recommendations in NICE clinical guideline 48 it had cited that the European guidelines for the management of STEMI recommend dual antiplatelet therapy for 12 months.

The ERG also commented that in the key trial all patients with STEMI received at least 6 months dual antiplatelet therapy regardless of the type of stent they received. However, the ERG highlighted that 'Drug-eluting stents for the treatment of coronary artery disease' (NICE technology appraisal guidance 152) recommends dual antiplatelet therapy for 3 months following treatment with a bare-metal stent. The ERG considered that treatment with dual antiplatelet therapy for 3 months will apply only to patients who have STEMI because 'Unstable angina and NSTEMI' (NICE clinical guidance 94) recommended that patients with NSTEMI receive dual antiplatelet therapy for 12 months.

1.2.2 Intervention

The ERG noted that the recommended use of ticagrelor is for a single course of treatment with ticagrelor plus aspirin for up to 12 months, and that the manufacturer does not expect patients to receive repeated courses of ticagrelor.

1.2.3 Comparators

The ERG noted that for patients who are to be managed with PCI, the two relevant comparators are the $P2Y_{12}$ inhibitors prasugrel and clopidogrel, and for patients who are not to be managed with PCI, clopidogrel is the relevant comparator. The ERG agreed with the manufacturer's assertion that recent use of prasugrel in UK clinical practice is low.

In the absence of any direct randomised control trial evidence of the relative efficacy of ticagrelor and prasugrel, the manufacturer cited data (from a paper published independently by a third party) that describes the results of an indirect analysis between ticagrelor and prasugrel. The ERG agreed with the manufacturer's conclusion that the two trials were too different in patient population and design to be appropriately compared, and highlighted that similar criticisms had been voiced by independent reviewers. The ERG concluded that the indirect analysis was inappropriate and its results should be interpreted with caution.

1.2.4 Outcomes

The ERG noted that the manufacturer's submission addressed the outcomes: mortality, thrombotic cardiovascular events, adverse effects of treatment and health-related quality of life, but did not address the outcome measure 'need for revascularisation'. In the PLATO trial nearly all patients with STEMI received revascularisation while for patients with NSTEMI or unstable angina it was left to the investigators' discretion as to whether the patient was managed medically or surgically. The ERG considered the manufacturer's explanation to be acceptable if the NICE scope was interpreted as referring to changing the immediate mode of treatment (that is, revascularisation) within the trial. However, if this outcome measure referred to additional, unplanned revascularisation following any index procedure, this had not been addressed in the manufacturer's submission.

The ERG noted that the outcome data for recurrent ischaemia, reported by the manufacturer were not in the clinical section of the submission but are in the published paper for the PLATO trial.

1.2.5 Economic evaluation

The ERG commented that the manufacturer's economic analysis was in line with that stipulated in the final scope issued by NICE.

1.3 Statements from professional/patient groups and nominated experts

The clinical specialists stated that standard therapy includes aspirin in combination with clopidogrel or prasugrel and that there is heterogeneity across the UK regarding the default $P2Y_{12}$ inhibitor used in clinical practice. The experts confirmed that ticagrelor would be initiated at hospital admission and then continued in secondary care, noting that it is not yet available clinically and that there are no UK guidelines regarding its use.

2 Clinical effectiveness evidence

2.1 Clinical effectiveness in the manufacturer's submission

2.1.1 Direct comparison (ticagrelor versus clopidogrel)

The manufacturer identified one trial in its submission to NICE. The PLATO trial was an international, multicentre, randomised, double-blind, double-dummy parallel group, phase III study. The trial evaluated the efficacy and safety of ticagrelor plus aspirin compared with clopidogrel plus aspirin over 12 months in people with ACS.

In the trial a total of 18,624 adult patients from 43 countries (including 18 UK centres, n = 281) were admitted to hospital with ACS, with or without ST-segment elevation (see page 38 of the manufacturer's submission for details

of eligibility criteria for PLATO), and were randomised to either ticagrelor plus aspirin (n = 9333) or clopidogrel plus aspirin (n = 9291).

A summary of the baseline characteristics of participants in the PLATO study is shown in table 1. Please refer to page 39 of the manufacturer's submission for further details.

Table 1 Baseline characteristics of participants in the PLATO study

Characteristic	Ticagrelor group (n=9333)	Clopidogrel group (n=9291)
Median age (years)	62.0	62.0
Age 75 years or older (%)	15.0	16.0
Females (%)	28.4	28.3
Median body weight (kg)	80.0	80.0
Body weight less than 60 kg (%)	7.0	7.1
Median body-mass index (BMI)	27	27
Race (%)		
White	91.8	91.6
Black	1.2	1.2
Asian	5.8	6.0
Other	1.2	1.2
Positive troponin I test at study entry (%)	85.3	86.1
Final diagnosis of ACS (%)		
STEMI	37.5	38.0
NSTEMI	42.9	42.5
Unstable angina	16.6	16.8
Other / missing data	3.0	2.7
ACS = acute coronary syndromes. STEMI = ST-segment-elevation myocardial infarction. NSTEMI = non-ST-segment-elevation myocardial infarction.		

Most patients were given 75 to 100 mg of aspirin daily unless it was not tolerated. For those who had not previously been receiving aspirin, 325 mg was the preferred loading dose; 325 mg was also permitted as the daily dose for 6 months after stent placement. In addition, patients in the ticagrelor plus aspirin arm received 180 mg of ticagrelor as the loading dose, followed by 90 mg of ticagrelor twice daily thereafter. Patients in the clopidogrel plus

aspirin arm received 300 to 600 mg of clopidogrel as the loading dose, followed by 75 mg of clopidogrel daily thereafter. Follow-up was planned for 12 months but if 1780 primary end point events were reached then patients were allowed to leave the study at their 6 or 9 month visit. The number of events that had actually occurred by the time the study was concluded was 1878. The median duration of treatment was 9.1 months.

The primary end point of the trial was a composite time to death from vascular causes, myocardial infarction or stroke. For patients in whom early invasive management was planned at randomisation, the first pre-specified secondary end point was the primary composite end point. Additional secondary end points (analysed for the entire study population) included the composite of death from any cause, myocardial infarction and stroke; the composite of death from vascular causes, myocardial infarction, stroke, severe recurrent cardiac ischemia, recurrent cardiac ischaemia, transient ischaemic attack or other arterial thrombotic events; myocardial infarction alone; death from vascular causes alone; stroke alone; and death from any cause. The PLATO trial included a pre-specified health economics and quality of life sub-study, in which the EQ-5D questionnaire was administered in all countries in the study where an official language version of EQ-5D was available, at discharge from the index visit, at 6 months, and at the end of treatment.

2.1.2 Results of PLATO study

The key outcomes from the PLATO trial are summarised in table 2 (intention-to-treat population)

Table 2 PLATO trial results (manufacturer's submission page 47)

	Ticagrelor Number of patients with events n = 9333 (Kaplan Meier %/12 months)	**Clopidogrel Number of patients with events n = 9291 (Kaplan Meier %/12 months)**	**HR for ticagrelor (95% CI)**	**p value**
Primary end point				
Death from vascular causes, MI, stroke	864 (9.8)	1014 (11.7)	0.84 (0.77 to 0.92)	< 0.001
Secondary end points				
Death from any cause, MI or stroke	901 (10.2)	1065 (12.3)	0.84 (0.77 to 0.92)	< 0.001
Death from vascular causes, MI, stroke, severe recurrent ischaemia, recurrent ischaemia, TIA or other arterial thrombotic event	1290 (14.6)	1456 (16.7)	0.88 (0.81 to 0.95)	< 0.001
MI	504 (5.8)	593 (6.9)	0.84 (0.75 to 0.95)	0.005
Death from vascular causes	353 (4.0)	442 (5.1)	0.79 (0.69 to 0.91)	0.001
Stroke	125 (1.5)	106 (1.3)	1.17 (0.91 to 1.52)	0.22
Ischaemic stroke	96 (1.1)	91 (1.1)		0.74
Haemorrhagic stroke	23 (0.2)	13 (0.1)		0.10
Unknown type of stroke	10 (0.1)	2 (0.02)		0.04
Death from any cause (exploratory analysis)	399 (4.5)	506 (5.9)	0.78 (0.69 to 0.89)	< 0.001
Death from causes other than vascular causes (exploratory analysis)	46 (0.5)	64 (0.8)	0.71 (0.49 to 1.04)	0.08
Severe recurrent ischaemia	302 (3.5)	345 (4.0)	0.87 (0.74 to 1.01)	0.08
Recurrent ischaemia	500 (5.8)	536 (6.2)	0.93 (0.82 to 1.05)	0.22
HR = hazard ratio. CI = confidence interval. MI = myocardial infarction. TIA = transient ischaemic attack.				

The manufacturer noted that when the components of the primary end point (incidence of MI, death from vascular causes and stroke) were considered

individually, the reduction in the primary end point was seen to be driven by approximately equal, statistically significant, reductions in the incidence of MI (hazard ratio [HR] 0.84, 95% confidence interval [CI] 0.75 to 0.95; p = 0.005) and death from vascular causes (HR 0.79, 95% CI 0.69 to 0.91; p = 0.001), because there was no statistically significant difference in the overall rate of stroke between the two arms, although the number of strokes was higher in the ticagrelor arm.

An exploratory analysis of total mortality indicated a statistically significant difference in favour of ticagrelor for the outcome of death from any cause (HR = 0.78; 95% CI 0.69 to 0.89; nominal p < 0.001). The manufacturer also reported the results of an exploratory analysis on the rate of stent thrombosis in patients who received a stent during the trial (n = 11,289), which indicated that the rate of definite stent thrombosis at 1 year was statistically significantly lower in the ticagrelor arm (1.3%) than in the clopidogrel arm (1.9%), with a HR of 0.67 (95% CI 0.50 to 0.91; nominal p = 0.009).

An analysis of the incidence of primary composite events over time in the trial indicated that early benefits are observed within the first 30 days of ticagrelor treatment compared with clopidogrel with an absolute risk reduction of 0.6% at 30 days. For patients who have received treatment for 360 days, the absolute risk reduction increases to 1.9%. The benefit is maintained over time with a relative risk reduction of around 16% over the entire duration of the study. A graphical depiction is presented on page 48 of the manufacturer's submission.

An analysis of the primary end point was conducted in several pre-defined subgroups (listed on page 49 of the manufacturer's submission) and the manufacturer's submission stated that treatment interaction significance levels of less than 0.05 occurred in three groups: geographic region; body weight above or below gender-specific median; and use of lipid-lowering drugs at randomisation. Overall, clinical outcomes were consistent across all major subgroups, including unstable angina, NSTEMI and STEMI, with hazard ratios

of 0.96 (95% CI 0.75 to 1.22), 0.83 (95% CI 0.73 to 0.94) and 0.84 (95% CI 0.34 to 1.00) respectively.

Health-related quality of life scores were elicited from patients with ACS using EQ-5D UK tariff. No differences were found between ticagrelor and clopidogrel arms for any of the items on the EQ-5D.

2.1.3 Adverse events

The manufacturer reported safety issues from the PLATO study, specifically bleeding, dyspnoea and ventricular pauses. Bleeding events reported in PLATO were also mapped onto the Thrombolysis in Myocardial Infarction (TIMI) scale by applying an algorithm to the bleeding events. Approximate comparison between bleeding events assessed by PLATO and TIMI criteria are shown on page 73 of the manufacturer's submission. There was no significant difference in the primary safety end point of 'major' bleeding between ticagrelor and clopidogrel (11.6% versus 11.2% respectively, p = 0.43) and these findings were consistent across all major subgroups. Non-CABG-related study-defined major bleeding and major or minor bleeding events were significantly higher in the ticagrelor group (HR 1.19; 95% CI 1.02 to 1.38; p = 0.03 and HR 1.11 95% CI 1.03 to 1.20; p = 0.008, respectively). Intracranial bleeding was more common in the ticagrelor group than in the clopidogrel group, with fatal intracranial bleeding being significantly more common in the ticagrelor group (HR not reported; p = 0.02). Non-intracranial fatal bleeding was, however, significantly higher in the clopidogrel group (HR not reported; p = 0.03).

Dyspnoea was significantly higher with ticagrelor than clopidogrel in the PLATO study (13.8% versus 7.8% respectively; p <0 .001). The rate of discontinuation due to dyspnoea was also significantly higher with ticagrelor than with clopidogrel (0.9% versus 0.1% respectively; p = <0.001). The investigator considered dyspnoea to be caused by ticagrelor in 2.2% of patients. Holter monitoring detected more ventricular pauses (of length greater than or equal to 3 seconds) during the first week in the ticagrelor group than in

the clopidogrel group, but such episodes were infrequent at 30 days and rarely associated with symptoms. In addition, there was no difference in the need for a pacemaker between the two treatment groups. Significantly greater increases from baseline in levels of uric acid and serum creatine were detected in the ticagrelor group compared with the clopidogrel group; $p < 0.001$ for both events throughout the study. For further details on adverse effects see tables 5.19 and 5.20, on pages 73 and 74 respectively, of the manufacturer's submission.

2.1.4 Subgroups

The manufacturer presented six subgroup analyses of the PLATO study. The manufacturer stated that five of these were pre-specified sub-groups: PLATO-INVASIVE; PLATO-MEDICAL (non invasive); PLATO-STEMI; PLATO-DIABETES; PLATO-GENETICS and one was a post-hoc subgroup: PLATO-CABG. The results of these subgroup analyses were generally consistent with the primary analysis. For further details on the subgroups see pages 50–7 and page 72 of the manufacturer's submission.

2.1.5 Indirect comparison (ticagrelor versus prasugrel)

The manufacturer identified two studies that provided data for an indirect comparison of ticagrelor and prasugrel; the PLATO trial and TRITON-TIMI 38 which compared prasugrel with clopidogrel in patients (n = 13,608) with ACS who were to be treated with primary or planned PCI. The manufacturer noted that there were general similarities between the trials, such as having an ACS population, using a clopidogrel comparator and having the same composite primary efficacy end point. However, there were some important differences between these two studies that made an indirect comparison of the relative benefits of prasugrel versus clopidogrel (in TRITON-TIMI 38) and ticagrelor versus clopidogrel (in PLATO) – and, by inference, prasugrel versus ticagrelor – problematic and potentially inappropriate. These differences included differences in the target population, in timing of doses and size of loading doses of clopidogrel, and in assessment of MI due to different timing of PCI in

the two studies. See pages 61–4 of the manufacturer's submission for further details of these differences. For the purposes of health economic modelling the results of a published indirect comparison of the TRITON-TIMI 38 and the PLATO trial, conducted by an independent group, were incorporated in the manufacturer's submission. The results from this publication were expressed as odds ratios and were converted to relative risks for input into the model (see page 66 of the manufacturer's submission). The authors of the publication state that the indirect comparison showed no significant differences in overall death, MI, stroke, or the composite of these outcomes. Prasugrel was associated with a significantly lower risk of any major bleeding and major bleeding associated with bypass grafting, although the risk was similar with both prasugrel and ticagrelor for major bleeding not related to bypass surgery. The authors concluded that prasugrel and ticagrelor are superior to clopidogrel for ACS; that prasugrel and ticagrelor have similar efficacy and safety but prasugrel was associated with fewer stent thromboses, but also with more bleeding events.

2.2 Evidence Review Group comments

The ERG conducted its own literature searches and concluded that no relevant published studies had been excluded in the manufacturer's submission. The ERG agreed that the PLATO trial is the only trial relevant to the decision problem.

The ERG considered the PLATO trial to be well designed and the trial randomisation and blinding processes to be robust. Although only 281 patients in the PLATO trial were from UK centres, the ERG considered that enough patients were derived from other EU countries with similar care pathways to the UK. The ERG noted that there was a considerable difference in both the mean age and the proportion of older patients in England and Wales compared with the PLATO trial. However in the manufacturer's economic evaluation, the event rates of the PLATO trial were age-adjusted to

more accurately reflect the cost effectiveness of ticagrelor for the population with ACS in England and Wales.

The ERG noted that the regional analysis suggests that in the USA, patients randomised to clopidogrel did better than those randomised to ticagrelor – this is currently a focus of deliberation of the FDA.

The ERG considered that compliance was well balanced across the two treatment arms.

The ERG further noted that there is unlikely to be any impact from the reported protocol deviations because they were balanced across the two treatment groups (3.1% in the ticagrelor group versus 3.2% in the clopidogrel group) and only a small proportion of patients were affected (3.2% in total).

The ERG noted that the direct evidence from the trial may not be able to support a recommendation for the four STEMI subgroups based on current NICE guidance, which recommends the following:

- STEMI without stenting – dual antiplatelet therapy for at least 4 weeks (NICE clinical guideline 48).
- STEMI with bare-metal stents – dual antiplatelet therapy for 3 months (NICE technology appraisal guidance 152).
- STEMI with drug-eluting stents – dual antiplatelet therapy for 12 months (NICE clinical guideline 48).

The ERG considered that the trial reflects current clinical practice and all patients had received antiplatelet treatment at a clinically meaningful dose.

The ERG noted that the manufacturer excluded ‘silent’ MIs (defined as development of new or presumed pathological Q waves in the absence of symptoms of cardiac ischaemia) from the MI count in the primary outcome. The ERG considered the secondary end points and their components to be standard end points as used in the field of cardiology. It noted however, that it

was not possible, from the data provided in the manufacturer's submission, to compare absolute rates of stroke and MI across the two arms of the trial and that only time to first event data were presented. The ERG was confident that the bleeding categorisation method employed by the manufacturer was relevant and robust.

The ERG considered that all patients should have been followed up for 12 months.

The ERG expressed concerns regarding the components of the primary efficacy composite end point. First, the requirement that all components of the end point should be of similar importance to patients was not satisfied, because the values of the mean utility scores during the first 12 months used in the manufacturer's economic evaluation were 0.246 for vascular death, 0.812 for MI and 0.736 for stroke. Second, there were differences in the frequencies of component end points observed in the trial (in 18,624 participants there were 795 vascular deaths, 1097 MIs and 231 strokes). Therefore, the criteria that the more or less important end points occured with similar frequency were not met. Third, the hazard ratio of the component end point of stroke differed in direction to that of the other two components, thus not meeting the criteria that component end points are those that are likely to have similar relative risk reductions with narrow confidence intervals. The ERG concluded that the results of the overall composite end point should be interpreted cautiously and the potential for increased risk of stroke should be discussed further. The ERG also noted that cumulative incidence survival curves would have been more appropriate than the Kaplan–Meier survival curves relating to the primary efficacy end point presented in the manufacturer's submission. In addition, the ERG considered it inappropriate that the sample size calculation for the trial was based on an expected primary composite end point, because the definition of the primary end point was time to first occurrence of the composite of MI, stroke or death from vascular causes. It would therefore have been more appropriate to use a

survival measure such as a hazard ratio, rather than a measure of simply whether patients experienced an event or not.

The ERG noted that the consistency of effects on efficacy and safety end points was explored in 25 pre-specified subgroups and eight post-hoc subgroups, without adjustment for multiple comparisons. The ERG expressed concern about the large number of subgroups and possible overemphasis of any significant results from these analyses.

With regard to the indirect comparison of ticagrelor and prasugrel, the ERG considered that any comparison between the PLATO and TRITON-TIMI 38 trials was problematic. The ERG concluded that the use of the results from the published indirect analysis was inappropriate. See pages 44−7 of the ERG report for further details.

2.3 Statements from professional/patient groups and nominated experts

The clinical specialist noted that the results from the PLATO study provided evidence of the clinical benefit of ticagrelor compared with clopidogrel, highlighting that the clinical benefit included an absolute mortality reduction, which was unusual. The specialist however noted that the non-CABG bleeding events were higher in the ticagrelor group, and that the dyspnoea side effects would need careful consideration because they would be unfavourable from the patients' perspective. The professional groups considered that it is unlikely that a head-to-head trial comparing ticagrelor to prasugrel would be forthcoming. They expressed concerns about the side effects, but stated that these are reversible.

The professional groups noted that ticagrelor is an important additive agent to the adjunctive therapy available for ACS. Mortality benefit with no overall excess bleeding is a very important consideration, as are the rapid onset and offset duration of action, meaning that if a patient needs an operation then the antiplatelet agent can be discontinued closer to the proposed procedure with

greater safety with regard to bleeding. Clinical specialists suggest that ticagrelor may be clinically more desirable in patients who need antiplatelet protection leading up to CABG.

3 Cost effectiveness

3.1 Cost effectiveness in the manufacturer's submission

3.1.1 Economic model (direct comparison)

The manufacturer did not identify any publications that evaluated the cost effectiveness of ticagrelor for the treatment of ACS. Therefore, the manufacturer developed a new economic model. However, nine economic evaluations were identified that were considered relevant to inform the structure, assumptions and model inputs for the cost-effectiveness analysis of ticagrelor for the treatment of ACS in the UK. For further details of these evaluations, see pages 85−9 of the manufacturer's submission.

The manufacturer's cost−utility model was a two-part construct with a 1-year decision tree, based on data from the PLATO study, and a Markov model for long-term extrapolation for a lifetime horizon, to ensure that all major clinical and resource generating events that a patient may experience throughout the course of their remaining life are captured. The main comparator used in the model was clopidogrel plus aspirin and the patient group presented in the base-case economic evaluation was defined as patients with ACS (STEMI, NSTEMI and unstable angina); including patients managed medically, and those managed with PCI or CABG as per the licensed indication.

There were four mutually exclusive health states in the 1-year decision tree: no further event, non-fatal MI, non-fatal stroke and death from any cause. At the end of the 1-year period represented by the decision tree, patients were allocated to one of four of the six mutually exclusive health states in the Markov model: no further event, non-fatal MI, post MI, non-fatal stroke, post stroke and death. The manufacturer stated that the reasoning behind this

construct with regard to the 'tunnel' states (non-fatal MI and non-fatal stroke) is to allow for a worse prognosis the first year after a non-fatal event compared with second and subsequent years. Costs and health outcomes are discounted at 3.5%. A half-cycle correction is used to adjust costs and outcomes simulated within the Markov model.

Costs and clinical outcomes, in terms of life years and QALYs, continue to accrue beyond the trial follow-up period of 1 year; however, no treatment effect is assumed beyond 1 year. This means that the transition probabilities between states in the Markov model are the same for both treatment arms, the only difference being the number of patients who start the Markov model in each state, which is based on the output of the 1-year decision tree.

The main assumptions underlying the economic analysis include:

- Adverse events (for example, bleeding) were not modelled explicitly; however, both costs and health-related quality of life decrements associated with all adverse events are still included in the analysis because they are part of the individual patient level data from the PLATO HECON sub-study that were used to estimate costs and QALYs for the different nodes of the short-term decision tree.
- It was assumed that adverse events such as bleeding and dyspnoea have no long-term prognostic impact beyond the 12 month duration of the trial.
- The probability of having a non-fatal MI or non-fatal stroke at least 1 year after the index ACS event was assumed to be constant at 3.15% and 1.02% respectively.
- The relative risk (compared with standard UK life tables) of dying at least 1 year after having a subsequent MI was assumed to be the same as that of dying at least 1 year after the index ACS event.
- No discontinuations other than due to death were included in the model.

For the 1 year decision tree, a parametric time-to-event survival model with a Weibull distribution was used to determine the baseline risk and an HR was

applied to the baseline risk. Data used in the 1-year decision tree were derived from the PLATO study. The manufacturer estimated an age-adjusted event rate for the clopidogrel arm in a UK setting to ensure that the economic evaluation would be generalisable to the UK population with ACS (mean age of PLATO patients = 62.2 years; compared with reported age of UK patients with ACS in 2009–10 = 69.7 years). In the Markov model, with the exception of the probabilities for transitioning from the no event health state to the non-fatal MI or non-fatal stroke health states, the probabilities of transitioning between all other health states were taken from standard UK life tables. For the exceptions stated above, the transition probabilities were taken from a study commissioned by the manufacturer, which analysed combined data from the Myocardial Ischemia National Audit Project and the General Practice Research Database. See page 129 of the manufacturer's submission for more information on how the clinical trial data were used in the model.

3.1.2 Utilities

The 12-month cohort in the PLATO-HECON study was used to calculate the utility accrued in the study (resulting in the average utility value over the 12 month period). Utility values were elicited from ACS patients using EQ-5D UK tariff (time trade-off method). In addition, the manufacturer conducted a review of utility scores via a literature search to ensure a level of consistency between the study and literature utility values. The utility values from the literature were used within the sensitivity analyses, and were lower than those reported in the PLATO-HECON sub-study. However the manufacturer stated that the relative difference between the two alternative sets of values was consistent across the different health states. The utility scores from both the PLATO-HECON sub-study and the published literature were adjusted downwards by 0.0328 to reflect characteristics of the UK population. Because utility decreases with age, a utility decrement of 0.004 was applied to each cycle beyond the first year to take account the ageing population in the Markov model. A summary of the quality of life values used to inform the cost-effectiveness analysis is presented in table 3.

Table 3 Summary of the quality of life values used to inform the base-case analysis (manufacturer's submission page 175)

State	Utility value	Standard error	Reference in submission	Justification
1-year decision tree				
No event (ticagrelor)	0.840	0.003	PLATO-HECON sub- study (MS, section 6.4.3)	Largest collection of EQ-5D questionnaires in any ACS study. Utility scores meet the criteria set out for the reference case
Non-fatal MI (ticagrelor)	0.786	0.014		
Non-fatal stroke (ticagrelor)	0.709	0.062		
Vascular death (ticagrelor)	0.218	0.023		
Non-vascular death (ticagrelor)	0.171	0.042		
Death from any cause (ticagrelor)	0.211	0.021		
No event (clopidogrel)	0.844	0.003		
Non-fatal MI (clopidogrel)	0.774	0.014		
Non-fatal stroke (clopidogrel)	0.695	0.032		
Vascular death (clopidogrel)	0.210	0.020		
Non-vascular death (clopidogrel)	0.270	0.057		
Death from any cause (clopidogrel)	0.220	0.019		
Markov model				
No event	0.842	0.002	As above	As above
Non-fatal MI	0.779	0.010	As above	As above
Post MI	0.821	0.038	As above plus Lacey et al 2003[a]	Evidence HRQL improved over time
Non-fatal stroke	0.703	0.010	As above	
Post stroke	0.703	0.038	As above plus assumption[b]	No evidence HRQL improves over time
Death	0.000	N/A	N/A	Convention

[a] Relative difference between the two values was applied to the MI utility from PLATO to give an estimate of the expected utility. [b] Utility for stroke will remain the same irrespective of the number of years after the event. MI = myocardial infarction. ACS = acute coronary syndromes. MS = manufacturer's submission. HRQL = health-related quality of life. N/A = not applicable.

3.1.3 Costs

The costs for the generic drugs clopidogrel and aspirin, were taken from the NHS Electronic Drug Tariff, November 2010. The key drug costs used in the economic evaluation were: aspirin 28-pack = £0.82; clopidogrel 30-pack = £3.40; ticagrelor 28-pack = £54.60. A pre-specified sub-study was undertaken to measure resource use and determine costs in all patients participating in the PLATO study. Hospitalisations, interventions, investigations and bleeding-related healthcare consumption were recorded for all patients, to estimate total healthcare costs associated with ticagrelor and clopidogrel within the PLATO study. Resource use was categorised into two time periods: index hospitalisation (randomisation to time of discharge) and post-index hospitalisation (day after discharge from index hospitalisation to the end of study). The manufacturer also considered the additional renal check required according to the SPC in a sensitivity analysis.

The manufacturer identified inconsistencies in the 'resource use table' during a final review of the 'with-in trial economic analysis'. The manufacturer presented clarifications in its addendum 'Impact of revised resource use on results submitted to NICE'. The revisions to the resource use resulted in a small increase of the health state costs (see table 4).

Table 4 Original and revised mean cost estimates used for the health states in the base-case analysis

Health state	Mean cost estimates	
	Original	Revised
No event (ticagrelor)	£8544	£8573
Non-fatal MI (ticagrelor)	£16,643	£16,767
Non-fatal stroke (ticagrelor	£15,394	£15,455
CV death (ticagrelor)	£11,077	£11,261
Non-CV death (ticagrelor)	£17,180	£17,275
All cause mortality (ticagrelor)	£11,753	£11,926
No event (clopidogrel)	£8633	£8676
Non-fatal MI (clopidogrel)	£16,362	£16,563
Non-fatal stroke (clopidogrel	£17,483	£17,576
CV death (clopidogrel)	£11,501	£11,620
Non-CV death (clopidogrel)	£27,920	£28,332
All cause mortality (clopidogrel)	£13,915	£14,078
MI = myocardial infarction. CV = cardiovascular.		

3.1.4 Results

The results of the base-case analyses (time horizon 40 years) and using different time horizons are presented in table 5.

Table 5 Deterministic results with costs and effects discounted (manufacturer's revised results, addendum page 3)

Time horizon	Ticagrelor	Clopidogrel	Incremental	ICER
40 years (base case)				
Costs	£14,178	£13,799	£379	–
Life-years	7.736	7.606	0.129	£2929
QALYs	6.382	6.275	0.108	£3521
20 years				
Costs	£14,154	£13,776	£378	–
Life-years	7.701	7.572	0.129	£2,936
QALYs	6.354	6.247	0.107	£3,529
10 years				
Costs	£13,257	£12,903	£354	–
Life-years	6.412	6.306	0.106	£3321
QALYs	5.302	5.213	0.089	£3970
5 years				
Costs	£11,765	£11,453	£313	–
Life-years	4.068	4.004	0.065	£4844
QALYs	3.371	3.317	0.055	£5728
1 year				
Costs	£10,017	£9752	£265	–
Life-years	0.969	0.961	0.008	£31,177
QALYs	0.797	0.789	0.008	£33,764

ICER = incremental cost-effectiveness ratio. QALY = quality-adjusted life year.

The manufacturer also presented ICERs for a range of subgroup populations for the base case (40 years) and using different time horizons: STEMI, NSTEMI and unstable angina, which are presented in table 6.

Table 6 Revised results for the base-case analysis and using different time horizons for the subgroups: taken from addendum, pages 4−6

Subgroup	Time horizon	Incremental costs (£)	Incremental QALYs	ICER
STEMI (ticagrelor versus clopidogrel)	40 years	306	0.120	£2551
	20 years	303	0.118	£2568
	10 years	267	0.090	£2968
	5 years	225	0.052	£4313
	1 year	181	0.007	£27,029
NSTEMI (ticagrelor versus clopidogrel	40 years	511	0.098	£5217
	20 years	511	0.098	£5219
	10 years	496	0.087	£5711
	5 years	460	0.056	£8138
	1 year	412	0.009	£5,659
unstable angina (ticagrelor versus clopidogrel)	40 years	482	0.091	£5310
	20 years	481	0.090	£5345
	10 years	454	0.071	£6402
	5 years	418	0.042	£10,032
	1 year	378	0.005	£77,100
QALY = quality-adjusted life year. ICER = incremental cost-effectiveness ratio. STEMI = ST-segment-elevation myocardial infarction.				

The manufacturer carried out a number of deterministic sensitivity analyses to the base case (no results using the revised resource data were submitted to NICE) and showed the effects of changing 43 model parameters. Only the change to the costs of the no event health state impacted substantially on the results. When the cost of the ticagrelor no event health state was set to its lowest, ticagrelor dominated clopidogrel. When the cost of the clopidogrel no event health state was set to its lowest, the ICER was £21,000 per QALY gained. Changes in all other parameters did not increase the ICER beyond £7620.

Scenario analyses were run using 0% and 6% discount rates, using published utility values, removing baseline utility adjustment and removing utility decrement per cycle. The results (no revised analyses submitted to NICE) of the scenario analyses showed that the comparison of ticagrelor versus

clopidogrel yields a stable, low ICER despite substantial variations in structure and methodological input (see table 6.64, page 217 of manufacturer's submission).

The cost-effectiveness acceptability curve shows that at a willingness to pay of £5000 per QALY gained, the probability of ticagrelor being cost effective compared with clopidogrel is 76.6%. At a willingness to pay of £20,000 per QALY gained, the probability of ticagrelor being cost effective compared to clopidogrel is 99.9%.

3.1.5 Indirect comparison

The manufacturer's submission also provided results for ticagrelor versus prasugrel for the subgroup receiving PCI, based on the results of a published indirect comparison of the PLATO and TRITON 38 trials. Because of the small number of patients who participated in the TRITON 38 quality of life sub-study, utility information from the literature, rather than empirical data from the trial, was incorporated into the model. If costs from the PLATO-HECON sub-study were not available, NHS reference costs were used in the analysis versus prasugrel. The cost of prasugrel was taken from MIMS, October 2010. The results are presented in table 7. It is noted that the manufacturer stated that the results of the indirect comparison should be viewed with extreme caution.

Table 7 Results of comparison of ticagrelor versus prasugrel

Subgroup	Time horizon	Incremental costs (£)	Incremental QALYs	ICER
Invasive (received PCI)	40 years	227	0.065	£3482
	20 years	222	0.062	£3598
	10 years	193	0.042	£4562
	5 years	165	0.023	£7047
	1 year	N/A	N/A	N/A
QALY = quality-adjusted life year. ICER = incremental cost-effectiveness ratio. PCI = percutaneous coronary intervention. N/A = Not applicable.				

3.2 Evidence Review Group comments

The ERG raised the following concerns regarding the economic evaluation presented in the manufacturer's submission.

The ERG highlighted concerns about the comparator included in the economic evaluation for patients with STEMI who received bare-metal stents. The manufacturer considered that the STEMI group represented a homogenous population and estimated a single ICER. However, within this subgroup there are four distinct populations as mentioned previously: STEMI without stenting, STEMI with drug-eluting stent, STEMI with bare-metal stents and STEMI with other treatment (e.g. CABG). The model also assumed that all patients receive aspirin as a long-term preventive treatment, whereas in England and Wales cardiovascular patients with multivascular disease have long-term clopidogrel treatment.

The ERG noted that the PLATO trial design did not involve uniform follow-up for all participants, because patients received treatment for 6, 9 or 12 months depending on their time of enrolment relative to the start of the study. Therefore, a limited proportion of patients were followed-up for 12 months in the trial. This increased the uncertainty in the estimates of the final disposition of patients at the conclusion of the trial, which was the prime driver of long-term benefits for patients in the Markov model.

The ERG noted that the model featured two separate pathways. Patients experiencing a non-fatal MI as their first event at any time during a model cycle remain in that state to the end of the cycle, and then progress to the post-MI state for all succeeding cycles until they die (whether from carciovascular or non-cardiovascular causes). In parallel, patients may have a non-fatal stroke as their first event during a period, and then progress to the post-stroke state until they die. The ERG considered that this structure does not represent real-world clinical experience, because it does not allow patients to have multiple cardiovascular events in their lifetime. The consequence of

this is that future costs and benefits, in both groups, could be inaccurately estimated. A further simplification noted was the use of fixed transition probabilities for the risk of previously event-free patients experiencing a first non-fatal MI or stroke throughout the long-term Markov model. Since a patient's age, accumulating experience of previous serious cardiovascular events, and their sequelae (such as disability), are known to alter risks significantly over time, the ERG considered that this omission may lead to inaccurate estimation of future events, costs and progressive changes in patient outcomes and quality of life.

The ERG was concerned that the model applied an average utility score, whereas clinical experience showed that ACS patients experience an initial utility decrement which steadily diminishes. As such, the ERG noted that the ICER at 12 months may be an underestimate.

The ERG noted that the subgroups of interest in the economic evaluation did not reflect the subgroups of interest in the clinical section of the manufacturer's submission. The ERG was therefore unable to verify the clinical effectiveness data related to the NSTEMI and unstable angina subgroups used in the model. The ERG also noted that the unstable angina subgroup was treated as a homogeneous group in the manufacturer's submission whereas, in clinical practice, patients are typically categorised into low, medium and high risk groups using the GRACE classification.

The ERG noted that the manufacturer adjusted the age of the trial patients to ensure the economic evaluation would be generalisable to the UK population with ACS.

The ERG noted some potential problems with the method used:

- the assumption of a Weibull common function for both sets of data may not be sufficiently accurate to represent the trial data

- the use of a binary variable to represent age differences may not be accurate, given that generally age influences event rates as an increasing curvilinear function
- the absence of gender as an adjustment variable is questionable, because cardiovascular risks are generally lower for women than men of the same age.

The ERG tested the impact of using model estimates rather than original trial data and these showed a mortality difference of 1.36%, compared with 1.26% in the model (with no age adjustment). This represents an 8% underestimate of likely benefits and an overestimate of the ICER.

3.2.1 Exploratory analyses undertaken by the ERG

The ERG acknowledged that healthcare resource use was estimated in the model using data from a parallel health economic study, which collected details of hospital care received by patients during the trial. However, it noted that these data were collected for only 57.4% of the trial population, and no information was available about how this subset was selected for the sub-study. Moreover, the ERG noted that for each patient category in the model, the resource use rate per patient was calculated separately for each treatment arm, and these rates were multiplied by a corresponding unit cost and totalled to arrive at an overall estimated hospital care cost per patient for the first 12 month period. The ERG considered that there were some important issues relating to this type of resource analysis, and conducted a combined analysis of resource use (taking all patient groups together), making some notional adjustments for double-counting. Results suggested that any difference between clopidogrel and ticagrelor is more likely to be around £100 per patient rather than the £371 per patient shown in the manufacturer's base case results, which would have the effect of doubling the estimated ICER after 12 months.

The ERG also noted that the manufacturer's base-case analysis applied estimated costs for the study drugs on the basis of 100% use in the trial period, despite clear evidence of early deaths in both of the trial arms as well as recorded treatment withdrawals and some poor compliance. The ERG incorporated trial data on drug use instead. It noted that this had the effect of reducing the average cost of both drugs substantially, and the incremental drug cost of ticagrelor compared with clopidogrel from £651 to £507 per patient.

Appliying the ERG's amended age adjustment, resource use, and costs of study drugs to the manufacturer's model resulted in a 42% increase in the submitted 1-year ICER from £36,177 to £51,204 per QALY gained. However, the ERG emphasised that both the incremental costs and additional benefits from using ticagrelor in place of clopidogrel were very small after a maximum of 12 months' treatment, and were subject to considerable uncertainty.

The ERG conducted a wide-ranging sensitivity analysis, calculating overall deterministic cost-effectiveness estimates for all combinations of four long-term variables (for details of these variables, see page 79 of the ERG report). Table 8 summarises the range of ICERs obtained, for the base case of 40 years, in each case.

Table 8 Overall 40 year cost-effectiveness results from the sensitivity analysis of long-term model variables (ERG report page 80)

	Best result	Central result	Worst result
All patients			
Incremental cost	£1131	£1017	£891
Incremental QALYs	0.332	0.129	0.050
ICER	£3407	£7897	£17,820
STEMI			
Incremental cost	£1181	£1337	£941
Incremental QALYs	0.333	0.151	0.051
ICER	£3551	£8872	£18,597
NSTEMI			
Incremental cost	£1114	£821	£874
Incremental QALYs	0.333	0.114	0.051
ICER	£3350	£7215	£17,307
Unstable angina			
Incremental cost	£1124	£1026	£884
Incremental QALYs	0.330	0.112	0.048
ICER	£3405	£9131	£18,378

QALY = quality adjusted life year. ICER = incremental cost effectiveness ratio. STEMI = ST-segment elevation myocardial infarction. NSTEMI = non-ST-segment myocardial infarction.

The ERG concluded that the most extreme combination of assumptions resulted in an estimated ICER for ticagrelor below £20,000 per QALY gained for each of the specified populations, compared with 12 months' clopidogrel treatment.

However, the ERG highlight that the cost-effectiveness claims for ticagrelor depend crucially upon the absolute reduction in 12 month mortality observed in PLATO for ticagrelor compared with clopidogrel. At earlier time points in the trial, the overall survival difference was much smaller and less significant between the two treatments. The ERG state that in the absence of additional evidence allowing indirect comparison of clopidogrel plus aspirin with

clopidogrel alone and with aspirin alone at 30 days, 90 days and 12 months, some uncertainty remains about whether the PLATO trial provides sufficient evidence to determine the true cost effectiveness of ticagrelor compared with clopidogrel, particularly for STEMI patients.

Finally, the ERG noted that there are no head-to-head trial data comparing ticagrelor with prasugrel. The ERG agreed with the manufacturer that sufficient clinical evidence is not yet available for a credible indirect comparison of ticagrelor versus prasugrel for patients with ACS. They concluded that the comparative effectiveness and safety of ticagrelor compared with prasugrel remains unknown.

4 Equalities issues

No equality and diversity issues relating to population groups protected by equality legislation were highlighted when the scope for this appraisal was developed or in any of the submissions.

5 Authors

Raisa Sidhu, Joanna Richardson, with input from the Lead Team (Sanjeev Patel, Cliff Snelling and John Cairns).

Appendix A: Sources of evidence considered in the preparation of the premeeting briefing

A The Evidence Review Group (ERG) report for this appraisal was prepared by Liverpool Reviews and Implementation Group (LRiG):

- Bagust A, Boland A, Blundell M et al. Ticagrelor for the treatment of acute coronary syndromes, February 2011

B Submissions or statements were received from the following organisations:

I Manufacturer/sponsor:

- AstraZeneca

II Professional/specialist, patient/carer and other groups:

- British Cardiovascular Society
- Royal College of Physicians
- British Cardiovascular Intervention Society
- Oxfordshire PCT
- Heart Care Partnership
- Bradford and Airedale Teaching PCT

C Additional references used:

Biondi-Zoccai G, Lotrionte M, Agostoni P et al. Adjusted indirect comparison meta-analysis of prasugrel versus ticagrelor for patients with acute coronary syndromes. International Journal of Cardiology, 2010.

National Institute for Health and Clinical Excellence (2010) The management of unstable angina and non ST elevation myocardial infarction. NICE clinical guideline 94. London: National Institute for Health and Clinical Excellence. Available from www.nice.org.uk/guidance/CG94

National Institute for Health and Clinical Excellence (2008) Drug-eluting stents for the treatment of coronary artery disease. NICE technology appraisal guidance 152. London: National Institute for Health and Clinical Excellence. Available from www.nice.org.uk/guidance/TA152

National Institute for Health and Clinical Excellence (2007) Secondary prevention in primary and secondary care for patients following a myocardial infarction. NICE clinical guideline 48. London: National Institute for Health and Clinical Excellence. Available from www.nice.org.uk/guidance/CG48