NICE National Institute for Health and Care Excellence

NICE guidance

Ticagrelor for the treatment of acute coronary syndromes

Technology appraisal guidance
Published: 26 October 2011

www.nice.org.uk/guidance/ta236

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 is 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.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

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 Recommendations

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

- with ST-segment-elevation myocardial infarction (STEMI) – defined as ST elevation or new left bundle branch block on electrocardiogram – that cardiologists intend to treat with primary percutaneous coronary intervention (PCI) **or**
- with non-ST-segment-elevation myocardial infarction (NSTEMI) **or**
- admitted to hospital with unstable angina – defined as ST or T wave changes on electrocardiogram suggestive of ischaemia plus 1 of the characteristics defined in section 1.2. Before ticagrelor is continued beyond the initial treatment, the diagnosis of unstable angina should first be confirmed, ideally by a cardiologist.

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

2 The technology

2.1 Ticagrelor (Brilique, AstraZeneca) is an oral antagonist at the $P2Y_{12}$ adenosine diphosphate receptor, which inhibits platelet aggregation and thrombus formation in atherosclerotic disease. The summary of product characteristics (SPC) states that ticagrelor, co-administered with low-dose aspirin, is indicated for the prevention of atherothrombotic events in adult patients with ACS, defined as STEMI, NSTEMI or unstable angina. Patients with ACS who receive ticagrelor and aspirin may receive drugs only (medical management) or may also undergo revascularisation with PCI or CABG.

2.2 According to the SPC, treatment should be initiated with a loading dose of 180 mg ticagrelor (2 tablets of 90 mg) and then continued at 90 mg twice a day for up to 12 months. Patients taking ticagrelor should also take low-dose aspirin daily, unless specifically contraindicated. Following an initial loading dose of aspirin, the maintenance dose is 75 to 150 mg per day.

2.3 Ticagrelor is contraindicated in patients with active pathological bleeding, a history of intracranial haemorrhage, or moderate-to-severe hepatic impairment. Co-administration of ticagrelor with a strong CYP3A4 inhibitor (for example, ketoconazole, clarithromycin, nefazodone, ritonavir, or atazanavir) is also contraindicated. The most commonly reported adverse reactions to treatment with ticagrelor include dyspnoea, epistaxis, gastrointestinal haemorrhage, subcutaneous or dermal bleeding, and bruising. For full details of adverse effects and contraindications, see the SPC.

2.4 The manufacturer stated in its submission that the cost of 90 mg tablets of ticagrelor is £54.60 for a pack of 56 tablets (28 days). Costs may vary in different settings because of procurement discounts.

3 The manufacturer's submission

The Appraisal Committee considered evidence submitted by the manufacturer of ticagrelor and a review of this submission by the Evidence Review Group (ERG). This evidence related to the clinical and cost effectiveness of ticagrelor plus aspirin.

Clinical effectiveness

3.1 For the comparison of ticagrelor plus aspirin with clopidogrel plus aspirin, the manufacturer identified 1 trial, the PLATO trial, an international, multicentre, randomised, double-blind, double-dummy, parallel group, phase 3 study. The trial evaluated the efficacy and safety of ticagrelor plus aspirin compared with clopidogrel plus aspirin over 12 months in people with ACS whose symptoms began up to 24 hours before their admission to hospital. In the trial, 18,624 adult patients with ACS with or without ST-segment elevation on electrocardiogram from 43 countries including 18 UK centres (n=281) were admitted to hospital, and randomised to either ticagrelor plus aspirin (n=9,333) or clopidogrel plus aspirin (n=9,291). In the ticagrelor group, patients received a loading dose of 180 mg of ticagrelor, then 90 mg twice a day. Patients randomised to clopidogrel received loading doses of 300 to 600 mg of clopidogrel, then 75 mg every day thereafter. Patients did not need loading doses of clopidogrel if they had taken clopidogrel before admission or had received clopidogrel after admission but before randomisation (median approximately 5 hours). In the time between admission and randomisation, 46% of patients in both the ticagrelor and clopidogrel groups received clopidogrel. All patients also received aspirin (in addition to ticagrelor or clopidogrel) with a loading dose of 325 mg, then 75 to 100 mg daily. Patients already taking aspirin did not need a loading dose of aspirin.

3.2 The primary end point was time to first event (a composite of myocardial infarction, stroke or death from vascular causes). The planned duration of treatment and follow-up was 12 months. If before this time 1,780 individuals had a primary end point event, then patients who had not yet been followed for 12 months would finish the study at their 6 or 9-month visit. At the end of the trial, 1,878 participants had experienced events, and the median duration of treatment was 9.1 months. Secondary end points included: myocardial infarction;

stroke; death from vascular causes; death from any cause; a composite of myocardial infarction, stroke and death from any cause; and a composite of myocardial infarction, stroke, severe recurrent cardiac ischaemia, recurrent cardiac ischaemia, transient ischaemic attack, other arterial thrombotic events and death from vascular causes.

3.3 The results showed that the relative risk of experiencing a primary end point event was 16% lower in the ticagrelor group compared with the clopidogrel group (hazard ratio [HR] 0.84; 95% confidence interval [CI] 0.77 to 0.92; p<0.001). Of the components of the primary end point, randomisation to ticagrelor plus aspirin reduced the incidence of myocardial infarction (HR 0.84; 95% 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), but not of stroke (HR 1.17; 95% CI 0.91 to 1.52). Randomisation to ticagrelor plus aspirin reduced the absolute risk of experiencing the primary end point from 11.7% to 9.8% at 12 months (absolute risk reduction 1.9%) compared with clopidogrel plus aspirin.

3.4 The manufacturer explored the consistency of effects and safety end points in 25 pre-specified subgroups and 8 post-hoc subgroups. An analysis was conducted of the primary end point in several predefined subgroups. The manufacturer's submission stated that analyses showed statistically significant differences in treatment efficacy in 3 groups: geographic region; body weight above or below a gender-specific median; and use of lipid-lowering drugs at randomisation. The HRs by type of ACS at presentation – unstable angina, NSTEMI and STEMI – were 0.96 (95% CI 0.75 to 1.22), 0.83 (95% CI 0.73 to 0.94) and 0.84 (95% CI 0.72 to 0.98) respectively with a non-statistically significant test for interaction (p=0.41). The manufacturer presented 6 analyses in subgroups that included patients whose condition was managed invasively, managed medically, patients with STEMI, patients with diabetes, patients with genetic polymorphisms, and patients undergoing CABG. The results of these 6 subgroup analyses were generally consistent with the primary analysis.

3.5 The manufacturer reported adverse events from the PLATO study, specifically bleeding, dyspnoea and ventricular pauses. There was no statistically significant difference in the primary safety end point of 'major' bleeding between the ticagrelor plus aspirin and clopidogrel plus aspirin groups (11.6% versus 11.2% respectively; p=0.43), or in the end point of bleeding defined by the Thrombolysis

in Myocardial Infarction (TIMI) scale. Both were analysed according to which treatment a patient took, rather than to which a patient had been randomised; these findings were consistent across all major subgroups. Patients randomised to ticagrelor experienced more overall major and minor bleeding (HR 1.11; 95% CI 1.03 to 1.20; p=0.008) as well as more major bleeding not related to CABG (HR 1.19; 95% CI 1.02 to 1.38; p=0.03). Intracranial bleeding was more common in the ticagrelor plus aspirin group than in the clopidogrel plus aspirin group, with fatal intracranial bleeding statistically significantly more common in the ticagrelor plus aspirin group (HR not reported; p=0.02). Fatal bleeding excluding intracranial bleeding was statistically significantly more common in the clopidogrel plus aspirin group (HR not reported; p=0.03). There was no difference between the 2 groups in relation to overall fatal bleeding (0.3% in each group). Patients randomised to ticagrelor experienced dyspnoea statistically significantly more often than patients taking clopidogrel (13.8% versus 7.8% respectively; p<0.001). More patients taking ticagrelor plus aspirin discontinued treatment because of dyspnoea than patients taking clopidogrel plus aspirin (0.9% versus 0.1% respectively; p<0.001). Holter monitoring detected more ventricular pauses of 3 seconds or longer during the first week in the ticagrelor plus aspirin group than in the clopidogrel plus aspirin group, but these occurred infrequently at 30 days of treatment and were rarely associated with symptoms. Patients treated with ticagrelor had statistically significantly greater increases from baseline in levels of serum uric acid and serum creatinine compared with those on clopidogrel (p<0.001 for both events throughout the study).

3.6 The manufacturer identified no trials directly comparing ticagrelor plus aspirin with prasugrel plus aspirin. Instead, the manufacturer identified 2 trials comparing prasugrel plus aspirin with clopidogrel plus aspirin that provided data for an indirect comparison: the PLATO trial (ticagrelor plus aspirin compared with clopidogrel plus aspirin) and TRITON-TIMI 38, which compared prasugrel plus aspirin with clopidogrel plus aspirin in patients (n=13,608) with ACS and scheduled PCI. The manufacturer took the view that the trials were not comparable and, by inference, a comparison between prasugrel and ticagrelor based on these trials was inappropriate and should be viewed with caution. The manufacturer noted that the PLATO and TRITON-TIMI 38 trials were similar in many ways, both including populations with ACS, both comparing the intervention plus aspirin to clopidogrel plus aspirin, and both sharing the same primary end point. However, there were important differences in the use of PCI

and medical management, in the size and timing of the loading dose of clopidogrel, and in assessing myocardial infarction. Although the manufacturer considered the indirect comparison inappropriate, it cited a published paper based on the PLATO and TRITON-TIMI 38 trials that showed no statistically significant differences in the occurrence of myocardial infarction, stroke, death from any cause or the composite of these outcomes between the 2 drugs. Ticagrelor plus aspirin was associated with a statistically significantly lower risk of major bleeding and major bleeding specifically associated with bypass grafting than prasugrel plus aspirin. The risk of major bleeding not related to CABG did not differ between patients taking prasugrel and those taking ticagrelor.

3.7 The PLATO trial included a pre-specified sub-study of health economics and quality of life that evaluated the health-related quality of life for ticagrelor plus aspirin compared with clopidogrel plus aspirin. Investigators administered the EuroQual 5D (EQ-5D) questionnaire to 8,840 patients at discharge from hospital for the index ACS event, again at 6 months, and at the end of treatment in all countries where a version of EQ-5D in the country's official language was available. No differences in any of the items on the EQ-5D were found between the ticagrelor plus aspirin group and the clopidogrel plus aspirin group.

Cost effectiveness

3.8 The manufacturer did not identify any publications that evaluated the cost effectiveness of ticagrelor for the treatment of ACS. The manufacturer developed a new economic model, informed by 9 existing economic evaluations. For the health economics evaluation of ticagrelor plus aspirin compared with prasugrel plus aspirin, the manufacturer presented the results of a published indirect comparison of the TRITON-TIMI 38 trial and the PLATO trial, conducted by an independent group.

3.9 The manufacturer constructed a 2-part cost–utility model with a 1-year decision tree to model effectiveness based on data from the PLATO study, and a Markov model to extrapolate costs and benefits to a lifetime horizon (40 years), and to incorporate major clinical events. Patients in the model had ACS (STEMI, NSTEMI or unstable angina) and included patients whose condition was managed medically or with PCI or CABG; the model therefore reflected the marketing

authorisation for ticagrelor. The model compared ticagrelor plus aspirin with clopidogrel plus aspirin.

3.10 The 1-year decision tree contained 4 mutually exclusive health states: non-fatal myocardial infarction, non-fatal stroke, death from any cause, and no further event. The Markov model included 6 states: non-fatal myocardial infarction, post-myocardial infarction, non-fatal stroke, post-stroke, death, and no further event. Non-fatal myocardial infarction and non-fatal stroke were tunnel states, which allowed for a worse prognosis the first year after a non-fatal event compared with second and subsequent years. After the first year following a non-fatal event, patients proceeded to 1 of 4 mutually exclusive health states: post-myocardial infarction, post-stroke, death or no further event. Costs and health outcomes were discounted at 3.5%. The Markov model used a half-cycle correction to adjust for simulated costs and outcomes. The model did not permit a patient to discontinue treatment for any reason other than death.

3.11 In the model, costs, life years, and quality-adjusted life years (QALYs) accrued beyond the first year of treatment with ticagrelor or clopidogrel; however, the model assumed that the beneficial effect of ticagrelor does not persist beyond 1 year. This means that the transition probabilities between states in the Markov model were the same for both treatment arms; the only difference between treatment arms was the number of patients who started the Markov model in each state, which was based on the output of the 1-year decision tree. Adverse events (notably bleeding) were not included in the structure of the model, but the increased costs and decreased health-related quality of life associated with adverse events recorded in PLATO (as part of PLATO-HECON) were included in the first year (decision tree) of the model. The manufacturer assumed that adverse events including bleeding and dyspnoea have no lasting effects beyond the 12-month duration of the trial. To model the incidence of cardiovascular complications beyond 1 year (in the Markov component of the model), the manufacturer assumed a constant probability of 3.15% per year for non-fatal myocardial infarction and 1.02% per year for non-fatal stroke. The risk of death from MI after the index event (STEMI, NSTEMI or unstable angina) was assumed to be the same as that of death at least 1 year after the index ACS event.

3.12 For the 1-year decision tree, the manufacturer used a parametric time-to-event survival model with a Weibull distribution to determine the baseline risk (that is,

the risk of cardiovascular events and death in the clopidogrel group). The manufacturer then applied HRs reflective of the effectiveness of ticagrelor from the PLATO study to this baseline risk to determine the risk in patients taking ticagrelor. Using data in the 1-year decision tree derived from the PLATO study, the manufacturer estimated from patients in the clopidogrel group age-adjusted event rates (myocardial infarction, stroke, death from any cause and death from vascular causes) for a UK population with ACS (mean age of PLATO patients, 62.2 years; reported age of UK patients with ACS in 2009 to 2010, 69.7 years). In the Markov model, the transition probabilities from the no event health state to each of the non-fatal myocardial infarction or non-fatal stroke health states were estimated from a study that the manufacturer commissioned from the Myocardial Ischaemia National Audit Project and the General Practice Research Database. The probabilities of transitioning between all other health states were based on relative risks applied to the probability of death in standard life tables.

3.13 The manufacturer used the 12-month cohort (patients who were eligible for a 12-month follow-up) in the PLATO-HECON study to calculate the utility accrued in the study and reported it as the average utility value for a patient over the 12-month period using the EQ-5D. The manufacturer performed a literature search to assess the relationship between utility values in the PLATO study and in the literature. The lower values from the literature were used in sensitivity analyses. The utility scores from both the PLATO-HECON substudy and the literature were adjusted downwards by 0.0328 to better reflect the patient population that would be treated in UK clinical practice. In addition, because utility decreases with age, the manufacturer applied a utility decrement of 0.004 in the Markov model to each cycle beyond the first year.

3.14 The costs for the generic drugs clopidogrel and aspirin were taken from the NHS Drug Tariff, November 2010. The cost of the drugs used in the economic evaluation were: aspirin 28-pack, £0.82; clopidogrel 30-pack, £3.40; and ticagrelor 28-pack, £54.60. The PLATO-HECON substudy measured resource use and determined costs for all patients participating in the PLATO study by recording admissions to hospital, interventions, investigations, blood products, re-operations due to bleeding, and use of concomitant or study drugs to estimate total healthcare costs associated with ticagrelor and clopidogrel. Resource use included costs from randomisation to the time of discharge from hospital, as well as after discharge from hospital to the end of the PLATO study. The manufacturer

also included in sensitivity analyses the costs of a visit to the GP and of a blood test to check renal function, as stipulated in the SPC for ticagrelor.

3.15 In its deterministic base case (40-year time horizon), the manufacturer's model estimated that ticagrelor provides an incremental health gain of 0.108 QALYs compared with clopidogrel, at an incremental cost of £379, resulting in an incremental cost-effectiveness ratio (ICER) of £3,521 per QALY gained. The manufacturer also presented results using time horizons of 1 year, 5 years, 10 years and 20 years: the ICER differed substantially from the base-case ICER only when using the 1-year time horizon, with an ICER of £33,764 per QALY gained. The manufacturer also presented base-case ICERs for the subgroups of ACS specified in the scope, which were £2,551 per QALY gained for STEMI, £5,217 per QALY gained for NSTEMI and £5,310 per QALY gained for unstable angina.

3.16 The manufacturer carried out deterministic sensitivity analyses to the base case and showed the effects of changing 43 model parameters. Only the change to the costs of the 'no further event' health state impacted substantially on the results. When the cost of the 'no further event' health state for ticagrelor plus aspirin was set to its lowest, ticagrelor plus aspirin dominated clopidogrel plus aspirin (that is, ticagrelor plus aspirin was more effective and less expensive than clopidogrel plus aspirin), whereas when the cost of the clopidogrel plus aspirin 'no further 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 £7,620.

3.17 The manufacturer ran scenario analyses for 0% and 6% discount rates, using published rather than PLATO-derived utility values, removing the 0.0328 downwards utility adjustment and removing the age-related decrease in utility per cycle. The results of the scenario analyses showed that the ICER for ticagrelor plus aspirin compared with clopidogrel plus aspirin ranged from £2,358 to £4,699 per QALY gained.

3.18 The cost-effectiveness acceptability curve showed that at £5,000 per QALY gained, the probability of ticagrelor plus aspirin being cost effective compared with clopidogrel plus aspirin was 76.6%. At £20,000 per QALY gained, the probability of ticagrelor plus aspirin being cost effective compared with

clopidogrel plus aspirin was 99.9%.

3.19 The manufacturer's submission also provided results for ticagrelor plus aspirin compared with prasugrel plus aspirin for the subgroup receiving PCI, based on the results of a published indirect comparison of the PLATO and TRITON-TIMI 38 trials. Because of the small proportion of patients who participated in the TRITON-TIMI 38 substudy of quality of life (EQ-5D was collected in only 461 of 13,608 patients at baseline), the model incorporated utility information from the literature, rather than from the substudy. If costs from the PLATO-HECON substudy were not available, the manufacturer used NHS reference costs in the analysis for prasugrel plus aspirin. The manufacturer obtained the cost of prasugrel from MIMS, October 2010. The analysis of ticagrelor plus aspirin compared with prasugrel plus aspirin resulted in an incremental cost of £227, incremental QALYs of 0.065 and an ICER of £3,482 per QALY gained, with a 40-year time horizon. The manufacturer stated that the results of the indirect comparison should be viewed with caution because of the problems associated with the indirect comparison of ticagrelor plus aspirin with prasugrel plus aspirin discussed in section 3.6.

ERG comments

3.20 The ERG conducted a literature search and agreed that the PLATO trial was the only trial relevant to the decision problem. The ERG considered that the PLATO trial was well designed with robust processes for randomisation and blinding. It noted that compliance and deviations in protocol were similar across treatment arms. Although only 281 patients in the PLATO trial were from centres in the UK, the ERG considered that they were not dissimilar to other European participants. The ERG also noted that participants in the PLATO trial were younger than patients with ACS in England and Wales, but that the manufacturer's model accounted for this difference.

3.21 The ERG noted that for patients with STEMI not undergoing PCI, NICE recommends dual antiplatelet therapy (clopidogrel plus aspirin) for at least 4 weeks (from NICE's previous guideline on MI: secondary prevention, now replaced by NICE's guideline on myocardial infarction: cardiac rehabilitation and prevention of further cardiovascular disease). From statements in the 'clinical

need and practice' and 'evidence and interpretation' sections of NICE's technology appraisal guidance on drug-eluting stents for the treatment of coronary artery disease, the ERG concluded that standard practice for STEMI should include dual antiplatelet therapy for 3 months for patients undergoing revascularisation with bare-metal stents and 12 months for patients undergoing revascularisation with drug-eluting stents.

3.22 The ERG considered that the PLATO trial reflects current clinical practice and that all patients received antiplatelet treatment at a clinically appropriate dose. The ERG was satisfied with the manufacturer's means of categorising adverse events from bleeding. The ERG expressed concerns about the components of the primary efficacy end point in the PLATO trial. Firstly, the primary end point was inconsistent with the concept that all components of an end point should be of similar importance to patients. For example, the average utility values from the 12-month cohort in the PLATO-HECON study used in the manufacturer's model differed by end point and were 0.246 for death from a vascular cause, 0.812 for myocardial infarction and 0.736 for stroke. Secondly, the primary end point was inconsistent with the concept that all components of an end point occur with similar frequencies. For example, in 18,624 participants there were 795 vascular deaths, 1,097 myocardial infarctions and 231 strokes during the median 9.1-month follow-up in the PLATO study. Thirdly, the primary end point was inconsistent with the concept that the effect of a treatment should have an effect of similar magnitude and direction on all components of a primary end point. For example, in the PLATO study, the HR for stroke (non-significantly higher with ticagrelor) differed from those for myocardial infarction and death from vascular causes (significantly lower with ticagrelor). The ERG concluded that the results of the overall composite end point should be interpreted cautiously. The ERG also noted that the manufacturer excluded 'silent' myocardial infarctions (defined as new or presumed pathological Q waves on ECG in the absence of symptoms). The ERG considered that the secondary end points and their components reflected those used in other cardiovascular trials.

3.23 The ERG noted that the manufacturer tested whether the effectiveness and safety of ticagrelor plus aspirin compared with clopidogrel plus aspirin differed across 25 pre-specified and 8 post-hoc subgroups, without adjustment for multiple comparisons. The ERG expressed concern about the large number of subgroups and potential overemphasis of any statistically significant results from

these analyses, which might have occurred by chance alone. With these caveats noted, the ERG observed that the regional analysis showed that in the USA, patients randomised to ticagrelor plus aspirin did worse than those randomised to clopidogrel plus aspirin.

3.24 For patients with STEMI who receive bare-metal stents, the ERG highlighted concerns about the comparator treatment included in the economic evaluation. It interpreted NICE's technology appraisal guidance on drug-eluting stents for the treatment of coronary artery disease as stating that dual antiplatelet therapy for 3 months was standard practice for patients undergoing revascularisation with bare-metal stents, whereas for patients undergoing revascularisation with drug-eluting stents, NICE's previous guideline on MI: secondary prevention (now replaced by NICE's guideline on myocardial infarction: cardiac rehabilitation and prevention of further cardiovascular disease) recommends dual antiplatelet therapy for 12 months. Another concern of the ERG was that the manufacturer treated the STEMI group as a homogeneous population and estimated a single ICER. By contrast, the ERG believed that STEMI has 4 distinct populations differing by treatment: STEMI with medical management, STEMI revascularised with drug-eluting stent, STEMI revascularised with bare-metal stent and STEMI with other intervention (for example, CABG).

3.25 The ERG stated that as the trial was designed to test the efficacy of 12 months of treatment, all patients should have been treated for 12 months. The ERG noted that the PLATO trial design did not involve uniform duration of treatment, instead, the protocol stipulated that patients could leave the study at their 6- or 9-month visit if a predetermined number of primary end-point events had occurred by that time. Approximately 44% of patients were followed up for 12 months in the trial. This increased the uncertainty in the estimates of effectiveness at the conclusion of the trial, which in turn was the prime driver of the Markov model and, therefore, the long-term benefits for patients.

3.26 The ERG noted that the model featured 2 separate paths. In 1 path, after first presentation with ACS, patients may have a subsequent non-fatal myocardial infarction at any time during the decision-tree part of the model and remain in the non-fatal myocardial infarction health state to the end of the decision-tree part of the model, then progress to the 'post-myocardial infarction' state for all remaining cycles until death (whether from cardiovascular or non-cardiovascular causes).

Similarly, patients may instead have a non-fatal stroke as their first event (after the initial presentation with ACS) during a cycle, and then progress to the post-stroke state until death. The ERG considered that this structure does not represent reality, because it does not allow patients to have more than 1 myocardial infarction, more than 1 stroke, or both myocardial infarctions and strokes in their lifetime following their initial presentation with ACS, and that this may bias future costs and benefits. The ERG also noted that the model simplified the natural history of treated cardiovascular disease by keeping constant the transition probability of previously event-free patients (since initial treatment for ACS) experiencing a non-fatal myocardial infarction or stroke throughout the long-term Markov model. The modelling ignored the increase in risk associated with other factors, notably, increasing age. The ERG considered that this omission may have led to the manufacturer's model inaccurately estimating future events, costs and progressive changes in the outcomes and quality of life of patients.

3.27 The ERG was concerned that the model applied an average utility score for the first year, whereas clinical experience showed that ACS patients experience an initial decline in utility that steadily improves. Therefore, the ERG noted that the ICER at 12 months may be an underestimate.

3.28 The ERG noted that in the manufacturer's submission the subgroups of interest in the economic evaluation did not reflect the subgroups of interest in the clinical section. The ERG could not verify the estimates of clinical effectiveness used in the manufacturer's model ascribed to ticagrelor in patients with NSTEMI or unstable angina. The ERG also noted that the manufacturer considered the subgroup with unstable angina as a homogeneous group whereas, in clinical practice in England and Wales, physicians typically categorise patients into lowest, low, intermediate, high and highest risk groups using the Global Registry of Acute Coronary Events (GRACE) classification and treat them accordingly.

3.29 The ERG noted that the manufacturer adjusted the age of the modelled patients to reflect the UK population with ACS. The ERG noted potential problems with the methods chosen by the manufacturer, which may have led to inaccuracies. The ERG established that these inaccuracies represented an 8% underestimate of benefits from ticagrelor plus aspirin compared with clopidogrel plus aspirin and suggested that the ICER presented by the manufacturer may be an overestimate.

3.30 The ERG acknowledged that use of healthcare resources was estimated in the model using data from an imbedded health economic study, which collected details of hospital care received by patients during the PLATO trial. For the purposes of the model, only data for those patients in the 12-month cohort were included. This cohort comprised of patients who, based on timing of enrolment, had the potential to receive 12 months treatment with ticagrelor. The ERG also noted that for each patient category in the model, the resources used by each patient were calculated separately for each treatment arm, and these were multiplied by a corresponding unit cost and totalled for an estimated hospital-care cost per patient for the first 12-month period. The ERG had some concerns relating to this type of resource analysis, and conducted a combined analysis of resource use (taking the ticagrelor and clopidogrel groups together), making some adjustments for double-counting of costs. Results suggested that the health state costs with ticagrelor were £100 lower (rather than £371 lower, as in the manufacturer's base-case) than the health state costs of clopidogrel, which would have the effect of doubling the estimated ICER at the 1-year time horizon.

3.31 The ERG noted that the manufacturer's base-case analysis estimated costs for the study drugs assuming 100% use in the trial period, despite evidence of deaths before the end of follow-up, treatment withdrawals, and poor adherence in some participants. The ERG instead incorporated data on drug use from the PLATO trial and noted that this reduced the average cost of both ticagrelor and clopidogrel substantially, and the difference in drug costs of ticagrelor plus aspirin compared with clopidogrel plus aspirin reduced from £651 to £507 per patient. Applying 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 manufacturer's ICER for the 1-year time horizon from £36,177 to £51,204 per QALY gained. However, the ERG emphasised that both the incremental costs and additional benefits associated with ticagrelor plus aspirin compared with clopidogrel plus aspirin were very small at longer time horizons, and subject to considerable uncertainty.

3.32 The ERG conducted a wide-ranging sensitivity analysis, calculating overall deterministic cost-effectiveness estimates for all combinations of 4 long-term variables – survival gain at 12 months, life expectancy at 12 months, the mean long-term utility value and the mean long-term discounted cost per patient year. The most favourable ICERs for ticagrelor plus aspirin are £3,407 per QALY gained

for all patients, £3,551 per QALY gained for the STEMI group, £3,350 per QALY gained for the NSTEMI group and £3,405 per QALY gained for the group with unstable angina. Incorporating the least favourable combination of assumptions resulted in an estimated ICER for ticagrelor plus aspirin below £20,000 per QALY gained for each of the specified populations compared with 12 months' clopidogrel plus aspirin treatment. The central estimates from these sensitivity analyses were £7,897 per QALY gained for all patients, £8,872 per QALY gained for the STEMI group, £7,215 per QALY gained for the NSTEMI group and £9,131 for the subgroup with unstable angina.

3.33 The ERG noted that there are no head-to-head trial data comparing ticagrelor plus aspirin with prasugrel plus aspirin. With regard to the indirect comparison of ticagrelor plus aspirin with prasugrel plus aspirin, the ERG considered that any comparison of the PLATO and TRITON-TIMI 38 trials posed problems. The ERG agreed with the manufacturer that sufficient clinical evidence is not yet available for a credible indirect comparison of ticagrelor plus aspirin compared with prasugrel plus aspirin for patients with ACS. It concluded that the effectiveness and safety of ticagrelor compared with prasugrel remains unknown.

3.34 Full details of all the evidence are in the manufacturer's submission and the ERG report.

4 Consideration of the evidence

4.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of ticagrelor, having considered evidence on the nature of ACS and the value placed on the benefits of ticagrelor by people with these conditions, those who represent them, and clinical specialists. It also took into account the effective use of NHS resources.

4.2 The Committee discussed the clinical management of ACS. It heard from the clinical specialists that, in the UK, treatment options for people with STEMI are prasugrel plus aspirin or clopidogrel plus aspirin, along with PCI with a bare-metal or drug-eluting stent followed by dual antiplatelet treatment. The Committee heard that the duration of treatment of clopidogrel does not vary whether a stent is bare-metal or drug-eluting, because all people with ACS who undergo PCI, in the acute setting, are treated with clopidogrel plus aspirin for 12 months. The Committee heard that in UK clinical practice people with NSTEMI are offered treatments depending on their GRACE or TIMI score; medical management is an option for people at lowest risk of future adverse cardiovascular events, whereas people at higher risk would be offered PCI and subsequent dual antiplatelet therapy with clopidogrel and aspirin. The Committee heard from the clinical specialists that in the UK most people with NSTEMI undergo PCI. The Committee understood that of people in the UK with ACS, few have unstable angina and often do not need revascularisation, but do receive dual antiplatelet therapy with clopidogrel and aspirin. The clinical specialists stated that in the UK it is unusual for a patient with STEMI to undergo CABG and that approximately 10% of patients with NSTEMI undergo CABG.

Clinical effectiveness

4.3 The Committee considered the evidence for the clinical effectiveness of ticagrelor compared with clopidogrel. The Committee noted that the manufacturer based its submission on a large trial, PLATO, which compared ticagrelor plus aspirin with clopidogrel plus aspirin. The Committee noted that ticagrelor plus aspirin reduced the relative risk of myocardial infarction, stroke

and death from vascular causes by 16% compared with clopidogrel plus aspirin. The Committee also noted that if the components of the primary end point were considered individually, the reductions in myocardial infarction and death from vascular causes were statistically significant (16% and 21% respectively) for patients randomised to the ticagrelor plus aspirin group. The Committee also noted the non-statistically significant increase in the incidence of stroke, in particular haemorrhagic stroke, in patients randomised to the ticagrelor group. The Committee considered the clinical evidence for ticagrelor plus aspirin compared with clopidogrel plus aspirin in the subgroups of patients that were specified in the scope (STEMI, NSTEMI and unstable angina) and noted that the test for interaction showed no statistical difference between the groups (p=0.41), interpreting this as no difference in the effectiveness between treatments by clinical presentation of ACS. The Committee noted that the manufacturer had performed a large substudy of quality of life based on EQ-5D scores, which indicated no difference in the quality of life between people taking ticagrelor plus aspirin and those taking clopidogrel plus aspirin.

4.4 The Committee heard from the clinical specialists that in general the trial was representative of the population in the UK, although the trial had a younger population and a higher proportion of men than the population with ACS in the UK. The Committee understood that the manufacturer had accounted for age in its analysis. The Committee noted comments from consultees and commentators questioning the generalisability of the PLATO trial to UK clinical practice because most of the patients presenting with ACS in the UK would receive medical therapy only whereas 21% of patients in the PLATO trial received medical therapy only. However, the Committee noted the clinical specialists' testimonies that most STEMI and NSTEMI patients would receive PCI. The Committee was also aware that results of the PLATO study showed no statistically significant difference in effectiveness between the patients whose condition was managed medically or otherwise. The Committee concluded that the trial was broadly reflective of clinical practice in the UK.

4.5 The Committee was aware that nearly half (46%) of all patients in the study received clopidogrel in hospital before randomisation, and that of those randomised to clopidogrel, only approximately one-fifth received a loading dose in the range (600 to 675 mg) recommended in the UK (600 mg). The Committee also noted that not all patients in the PLATO trial received treatment for

12 months and that the median duration of treatment was 9 months. The Committee heard that the results presented included those censored before 12 months. The Committee noted that the Kaplan–Meier curves depicting the 2 arms of the trial separated as early as 1 month and up to 1 year and, therefore, concluded that neither the difference in loading doses of clopidogrel nor censoring was likely to have substantially biased the results.

4.6 The Committee understood that ticagrelor is administered twice a day compared with once a day with clopidogrel and heard from the patient experts that, in practice, people may be less likely to take drugs twice a day. The Committee noted that no clear differences had been established on adherence between once-a-day clopidogrel and twice-a-day ticagrelor. The Committee noted comments from consultees and commentators that, particularly with a gastrointestinal bleed, the fast offset (time taken for ticagrelor to become inactive after it is stopped) could put a patient at increased risk of myocardial infarction and stroke more quickly than had the patient been taking clopidogrel, and with insufficient time to consult a cardiologist. However, the Committee heard from the manufacturer that missing a dose of ticagrelor would not result in a lower level of platelet activation than if the patient were treated with clopidogrel without missing a dose. The Committee heard that when a CABG is planned, the marketing authorisation recommends stopping ticagrelor 7 days before the procedure, suggesting that the offset is not as fast as had been suggested in the consultation comments. The Committee also noted comments from consultees and commentators that treatment with ticagrelor should be limited to people who clinicians have counselled on the importance of adherence. The Committee heard from the clinical specialists that people taking clopidogrel or ticagrelor would usually receive information to ensure that they understand why adherence is important and why stopping treatment early might increase the risk of recurrent cardiovascular disease. Therefore, the Committee agreed that advice on adherence should not explicitly be factored into the recommendations. Lastly, the Committee noted that most patients with cardiovascular disease take drugs twice a day, including statins in the evening. The Committee concluded that in the 'real world' setting, the need to take medication twice a day rather than once a day would be unlikely to substantially reduce the effectiveness of ticagrelor plus aspirin relative to clopidogrel plus aspirin.

4.7 The Committee discussed the concerns about safety and adverse effects

associated with ticagrelor. The Committee heard that dyspnoea (shortness of breath), ventricular pauses, increases in serum uric acid and increases in serum creatinine from baseline were statistically significantly more common in the ticagrelor group compared with the clopidogrel group, and noted that patients randomised to ticagrelor were more likely to discontinue the study drug because of adverse reactions. The Committee heard from the patient experts that dyspnoea frustrated patients with ACS and the clinical specialists stated that a patient randomised to ticagrelor was 9 times as likely to discontinue the study because of dyspnoea as a patient randomised to clopidogrel, but that the absolute risk, at less than 1%, was small. The Committee heard from the manufacturer that the effects of dyspnoea were limited mainly to mild episodes. The Committee noted no statistically significant difference in the primary safety end point of major bleeding between ticagrelor plus aspirin and clopidogrel plus aspirin but that patients on ticagrelor plus aspirin experienced more overall major and minor bleeding as well as more major bleeding not related to CABG. The Committee considered that the mortality benefit associated with ticagrelor outweighed the risks and concluded that ticagrelor was a clinically effective treatment option for people with ACS.

4.8 The Committee discussed whether ticagrelor plus aspirin would be more or less effective in any subgroups including patients with STEMI, NSTEMI or unstable angina. The Committee noted that several additional subgroups were presented in the trial. The Committee noted that among those defined in the scope (STEMI, NSTEMI, unstable angina) there was no statistically significant evidence of heterogeneity, consistent with no difference in effectiveness of ticagrelor compared with clopidogrel by clinical presentation of ACS. The Committee appreciated that the numbers of patients by subgroup may have been too small to detect a difference in effectiveness. The Committee heard from the manufacturer that it had not corrected for multiple comparisons when analysing the many subgroups. The Committee noted the comment from a consultee saying that patients with unstable angina are unlikely to benefit from ticagrelor because subgroup analysis shows benefit only for patients whose blood tests following the index event were positive for troponin. The Committee noted, however, that neither the test for interaction by clinical presentation of ACS nor the test for interaction by whether a patient had a positive or negative test for troponin were positive (p value for interaction 0.41 and 0.29 respectively). Lastly, no evidence of statistical or biological plausibility was presented to support effect modification

by presentation of ACS, and there are no trials using ticagrelor for the primary prevention of cardiovascular disease. Therefore, the Committee concluded that providing specific recommendations only for patients with STEMI and NSTEMI and excluding those with unstable angina would be speculative, would counter the statistical evidence, and would risk excluding patients who could benefit from treatment with ticagrelor.

4.9 The Committee was aware of comments from consultees and commentators that the estimate of total mortality remained 'exploratory'. This was because the analysis plan for PLATO stated that secondary end points should be tested individually in a pre-specified order, so mortality should not have been included because it followed the non-statistically significant result for stroke. The Committee was aware that the result for the association between ticagrelor and total mortality, while exploratory, had a HR of 0.78 and a 95% CI of 0.69 to 0.89, so was likely to reflect a real decrease in total mortality associated with ticagrelor plus aspirin.

4.10 The Committee noted the concerns around the indirect comparison of ticagrelor plus aspirin and prasugrel plus aspirin highlighted in the manufacturer's submission and reiterated by the ERG. The Committee concurred with this view and concluded that the relative effectiveness of ticagrelor plus aspirin and prasugrel plus aspirin was uncertain. The Committee concluded that no separate recommendations could be made for ticagrelor compared with prasugrel.

Cost effectiveness

4.11 The Committee considered the estimates of cost effectiveness presented in the manufacturer's submission and noted that all ICERs for ticagrelor were below £5,400 for the whole population in which ticagrelor is licensed and the subgroups. The Committee was aware of the concerns raised by the ERG around the structure of the model adopted in the manufacturer's submission, and agreed that the assumption that patients could not experience multiple cardiovascular events over-simplified the clinical course of patients with ACS. The Committee noted that if the model had included the possibility of more than 1 cardiovascular event after the index event, and had accounted for the increased risk of a cardiovascular event associated with having had prior events, then the ICERs for

ticagrelor compared with clopidogrel would be lower than in the manufacturer's base case. This is because at the end of the 1-year decision tree, more patients on clopidogrel than on ticagrelor had experienced a myocardial infarction or stroke, and were therefore at higher risk of experiencing another event. The Committee was aware of the ERG's concerns over the method used to adjust for age, but agreed that this would not result in major changes to the ICERs. The Committee also noted that it would have been more appropriate to incorporate a utility value that reflected clinical practice rather than modelling the average utility score, but acknowledged that this too was unlikely to have a large impact on the ICERs. The Committee noted comments from consultees that the adverse event profile should be fully built into the structure of the economic model. The Committee was aware that the 1-year decision tree part of the economic model took account of all costs and changes in quality of life associated with the adverse events of treatment.

4.12 The Committee was aware of the ERG's concerns about the manufacturer's method of estimating resource use and costs. It was aware that these limitations could skew the differences in total costs between the 2 treatment arms. The Committee accepted the ERG's adjustments to the manufacturer's model and noted the resulting estimates of cost effectiveness. The Committee agreed that the central ICERs from the ERG's sensitivity analysis (£7,897 per QALY gained for all ACS, £8,872 per QALY gained for STEMI, £7,215 per QALY gained for NSTEMI and £9,131 per QALY gained for unstable angina) represented the most plausible estimates for the cost effectiveness of ticagrelor compared with clopidogrel. The Committee noted that the ICERs produced with this analysis were within the range normally considered to be a cost-effective use of NHS resources and therefore ticagrelor plus low-dose aspirin should be recommended as a treatment option for up to 12 months in adults with ACS. However, the Committee agreed that the patient populations for STEMI and unstable angina needed to be further specified.

4.13 The Committee noted that the inclusion criteria in the PLATO trial for patients with STEMI, defined as ST elevation or new left bundle branch block on electrocardiogram, included the 'intention to perform primary PCI'. The Committee therefore agreed that only patients with STEMI that cardiologists intend to treat with primary PCI should be treated with ticagrelor. The Committee heard that there is a spectrum of severity with respect to unstable angina. The

Committee was aware that in clinical practice in the UK a diagnosis of unstable angina could be made using less stringent criteria than those defined in the PLATO trial. The Committee agreed that only patients with unstable angina aligned with the definition in the PLATO trial should be treated with ticagrelor. The Committee noted that the definition of unstable angina in the PLATO trial was that patients were hospitalised and had to have ST-segment changes on electrocardiography indicating ischemia, and that patients had at least 1 of the following characteristics: age 60 years or older; previous myocardial infarction or CABG; coronary artery disease with stenosis of 50% or more in at least 2 vessels; previous ischaemic stroke, transient ischaemic attack, carotid stenosis of at least 50%, or cerebral revascularisation; diabetes mellitus; peripheral arterial disease; or chronic renal dysfunction, defined as a creatinine clearance of less than 60 ml per minute per 1.73 m^2 of body-surface area. The Committee was aware that it may be necessary to start treatment with ticagrelor immediately when a patient presents with symptoms. However, the Committee was concerned that a wrong diagnosis of unstable angina could result in the patient unnecessarily taking ticagrelor. The Committee therefore agreed that it would be appropriate to specify that before ticagrelor is continued beyond the initial treatment, the diagnosis of unstable angina should first be confirmed, ideally by a cardiologist.

4.14 The Committee noted the comments from consultees and commentators about whether 'lowest risk' patients (that is, patients who have a 6-month mortality of 1.5% or less as defined by the GRACE scoring system) should receive ticagrelor, given that NICE's previous guideline on unstable angina and NSTEMI (now replaced by NICE's guideline on acute coronary syndromes) stipulates that these patients would not receive clopidogrel because the harms potentially outweigh the benefits. The Committee concluded that, because patients potentially suitable for treatment with ticagrelor with unstable angina must have at least 1 specific risk factor for myocardial infarction as well as ST-segment changes on electrocardiography, these patients would therefore not be classed as 'lowest risk'.

4.15 The Committee heard from the primary care trust expert that although treatment with ticagrelor relative to clopidogrel appeared cost effective within the range considered to represent good value for money by NICE, the high incidence of ACS in England and Wales means that ticagrelor would substantially impact budgets were it approved for use. The primary care trust expert noted that this

would invariably lead to reduced spending elsewhere for health, which would include cardiology services. The Committee noted further comments received from consultees that affordability was an issue that NHS commissioners needed to consider 'very seriously'. Although the Committee agreed that that budget impact would be substantial, it was possible that any services displaced might be less cost effective than ticagrelor relative to clopidogrel. Moreover, the Committee noted that NICE's guide to the methods of technology appraisal states that budget impact and affordability are not relevant to its decision making.

5 Implementation

5.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 3 months of its date of publication.

5.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final draft guidance.

5.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has acute coronary syndrome and the healthcare professional responsible for their care thinks that ticagrelor is the right treatment, it should be available for use, in line with NICE's recommendations.

6 Recommendations for further research

6.1 Clinical trials should be conducted comparing ticagrelor with prasugrel in people with ACS.

6.2 Further research into whether ticagrelor is particularly beneficial in any clinical or biological subgroups would be useful.

7 Appraisal Committee members and NICE project team

Appraisal Committee members

The Appraisal Committee is 1 of NICE's standing advisory committees. Its 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. The Appraisal Committee meets 3 times a month except in December, when there are no meetings. The Committee membership is split into 3 branches, each with a chair and vice chair. Each branch considers its own list of technologies, and ongoing topics are not moved between the branches.

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.

Dr Amanda Adler (Chair)
Consultant Physician, Addenbrooke's Hospital

Dr Ray Armstrong
Consultant Rheumatologist, Southampton General Hospital

Dr Jeff Aronson
Reader in Clinical Pharmacology, University Department of Primary Health Care, University of Oxford

Dr Peter Barry
Consultant in Paediatric Intensive Care, Leicester Royal Infirmary

Dr Michael Boscoe
Consultant Cardiothoracic Anaesthetist, Royal Brompton and Harefield NHS Foundation

Trust

Professor John Cairns
Professor of Health Economics Public Health and Policy, London School of Hygiene and Tropical Medicine

Dr Mark Chakravarty
External Relations Director, Pharmaceuticals and Personal Health, Oral Care Europe

Mr Mark Chapman
Health Economics and Market Access Manager, Medtronic UK

Professor Fergus Gleeson
Consultant Radiologist, Churchill Hospital, Oxford

Mrs Eleanor Grey
Lay member

Dr Neil Iosson
General Practitioner

Mr Terence Lewis
Lay Member

Dr Ruairidh Milne
Director of Strategy and Development and Director for Public Health Research at the NIHR Evaluation, Trials and Studies Coordinating Centre at the University of Southampton

Dr Rubin Minhas
General Practitioner and Clinical Director, BMJ Evidence Centre

Dr Peter Norrie
Principal Lecturer in Nursing, DeMontfort University

Dr Sanjeev Patel
Consultant Physician and Senior Lecturer in Rheumatology, St Helier University Hospital

Dr John Pounsford

Consultant Physician, Frenchay Hospital, Bristol

Dr Casey Quinn
Lecturer in Health Economics, Division of Primary Care, University of Nottingham

Dr John Rodriguez
Assistant Director of Public Health, NHS Eastern and Coastal Kent

Mr Navin Sewak
Primary Care Pharmacist, NHS Hammersmith and Fulham

Mr Roderick Smith
Finance Director, West Kent Primary Care Trust

Mr Cliff Snelling
Lay Member

Professor Ken Stein (Vice Chair)
Professor of Public Health, Peninsula Technology Assessment Group (PenTAG), University of Exeter

Professor Andrew Stevens
Professor of Public Health, Department of Public Health and Epidemiology, University of Birmingham

Dr Rod Taylor
Professor in Health Services Research, Peninsula Medical School, Universities of Exeter and Plymouth

Mr Tom Wilson
Director of Contracting and Performance, NHS Tameside and Glossop

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.

Raisa Sidhu
Technical Lead

Joanna Richardson
Technical Adviser

Jeremy Powell
Project Manager

8 Sources of evidence considered by the Committee

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

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

The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, the ERG report and the appraisal consultation document (ACD). Manufacturers or sponsors were also invited to make written submissions. Professional or specialist, patient or carer groups, and other consultees, had the opportunity to give their expert views. Manufacturers or sponsors and professional or specialist and patient or carer groups also have the opportunity to appeal against the final appraisal determination.

Manufacturers or sponsors:

- AstraZeneca

Professional or specialist, and patient or carer groups:

- Action Heart
- British Cardiovascular Intervention Society (BCIS)
- British Cardiovascular Society
- British Heart Foundation
- Heart Care Partnership (UK)
- HEART UK
- Royal College of Nursing
- Royal College of Physicians

- South Asian Health Foundation

Other consultees:

- Department of Health
- NHS Bradford and Airedale
- Oxfordshire PCT
- Welsh Assembly Government

Commentator organisations (did not provide written evidence and without the right of appeal):

- Bristol–Myers Squibb
- British National Formulary
- British Society for Cardiovascular Research
- Commissioning Support Appraisals Service
- Daiichi Sankyo
- Department of Health, Social Services and Public Safety for Northern Ireland
- Eli Lilly
- Healthcare Improvement Scotland
- Medicines and Healthcare products Regulatory Agency (MHRA)
- Sanofi–Aventis

The following individuals were selected from clinical specialist and patient expert nominations from the non-manufacturer or sponsor consultees and commentators. They gave their expert personal view on ticagrelor by attending the initial Committee discussion and providing written evidence to the Committee. They are invited to comment on the ACD.

- Nick Curzen, nominated by the Royal College of Physicians – clinical specialist
- Professor Anthony Gershlick, Consultant Cardiologist, University Hospitals of

Leicester, nominated by the Royal College of Physicians, Consultant Cardiologist, Southampton University Hospitals – clinical specialist

- Liz Clark, nominated by the Heart Care Partnership – patient expert
- John Miller, nominated by the Heart Care Partnership – patient expert

The following individuals were nominated as NHS Commissioning experts by the selected PCT allocated to this appraisal. They gave their expert and NHS commissioning personal view on ticagrelor by attending the initial Committee discussion and providing written evidence to the Committee. They are invited to comment on the ACD.

- Greg Fell, Consultant in Public Health, NHS Bradford and Airedale selected by NHS Bradford and Airedale – NHS Commissioning expert

Representatives from the following manufacturer or sponsor attended Committee Meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- AstraZeneca

Update information

February 2014: Implementation section updated to clarify that ticagrelor is recommended as an option for treating acute coronary syndromes.

ISBN: 978-1-4731-6689-9