NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Ticagrelor for the treatment of acute coronary syndromes

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the manufacturer or sponsor of the technology, national professional organisations, national patient organisations, the Department of Health and the Welsh Assembly Government and relevant NHS organisations in England. Consultee organisations are invited to submit evidence and/or statements and respond to consultations. They are also have right to appeal against the Final Appraisal Determination (FAD). Consultee organisations representing patients/carers and professionals can nominate clinical specialists and patient experts to present their personal views to the Appraisal Committee.

Clinical specialists and patient experts – Nominated specialists/experts have the opportunity to make comments on the ACD separately from the organisations that nominated them. They do not have the right of appeal against the FAD other than through the nominating organisation.

Commentators – Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement. They are invited to respond to consultations but, unlike consultees, they do not have the right of appeal against the FAD. These organisations include manufacturers of comparator technologies, NHS Quality Improvement Scotland, the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Information Authority and NHS Purchasing and Supplies Agency, and the *British National Formulary*).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but may be summarised by the Institute secretariat – for example when many letters, emails and web site comments are received and recurring themes can be identified.

Comments received from consultees

Consultee	Comment	Response
AstraZeneca	***Are the provisional recommendations sound and a suitable basis for guidance to the NHS?*** While the provisional recommendations provide a suitable basis for guidance to the NHS we would recommend that consideration is given to the following in order to provide further clarification: • Specifying that ticagrelor should be used in combination with low dose aspirin • Specifying the duration of treatment with ticagrelor as 12 months • Amending the recommendation for unstable angina to remove the requirement for diagnosis to be confirmed by a cardiologist <u>Low dose aspirin</u> In order to reflect the Summary of Product Characteristics we request that the recommendations specify that 'ticagrelor in combination with low dose aspirin is recommended as a treatment option'. <u>Duration of treatment</u> The current recommendations make no reference to the duration of treatment with ticagrelor. This may result in a variation in the duration of treatment, with some patients potentially receiving treatment for suboptimal periods and others for periods greater than 12 months, for which a benefit has not yet been established. Both the clinical and cost-effectiveness data submitted and discussed by the Appraisal Committee are based on a 12 month treatment duration with the data clearly demonstrating benefits of ticagrelor in terms of improved efficacy and cost-effectiveness when compared with clopidogrel. We would therefore recommend that in order to improve the current recommendations and ensure all patients receive treatment for the appropriate duration of time the following statement is added at the end of section 1.1: 'The recommended treatment duration for ticagrelor (in combination with low dose aspirin) for adults with ACS is 12 months'. <u>Unstable angina - Confirming diagnosis</u> The current recommendation for unstable angina specifies that 'after treatment is initiated it should only be continued if the diagnosis is confirmed by a cardiologist'. This does not reflect current clinical practice where diagnosis is confirmed by different clinicians according to local treatment protocols. Specifying a cardiologist will require a change to current treatment protocols and a change to clinical practice. It should	Comments noted. The recommendation now states 'Ticagrelor in combination with low-dose aspirin' in accordance with the Summary of Product Characteristics. The Summary of Product Characteristics states that "Treatment is recommended for up to 12 months unless discontinuation of Brilique is clinically indicated". NICE issues guidance in accordance with the marketing authorisation and the Committee considered that the recommendation must reflect the SPC. Therefore the recommendation now states that 'Ticagrelor in combination with low-dose aspirin is recommended for up to 12 months'. The Committee was aware

	also be noted that the requirement for a cardiologist to confirm diagnosis is not a requirement within NICE guideline for unstable angina and NSTEMI (CG94). In order to reflect current clinical practice and also avoid confusion with CG94 we would recommend that the current text is revised as follows with reference to a cardiologist removed 'After treatment is initiated it should only be continued if the diagnosis is confirmed ~~by a cardiologist~~'	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 for up to 12 months. The Committee therefore agreed that it would be appropriate to specify that before treatment is continued beyond the initial treatment, the diagnosis of unstable angina should first be confirmed, ideally by a cardiologist.
AstraZeneca	***Has all of the relevant evidence been taken into account?*** We can confirm that all relevant evidence has been taken into account.	Comment noted.
AstraZeneca	***Are the summaries of clinical and cost-effectiveness reasonable interpretations of the evidence?*** While the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence there are a number of areas which would benefit from additional clarification and we have highlighted these in the attached table. In addition there are two areas which are factually incorrect and require amending. The first of these relates to the last sentence in section 3.6 where ticagrelor and prasugrel have been transposed. The sentence should read: 'Ticagrelor ~~prasugrel~~ was associated with a significantly lower risk of any major bleeding and major bleeding associated with bypass surgery than prasugrel ~~ticagrelor~~' The second relates to section 3.30 where it states: 'The ERG acknowledged that the 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. However, it noted that these data were collected for only 57.4% of the trial population,	Comment noted Comment noted. Comment noted. This change is reflected in section 3.6 of the Final Appraisal Determination (FAD).

	and the manufacturer provided no information about how this subset was selected.' This statement is incorrect. Resource use was collected for all patients within the PLATO study; however, for the purposes of the model, only data for the 12 month cohort were used to estimate the one year costs. This ensured that the resource costs accurately reflected a 12-month treatment duration as per the time horizon of the short-term decision tree portion of the model. 'The ERG acknowledged that the 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. ~~However, it noted that these data were collected for only 57.4% of the trial population, and the manufacturer provided no information about how this subset was selected.~~ 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.	Comment noted. Section 3.30 of the FAD has been reworded to reflect this change.
AstraZeneca	***Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief?*** No ***Are there any equality related issues that need special consideration and are not covered in the appraisal consultation document?*** No	Comments noted.
AstraZeneca	Page 4, section 2.1: For clarification the final sentence in this section would benefit from the addition of 'medical management' e.g. 'Patients with acute coronary syndromes who receive ticagrelor and aspirin may receive drugs only (medical management) or may also undergo revascularisation with PCI or CABG'	Comment noted. This change has been incorporated in section 2.1 of the FAD.
AstraZeneca	Page 6, section 3.2: Again for clarification the final sentence would benefit from the addition of 'CABG' and 'invasive procedure' e.g. 'In the subgroup of patients for whom PCI and CABG (invasive procedure) was planned at randomisation, the first pre-specified end point was the same as the primary endpoint (that is, the composite of myocardial infarction, stroke and death from any cause)'	Comment noted. This sentence has been removed from the FAD.
AstraZeneca	Page 6, section 3.3: While section 3.2 refers to the secondary endpoints of the PLATO study with	Comment noted. This

	regards to study design details of the actual results are not presented in section 3.3. In order to inform the reader of these results and also reflect both the AstraZeneca submission and the ERG report we recommend the addition of the following text to the end of section 3.3: 'For the secondary endpoints ticagrelor reduced the incidence of MI (HR [95%CI] = 0.84 [0.75-0.95], p=0.005) and death from vascular causes (HR [95%CI] = 0.79 [0.69-0.91], p=0.001). There was no effect observed on the rate of stroke. An exploratory analysis of total mortality identified a lower incidence in the ticagrelor arm of the study. Death from any cause occurred with an event rate of 4.5% per year in the ticagrelor treatment group compared to 5.9% per year in the clopidogrel treatment group (HR [95%CI]) = 0.78 [0.69-0.89], nominal p<0.001)'.	suggestion has not been incorporated into the FAD as, given that the secondary endpoints are the components of the primary end point, this would be a repetition of section 3.3. Comment noted. This suggestion has not been incorporated into the FAD. The FAD contains the key clinical data from the source documents. The manufacturer's submission and ERG report in full are also in the public domain.
AstraZeneca	Page 7, section 3.5: The current sentence '*Patients randomised to ticagrelor experienced more bleeds (major or minor) not related to CABG (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'* is confusing and does not clearly distinguish between the rates of different bleeds. In order to clearly document the different types of bleeds we would recommend amending the current sentence as follows: '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).' For clarification in relation to fatal bleeding for the ticagrelor and clopidogrel groups we would recommend the addition of the following sentence: 'Fatal bleeding not attributed to intracranial bleeding was significantly higher in the clopidogrel group (HR not reported; p = 0.03). There was no difference between the two groups in relation to overall fatal bleeding (0.3% in each group).' Ticagrelor needs to be added to the following sentence: '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 these occurred infrequently at 30 days and were rarely associated with symptoms'.	Comment noted. This suggestion has been incorporated into the FAD in section 3.5. Comment noted. This suggestion has been incorporated into the FAD in section 3.5. Comment noted. This typing error has been rectified in the FAD in section 3.5.

AstraZeneca	Page 8, section 3.5: In order to accurately reflect the duration increases in serum uric acid and serum creatinine with ticagrelor compared with clopidogrel the following text should be added at the end of section 3.5: 'Patients randomised to ticagrelor had 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 but there was no difference between the two groups by 1 month following discontinuation of treatment.	Comment noted. This suggestion has not been incorporated into the FAD. The FAD contains the key clinical data from the source documents. The manufacturer's submission and ERG report in full are also in the public domain.
AstraZeneca	Page 8, section 3.6: Within the PLATO study investigators specified whether patients were to receive initial revascularisation – this should be reflected in the current text as follows: 'TRITON-TIMI 38 enrolled patients with ACS who were managed invasively with PCI, whereas in PLATO investigators prespecified whether patients were to receive initial revascularisation or medical therapy alone'	Comment noted. This change has not been incorporated in section 3.6 of the FAD as this section has been rewritten.
AstraZeneca	Page 9, section 3.6: Within section 3.6 no reference is made to the proportion of patients who underwent CABG in the TRITON and PLATO studies. In order to provide this information to the reader and accurately reflect the data we would recommend the addition of the following sentence at the end of section 3.6: 'The risk of major bleeding not related to bypass surgery did not differ between the prasugrel and ticagrelor groups. CABG accounted for only 3.2% in TRITON compared with 10.2% in PLATO'	Comment noted. This suggestion has not been incorporated into the FAD. The FAD contains the key clinical data from the source documents. The manufacturer's submission and ERG report in full are also in the public domain.
AstraZeneca	Page 20, section 4.2: In order to accurately reflect the Appraisal Committee discussions the following sentence should be amended as follows: 'The Committee heard that the dose of clopidogrel does not vary whether a bare-metal stent or drug-eluting stent is used, because all people with ACS undergoing PCI (in the acute setting) are treated with clopidogrel for 12 months'.	Comment noted. This change is reflected in section 4.2 of the FAD.
Department of Health	I wish to confirm that the Department of Health has no substantive comments to make regarding this consultation.	Comment noted.
Oxfordshire PCT	***Evidence of clinical and cost-effectiveness*** We are content that the PLATO study with its attendant sub assessments is the relevant trial and that no other evidence has been missed. We have also looked at the quoted costs for treatment which are put forward within the manufacturer's submission and they appear to be an accurate reflection of NHS costs	Comments noted.

	which accrue in ACS. We paid particular attention to the comparison of costs between clopidogrel and ticagrelor because of the considerable variation in the 12 month costs of the drugs (quoted as £42.16 and £713.70 respectively). The cost-effectiveness argument therefore relies upon the anticipated reduction in vascular events seen in the PLATO trial and, as far as we could tell this was accurate. We have concerns regarding the adverse event profile and its incorporation into the costs (page 14 of 292 in the manufacturer's submission dated 12th November 2010) taken from the trial. If the incidences of bleeding and dyspnoea in general use result in more referrals (as they could since trial patients will be more intensively monitored than in general practice) then the costs will be higher than in the trial. This would impact adversely upon the cost-effectiveness. However, we are unable to make an estimate of increased costs.	Comment noted. This concern was discussed by the Committee and section 4.11 of the FAD has been updated to clarify 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.
Oxfordshire PCT	Ticagrelor has a rapid onset of action and equally rapid reversibility. Whilst this can be an advantage for patients before surgery, it does mean that for the patient to achieve benefit they must comply with treatment. We understand that patients were admitted to the trial only if they were likely to be able to comply, and that the trial (Section B1, page 2 of 31 in the manufacturer's clarification letter to NICE dated 17th December 2011), employed methods estimating compliance. Consequently we disagree somewhat with the Appraisal Committee's conclusion in paragraph 4.6 that "decreased compliance would be unlikely to significantly reduce the effectiveness of ticagrelor plus aspirin relative to clopidogrel plus aspirin in the real world setting". It is because ticagrelor has a more rapid reversibility that compliance with ticagrelor compared with clopidogrel is of greater significance. In the 'real world' compliance with long term medications has generally been accepted as about 70% (there is a broad range). We would like to see an addition to criterion 1.1 stating that use should be limited to patients who have been counselled on the importance of compliance with the treatment regime.	Comment noted. This concern around compliance was discussed by the Committee and section 4.6 of the FAD reflects this discussion.
Oxfordshire PCT	We would also request that it is made explicit, within the criteria for recommendation for use within the NHS, that treatment should not be continued for more than 12 months in line with the PLATO study and the posology section of the Summary of Product Characteristics. We base this upon our local experience of the use of clopidogrel for the prevention of vascular events following ACS, when GPs found it difficult to know if they ought to stop therapy, without specific guidance to do so.	Comment noted. The recommendations now state that 'Ticagrelor in combination with low-dose aspirin is recommended for up to 12 months...'

Oxfordshire PCT	***Discrimination and equality issues*** We have found no aspects relating to unlawful discrimination or equality related issues.	Comment noted.
Oxfordshire PCT	It would be helpful if, when quoting risks and benefits, the commentary on the consideration of evidence would always make clear when a figure is that of the relative risk or the absolute risk. Paragraph 3.3 states "patients in the ticagrelor group were 16% less likely to experience a primary end point". This is a relative risk reduction – the same paragraph later is explicit when using absolute risk reduction.	Comment noted. Section 3.3 of the FAD has been updated to clarify this refers to the relative risk.
NHS Bradford and Airedale	**1a. FDA review:** A critical part of the FDAs seeming concern about granting market access to this medicine is the seeming differential between US patients and non US patients. There is an apparent advantage of clopidogrel in US patients (lower event rate) compared to non US and PLATO overall. We would consider this does require further investigation. Taking into account the view expressed in the TA Committee meeting that "it is licensed here, therefore the US FDA view is not important", we do feel that the issues highlighted by the FDA reviewer need careful consideration as they may have a bearing on the real world effectiveness. Our interpretation of the FDA report is that they were less impressed with data on efficacy – and there are important nuances in both the clinical and statistical interpretation of the data that might easily be overlooked, but would have a bearing on the real life effectiveness.	Comment noted. Ticagrelor has been granted Marketing Authorisation in the US as of July 2011. Please note that the Committee makes a decision on cost-effectiveness in accordance with the marketing authorisation granted by the European Medicines Authority. If a drug has received marketing authorisation, it is beyond the NICE remit to challenge this. All clinical data is, however, reflected in the economic model and therefore in the cost-effectiveness estimates. All available data feeds into Committee deliberations.
NHS Bradford and Airedale	**1b. Subgroups:** Efficacy of Ticagrelor vs. clopidogrel in various pre-planned sub-group analyses of PLATO was clear - although not all reached statistical significance (taken from DTB review article): • patients in whom invasive management was planned at randomisation (9.0% vs. 10.7% at 360 days, HR 0.84, 95% CI 0.75 to 0.94; NNT 59); • those with STEMI and planned primary PCI (9.4% vs. 10.8%, HR 0.87, 95% CI 0.75 to 1.01); • those with diabetes (HR 0.88, 95% CI 0.76 to 1.03); • those with creatinine clearance below 60mL/minute (17.3% vs. 22.0%, HR 0.77, 95% CI 0.65 to 0.90; NNT 21). There seem uncertainties with respect to the optimal treatment schedule for different sub groups, and	Comment noted. The issue of subgroups was discussed by the Committee and its deliberations are outlined in section 4.8 of the FAD.

	treatment duration – first line, second line in clopidogrel non responders (genetic testing?)	
NHS Bradford and Airedale	**1c. Time to event:** The benefit of ticagrelor over clopidogrel was apparent within the first 30 days of therapy and persisted throughout the study period. The FDA reviewer questioned whether the treatment benefit was driven by statistically significant reductions in both vascular death (4.0% vs. 5.1%; p=0.001) and MI (5.8% vs. 6.9%; p=0.005). Ticagrelor does not appear to have an effect on stroke outcomes (HR 1.17, 95%CI 0.91-1.52, p=0.22).	Comment noted. Section 4.3 of the FAD indicates that that the Committee was aware of this and considered it in its deliberations.
NHS Bradford and Airedale	**1d. Exclusion criterion used in PLATO:** The SMC review highlighted that PLATO did not exclude patients already receiving treatment with clopidogrel and may have included a small proportion of patients who were poor responders to clopidogrel and therefore at higher risk of an ischaemic event. Clopidogrel patients also received different loading doses depending on whether or not they had already been receiving clopidogrel, and at the discretion of the investigator if undergoing PCI. Loading dose of clopidogrel is an issue - 70% of patients in PLATO did not have loading dose of 600mg of clopidogrel which is current clinical practice in the UK, Obviously this might have a bearing on the contextualisation of the results.	Comment noted. Section 4.5 of the FAD indicates that that the Committee was aware of this and considered it in its deliberations.
NHS Bradford and Airedale	**1e. Follow up – quoting from Marciniak / FDA review:** “There was one aspect of PLATO study conduct that was not good: the follow-up rate. By the sponsor’s statistics, about 5% of the patients died while about 82% had a final study visit (“completers” per the sponsor’s terminology). Hence about 13% of the patients (100% - 5% - 82%) had incomplete follow-up for determining the primary endpoint of CV death, myocardial infarction (MI), or stroke by the sponsor’s tallying.” This lack of follow up is a concern in terms of real world efficacy.	Comment noted. Section 4.5 of the FAD indicates that that the Committee was aware of this and considered it in its deliberations.
NHS Bradford and Airedale	**1f. Safety and adverse events:** There are nuances in data re adverse events need full exploration – both clinically and H Econ case. The safety issue common to platelet inhibitors is bleeding. Ticagrelor did produce more bleeding than clopidogrel. Although there was no significant difference in rates of major bleeding between the two groups (11.6% with ticagrelor vs. 11.2% with clopidogrel), ticagrelor was associated with a higher rate of major bleeding that was unrelated to CABG during 12 months of treatment. While major bleeds and less serious bleeds were substantially increased with ticagrelor, life-threatening and fatal bleeds were not significantly increased. The FDA primary clinical safety reviewer commented that most major bleeds were CABG-related (~ 75%) and most CABG bleeds were major (~85%). The risk of CABG-bleeding was increased in ticagrelor patients who did not wait until day 5 after stopping treatment to have CABG. Patients taking ticagrelor were significantly more likely to suffer from non-procedure related bleeding and	Comment noted. Section 4.7 of the FAD reflects the Committee’s discussion around adverse events. The concern around rapid reversibility was discussed by the Committee and section 4.6 of the FAD reflects this discussion.

	breathlessness than those taking clopidogrel. For example, in PLATO, dyspnea was significantly more common among ticagrelor patients than clopidogrel patients. So it's possible that ticagrelor will be associated with higher resource use because the dyspnea leads to more diagnostic testing and more ER visits. Dyspnoea was reported more commonly in those treated with ticagrelor than clopidogrel (13.8% vs. 7.8%). We note that in PLATO few seem to have discontinued on account of this - 13.8% vs. 7.8% with clopidogrel, p<0.001; NNH 17, leading to discontinuation of treatment in around 1% of patients. We are of the view that discontinuation on account of side effects would be higher in real life than in a trial (motivated, well supported patients etc). Combined with rapid reversibility, this poses a greater risk and are of the view that this needs to be fully explored in the economic analysis – probably through a sensitivity analysis. Discontinuation of study drug due to adverse events occurred more frequently with ticagrelor (7.4% vs. 6.0%, p < 0.001), which was also associated with more episodes of fatal intracranial bleeding (0.1% vs. 0.01%, p=0.02) but with fewer episodes of other types of fatal bleeding (0.1% vs. 0.3%, p=0.03) than clopidogrel.	
NHS Bradford and Airedale	**1g. Risks and bleed rates - length of treatment seems important:** PLATO study, ticagrelor was associated with a higher rate of major bleeding events unrelated to CABG than clopidogrel, including more instances of fatal intracranial bleeding. But the ticagrelor patients had fewer fatal bleeding events of other types, and overall bleeding rates were similar between the two groups. Obviously the recommended treatment course is one year. Any analysis of clinical and cost effectiveness, and real world use would need to be mindful of patients who will be on the drug for a long time. Bleeding rates are always expressed as rates—frequency divided by time—so if a patient takes a drug for a longer period of time, the likelihood he will experience bleeding is higher We would expect these issues to be built into the econ analysis, and are not clear it is at this moment. NHSBA would like assurance that the adverse event profile has been fully built into the economic analysis.	Comments noted. This concern was discussed by the Committee and Section 4.11 of the FAD has been updated to clarify 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.
NHS Bradford and Airedale	**1h. Onset / offset of action:** The fast-offset drug might be well-suited to coronary artery bypass patients or perhaps patients who have multivessel disease and are going to probably undergo bypass. This advantage does not extend to chronic antiplatelet drug users. As the effects of ticagrelor reverse rapidly, compliance may be particularly important for effective treatment, and patients may need additional counselling and surveillance in this respect. It is thought that about 20% of patients on clopidogrel don't adhere to their prescribed regimen. Although the "trough levels" of platelet inhibition are higher with ticagrelor than for clopidogrel when a patient	Comments noted. These concerns around compliance and rapid reversibility were discussed by the Committee and section 4.6 of the FAD reflects this discussion.

	misses a single dose, the level of platelet inhibition with ticagrelor drops off rapidly if a patient misses three or four doses. If there is a GI bleeding complication, leading the GI specialist to immediately take the patient off the antiplatelet drugs then with a slow-offset drug, there may be time for the cardiologist to consult with the GI specialist about the antiplatelet regimen, but taking a patient off of a fast-offset drug could put him or her at risk for MI and stroke very quickly. **1i. BD dosing – compliance:** especially if effects wear off quickly - an advantage can be turned into a disadvantage compared to clopi – PLATO demonstrated that more patients on ticagrelor than clopidogrel discontinued due to adverse events (7.4% vs. 6.0%, p<0.001; NNH 71). patients deemed unlikely to comply with the twice-daily regimen of ticagrelor were excluded from the pivotal PLATO study. We disagree with the conclusions of the Committee in 4.6 on compliance. Patients are always advised to take medicines as their doctor prescribes, there is a huge wealth of anecdotal clinical experience and peer reviewed evidence making clear that whilst such instructions are given that compliance is often poor. This is an important point in this particular medicine. There have been a number of recent and very well cited examples of where medicines have received market authorisation in Europe that that subsequently turned out to do more harm than good. We would wish to see a cautious approach to the introduction of this medicine.	
NHS Bradford and Airedale	**2. There are many important issues with respect to different methods of appraising value for money, population impact and affordability. Whilst we accept that affordability is not within the remit of the TA Committee it is a critical consideration.** **2a The difference in drug acquisition cost is stark, and well documented.** **2b Budget impact** NHSBA has seen various estimations of budget impact. Here we highlight the likely budget impact using the manufacturers own model. AZ Budget impact model. W Yorks. About £5m /yr in population of 2.1m - £240k / 100,000 pop In NHSBA (520k registered pop) the estimated impact is therefore in the region of £1.25m. Assuming, at best, a flat budget scenario this equates to £1.25m of investment we will not be making in other cardiology services. This is equivalent to 1.4% of the total prescribing budget for NHSBA. We note that the budget impact model is from the manufacturer therefore are of the impression it will be populated will with perhaps the most optimistic assumptions. It is not clear that the cost of treating side effects are built into the AZ model adequately – noting some of our concerns above. Some commentators have noted that the net cost may be lower due to lower resource use savings…….less readmissions etc. This seems incorporated into the AZ model. It is of note that NHS commissioners will not realise this cost without concurrent reductions in capacity – bed base in hospitals. Put most simply, if the bed is there it will be filled with another patient. Therefore whilst there may be a net	Comment noted. These issues were discussed by the Committee and section 4.15 of the FAD reflects this discussion.

saving to the NHS, this will NOT be realised by NHS commissioners. Calculating how much capacity to remove so as to realise cash savings will be difficult.
NHS Bradford and Airedale currently spends approx £67m on circulatory problems (of which £22.6 is on CHD). The additional estimated £1.25m that this drug may incur will be found from savings elsewhere in the cardiology spend, with reductions in spend in other parts of the programme and certainly very limited new investment. NHS Commissioners are required to make judgements about the relative value of investments. We would seek support of secondary and primary care clinicians in doing this.

2c Population impact seems modest, for a high cost and opportunity cost.

The population impact of introduction of ticagrelor is also an important consideration. Using our own data we can estimate admissions for ACS seems relatively stable – see table below.

Admissions for ACS 2008 / 09 to 2010 / 11

ICD10 code (primary)	2008 09	2009 10	2010 11
I20 – UA	1447	1166	1070
I21 - AMI	726	656	485
I22 – subsequent MI	140	144	173
I24 – other acute ischemic HD	8	25	224
	2321	1991	1952

The recent studies give a perspective on mortality.

Wallentin (main PLATO study). The one year CV mortality (primary end point) is 9.8% in ticag vs 11.7% in clopi – an absolute risk reduction of 1.9% (NNT of 54).
The James SK et al (BMJ 2011) sub group analysis on effectiveness of Tica v clopi in ACS patients planned for medical management gives a different perspective on CV mortality risk. This indicates (table 3) that 12% of ticagrelor patients died at 1yr, compared to 14.3% of clopidogrel. An absolute risk reduction of 2.3%.
Taking data on the primary outcome of PLATO - composite end point CV death – the absolute risk reduction (compared to clopidogrel) is 1.9%
Just considering ACS patients, application of this data to our local population of 1070 ACS admissions that are admitted would indicate the following (using the James et al estimates from BMJ)

		current Management	Ticagrelor	Net benefit
ACS admissions	CV Deaths	153.01	128.4	24.61
1070		14.3% CV death at 1yr	12% CV death at 1yr	net reduction in deaths

25 fewer deaths in a population of 1070 ACS admissions admitted. The net estimated drug cost is £686k (taking the figures on cost of ticagrelor and clopidogrel used above, and assuming all 1,100 are prescribed

	a 12m course of ticagrelor). This equates to approximately £30,000 per CV death avoided, and NHS commissioners do need to consider the opportunity cost of investments foregone that might represent better value for money. Obviously such an analysis is obviously very sensitive to time horizon, and the horizon above is 1 year. Obviously there are significant uncertainties in the epidemiology of ACS – and some discrepancies between different systems (eg HES and MINAP). In addition the actual decision to commence treatment with antiplatelet depends on risk stratification. **2d. Economics and cost effectiveness** Despite the issues and weaknesses cited above, PLATO did report a mortality benefit, this is an obvious and important driver of the QALY side of the ICER equation. It is clear that the ACD concludes that ticagrelor is a highly cost effective use of resources. The absolute benefit is relatively meagre. See Table 1 from the Wallentin et al paper in NEJM. That said, it is difficult to disagree with the findings of the ERG on their point estimates of ICER and CEACs. The methodology seems sound, though we would wish to see the sensitivity analysis cover in more detail some of the issues we highlight in section 1 It is worth noting that the ICERs are predicated on an NHS perspective. The ICERS will not work from a commissioner perspective unless the commissioner is able to realise savings from reduced admissions in cash terms – they will only do this through reduction in bed base in secondary care. **2e "Real world value for money" versus Incremental cost effectiveness ratios** The question that most, if not all commissioners will ask is whether the returns warrant the cost – an 18 fold cost difference compared to generic clopidogrel. The SMC review alluded to "drugs with a lower acquision cost". The SMC did not give any advice on where clopidogrel or ticagrelor might be preferentially used. The NICE ACD does not either. This issue of combining a relatively meagre absolute benefit with cost was adequately highlighted in the DTB review published recently. "To prevent one death from a vascular cause, stroke or myocardial infarction, 53 people would need to be treated with ticagrelor instead of clopidogrel for 12 months at a cost of £37,775; to treat the same number of people with generic clopidogrel would cost £1,626, so using ticagrelor would cost an extra £36,149 to prevent one death." (taken from NYRDTC report) This is obviously uncomfortable territory, but NHS Commissioners must ask this question explicitly, and it cannot be ignored. This is a very good example of where a "pure academic" approach to economic appraisal must sync with the real issues of affordability in practice, and a financially driven approach to cost benefit appraisal within short time horizons. This is a concept that the NHS simply cannot ignore. NHS commissioners recognise and are supportive of an economic approach to valuation of benefit over clinically and epidemiologically appropriate time horizons. However, they MUST live within a budget envelope and a 1 year time horizon. The budget impact of this drug is considerable. NICE clearly will find that it is highly cost effective – obviously that is very different from affordable. NHSBA and other NHS Commissioners will necessarily ask what services will be scaled back or cut, and whether the opportunity costs worth it? As a minimum, commissioners may seek to scale back the value of cardiology contracts, and may get into considering	

	specific interventions. Given that the NNT for a non fatal MI is approx 44 it ought to be possible to calculate the likely reduction in admissions for MI this drug will yield, and thus the size of contract reduction that might be possible. Most commissioners see this as a low priority development. From a commissioners perspective no there is not a compelling case for rapid introduction. We find the DTB conclusion compelling: "Although ticagrelor appears to offer some benefits over clopidogrel in ACS, it is much more expensive, requires twice-daily dosing and has unknown long-term safety. Consequently, we cannot currently recommend ticagrelor as first-line therapy in the management of patients with ACS."	

Comments received from clinical specialists and patient experts

Nominating organisation	Comment	Response
The Royal College of Nursing	The evidence considered seems comprehensive.	Comment noted.
The Royal College of Nursing	We would ask that the summaries of the clinical and cost effectiveness of this appraisal should be aligned to the clinical pathway followed by people with coronary disease. The preliminary views on resource impact and implications should be in line with established standard clinical practice.	Comment noted. Sections 4.2 and 4.4 in the FAD in particular take note of the views of the clinicians present at the Appraisal Committee Meeting regarding the treatment pathway as well as the generalisability of the trial to UK clinical practice.
The Royal College of Nursing	Nurses working in this area of health have reviewed the recommendations of the Appraisal Committee and do not have any other comments to add. The RCN would welcome guidance to the NHS on the use of this health technology.	Comment noted.
The Royal College of Nursing	We are not aware of any specific issue at this stage. However, it would be helpful to know if NICE will publish the equality analysis for this appraisal. We would also ask that any guidance issued should show that an analysis of equality impact has been considered and that the guidance demonstrates an understanding of issues relating to all the protected characteristics where appropriate.	Comment noted. The impact on equality has been assessed during this appraisal according to the principles of the NICE Equality scheme. The 'Equality Impact Assessment' form, which reflects any equalities issues that may have arisen right from the scoping stage to the development of final guidance will be published along with the final guidance.

Nominating organisation	Comment	Response
BCS/BCIS/RCP	Page 3, section 1.1, under “unstable angina” A comment should be added that benefit was only observed for ticagrelor in troponin positive patients	Comment noted. This change has not been incorporated. Section 4.8 of the FAD reflects the discussion on this issue.
BCS/BCIS/RCP	Page 7, section 3.5: In relation to comments about bleeding, it should be specifically stated that rates of major bleeding were significantly higher with ticagrelor compared to clopidogrel in the patients who did not undergo CABG. The rate of CABG in both groups was about 10% and therefore the risk of major bleeding was significantly greater in around 90% of potential candidates for ticagrelor.	Comment noted. Section 3.5 of the FAD has been updated to reflect this change.
BCS/BCIS/RCP	Page 20, section 4.2: The last 2 sentences are not accurate. (a) Patients with unstable angina are relatively uncommon and treated according to their clinical risk. Often they do not require revascularisation. Patients with unstable angina are unlikely to benefit from ticagrelor because subgroup analysis shows benefit only for troponin positive patients and unstable angina is troponin negative by definition. (b) I disagree that it is unusual for ACS patients in the UK to undergo CABG. It is unusual for STEMI patients to undergo CABG, but around 10% of NSTEMI patients do undergo CABG, as reflected in this study.	Comment noted. Section 4.2 of the FAD has been updated.
BCS/BCIS/RCP	Page 22, 4.7 I think the issues raised in point 2 re major bleeding should be included again here under “safety concerns”.	Comment noted. Section 4.7 of the FAD has been updated to reflect discussions at the second Committee meeting.
BCS/BCIS/RCP	The FDA have approved Ticagrelor - should NICE have a condition (as per their "blackbox" warning) re the need for a maximum dose of aspirin - i.e. no > than 100 mg We need to know something about minimum and maximum timing of recommended dose (the median time of the study was 9 months) and the curves (treated versus control) do not separate for a month	Comments noted. As per the Summary of Product Characteristics, the recommendations state that ‘Ticagrelor in combination with low-dose aspirin is recommended for up to 12 months as a treatment...’
BCS/BCIS/RCP	We need to emphasize there is a difference (excess + 22%) in non CABG bleeding	Comment noted. Section 4.7 of the FAD has been updated to reflect discussions at the second Committee meeting.
British Heart Foundation	The BHF would like to approve the recommendations.	Comment noted.

Comments received from commentators

Commentator	Comment	Response
Daiichi Sankyo UK and Eli Lilly and Company	We acknowledge that overall the PLATO trial was a well designed trial with some significant findings. The trial presented clinical data for a broad range of patient subgroups however the concurrent cost effectiveness of these subgroups was insufficiently explored, in particular invasively/non-invasively managed patients as specified in the scope. Identifying the clinical and cost effectiveness benefits in important patient subgroups is of interest to clinicians and patients.	Comment noted. The discussion on subgroups is reflected in section 4.8 of the FAD. In addition, the recommendations for further research (section 6) state that further research into whether ticagrelor is particularly beneficial in any clinical or biological subgroups would be useful.
Daiichi Sankyo UK and Eli Lilly and Company	In general we consider the clinical and cost effectiveness summaries of ticagrelor to be reasonable interpretations of the evidence presented. However we feel that more detailed cost effectiveness analyses in important patient subgroups would help to ensure appropriate use of this treatment in real life practice.	Comment noted. The discussion on subgroups is reflected in section 4.8 of the FAD. In addition, the recommendations for further research (section 6) state that further research into whether ticagrelor is particularly beneficial in any clinical or biological subgroups would be useful.
Daiichi Sankyo UK and Eli Lilly and Company	We agree with the Appraisal Committee's view that the PLATO trial is broadly representative of UK clinical practice except for the proportion of patients that were medically managed in the PLATO trial population. It is estimated that the majority of ACS patients in the UK are medically managed with approximately 15-20% of ACS patients undergoing PCI (estimated from Ludman 2010). In PLATO, only 5216 (28%) of patients were planned to be medically managed and of these, only 3948 patients were truly medically managed (21% of the PLATO trial population) which is a proportion not reflective of UK clinical practice. We question the generalisability of the medically managed PLATO trial population and would usually expect this to be considered given the heterogeneity amongst the ACS population and the differing levels of risk.	Comment noted. This discussion is reflected in section 4.4 of the FAD.

Commentator	Comment	Response
Daiichi Sankyo UK and Eli Lilly and Company	The manufacturer has not performed its own indirect comparison of ticagrelor and prasugrel stating it would be difficult due to differences in clinical trial design of the TRITON-TIMI 38 and PLATO studies. The Evidence Review Group (ERG) concurred with this decision. However, the manufacturer used results from an independent indirect comparison (Biondi-Zoccai 2010 - recommended to be viewed with caution due to the inherent differences between the trials) in an economic model to generate an ICER for ticagrelor versus prasugrel. The Evaluation Report states that the economic model used to generate these ICERs was not reviewed by the ERG. We request that the cost effectiveness information of ticagrelor compared with prasugrel (section 3.19) is removed from the guidance as an indirect comparison was deemed inappropriate and the ICER generated using inputs from the independent indirect comparison has not been reviewed by the ERG.	Comment noted. Section 4.10 of the FAD is clear in stating that the no separate recommendations could be made for ticagrelor plus aspirin compared with prasugrel plus aspirin owing to concerns around the indirect comparison of ticagrelor plus aspirin and prasugrel plus aspirin highlighted in the manufacturer's submission and reiterated by the ERG. As this evidence was presented to the Committee, reference to it cannot be removed from the evidence section of the FAD.
Daiichi Sankyo UK and Eli Lilly and Company	It should be noted that the total mortality analysis is exploratory. The statistical analysis plan for PLATO states that the secondary endpoints should be tested individually in a pre-specified order until the first non-significant difference was found between the two groups. The US Food and Drug Administration (FDA) Advisory Committee Briefing Document for ticagrelor reports that total mortality was the last endpoint to be analysed in the predefined hierarchy and while nominally positive for ticagrelor, formal statistical testing ceased when significance was not reached for stroke (FDA 2010). The exploratory nature of the total mortality analysis is recognised in the ERG report.	Comment noted. Please refer to section 4.9 in the FAD which addresses this concern.
Daiichi Sankyo UK and Eli Lilly and Company	Although the provisional recommendations are predominantly based on the appropriate review of the clinical and cost effectiveness evidence presented by the manufacturer for ticagrelor, more specific guidance on the use of ticagrelor in important patient subgroups would be of benefit to clinicians and ensure ticagrelor is used in appropriate patients.	Comment noted. The discussion on subgroups is reflected in section 4.8 of the FAD. In addition, the recommendations for further research (section 6) state that further research into whether ticagrelor is particularly beneficial in any clinical or biological subgroups would be useful.
Daiichi Sankyo UK and Eli Lilly and Company	We do not agree that the method for generating ICERs for ticagrelor versus prasugrel was suitable as they are based on an independent indirect comparison which was deemed inappropriate and the analysis was not reviewed by the ERG.	Comment noted. No separate recommendations were made for ticagrelor plus aspirin compared with prasugrel plus aspirin.

Commentator	Comment	Response
Daiichi Sankyo UK and Eli Lilly and Company	Lastly, we would also like to see further clarification about the proposed date for review. It has been proposed in the ACD that this guidance will be incorporated into forthcoming NICE clinical guidelines on 'The management of myocardial infarction with ST-segment elevation', however this only relates to one aspect of this guidance. Hence, further clarification regarding the proposed date of review for all recommendations would be of interest.	Comment noted. Section 8 has been updated.

Comments received from members of the public

Role*	Section	Comment	Response
NHS Professional 1	1	Agree with this recommendation	Comment noted.
	2	Suggest no changes	Comment noted.
	3	Endorse the comments of our nominated experts on bleeding risk noting the excess risk of bleeding in non CABG patients.	Comment noted. Sections 3.5 and 4.7 of the FAD have been updated to reflect these changes.
	4	Endorse the comments of our expert on the use of CABG to treat patients with NSTEMI (about 10% of cases) and on the incorporation of bleeding in to the section on safety.	Comment noted. Sections 4.2 and 4.7 of the FAD have been updated to reflect these changes.
	5	Suggest no changes	Comment noted.
	6	Agree with these comments	Comment noted.
	7	No comments	Comment noted.
	8	No comments	Comment noted.

* When comments are submitted via the Institute's web site, individuals are asked to identify their role by choosing from a list as follows: 'patent', 'carer', 'general public', 'health professional (within NHS)', 'health professional (private sector)', 'healthcare industry (pharmaceutical)', 'healthcare industry'(other)', 'local government professional' or, if none of these categories apply, 'other' with a separate box to enter a description.

Role*	Section	Comment	Response
NHS Professional 2	1	The groups have specifically been guided by the clinical trial clarification, this may be somewhat unrealistic to apply into every day practice and scoring systems (e.g. GRACE) are in routine practice as a guide to the use of antiplatelet agents following recommendations by NICE. We would request a consideration that the position of ticagrelor in UA/NSTEMI sub-group should be determined by 6 month mortality in accordance to the recently published NICE guideline on UA/NSTEMI. We would welcome clarification on the use of ticagrelor in the use of low risk patients and in particular noting that clopidogrel is considered not appropriate in patients who have a 6 mortality of 1.5%. We request this is made explicitly clear that this is also applicable to ticagrelor.	Comment noted. The discussion on this issue is reflected in section 4.14 of the FAD.
	4	It will helpful as part of the consideration of evidence to ensure that a duration is explicitly recommended. Otherwise, there will be opportunity for inequity in prescribing that was seen with both clopidogrel and prasugrel. When clopidogrel TA was first published, many were prescribing for just 1 month, or 3 months following publication of SIGN. It was only when NICE published further clarification that up to 12 months meant for 12 months did care subsequently change. This variability was again recognised with the subsequent TA on prasugrel as no duration is stipulated leading to great variability in the durations of prasugrel ranging from 1 month to 15 months in accordance with the clinical trial publication. To help offer clear clarity, it will be most helpful if NICE was to offer a recommendation for duration based on evidence to guide clinical practice	Comment noted. The Summary of Product Characteristics states that “Treatment is recommended for up to 12 months unless discontinuation of Brilique is clinically indicated”. NICE issues Guidance in accordance with the marketing authorisation and the Committee considered that the recommendation must reflect the SPC. Therefore the recommendation now states that ‘Ticagrelor in combination with low dose aspirin is recommended for up to 12 months...’.
UK Clinical Pharmacy Association	1	The duration is not explicitly recommended. There is therefore an opportunity for inequity in prescribing that was seen with both clopidogrel and prasugrel. When clopidogrel TA was first published, many were prescribing for just 1 month, or 3 months following publication of SIGN. It was only when NICE published further clarification that up to 12 months meant for 12 months did care subsequently change. This variability was again recognised with the subsequent TA on prasugrel as no duration is stipulated leading to great variability in the durations of prasugrel ranging from 1 month to 15 months in accordance with the clinical trial publication. To help offer clear clarity, it will be most helpful if NICE was to offer a recommendation for duration based on evidence to guide clinical practice.	Comment noted. The Summary of Product Characteristics states that “Treatment is recommended for up to 12 months unless discontinuation of Brilique is clinically indicated”. NICE issues Guidance in accordance with the marketing authorisation and the Committee considered that the recommendation must reflect the SPC. Therefore the recommendation now states that ‘Ticagrelor in combination with low dose aspirin is recommended for up to 12 months...’.

Role*	Section	Comment	Response
	4	1) The group have specifically been guided by the clinical trial clarification. This may be somewhat unrealistic to apply into every day practice, and scoring systems (e.g. GRACE) are in routine practice as a guide to the use of antiplatelet agents following recommendations by NICE. UKCPA would request a consideration that the position of ticagrelor in UA/NSTEMI sub-group should be determined by 6 month mortality in accordance with the recently published NICE guideline on UA/NSTEMI. We would welcome clarification on the use of ticagrelor in the use of low risk patients. 2) NICE currently stipulates that any patient with UA/NSTEMI who has a 6 month mortality of 1.5% should not be offered clopidogrel as the risks potentially outweigh the benefits. We would suggest this equally applies to ticagrelor and is clarified in the recommendation.	Comment noted. The discussion on this issue is reflected in Section 4.14 of the FAD.