NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Ticagrelor for secondary prevention of atherothrombotic events after myocardial infarction [ID813]

The following documents are made available to the consultees and commentators:

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

2. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   - **AstraZeneca**
   - **British Cardiovascular Society**

   'No Comment' response received for the Department of Health and Royal College of Nursing

3. **Comments on the Appraisal Consultation Document received through the NICE website**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SingleTechnology Appraisal

Ticagrelor for preventing atherothrombotic events after myocardial infarction

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 companies, national professional organisations, national patient organisations, the Department of Health and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal determination (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation.

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health, Social Services and Public Safety for Northern Ireland).

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 NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comments received from consultees

Consultee	Comment [sic]	Response
Astra Zeneca	The appraisal is currently entitled: "Ticagrelor for preventing atherothrombotic events after myocardial infarction". This title is not well aligned with the marketing authorisation (patients with a history of myocardial infarction, of at least one year ago). The current appraisal title brings the potential for confusion, particularly as ticagrelor (90mg) is licensed for use in the 12 months immediately after myocardial infarction, which is not the focus of this appraisal. We request that the title of the appraisal be amended to: "Ticagrelor for preventing atherothrombotic events in patients with a history of myocardial infarction"	Comment noted. Unfortunately the title of the appraisal cannot be amended at this stage of appraisal process. Section 2 of the document clarifies the details of the indication under appraisal.
Astra Zeneca	AZ welcomes the draft recommendations of NICE. There is opportunity to refine the wording in Section 1 (and subsequently repeated in Section 4.14 and in the Summary of appraisal committee's key conclusions), so as to ensure full clarity with regards to the population to which the draft recommendation relates and to reduce any potential for confusion regarding cessation of treatment: a) There is potential for what constitutes "a high risk of developing atherothrombotic events" to be open to different interpretations. As such it would be helpful if the definition used in the appraisal was specified. In practice this means specifying the five enrichment factors for CV risk used in the PEGASUS-TIMI 54 trial (please see suggested wording below). b) The first bullet contains a misspelling of "infarction". c) The second bullet point is ambiguous and could be misinterpreted to mean that patients should continue ticagrelor 60mg BID with low-dose aspirin without interruption (i.e. once they initiate treatment they must continue without interruption for up to 3 years). To address this, please consider merging this bullet with the first one. d) The final bullet contains the misspelling "aspirinis". e) The final bullet point is ambiguous and could be misinterpreted to mean that patients should stop taking both ticagrelor 60mg BID and low-dose aspirin when clinically indicated or after a maximum of 3 years. It must be made clear that	Comment noted. The recommendation has changed after the second committee meeting. Please see the final appraisal determination document.

Consultee	Comment [sic]	Response
	the maximum treatment duration of 3 years applies only to ticagrelor 60mg. We propose the following wording be used, so as to address the above points: "1.1 Ticagrelor 60 mg BID, in combination with low-dose aspirin, is recommended as an option as a continuation therapy for preventing atherothrombotic events in people who have a history of myocardial infarction and a high risk of developing further atherothrombotic events, only if: • they have had a myocardial infarction at least a year ago, have already taken ticagrelor 90 mg in combination with aspirin for 1 year and ticagrelor 60 mg in combination with aspirin is continued without interruption and • treatment with ticagrelor 60 mg BID is stopped when clinically indicated or after a maximum of 3 years."	
Astra Zeneca	1.2 For the purposes of this guidance "a high risk of developing atherothrombotic events" is defined as presence of at least one of the following five risk factors: • Age ≥65 years, • OR diabetes mellitus requiring medication, • OR a second prior MI, • OR evidence of multivessel coronary artery disease • OR chronic non-end stage renal dysfunction (creatinine clearance <60ml/min). 1.3 This guidance is not intended to affect the position of patients whose treatment with ticagrelor 60 mg BID, in combination with aspirin as a continuation therapy, was started within the NHS before this guidance was published. Treatment of those patients may continue without change to whatever funding arrangements were in place for them before this guidance was published until they and their NHS clinician consider it appropriate to stop."	Comment noted. The recommendation now covers the full marketing authorisation. Section 4.3 refers to the summary of product characteristics where patients who have high risk of subsequent atherothrombotic events are listed.
Astra Zeneca	Please include a registered trademark for Brilique™ throughout the document.	Comment noted. Unfortunately this cannot be included in the guidance in line with NICE style
Astra Zeneca	Please ensure that the licensed doses for each marketing authorisations are made clear and that the full marketing authorisation for the 60 mg BID is captured: To achieve the latter we suggest amending the second paragraph to read: "This marketing authorisation allows ticagrelor 60 mg BID to be initiated as continuation therapy after initial 1-year treatment with ticagrelor 90 mg BID or another Adenosine diphosphate (ADP) receptor inhibitor. Treatment can also be initiated up to 2 years from the MI, or within 1 year after stopping previous ADP	Comment noted. Section 2 clarifies the dose and twice daily schedule. Thereafter, ticagrelor 60 mg twice daily plus aspirin is referred to as ticagrelor. This is detailed in the first paragraph of section 4.

Consultee	Comment [sic]	Response
	receptor inhibitor treatment."	
Astra Zeneca	Please note that the correct price of ticagrelor 60mg is £54.60 for a 56 tablet pack (28-day supply).	Comment noted, price corrected
Astra Zeneca	Please insert a space between “event,and” to read “event, and”.	Comment noted, space inserted
Astra Zeneca	The full stop should be removed at “clopidogrel.and”.	Comment noted. Typing mistake corrected.
Astra Zeneca	a) Please correct the following in parentheses: “(approximately 1 in 5 people who are event-free in the first year after a myocardial infarction go on to experience a further myocardial infarction, stroke or within the subsequent 3 years) to read “(approximately 1 in 5 people who are event-free in the first year after a myocardial infarction go on to experience a further myocardial infarction, stroke or cardiovascular death within the subsequent 3 years).” b) As for the equivalent comment made at section 1, please include the bolded “The committee was aware that patients enrolled into PEGASUS-TIMI 54, the trial which formed the basis of the company submission, had a history of myocardial infarction of at least 12 to 36 months, at least 1 additional risk factor for subsequent atherothrombotic events (age ≥65 years, diabetes mellitus requiring medication, a second prior MI, evidence of multivessel coronary artery disease or chronic non-end stage renal dysfunction)” c) Please remove the extra space in the final sentence (“aspirin in” to be changed to “aspirin in”).	Comment noted, typing mistakes have been corrected.
Astra Zeneca	The references to “the last antiplatelet” and “previous antiplatelet” are incorrect and should be corrected to read “ADP receptor inhibitor”. This is important because aspirin is an antiplatelet agent and this could cause confusion.	Comment noted, see FAD section 4.3.
Astra Zeneca	It is more correct to say that the we “explored the feasibility of conducting an indirect comparison of ticagrelor with clopidogrel in combination with aspirin”, rather than considered undertaking one.	Comment noted. The sentence has been amended as suggested.
Astra Zeneca	a) Please implement suggested changes from Section 1.1 to the bullet points in this section. b) There is a reference in this section to a section 4.16, but this does not appear in the ACD. c) The section ends with a comma, rather than a full stop.	Comment noted. Section 1.1 has been amended. Section numbering has been changed. Comma has been replaced with the full stop.
Astra Zeneca	a) Please amend the appraisal title, as per earlier comment b) Key conclusion: Please implement suggested changes from Section 1.1	Comments noted. Typing mistakes have been corrected

Consultee	Comment [sic]	Response
	to the bullet points in this section c) Relevance to general clinical practice in the NHS: • Aligned to earlier comment, please replace “previous treatment with an antiplatelet agent” to “previous treatment with an ADP receptor inhibitor” • “in the trialIn practice”, to read “in the trial. In practice” d) Equalities considerations and social value judgements: • Space needed: “stroke,gastrointestinal bleed” to read “stroke, gastrointestinal bleed” • Space needed: “anticoagulation therapy.The” to read “anticoagulation therapy. The”	

Comments received from clinical experts and patient experts

Nominating organisation	Comment [sic]	Response
British Cardiovascular Society	1) Questionable basis for decision-making based on trial subgroup which might overestimate efficacy and safety of ticagrelor In addition to PEGASUS-TIMI 54, NICE considered data submissions from Astra Zeneca which focused on the trial’s subgroup of patients who had an MI between one to two years previously (and who were at increased risk of atherothrombotic events). This seems to have been based on the company’s marketing authorisation, on its assumption that few patients more than two years from an MI received dual antiplatelet therapy, and on the assertion that this subgroup derives greater clinical benefit than patients whose MI was more distant. NICE concluded that it was appropriate to focus its decision making on this subgroup, as opposed to the whole study population which included patient entry up to three years following MI. Several subgroup analyses, including time from qualifying (MI) event, were pre-specified in the trial protocol (which can be found online). Rates of the primary efficacy and safety endpoints in patients randomised to ticagrelor 60 mg twice daily or placebo were presented in supplementary figures in the online appendix to the PEGAGSUS-TIMI 54 publication in the New England Journal of Medicine. Rates of cardiovascular death, MI or stroke were 7.79% v 9.74% (HR 0.77; 95% CI 0.66-0.90), respectively, in patients who entered the trial within two years of MI and 7.76% v 7.94% (HR 0.96; 95% CI 0.79-1.17) in patients who entered the trial two or more years after MI. There was no significant interaction between time from MI and the primary efficacy endpoint (P=0.09) or between time from MI and the rates of TIMI major bleeding (P=0.23). The statistical grounds for using this subgroup to assess the efficacy and safety of ticagrelor as opposed to the main trial results is, therefore, not clear. The majority of	Comment noted. The issue was discussed at the committee meeting and recommendation is now in line with the full marketing authorisation..

	the other pre-specified subgroup analyses showed a significant reduction in the rates of the primary efficacy endpoint in one but not the other of the comparators (e.g. men v women, caucasians v non-caucasians, prior PCI v no prior PCI, etc.) but, quite appropriately, NICE did not recommend treatment with ticagrelor only in the groups "benefiting" in these analyses, for example men and not women. Decision-making based on this subgroup, as opposed to the whole study population, selects the most positive results in favour of ticagrelor, yet it is not clear that this is a valid strategy and it is one which may overestimate the clinical efficacy and underestimate the side effects of ticagrelor. BCS believes this analysis may prejudice the results and recommends that NICE reviews its decision-making based on the subgroup of patients who were treated within two years of MI rather than the whole study population.	
The British Cardiovascular Society	2) Potential overestimation of cost-effectiveness Analogous to point 1), the subgroup of patients within two years of MI was also used in the cost-effectiveness analyses of the drug. The greater risk reduction in this group compared with the trial population as a whole likely contributed to a more favourable estimate of the cost-effectiveness of ticagrelor.	Comment noted
The British Cardiovascular Society	3) Specification of timing of initiation of ticagrelor Having chosen to base its analysis of efficacy, safety, and cost-effectiveness on the subgroup of patients who were randomised to receive ticagrelor or placebo within two years of MI, it seems inconsistent for NICE not to specify this timeframe (between one to two years from MI) in its recommendation for the introduction of ticagrelor.	Comment noted. As the recommendation is now for the full marketing authorisation it is no longer necessary to clarify the timeframe of treatment in relation to the MI.
The British Cardiovascular Society	4) Inappropriate restriction of ticagrelor to patients who received ticagrelor in the first 12 months after myocardial infarction The draft NICE recommendations appear to restrict the use of ticagrelor beyond 12 months after MI to those patients who have already been treated with ticagrelor. It is acknowledged that ticagrelor (in combination with Aspirin) is commonly used in contemporary UK practice to treat "high risk" patients, but there seems no good clinical reason to exclude patients who have been treated with a different ADP antagonist in the first year after MI. BCS does not accept the argument that switching anti-platelet agents is complicated; it happens quite commonly already (not least because ticagrelor is often poorly tolerated in the first year post MI, requiring a switch over to clopidogrel, for example). Furthermore, as NICE acknowledges, 84% of patients in PEGASUS-TIMI 54 received an anti-plalet agent other than ticagrelor (usually clopidogrel) in the first year after MI. The draft recommendations are not consistent with the trial evidence and make little clinical sense.	Comment noted. Restriction has been removed from the guidance.

The British Cardiovascular Society	5) Specification of ticagrelor dosing in recommendations The draft recommendations refer to “ticagrelor 60 mg”. The dosing regimen is 60 mg twice daily and this should be specified in the recommendations to avoid confusion. Guidelines and technology appraisals are frequently read without reference to the evidence behind them.	Comment noted. Section 2 clarifies the dosing.
The British Cardiovascular Society	6) Definition of high risk patients It is not clear from the draft NICE recommendations what constitutes patients who are at “high risk of developing atherothrombotic events.” BCS believes that this group should be defined so that appropriately high-risk patients are considered for treatment and, conversely, so that lower risk patients who are likely to gain less or be harmed by prolonged dual anti-platelet therapy are not selected for treatment.	Comment noted. The recommendation now covers the full marketing authorisation. Section 4.3 refers to the summary of product characteristics where patients who have high risk of subsequent atherothrombotic events are listed.
The British Cardiovascular Society	7) Specification of exclusions from ticagrelor use In PEGASUS TIMI 54, the use of ticagrelor resulted in a significant increase in the rate of major bleeding (2.3% v 1.06%; $p<0.001$) despite exclusion from the study of patients who were at high risk of bleeding, such as patients who required oral anticoagulation. There is therefore no safety or efficacy data relating to this population and a credible mechanism for potential harm. BCS believes that the technology appraisal recommendations should specify that ticagrelor is not recommended for this indication in patients who are at high risk of bleeding such as those who require oral anticoagulation since they were excluded from the only relevant trial.	Comment noted. The recommendation is now for the population covered by the marketing authorisation.

AZ Comments on ACD

Appraisal Title

The appraisal is currently entitled: "Ticagrelor for preventing atherothrombotic events after myocardial infarction". This title is not well aligned with the marketing authorisation (patients with a *history of* myocardial infarction, of at least one year ago). The current appraisal title brings the potential for confusion, particularly as ticagrelor (90mg) is licensed for use in the 12 months immediately after myocardial infarction, which is not the focus of this appraisal.

We request that the title of the appraisal be amended to:

"**Ticagrelor for preventing atherothrombotic events in patients with a history of myocardial infarction**"

1 Recommendations

AZ welcomes the draft recommendations of NICE.

There is opportunity to refine the wording in Section 1 (and subsequently repeated in Section 4.14 and in the Summary of appraisal committee's key conclusions), so as to ensure full clarity with regards to the population to which the draft recommendation relates and to reduce any potential for confusion regarding cessation of treatment:

a) There is potential for what constitutes "a high risk of developing atherothrombotic events" to be open to different interpretations. As such it would be helpful if the definition used in the appraisal was specified. In practice this means specifying the five enrichment factors for CV risk used in the PEGASUS-TIMI 54 trial (please see suggested wording below).
b) The first bullet contains a misspelling of "infarction".
c) The second bullet point is ambiguous and could be misinterpreted to mean that patients should continue ticagrelor 60mg BID with low-dose aspirin without interruption (i.e. once they initiate treatment they must continue without interruption for up to 3 years). To address this, please consider merging this bullet with the first one.
d) The final bullet contains the misspelling "aspirinis".
e) The final bullet point is ambiguous and could be misinterpreted to mean that patients should stop taking <u>both</u> ticagrelor 60mg BID <u>and</u> low-dose aspirin when clinically indicated or after a maximum of 3 years. It must be made clear that the maximum treatment duration of 3 years applies only to ticagrelor 60mg.

We propose the following wording be used, so as to address the above points:

"1.1 Ticagrelor 60 mg BID, in combination with low-dose aspirin, is recommended as an option as a continuation therapy for preventing atherothrombotic events in people who have a history of myocardial infarction and a high risk of developing further atherothrombotic events, only if:

- **they have had a myocardial infarction at least a year ago, have already taken ticagrelor 90 mg in combination with aspirin for 1 year and ticagrelor 60 mg in combination with aspirin is continued without interruption and**
- **treatment with ticagrelor 60 mg BID is stopped when clinically indicated or after a maximum of 3 years."**

1.2 For the purposes of this guidance "a high risk of developing atherothrombotic events" is defined as presence of at least one of the following five risk factors:

- **Age ≥65 years,**
- **OR diabetes mellitus requiring medication,**
- **OR a second prior MI,**
- **OR evidence of multivessel coronary artery disease**
- **OR chronic non-end stage renal dysfunction (creatinine clearance <60ml/min).**

1.3 This guidance is not intended to affect the position of patients whose treatment with ticagrelor 60 mg BID, in combination with aspirin as a continuation therapy, was started within the NHS before this guidance was published. Treatment of those patients may continue without change to whatever funding arrangements were in place for them before this guidance was published until they and their NHS clinician consider it appropriate to stop."

2 The technology

Description of the technology

Please include a registered trademark for Brilique™ throughout the document.

Marketing authorisation

Please ensure that the licensed doses for each marketing authorisations are made clear and that the full marketing authorisation for the 60 mg BID is captured:

To achieve the latter we suggest amending the second paragraph to read:
"This marketing authorisation allows ticagrelor 60 mg BID to be initiated as continuation therapy after initial 1-year treatment with ticagrelor 90 mg BID or another Adenosine diphosphate (ADP) receptor inhibitor. Treatment can also be initiated up to 2 years from the MI, or within 1 year after stopping previous ADP receptor inhibitor treatment."

Price

Please note that the correct price of ticagrelor 60mg is **£54.60** for a 56 **tablet** pack (28-day supply).

4 Committee discussion

Please insert a space between "event,and" to read **"event, and"**.

4.2 Clinical management

The full stop should be removed at "clopidogrel.and".

4.3 Clinical management

a) Please correct the following in parentheses: "(approximately 1 in 5 people who are event-free in the first year after a myocardial infarction go on to experience a further myocardial infarction, stroke or within the subsequent 3 years) to read **"(approximately 1 in 5 people who are event-free in the first year after a myocardial infarction go on to experience a further myocardial infarction, stroke or cardiovascular death within the subsequent 3 years)."**

b) As for the equivalent comment made at section 1, please include the bolded "The committee was aware that patients enrolled into PEGASUS-TIMI 54, the trial which formed the basis of the company submission, had a history of myocardial infarction of at least 12 to 36 months, at least 1 additional risk factor for subsequent atherothrombotic events **(age ≥65**

years, diabetes mellitus requiring medication, a second prior MI, evidence of multivessel coronary artery disease or chronic non-end stage renal dysfunction)"

c) Please remove the extra space in the final sentence ("aspirin in" to be changed to **"aspirin in"**).

4.4 Decision problem (population)

The references to "the last antiplatelet" and "previous antiplatelet" are incorrect and should be corrected to read **"ADP receptor inhibitor"**. This is important because aspirin is an antiplatelet agent and this could cause confusion.

4.5 Decision problem (comparator)

It is more correct to say that the we "**explored the feasibility of conducting** an indirect comparison of ticagrelor with clopidogrel in combination with aspirin", rather than considered undertaking one.

4.14 Cost effectiveness

a) Please implement suggested changes from Section 1.1 to the bullet points in this section.
b) There is a reference in this section to a section 4.16, but this does not appear in the ACD.
c) The section ends with a comma, rather than a full stop.

Summary of appraisal committee's key conclusions

a) Please amend the appraisal title, as per earlier comment
b) Key conclusion: Please implement suggested changes from Section 1.1 to the bullet points in this section
c) Relevance to general clinical practice in the NHS:
    - Aligned to earlier comment, please replace "previous treatment with an antiplatelet agent" to **"previous treatment with an ADP receptor inhibitor"**
    - "in the trialIn practice", to read **"in the trial. In practice"**
d) Equalities considerations and social value judgements:
    - Space needed: "stroke,gastrointestinal bleed" to read **"stroke, gastrointestinal bleed"**
    - Space needed: "anticoagulation therapy.The" to read **"anticoagulation therapy. The"**

5.3 Implementation

Space needed: "without interruptionand " to read **"interruption and ".**

[redacted] *05/09/2016*

Ticagrelor for preventing atherothrombotic events after myocardial infarction

BCS response to NICE consultation

Based upon the results of PEGASUS-TIMI 54, The British Cardiovascular Society (BCS) believes that Ticagrelor 60 mg twice daily, taken in combination with Aspirin, may be of potential clinical benefit in patients who have sustained a prior myocardial infarction (MI) and who are at increased risk of further cardiovascular events. BCS therefore believes it is reasonable for this treatment regimen to be recommended as an option for this group of patients. However, BCS has several comments regarding the precise recommendations and the way these where formulated as described in the "Committee discussion" section of the NICE Appraisal consultation document, Ticagrelor for preventing atherothrombotic events after myocardial infarction.

1) Questionable basis for decision-making based on trial subgroup which might overestimate efficacy and safety of ticagrelor

In addition to PEGASUS-TIMI 54, NICE considered data submissions from Astra Zeneca which focused on the trial's subgroup of patients who had an MI between one to two years previously (and who were at increased risk of atherothrombotic events). This seems to have been based on the company's marketing authorisation, on its assumption that few patients more than two years from an MI received dual antiplatelet therapy, and on the assertion that this subgroup derives greater clinical benefit than patients whose MI was more distant. NICE concluded that it was appropriate to focus its decision making on this subgroup, as opposed to the whole study population which included patient entry up to three years following MI.

Several subgroup analyses, including time from qualifying (MI) event, were pre-specified in the trial protocol (which can be found online). Rates of the primary efficacy and safety endpoints in patients randomised to ticagrelor 60 mg twice daily or placebo were presented in supplementary figures in the online appendix to the PEGAGSUS-TIMI 54 publication in the New England Journal of Medicine. Rates of cardiovascular death, MI or stroke were 7.79% v 9.74% (HR 0.77; 95% CI 0.66-0.90), respectively, in patients who entered the trial within two years of MI and 7.76% v 7.94% (HR 0.96; 95% CI 0.79-1.17) in patients who entered the trial two or more years after MI. There was no significant interaction between time from MI and the primary efficacy endpoint (P=0.09) or between time from MI and the rates of TIMI major bleeding (P=0.23). The statistical grounds for using this subgroup to assess the efficacy and safety of ticagrelor as opposed to the main trial results is, therefore, not clear. The majority of the other pre-specified subgroup analyses showed a significant reduction in the rates of the primary efficacy endpoint in one but not the other of the comparators (e.g. men v women, caucasians v non-caucasians, prior PCI v no prior PCI, etc.) but, quite appropriately, NICE did not recommend treatment with ticagrelor only in the groups "benefiting" in these analyses, for example men and not women. Decision-making based on this subgroup, as opposed to the whole study population, selects the most positive results in favour of ticagrelor, yet it is not clear that this is a valid strategy and it is one which may overestimate the clinical efficacy and underestimate the side effects of ticagrelor. BCS believes this analysis may prejudice the results and recommends that NICE reviews its decision-making based on the subgroup of patients who were treated within two years of MI rather than the whole study population.

2) Potential overestimation of cost-effectiveness

Analogous to point 1), the subgroup of patients within two years of MI was also used in the cost-effectiveness analyses of the drug. The greater risk reduction in this group compared with

the trial population as a whole likely contributed to a more favourable estimate of the cost-effectiveness of ticagrelor.

3) **Specification of timing of initiation of ticagrelor**

Having chosen to base its analysis of efficacy, safety, and cost-effectiveness on the subgroup of patients who were randomised to receive ticagrelor or placebo within two years of MI, it seems inconsistent for NICE not to specify this timeframe (between one to two years from MI) in its recommendation for the introduction of ticagrelor.

4) **Inappropriate restriction of ticagrelor to patients who received ticagrelor in the first 12 months after myocardial infarction**

The draft NICE recommendations appear to restrict the use of ticagrelor beyond 12 months after MI to those patients who have already been treated with ticagrelor. It is acknowledged that ticagrelor (in combination with Aspirin) is commonly used in contemporary UK practice to treat "high risk" patients, but there seems no good clinical reason to exclude patients who have been treated with a different ADP antagonist in the first year after MI. BCS does not accept the argument that switching anti-platelet agents is complicated; it happens quite commonly already (not least because ticagrelor is often poorly tolerated in the first year post MI, requiring a switch over to clopidogrel, for example). Furthermore, as NICE acknowledges, 84% of patients in PEGASUS-TIMI 54 received an anti-plalet agent other than ticagrelor (usually clopidogrel) in the first year after MI. The draft recommendations are not consistent with the trial evidence and make little clinical sense.

5) **Specification of ticagrelor dosing in recommendations**

The draft recommendations refer to "ticagrelor 60 mg". The dosing regimen is 60 mg twice daily and this should be specified in the recommendations to avoid confusion. Guidelines and technology appraisals are frequently read without reference to the evidence behind them.

6) **Definition of high risk patients**

It is not clear from the draft NICE recommendations what constitutes patients who are at "high risk of developing atherothrombotic events." BCS believes that this group should be defined so that appropriately high-risk patients are considered for treatment and, conversely, so that lower risk patients who are likely to gain less or be harmed by prolonged dual anti-platelet therapy are not selected for treatment.

7) **Specification of exclusions from ticagrelor use**

In PEGASUS TIMI 54, the use of ticagrelor resulted in a significant increase in the rate of major bleeding (2.3% v 1.06%; $p<0.001$) despite exclusion from the study of patients who were at high risk of bleeding, such as patients who required oral anticoagulation. There is therefore no safety or efficacy data relating to this population and a credible mechanism for potential harm. BCS believes that the technology appraisal recommendations should specify that ticagrelor is not recommended for this indication in patients who are at high risk of bleeding such as those who require oral anticoagulation since they were excluded from the only relevant trial.

Comments on the ACD Received from the Public through the NICE Website

Name	[redacted]
Role	Deputy Head of Prescribing and Medicines Mangement
Other role	
Organisation	[redacted]
Location	England
Conflict	
Notes	
Comments on individual sections of the ACD: **I don't think the text within the following bullet:** **ï, "ticagrelor 60 mg in combination with aspirin is continued without interruption"** **makes it very clear about whether patients who had a MI more than 1 year ago, but less than 3 years , who have had their ticagrelor 90mg stopped should be re-started on ticagrelor 60mg.**	
Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	