NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Prasugrel with percutaneous coronary intervention for treating acute coronary syndromes (review of technology appraisal guidance 182)

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.

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	Response
Daiichi Sankyo and Lilly	Thank you for opportunity to comment on the Appraisal Consultation Document (ACD) on prasugrel with percutaneous coronary intervention (PCI) for treating acute coronary syndrome (ACS).	Comment noted.
	Whilst we welcome the Appraisal Committee's continued recognition of prasugrel as a valuable treatment option in ACS patients undergoing a PCI for ST-elevation myocardial infarction (STEMI), when stent thrombosis has occurred during clopidogrel treatment and in patients with diabetes in these preliminary recommendations, prasugrel has equally compelling data in the non-ST-segment-elevation myocardial infarction (NSTEMI) patient population who are to undergo PCI:	Comment noted. The recommendation in the FAD has been amended in order to specify the dose of prasugrel (prasugrel 10 mg) and include people with unstable angina and NSTEMI. See FAD sections 1.1 and 4.3.16.
	In the licensed 10mg population (core clinical cohort) censored at 12 months (EMA recommended length of therapy) the benefit, measured as primary end point, is further improved. Non-CABG-related TIMI major bleeding is ameliorated and is no longer significantly different to clopidogrel. This improved risk of bleeding, together with significantly improved efficacy outcomes resulted in the net clinical benefit being further improved (from HR 0.89 to HR 0.79).[1] This should support a more positive opinion towards prasugrel use in the NSTEMI ACS population. <u>References</u> 1. De Servi S, Goedicke J, Schirmer A, Widimsky P. Clinical Outcomes for Prasugrel Versus Clopidogrel are consistent among patients from TRITON-TIMI 38 with Unstable Angina or Non-ST-Elevation Myocardial Infarction. European Heart Journal. 2013 34 (Abstract Supplement), 882	Comment noted. The recommendation in the FAD has been amended in order to specify the dose of prasugrel (prasugrel 10 mg) and include people with unstable angina and NSTEMI. See FAD sections 1.1 and 4.3.16

Consultee	Comment	Response
	Prasugrel offers clinicians a treatment option where a potent oral antiplatelet is considered appropriate for NSTEMI patients, and we urge the Appraisal Committee to reconsider their decision and recommend prasugrel for use in all NSTEMI patients. Not recommending prasugrel in the wider NSTEMI patient population could mean that optimal treatment is denied to suitable patients. Despite the original decision on prasugrel, and the subsequent decision on ticagrelor, NICE guidance in this complex clinical area has not resulted in consistent opinion amongst clinicians in England and Wales, as confirmed by the clinical experts at the Appraisal Committee meeting. This could lead to a variation in patient care. In addition, the need to treat NSTEMI patients who require a PCI in England and Wales more quickly is a key clinical issue that further supports the availability of potent antiplatelet treatment options. Consistent recommendations for the oral antiplatelets will allow the right patient to get the right medication and in the process generate more evidence that can inform further comparative research to adapt care to improve outcomes.	Comment noted. The recommendation in the FAD has been amended in order to specify the dose of prasugrel (prasugrel 10mg) and include people with unstable angina and NSTEMI. See FAD sections 1.1 and 4.3.16.
	The Assessment Group's primary analysis showed prasugrel to be a cost effective treatment option when compared to clopidogrel in all the subgroups considered – including ACS patients treated with PCI for Unstable Angina (UA) or NSTEMI without a diagnosis of diabetes mellitus. The Appraisal Committee's decision to make recommendations about cost effectiveness using a five year time horizon is unfair. It is contradictory to the guidance given by NICE in the Guide to the methods of technology appraisal 20132, and is inconsistent with what has been accepted in previous cardiology technical appraisals and guidelines (TA236 (Acute coronary syndrome – ticagrelor), TA210 (Vascular disease - clopidogrel and dipyridamole), TA182 (Acute coronary syndrome – prasugrel) and CG94 (Unstable angina and NSTEMI). Another point of inconsistency is the Appraisal Committee's reluctance to accept the extrapolation of the CAPRIE data, while the same and similar extrapolations were accepted in 2010. Finally, the reasoning behind the decision to reduce the time horizon (due to parameters being sensitive to assumptions) is unjustified, considering the robust sensitivity analysis suggests otherwise. In addition, we commented on the approaches and statements made in the ACD on the following topics: 1. Use of a 5 year time horizon as the base case 2. Prasugrel bleeding rates referred to in the ACD 3. Lack of indirect comparison 4. Base case results in Table 1	Comment noted. In response to comments received during consultation, the Committee reconsidered which time horizon was the most appropriate for its decision making. The Committee noted that the time horizon within which the results would fall to within the range usually considered to be cost effective by NICE is likely to be much less than 40 years. The Committee considered that despite uncertainty in the ICERs arising from the 40 year extrapolation, the results were sufficiently robust to permit their use, and concluded that the 40 year time horizon was the most appropriate for decision making. See FAD section 4.3.14. Comments noted. Please see detailed responses to each below.

Consultee	Comment	Response
	5. Correction: Section 4.1.17 6. Correction: Section 4.1.18 Providing guidance that enables physicians and patients the choice of agents (clopidogrel, prasugrel and ticagrelor) in acute coronary syndrome PCI patients in both NSTEMI and STEMI will allow more consistent clinical practice in this complex therapy area and the provision of evidence to support improved outcomes for patients who continue to be at high risk of mortality.	Comment noted.
	<u>1. Use of a 5 year time horizon as the base case</u> We have concerns about the Appraisal Committee's decision to make recommendations about cost effectiveness using a 5 year time horizon as the base case on which to base their decision. In using this time horizon, the incremental cost effectiveness ratio (ICER) for the UA or NSTEMI without diabetes subgroup is higher than the range usually considered cost effective by NICE. This approach conflicts with the guidance given in the NICE's Guide to the methods of technology appraisal 2013[2], which states that a lifetime time horizon for clinical and cost effectiveness should be adopted if: 1.a technology has an impact on the costs and outcomes over a patient's lifetime; 2.a treatment affects survival at a differential rate when compared with the relevant comparator. Following this guidance, it is appropriate that a treatment for ACS have a lifetime time horizon as it affects survival, as well as costs and outcomes over a patient's lifetime. In addition, the decision problem states that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs and outcomes between the technologies being compared.	Comment noted. In response to comments received during consultation, the Committee reconsidered which time horizon was the most appropriate for its decision making. The Committee noted that the time horizon within which the results would fall to within the range usually considered to be cost effective by NICE is likely to be much less than 40 years. The Committee considered that despite uncertainty in the ICERs arising from the 40 year extrapolation, the results were sufficiently robust to permit their use, and concluded that the 40 year time horizon was the most appropriate for decision making. See FAD section 4.3.14.
	Inconsistency with previous appraisals A lifetime time horizon has been accepted in other economic models in cardiology, such as those used to inform TA236 (Acute coronary syndrome – ticagrelor), TA210 (Vascular disease - clopidogrel and dipyridamole), TA182 (Acute coronary syndrome – prasugrel) and CG94 (Unstable angina and NSTEMI). The Appraisal Committee has recognised that extrapolation is often necessary in economic modelling due to limited long term data. Extrapolation based on data	Comment noted. In response to comments received during consultation, the Committee reconsidered which time horizon was the most appropriate for its decision making. The Committee noted that the time horizon within which the results would fall to within the range usually considered to be cost effective by NICE is likely to be much less than 40

Consultee	Comment	Response
	collected over 3 years or less is common in cardiology health economics. In the models for TA236 (Acute coronary syndrome – ticagrelor) and CG94 (Unstable angina and NSTEMI), extrapolation was derived from MINAP data, which was collected over 2 years. CAPRIE data was used in TA210 (Vascular disease - clopidogrel and dipyridamole) to estimate long term risk in a lifetime model, and was accepted by the NICE Appraisal Committee. However, the extrapolation of this CAPRIE data (which had a follow-up period of 3 years) is now being questioned in this appraisal. *Sensitivity analysis* A reason given by the Appraisal Committee for their decision to use the 5 year time horizon for the base case is that "…the cost-effectiveness of prasugrel was highly sensitive to changes in key model assumptions". We disagree with this statement. The Assessment Group conducted robust sensitivity analysis, assessing the sensitivity to changes in key model assumptions (both univariately and probabilistically) and clearly showed across all subgroups that the model was not highly sensitive to changes in key model assumptions. The range of the ICER with the univariate sensitivity analysis was generally within £2,000, and values fell well below the range considered to be cost effective by NICE (£20,000 - £30,000/QALY gained). In the model submitted in TA236 (Acute coronary syndrome – ticagrelor), these univariate ranges included parameters that varied by £30,000. In addition, our own analysis showed that when looking at values for UA/NSTEMI without diabetes (which had a deterministic incremental cost of £248 and incremental QALYs of 0.053 at 40 years - giving an ICER of £4,667), if the incremental cost is kept constant and the incremental QALYs decreased, a decrease of 85% would be required before the ICER crosses a £30,000/QALY threshold. Likewise, if the incremental QALYs remain constant and the incremental cost increases, the cost would need to increase by seven times before the £30,000/QALY threshold is crossed. Decreasing the QALY gains by 50% as well as increasing the costs by 50% (£496) led to an ICER of £18,717 - an ICER below a £20,000-£30,000/QALY threshold. Such alterations should be considered extreme, but still produce ICERs below the accepted thresholds. In using the 5 year ICER for prasugrel compared with clopidogrel in patients with UA or NSTEMI without diabetes, the Appraisal Committee concluded that prasugrel was not a cost effective use of NHS resources. This would not have been the case if a lifetime time horizon was used as the base case.	years. The Committee considered that despite uncertainty in the ICERs arising from the 40 year extrapolation, the results were sufficiently robust to permit their use, and concluded that the 40 year time horizon was the most appropriate for decision making. See FAD section 4.3.14. Comments noted. In response to comments received during consultation, the Committee reconsidered which time horizon was the most appropriate for its decision making. The Committee noted that the time horizon within which the results would fall to within the range usually considered to be cost effective by NICE is likely to be much less than 40 years. The Committee considered that despite uncertainty in the ICERs arising from the 40 year extrapolation, the results were sufficiently robust to permit their use, and concluded that the 40 year time horizon was the most appropriate for decision making. See FAD section 4.3.14.

Consultee	Comment	Response
	References 2. National Institute for Health and Care Excellence. Guide to the methods of technology appraisal 2013. London: NICE; 2013 (www.nice.org.uk)	
	2. Prasugrel bleeding rates referred to in the ACD It is stated a number of times throughout the ACD that prasugrel use leads to a greater incidence of (potentially fatal) bleeding compared to clopidogrel. These statements are misleading when referring to the bleeding rates observed when prasugrel is used according to its current label. In the core clinical group, no statistically significant difference in the rate of non-CABG-related TIMI major bleeding was noted between patients in the prasugrel and clopidogrel arms. A significant difference in favour of clopidogrel was only seen when major and minor bleeding events were combined.[3] In order to be consistent and clear throughout the ACD we suggest that all references in the ACD to the bleeding rates of prasugrel should relate to those observed in the core clinical cohort, as this is the data the recommendations are based on and reflect our licensed indication for the 10mg dose. References 3. Wiviott SD, Desai N, Murphy SA et al. Efficacy and safety of intensive antiplatelet therapy with prasugrel from TRITON-TIMI 38 in a core clinical cohort defined by worldwide regulatory agencies. Am J Cardiol. 2011 108:905-1	Comment noted. FAD sections 4.1.13, 4.1.16 and 4.3.6 have been amended to clarify that a significant difference in favour of clopidogrel (in terms of bleeding rates) was only seen when major and minor bleeding events were combined. In addition, the source of the bleeding rate data has been made explicit in the text (for example, in patients aged over 75 or weighing under 60 kg [section 4.1.17], the clinical specialists opinion [section 4.3.1], the ACCOAST and TRILOGY trial results [section 4.3.2], and the CURRENT-OASIS 7 trial results [section 4.3.4]).
	3. Lack of indirect comparison We understand why the Appraisal Committee wanted an indirect comparison between prasugrel and ticagrelor to assist them in the decision-making process. However, key differences in the pivotal trials of prasugrel and ticagrelor mean that a formal indirect comparison is highly problematic and potentially inappropriate. This lack of comparable data again highlights the need for further experience of all the licensed treatment options available, utilised in similar patients in clinical practice.	Comment noted. The Committee was aware of the rationale provided by both the manufacturer and the Assessment Group for not undertaking the indirect comparison. However given that ticagrelor is in established use in clinical practice and that it was included as a comparator in the final scope issued by NICE, the Committee agreed that an indirect comparison should have been performed, recognising that it would have been imperfect. See FAD section 4.3.12.
	4. Base case results in Table 1 We consider it inappropriate to report the ERG amended results from TA182	Comment noted. Table 1 has been amended and additional text has been added to provide further explanation of the data presented. See FAD section

Consultee	Comment	Response
	alongside the current MTA results for three reasons: 1. There is not enough information provided in the documentation for the current MTA or the previous STA (TA182) to replicate the finding for the subgroup UA/NSTEMI without diabetes, as such we are unable to confirm the accuracy of the analysis. 2. It is unclear which cohort (e.g. target patient group, overall ACS group) the subgroup has been drawn from and whether the 'full' subgroup is analysed or a median patient. It appears more likely the median patient has been used, whereas in the MTA model it was run for the entire patient group rather than the median patient. It was acknowledged in the previous TA that this is not appropriate. 3.The MTA process and the STA process, as well as the models used in the assessments are, not equivalent. However, the presentation of the results in Table 1 would not allow a general reader to understand either the difference in the TA process or the concerns that the manufacturer had with the ERG amendments or the concerns that ERG had with the structure of the model, but would suggest these results can be read alongside each other.	4.2.27.
	5. Correction: Section 4.1.17 Under section 4.1.17 (p. 14) in the ACD it is stated that for patients aged 75 years and older, weighing less than 60 kg or with a history of stroke or transient ischaemic attack there were "…no statistically significant differences between the 2 groups for the primary efficacy end point." The results for the primary safety end point (non-CABG-related TIMI major bleeding) were not significant either, but this is not explicitly stated in the text. In order to give a balanced view of the data, the non-significance of both end points should be presented in the same manner.	Comment noted. Section 4.1.17 of the FAD has been amended to explicitly state the results for the primary safety end point.
	6. Correction: Section 4.1.18 It is stated under section 4.1.18 (p. 15) in the ACD that "The Assessment Group noted that if the incidence of clinical myocardial infarctions was compared, there may be no differences in outcomes between the treatment arms." This statement is contradictory to our understanding of the Assessment Group's comments on p. 43 of the Assessment Report[4]. More clarity on what information this statement is based on is required if it is to be included in the ACD. References	Comment noted. Section 4.1.18 of the FAD has been amended to state that the manufacturer's re-analysis of myocardial infarctions provided a convincing case that prasugrel is effective across all types of myocardial infarction when compared with clopidogrel.

Consultee	Comment	Response
	4. Greenhalgh J, Bagust A, Boland A, Dwan K, Beale S, Fleeman N, McEntee J, Dundar Y, Richardson M, Fisher M. Prasugrel with percutaneous coronary intervention for treating acute coronary syndromes (review of TA182). The Liverpool Reviews and Implementation Group, The University of Liverpool, 2013	

Comments received from clinical specialists and patient experts

Nominating organisation	Comment	Response
Pumping Marvellous Foundation	Has all of the relevant evidence been taken into account? Yes to my knowledge	Comment noted.
	Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? Yes to my knowledge	Comment noted.
	Are the provisional recommendations sound and a suitable basis for guidance to the NHS? From a patient perspective they are	Comment noted. The recommendation in the FAD has been amended in order to specify the dose of prasugrel (prasugrel 10mg) and to include all people with acute coronary syndrome (that is unstable angina, NSTEMI and STEMI). See FAD sections 1.1 and 4.3.16.
	Can I please point out that our organisation is the Pumping Marvellous Foundation not just Pumping Marvellous as per page 58 which makes our representation inaccurate.	Comment noted. The name of your organisation has been amended.

Nominating organisation	Comment	Response
Royal College of Nursing	The Royal College of Nursing welcomes the opportunity to review this document. The RCN's response to the questions on which comments were requested is set out below: i) Has the relevant evidence has been taken into account? The evidence considered seems comprehensive. ii) Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? We would ask that the summaries of the clinical and cost effectiveness of this appraisal should be aligned to the clinical pathway followed by patients with acute coronary syndrome. The preliminary views on resource impact and implications should be in line with established standard clinical practice	Comment noted. Comment noted. The summaries of clinical and cost effectiveness in this appraisal are aligned to the clinical pathways presented in other NICE guidance, including the clinical guideline on myocardial infarction with ST-segment elevation (NICE clinical guideline 167), the clinical guideline on unstable angina and NSTEMI (NICE clinical guideline 94), the original appraisal of prasugrel (NICE technology appraisal guidance 182) and the appraisal of ticagrelor (NICE technology appraisal guidance 236).
	iii) Are the provisional recommendations sound and a suitable basis for guidance to the NHS? 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 recommendation in the FAD has been amended in order to specify the dose of prasugrel (prasugrel 10mg) and include all people with acute coronary syndrome (that is unstable angina, NSTEMI and STEMI) having primary or delayed percutaneous coronary intervention. See FAD sections 1.1 and 4.3.16.
	iv) Are there any aspects of the recommendations that need particular consideration to ensure that NICE avoids unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? We are not aware of any specific issue at this stage. We would ask that any guidance issued should show that an equality impact analysis has been considered and that the guidance demonstrates an understanding of issues	Comment noted. Potential equalities issues were considered throughout the process of producing this guidance, including during the scoping, ACD and FAD stage of the appraisal. No equality issues relevant to the Committee's recommendations were raised. See summary of Appraisal Committee's key conclusions – section 'Equalities considerations and social value judgements'.

Nominating organisation	Comment	Response
	relating to all the protected characteristics where appropriate.	

Comments received from commentators

Commentator	Comment	Response
AstraZeneca	Thank you for the opportunity to submit comments for the Appraisal Consultation Document (ACD) of the appraisal: Prasugrel with percutaneous coronary intervention for treating acute coronary syndrome (review of TA182) [ID648].	Comment noted.
	AstraZeneca would like to comment on the draft recommendation (1.2) that prasugrel, in combination with aspirin, be recommended as an option for patients with NSTEMI or UA with diabetes (of appropriate age and weight).	Comment noted. The recommendation in the FAD has been amended in order to specify the dose of prasugrel and include all people with acute coronary syndrome (that is unstable angina, NSTEMI and STEMI) having primary or delayed percutaneous coronary intervention. See FAD sections 1.1 and 4.3.16.
	• The Appraisal Committee's consideration of the evidence for clinical-effectiveness contemplated all patients with diabetes (4.3.8), rather than considering patients in line with the defined subgroups for the appraisal (STEMI with diabetes, NSTEMI or UA with diabetes). AstraZeneca recognises that the TRITON-TIMI 38 trial showed additional benefit for patients with diabetes but would argue that the findings for the NSTEMI or UA with diabetes cohort (in particular) are not generalisable to routine clinical practice in England and Wales. The recently updated SmPC for prasugrel states "In NSTEMI/UA patients, where coronary angiography is performed within 48 hours after admission, the loading dose should only be given at the time of PCI." (1). Data from the most recent UK BCIS Audit (2) shows that, in UK real world practice, the median delay from first hospital arrival to PCI in NSTEMI patients is 2.6 days (for those who are admitted directly to a PCI centre) or 4.3 days for those who undergo an inter-hospital transfer. Therefore prasugrel use is appropriate in only a minority of UK NSTEMI patients undergoing PCI, and any recommendation from the appraisal should be reflective of this point. In NSTEMI patients in the TRITON study (3, 4), the loading of prasugrel anti-platelet therapy occurred only after the coronary anatomy was known to be suitable for PCI. Therefore the timing of prasugrel loading (as extrapolated from the TRITON trial) is not representative of the current treatment pathways for many	In response to comments received during consultation, the Committee reconsidered the generalisability of the TRITON-TIMI 38 trial to clinical practice in England in regards to the timing of preloaded dose of clopidogrel. The Committee heard from the manufacturer of prasugrel during the 2nd Committee meeting that the management of patients with NSTEMI in clinical practice has changed since the publication of the original appraisal of prasugrel (NICE technology appraisal guidance 182) – as the 'door to needle time' for patients in England decreases, so too does the time for pre-loading with clopidogrel. The Committee agreed that there is still limited evidence on the importance of the timing of the clopidogrel loading dose and so its effect on patients' outcomes remains an issue. See FAD section 4.3.4. The Committee accepted that the difference between diagnosis and treatment meant that there is uncertainty about whether the results of the

Commentator	Comment	Response
	patients presenting with NSTEMI/UA and potentially delays the initiation of dual anti-platelet therapy where an earlier diagnosis of NSTEMI/UA has already been made. • In accordance with the above, the findings of the TRITON-based cost-effectiveness analysis should not be considered generalisable to patients in England and Wales with NSTEMI or UA with diabetes, given real world treatment practice. **References** 1) Summary of Product Characteristics Efient 5 and 10mg tablets. Available from http://www.medicines.org.uk/emc/medicine/21504/SPC 2) BCIS National Audit of Percutaneous Coronary Interventional Procedures Public Reports Available at http://www.bcis.org.uk/pages/page_box_contents.asp?pageid=697&navcatid=11 3) Wiviott SD et al. Evaluation of prasugrel compared with clopidogrel in patients with acute coronary syndromes: design and rationale for the TRial to assess Improvement in Therapeutic Outcomes by optimizing platelet InhibitioN with prasugrel Thrombolysis In Myocardial Infarction 38 (TRITON-TIMI 38). Am Heart J. 2006; 152:627-35. 4) Wiviott SD et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. New Engl J Med. 2007; 357:2001-15.	TRITON-TIMI 38 trial can be generalisable to patients with unstable angina and NSTEMI in England. However, the Committee acknowledged that there is a slight advantage of prasugrel over clopidogrel beyond the period when preloading is relevant (see FAD section 4.3.4) and that the ICERs are well within the range usually considered be cost effective by NICE (£20,000 to £30,000). The Committee therefore concluded that prasugrel should be recommended for patients with unstable angina or NSTEMI. See FAD section 4.3.16.
Healthcare Improvement Scotland	I have read it again and again I cannot find fault. It is a very impressive and comprehensive appraisal which summarises all the clinically relevant points and provides clear management plans which will be very helpful for the management of ACS across the UK and beyond. As the authors allude, the main problem in this area is the relative lack of studies with most of the appraisal dependent on various analyses of three (very large studies) and the lack of a direct head to head of the newer antiplatelet therapies. However one can only analyse and appraise existing research and I genuinely do not think the group could improve on what they have produced.	Comment noted. The recommendation in the FAD has been amended in order to specify the dose of prasugrel and include all people with acute coronary syndrome (that is unstable angina, NSTEMI and STEMI) having primary or delayed percutaneous coronary intervention. See FAD sections 1.1 and 4.3.16.

Comments received from members of the public

Role*	Section	Comment	Response
NHS professional	Section 1	State an intended duration of treatment for prasugrel, similar to the TA for Ticagrelor (TA236). The SPC for prasugrel suggests a treatment duration of "up to 12 months is recommended, unless the discontinuation of Efient is clinically indicated". Wording to this effect will minimise premature swapping to clopidogrel after discharge and equally prevent prolonged duration of dual antiplatelet therapy.	Comment noted. The Committee did not consider evidence regarding the duration of treatment with prasugrel and so were unable to include this in its recommendations. The Committee was aware that the summary of product characteristics for prasugrel stipulates that treatment for up to 12 months is recommended unless stopping prasugrel is clinically indicated. See FAD section 3.2
		The phrase "person is not at increased risk of bleeding that is …….60kg or more" is misleading as all patients taking aspirin and a second more potent antiplatelet (pras or ticagrelor) will be at increased risk of major bleeding compared to aspirin and clopidogrel. The target population identified by the manufacturer included as having optimal benefit from prasugrel were those under the age of 75, weigh 60kg AND with no history of stroke or TIA. Could the statement "not at increased risk of bleeding" be removed and "no history of stroke and TIA" be inserted:" NICE recommends prasugrel in combination with aspirin for up to a year as a possible treatment for preventing …….. in those under the age of 75 years, who weigh more than 60kg and have no history of stroke or TIA.	Comment noted. The recommendation in the FAD has been amended in order to specify the dose of prasugrel and include all people with acute coronary syndrome (that is unstable angina, NSTEMI and STEMI) having primary or delayed percutaneous coronary intervention. See FAD sections 1.1 and 4.3.16. The Committee was aware that the summary of product characteristics for prasugrel recommends a lower dose of 5mg prasugrel for patients aged 75 years or over and for patients less than 60kg. The Committee noted that it had not been presented with any evidence for the efficacy of the lower dose of prasugrel and therefore it agreed it would be inappropriate to make a recommendation for patients aged 75 years or over and patients weighing less than 60kg. See FAD section 4.3.11.
	Section 4	4.3.9 - the quoted rate of stent thrombosis of 25% in those taking clopidogrel seems very high - expected rates are usually around 2%	Comment noted. This figure was the opinion of the clinical specialists present at the 1st Committee meeting. FAD section 4.3.9 has been amended to state:

* When comments are submitted via the Institute's web site, individuals are asked to identify their role by choosing from a list as follows: 'patient', '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
			"The Committee heard from the clinical specialists that in around a quarter of patients having percutaneous coronary intervention, stent thrombosis can occur despite clopidogrel treatment."
NHS professional	Section 1	I hope that recent data published by the Freeman group showing a mortality advantage for Prasugrel over and above Clopidogrel in patients with STEMI treated with PPCI is included in the appraisal. Although this is not randomised data, it is "real world" data that is highly relevant I hope that recommendations include the use of the 5mg dose of Prasugrel. Since the last TA, more data on this dose is available including platelet function data (Generations and Feather trials) and clinical data (Trilogy trial. I would consider it reasonable to recommend the 5mg dose for patients <60kg and >75yr age rather than avoiding in this patient group.	Comment noted. The Committee was not presented with any data published by the Freeman Group and was therefore unable to take it into account in its decision making. Comment noted. The recommendation in the FAD has been amended in order to specify the dose of prasugrel and include all people with acute coronary syndrome (that is unstable angina, NSTEMI and STEMI) having primary or delayed percutaneous coronary intervention. See FAD sections 1.1 and 4.3.16. The Committee noted comments received during consultation that new data had become available on the 5 mg dose since the publication of the original appraisal of prasugrel, which included data from the TRILOGY trial. The Committee was aware that safety data for the 5 mg dose of prasugrel from the TRILOGY trial had led to an update of the information on the 5 mg dose in the drug's summary of product characteristics. However, the Committee noted that it had not been presented with any evidence for the efficacy of the lower dose of prasugrel, and so was not in a position to recommend prasugrel for these subpopulations. See FAD section 4.3.11.
	Section 4	I hope that recent data published by the Freeman group showing a mortality advantage for Prasugrel over and above Clopidogrel in patients with STEMI treated with PPCI is included in the appraisal. Although this is not randomised data, it is "real world" data that is highly relevant I hope that recommendations include the use of the 5mg dose of	Comment noted. The Committee was not presented with any data published by the Freeman Group and was therefore unable to take it into account in its decision making. Comment noted. The recommendation in the FAD

Role*	Section	Comment	Response
		Prasugrel. Since the last TA, more data on this dose is available including platelet function data (Generations and Feather trials)and clinical data (Trilogy trial. I would consider it reasonable to recommend the 5mg dose for patients <60kg and >75yr age rather than avoiding in this patient group.	has been amended in order to specify the dose of prasugrel and include all people with acute coronary syndrome (that is unstable angina, NSTEMI and STEMI) having primary or delayed percutaneous coronary intervention. See FAD sections 1.1 and 4.3.16. The Committee noted comments received during consultation that new data had become available on the 5 mg dose since the publication of the original appraisal of prasugrel, which included data from the TRILOGY trial. The Committee was aware that safety data for the 5 mg dose of prasugrel from the TRILOGY trial had led to an update of the information on the 5 mg dose in the drug's summary of product characteristics. However, the Committee noted that it had not been presented with any evidence for the efficacy of the lower dose of prasugrel, and so was not in a position to recommend prasugrel for these subpopulations. See FAD section 4.3.11.
	Section 7	I can not see any representation from the community of Intervention Cardiologists on this committee. I think it would be beneficial if such an individual could be recruited	Comment noted. The Appraisal Committees are standing committees that do not recruit members from specific specialities for specific appraisal topics. The Chair of the Appraisal Committee and the NICE project team select clinical specialists and patient experts from nominations by non-manufacturer consultees and commentators Clinical specialists in the specific field of an appraisal are invited to attend Committee meetings and to provide their opinion on practice in the UK. See sections 1.9, 3.4.12 to 3.4.20 of NICE's Guide to the Single Technology Appraisal Process. A professor of interventional cardiology and a consultant cardiologist attended the Appraisal Committee meeting as clinical specialists to answer questions to help clarify issues about the submitted evidence.

Summary of comments received from members of the public

Theme	Response
An intended duration of prasugrel treatment should be stated	Comment noted. The Committee did not consider evidence regarding the duration of treatment with prasugrel and so were unable to include this in its their recommendations. The Committee was aware that the summary of product characteristics for prasugrel stipulates that treatment for up to 12 months is recommended unless stopping prasugrel is clinically indicated. See FAD section 3.2.
'…person is not at increased risk of bleeding…' is misleading	Comment noted. The recommendation in the FAD has been amended in order to specify the dose of prasugrel and include all people with acute coronary syndrome (that is unstable angina, NSTEMI and STEMI) having primary or delayed percutaneous coronary intervention. See FAD sections 1.1 and 4.3.16. The Committee was aware that the summary of product characteristics for prasugrel recommends a lower dose of 5mg prasugrel for patients aged 75 years or over and for patients less than 60kg. The Committee noted that it had not been presented with any evidence for the efficacy of the lower dose of prasugrel and therefore it agreed it would be inappropriate to make a recommendation for patients aged 75 years or over and patients weighing less than 60kg. See FAD section 4.3.11.
Quoted rate of stent thrombosis seems very high	Comment noted. This figure was based on the opinion of 2 clinician specialists who attended the 1st Appraisal Committee meeting. The wording has been amended to imply that a quarter of patients is the upper limit. See FAD section 4.3.9.
Recommendation for patients < 60 kg or > 75 years should be considered	Comment noted. The Committee was aware that the summary of product characteristics for prasugrel recommends a lower dose of 5mg prasugrel for patients aged 75 years or over and for patients weighing less than 60 kg. The Committee noted that it had not been presented with any evidence for the efficacy of the lower dose of prasugrel and therefore it agreed it would be inappropriate to make a recommendation for patients aged 75 years or over and patients weighing less than 60kg. See FAD section 4.3.11.

Theme	Response
Intervention cardiologists should be represented on the Committee	Comment noted. The Appraisal Committees are standing committees that do not recruit members from specific specialities for specific appraisal topics. The Chair of the Appraisal Committee and the NICE project team select clinical specialists and patient experts from nominations by non-manufacturer consultees and commentators. See sections 1.9, 3.4.12 to 3.4.20 of NICE's Guide to the Single Technology Appraisal Process. Clinical specialists in the field of cardiology were invited to attend the 1st Committee meeting and to provide their opinion on practice in the UK. A professor of interventional cardiology and a consultant cardiologist attended the Appraisal Committee meeting as clinical specialists to answer questions to help clarify issues about the submitted evidence.