NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events (review of technology appraisal guidance 90)

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
Sanofi-aventis and Bristol-Myers Squibb	Sanofi-aventis/Bristol-Myers Squibb welcome the preliminary recommendations of the Appraisal Committee as described in the ACD and look forward to these recommendations progressing to full guidance over the coming months. We are pleased that the Appraisal Committee has included the multivascular patient group, a group at a high risk of further occlusive vascular events, in this review and has provided clear guidance.	Comment noted. See responses below.
Sanofi-aventis and Bristol-Myers Squibb (cont)	Antiplatelets and bleeding risk Sanofi-aventis/BMS would like to request the deletion of the following line in section 3.2. "There is an increased risk of bleeding from clopidogrel because of its antiplatelet activities." All antiplatelets, by virtue of their pharmacological properties can increase the risk of bleeding and therefore this is not solely confined to clopidogrel. This is supported by the SmPC of both MRD-ASA and clopidogrel, and the findings of the Academic Group on page 16 of Assessment Report.	Comment noted. This has been amended in the FAD. See FAD section 3.2.
Sanofi-aventis and Bristol-Myers Squibb (cont)	Clinical Trials The Committee considered 4 clinical trials in reviewing the evidence for this appraisal, CAPRIE, ESPS2, which were available before the publication of TA90 and PROFESS and ESPRIT, two newer trials published following TA90. The CAPRIE trial, comparing clopidogrel with aspirin resulted in a relative risk reduction of 8.7% (p=0.043) in the primary endpoint of first occurrence of the composite outcome of ischaemic stroke, myocardial infarction or vascular death. The PROFESS study, the largest antiplatelet trial in the secondary prevention of stroke, failed to reach its primary endpoint of recurrent stroke (hazard ratio 1.01, 95% confidence interval 0.92-1.11; p=0.78), but demonstrated that MRD-ASA and clopidogrel are broadly comparable in terms of their efficacy. However when MRD-ASA was compared to clopidogrel there was an increased risk of major haemorrhagic events (HR 1.15, 95% confidence interval 1.00-1.32) and intracranial haemorrhage (HR 1.42, 95% confidence interval 1.11-1.83).	Comment noted. The Committee has considered these trials and they are summarised in the FAD document. See FAD sections 4.1, 4.3.3.

Consultee	Comment	Response
Sanofi-aventis and Bristol-Myers Squibb (cont)	With the publication of PRoFESS, the clinical effectiveness of clopidogrel (75 mg once daily) has been shown to have similar efficacy and a more favourable side effect profile and better tolerability compared with twice daily MRD-ASA. In light of this new evidence from PRoFESS, in addition to the evidence from CAPRIE and comments from the patient experts regarding the value of reducing the number of tablets patients need to take, clopidogrel should be considered the treatment of choice for patients at risk of occlusive vascular events.	Comment noted. The Committee has considered the PRoFESS trial and it is summarised in the FAD document. See FAD sections 4.1, 4.3.3.
Sanofi-aventis and Bristol-Myers Squibb (cont)	<u>Cost-effectiveness</u> The wider use of clopidogrel in patients at risk of occlusive vascular events is further supported by the economic analyses undertaken by the Academic group which demonstrated that clopidogrel is a cost-effective treatment in this population at the tariff price of £10.90 as per BNF58. The Academic Group conducted analyses utilising both the branded and the generic price of clopidogrel. SA/BMS support the Appraisal Committee's decision to consider the tariff price of clopidogrel as the most relevant for this appraisal. We would like to reiterate that less than 3% of prescriptions written in the NHS are for branded clopidogrel (Plavix) and roughly less than 13% of prescriptions are dispensed as branded clopidogrel (Plavix). Of special interest is the group of patients who have had an ischaemic stroke. In the Assessment Report received in May 2010, the cost-effective strategy was MRD-ASA followed by ASA, followed by clopidogrel. In our response to that report we pointed out that the costs and QALYS between those treatment strategies with clopidogrel first (e.g. clopidogrel> ASA>MRD-ASA) and those with MRD-ASA first (MRD-ASA>ASA>clopidogrel) were very similar. The Academic Group ran additional analyses that demonstrated that these differences were small and led to unstable results due to the uncertainty arising from simulation error. The academic model is a patient level simulation where costs and QALYS are estimated over a randomly simulated cohort of patients. The uncertainty arising from simulation error is reduced by increasing the number of simulated patients. Hence, the number of simulated patients was increased from 2,000 to 10,000. This increase resulted in consistent results across runs but also indicated that treatment strategies with clopidogrel as first in the treatment sequence lie on the cost-effectiveness frontier.	Comment noted. The Committee considered the cost effectiveness analyses that used the prices of both generic and branded clopidogrel. It considered the analyses that used the generic price for clopidogrel to be appropriate. See FAD section 4.3.6. Comment noted. The Committee discussed the revised analyses from the Assessment Group and discussed the differences in the costs and QALYs between the strategies. The Committee recognised that the differences in the total costs and QALYs for the different treatment strategies each including clopidogrel, modified-release dipyridamole plus aspirin and aspirin were small. However, it noted that these were consistent in all analyses, and with a further reduction in the price of clopidogrel the differences in costs would be larger. See FAD section 4.3.11.

Consultee	Comment	Response
Sanofi-aventis and Bristol-Myers Squibb (cont)	The results of the PSA in addendum 3 confirmed the results of the deterministic analysis presented in addendum 2 that treatment strategies with clopidogrel first, lay on the cost-effectiveness frontier. At a WTP =£20,000/QALY the treatment strategies with clopidogrel first in the sequence has an estimated probability of being cost-effective of 68% and at a WTP=£30,000/QALY a probability of 73%. Of note, these analyses were undertaken at the clopidogrel tariff price of £10.90. This price has subsequently decreased to £5.13 which is lower than the price of MRD-ASA of £7.79 and will of course further improve the cost-effectiveness of clopidogrel. We are therefore confident that the preliminary recommendations will remain unchanged and will progress to final guidance over the coming months	Comment noted. No changes requested. Comment noted. The Assessment Group provided a reanalysis of the data for people who had had a myocardial infarction. This analysis used a price of clopidogrel of £5.13, reflecting the NHS tariff price for August 2010. The results showed that aspirin followed by clopidogrel remained the optimal treatment strategy. See FAD section 4.3.10.
Vascular Society	We are concerned about the risks of bleeding in patients taking clopidogrel therapy who require elective, or urgent surgery. Please detail what happened to these patients in the studies, and it would be very helpful if guidelines on management could be included.	Comment noted. A technology appraisal provides recommendations about the cost effectiveness of technologies. Considerations regarding the specific management of particular patient groups are more appropriately considered as part of a clinical guideline. No changes made to the FAD.
Vascular Society (cont)	An increasing number of patients are having a stent inserted for peripheral arterial stenoses. Although there is little current evidence, this issue should be highlighted, and it seems logical to recommend a similar regimen to coronary stents.	Comment noted. Recommendations for the use of clopidogrel and modified release dipyridamole in people having a stent inserted are outside the scope of this appraisal. No changes made to the FAD.

Consultee	Comment	Response
Department of Health	In NICE's recommendations and key conclusions, clopidogrel or dipyridamole are referred to as being 'recommended as a treatment option.' The general reader may find this terminology very confusing i.e. is the treatment in question **recommended** or is it **an option?** The two terms have different implications for the user. Our understanding is that NICE wishes to imply that, if a clinician regards the use of one of these drugs as clinically appropriate, then the one they refer to (clopidogrel or modified release dipyridamole depending on the indication) is the **recommended** one. Could you please consider making the terminology clearer so that the user knows whether, as in the example of ischaemic stroke (ACD section 1.1.1 page 29), clopidogrel **should** be used or **should be considered for use** or **may be used**. With the current wording and particularly the use of the words **"an option"**, we believe that the general reader could easily conclude that NICE means any one of these three interpretations, which could be potentially confusing.	Comment noted. The use of the phrase 'recommended as a treatment option' is consistent with other NICE guidance. The intention of the guidance is that where a technology is recommended by NICE, it should be considered for use. However, choice of treatment should still include consideration of any other available treatments. No changes made to the FAD.
Department of Health (cont)	Generic clopidogrel is cheaper than branded clopidogrel and so will obviously be preferred by the NHS on cost grounds. However as was noted on p. 73 of NICE's CG94 (unstable angina and NSTEMI guideline), generic versions of clopidogrel are often not the same compound as branded Plavix, which is clopidogrel hydrogen sulphate (because they are different clopidogrel salts), and that the evidence upon which recommendations are made usually refers to Plavix. Could you please consider making reference to this. Our understanding is that plavix and generic clopidogrel preparations are assumed as equal in their efficacy, but that this is not proven. (Please be assured that we are not disputing NICE's advice that the cheapest version of clopidogrel should be used when indicated. It is merely our view that the evidence base may not necessarily apply to these cheaper versions, when they are different compounds).	Comment noted. Different preparations of clopidogrel were discussed at the Committee meeting. All generic versions of clopidogrel have a marketing authorisation for the prevention of atherothrombotic events in adults who have had a MI (from a few days until less than 35 days), IS (from 7 days until less than 6 months) or established PAD. No changes to the FAD made.

Consultee	Comment	Response
Diabetes UK and Association of British Clinical Diabetologists (Joint Submission)	**Has all of the relevant evidence been taken into account?** Although people with diabetes were not considered as a separate subgroup in this appraisal, it would be valuable for the appraisal consultation document to acknowledge that people with diabetes are considered a high risk group, and once they have cardiovascular disease, are at increased risk of further occlusive vascular events. The conclusions of the appraisal will therefore have a bearing on the care of people with diabetes.	Comment noted. The populations included in the appraisal are people who have established peripheral arterial disease, or have a history of myocardial infarction, ischaemic stroke or transient ischaemic attack. These populations are at high risk of occlusive vascular events or further occlusive vascular events, and can include people with diabetes, who have cardio vascular disease. No changes to the FAD made.
Diabetes UK and Association of British Clinical Diabetologists (Joint Submission) (cont)	**Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** It would be pertinent, as with some other technology appraisals, that a recommendation is included to ensure that people requiring antiplatelet therapy are provided with information about the benefits, risks, side effects, method, volume and frequency of administration of each appropriate antiplatelet therapy. This is important to support individuals to make an informed decision in partnership with their healthcare professional, helping tailor care to the needs of the individual. The committee noted the contribution of patient experts that identified people value factors such as ease of administration and few side effects.	Comment noted. A series of audit support materials will be developed alongside the appraisal. These include criteria about the provision of information to patients. No changes made to the FAD.
Diabetes UK and Association of British Clinical Diabetologists (Joint Submission) (cont)	We welcome the fact that the recommendations acknowledge contraindications and where medications may not be tolerated. The contraindications highlighted in the SPCs underscore the need for appropriate screening for pre-existing conditions and complications that would inform decisions about treatment options. In line with the committees recognition that clinical specialists said they would value ”clear, straight forward, guidance”, it would be useful, when producing implementation support for this guidance, that a chart of the different treatment options, the recommendations, and the benefits, risks and side effects, is provided for clinical use.	Comment noted. No changes requested. Comment noted. A series of audit support materials will be developed alongside the appraisal. No changes to the FAD requested.

Consultee	Comment	Response
Diabetes UK and Association of British Clinical Diabetologists (Joint Submission) (cont)	**Conclusion** As identified in our prior joint submission, these technologies should be available as antiplatelet therapies provided they are considered safe and effective. Decisions about treatment choice should be individually tailored and made in partnership between the healthcare professional and person with diabetes. In considering the treatment options available the following factors should inform decision making: • Licensed indications of the treatment • Clinical suitability, efficacy and patient choice • Quality of life considerations including known side effects such as headaches, bleeding, gastritis, nausea, vomiting • medication administration • Risks, safety, and contraindications	Comment noted. This appraisal has been completed in accordance with the published guide to the methods of technology appraisal. A technology appraisal makes recommendations for the NHS about the cost effective use of technologies. Recommendations take account of efficacy including health related quality of life and adverse effects, as well as cost. The Committee makes recommendations only within the context of the marketing authorisation of the technologies under appraisal.
British Association of Stroke Physicians	1. Has all of the relevant evidence been taken into account? As discussed at the Appraisal Committee Meeting, the reasons for exclusion of the CHARISMA and MATCH trials was discussed, and it may be relevant to mention this within the context of the trials considered (or not considered). In addition, and as previously outlined in my letter, the EARLY Trial was not considered, which compares early aspirin and dipyridamole initiation with standard initiation.	Comment noted. The Committee discussed the exclusion of the MATCH and CHARISMA trials, but considered that these studied a combination of clopidogrel plus aspirin which was outside of the scope of this appraisal. Likewise, it noted comments made about the EARLY trial that compared early and standard initiation of treatment, but considered that this had been appropriately excluded from the Assessment Group's review. See FAD section 4.3.3.
British Association of Stroke Physicians (cont)	2. Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence. In Section 4.3.12, I think it would be more appropriate to say that patients with transient ischaemia attack are sometimes (rather than often) treated with clopidogrel. In addition in the Summary Table, I think it is important to reiterate that the preference for clopidogrel is based upon a generic (cheapest available) prescription.	Comment noted. The word in the FAD was amended from 'often' to 'sometimes'. See FAD section 4.3.12. Comment noted. The following sentence was added to the summary table: 'treatment with clopidogrel to prevent occlusive vascular events should be started with the least costly licensed preparation.'

Consultee	Comment	Response
British Association of Stroke Physicians (cont)	3. Are the provisional recommendations sound and a suitable basis for guidance to the NHS? In Section 1.5, it is my understanding that this statement refers to the possibility that benefit may extend beyond the current two year period recommended by the guidelines in respect of dual aspirin and modified release dipyridamole therapy. I wonder if this should be more explicitly stated in this section of the Provisional Recommendation.	Comment noted. The statement in section 1.5 is standard wording that is used to ensure that any patients receiving treatment with a technology in circumstances not recommended in guidance and who started treatment prior to publication of the guidance, do not have their treatment stopped when the revised guidance is published. The last sentence on section 4.3.4 has been amended to read: 'The Committee was persuaded that it was appropriate to examine the Assessment Group's analyses of cost effectiveness without specifying a limit on the duration of treatment.'
British Association of Stroke Physicians (cont)	4. Are there any aspects to the recommendation that need particular consideration to ensure we would avoid unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief? No I trust that these minor comments are contributory, as I believe the document overall is a fair and balanced statement of the current evidence, the presentations made to the Appraisal Committee, and the subsequent discussions.	Comment noted. No actions requested. Comment noted. No actions requested.
Royal College of Nursing	Feedback received from nurses working in this area of health suggest that there is no additional comments to be submitted on behalf of the Royal College of Nursing on the ACD for the above appraisal	Comment noted. No actions requested.
Welsh Assembly Government	Thank you for giving the Welsh Assembly Government the opportunity to comment. Please note that we have no comment to submit at this stage.	Comment noted. No actions requested.

Comments received from clinical specialists and patient experts

Nominating organisation	Comment	Response
Clinical specialist	The recommendations are fundamentally sound. The issue, however, is whether they could be simpler to make application in 'the real world' easier and therefore achieve greater clinical and cost effective benefit. This is a confusing area as the appraisal excludes atrial fibrillation (AF) and coronary revascularisation which are both common. It also overlaps with CG 48 and 94. It is crucial that the recommendations do not prevent formal (warfarin) anticoagulation of AF or dual antiplatelet therapy in appropriate patients following coronary revascularisation. The differences between the strategies is small compared to the difference in adding other therapy such as statins and ACE inhibitors. Recommendations must facilitate this multi-pronged attack not introduce confusion that reduces it. It is unfortunate that clopidogrel is not licenced for TIA although it is generally accepted that it can be safely and effectively used when the other agents are not tolerated – a form of words needs to be chosen that allows this to happen and certainly does not inhibit it which would be detrimental for a high risk patient group. This is confounded by the fact that the distinction between TIA and ischaemic stroke is not always clear cut (MRI deficit with brief symptoms).	Comment noted. The guidance section clarifies that the recommendations do not apply to stroke prevention in atrial fibrillation. A technology appraisal makes recommendations for the NHS about the cost effective use of technologies. The Committee can only make recommendations within the context of the marketing authorisation of the technologies under appraisal.
Clinical specialist (cont)	For simplicity it would be much easier if 1.1 could recommend Clopidogrel for all as first line therapy. This might now be more cost effective as the price has fallen further so again avoiding the document being out of date. A carefully worded addendum for TIA would be needed and alternatives itemised when not tolerated. If it cannot be this simple then as section 1 will be the most read it should add that aspirin can be used in PAD when clopidogrel not tolerated as in 4.3.8.	Comment noted. The Assessment Group provided a reanalysis of the data for people who had had a myocardial infarction. This analysis used a price of clopidogrel of £5.13, reflecting the NHS tariff price for August 2010. The results showed that the lower price had no effect on the optimum treatment strategy: aspirin followed by clopidogrel remained the optimal treatment strategy. See FAD section 4.3.10.

Nominating organisation	Comment	Response
Clinical specialist (cont)	The recommendations should probably recognise the arrival of newer agents such as prasugrel which is licenced and used after myocardial infarction – it might continue instead of clopidogrel in multi vessel disease although this will be outside evidence but some flexibility may need to be allowed but avoiding confusion. Not recognising this will make the document look out of date very quickly. It is less clear whether clopigogrel resistance will be a big issue in the near future but if it is then recommending, by implication, that resistant patients swap from prasugrel to clopidogrel will be unhelpful.	Comment noted. The Committee may only make recommendations about technologies that are listed as interventions in the appraisal. Recognition in the recommendations, of the arrival of newer agents such as prasugrel is outside the scope of the appraisal. No changes made to the FAD.
Clinical specialist (cont)	The definition of PAD may be needed somewhere as this is not as clear as for the other diagnoses in clinical practice.	Comment noted. Peripheral arterial disease is described in section 2.2 of the FAD.
Clinical specialist (cont)	Finally the issue of Proton Pump Inhibitors with Clopidogrel should be covered to avoid confusion	Comment noted. A technology appraisal makes recommendations about the clinical and cost effectiveness of a technology. Issues about the use of Proton Pump Inhibitors with clopidogrel are more appropriately dealt with in the context of a clinical guideline. No changes made to the FAD.

Comments received from commentators

Commentator	Comment	Response
	None received	

Comments received from members of the public

Role*	Section	Comment	Response
		None received	

* 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.