NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Consideration of consultation responses on review proposal

Review of TA52; Drugs for early thrombolysis in the treatment of acute myocardial infarction, and TA230; Bivalirudin for the treatment of ST-segment elevation myocardial infarction (STEMI).

TA52 was issued in October 2002.

The review date for this guidance was October 2005.

In January 2006, following consultation, the Institute made this guidance 'static'.

TA230 was issued in July 2011. The review date for this guidance is July 2014.

Background

At the GE meeting of 29 May 2012 it was agreed we would consult on the review plans for this guidance. A four week consultation has been conducted with consultees and commentators and the responses are presented below.

Proposal put to consultees:	NICE has been asked to develop a clinical guideline on 'the acute management of myocardial infarction with ST-segment-elevation' and a related quality standard on the 'management of acute coronary syndromes including myocardial infarction'. It is proposed that the recommendations of TA52 and TA230 are incorporated verbatim into the clinical guideline. The guideline developers may supplement the recommendations by placing them in the context of current clinical practice. It is further proposed that TA230 is moved to the static list and TA52 remains on the static list until such time as the clinical guideline into which they are incorporated is updated. Both technology appraisals will remain extant alongside the clinical guideline. This has the consequence of preserving the funding direction for TA52 and TA230.
Rationale for selecting this proposal	There is no new evidence to suggest that either TA52 or TA230 require update. It is therefore appropriate to incorporate them into the ongoing, related clinical guideline.

GE is asked to consider the original proposal in the light of the comments received from consultees and commentators, together with any responses from the appraisal team. It is asked to agree on the final course of action for the review.

Recommendation post consultation:	The recommendations of TA52 and TA230 will be incorporated verbatim into the clinical guideline. The guideline developers may supplement the recommendations by placing them in the context of current clinical practice and other relevant NICE guidance. TA230 will be moved to the static list and TA52 remains on the static list until such time as the clinical guideline into which they are incorporated is updated. Both technology appraisals will remain extant alongside the clinical guideline. This has the consequence of preserving the funding direction for TA52 and TA230.

Respondent	Response to proposal	Details	Comment from Technology Appraisals
Merck, Sharp & Dohme	Request change to matrix	Currently Merck Sharp & Dohme is listed in the provisional matrix as a possible comparator manufacturer (tirofiban). However please note that MSD divested this product to Iroko in 2010, and Iroko now holds the product licence.	Comment noted
Medicines and Healthcare Products Regulatory Agency	No comment	It seems that you are consulting simply on an administrative arrangement; there is nothing here involving new evidence or appraisal of new interventions. Therefore, we will not be commenting on this.	Comment noted

Respondent	Response to proposal	Details	Comment from Technology Appraisals
British Cardiac Intervention Society / British Cardiovascular Society	Agree (TA52) Disagree (TA230)	We agree that TA52 should be incorporated verbatim in to the guidelines and are confident that the development group will place the recommendation in to the context of current clinical practice in which the default treatment strategy for ST elevation MI (STEMI) is primary percutaneous coronary intervention (PCI). Given the importance of primary PCI in the treatment of ST elevation myocardial infarction (STEMI) and the vital role of anti-coagulant and anti-platelet therapy in this procedure, we agree that incorporation of guidelines on bivalirudin in to new STEMI guidelines would be appropriate. We strongly advise however against incorporation of TA230 verbatim. The field of anti-coagulant and anti-platelet therapy in primary PCI is rapidly evolving and many combinations of effective drugs are possible. In addition to the TA230 recommendation concerning the use of bivalirudin in primary PCI for STEMI, NICE has issued two further recommendations in this area, namely TA 182 concerning the use of prasugrel and TA 236 concerning the use of ticagrelor. These recommendations are each helpful when taken alone, but when viewed together with TA230 are leading to considerable confusion and disquiet among BCIS members who are of course those responsible for providing primary PCI services in the UK. While both ticagrelor and prasugrel are recommended as treatment options in primary PCI, NICE states that bivalirudin in combination with aspirin and clopidogrel is recommended (i.e. it is not considered as “an option”) for use in primary PCI. As NICE does not recommend the use of bivalirudin with ticagrelor or prasugrel (for which no good evidence exists), the many BCIS members who choose to use heparin plus dual anti-platelet therapy with aspirin and prasugrel or ticagrelor in accordance with TAs 182 and 236 are not compliant with TA230. Our firm opinion is that there is sufficient uncertainty about optimal anti-coagulant and anti-platelet therapy in primary PCI for STEMI to justify each of these treatment strategies and that bivalirudin in combination with aspirin and clopidogrel should be recommended as a treatment option in primary PCI for STEMI in the guidelines for STEMI.	Comments noted The ‘recommended’ wording in TA230 applies only to the context in which bivalirudin was considered in the single technology appraisal. Where other options are also appropriate, the wording does not prevent the guideline group giving guidance on all the alternatives. The guideline will incorporate both TA 230 and TA236. The summary of product characteristics for bivalirudin states that should be administered with aspirin and clopidogrel. The TA recommendation only applies to the use of bivalirudin within its licensed indication and would not apply in circumstances where an alternative to clopidogrel was used. By placing the recommendations in the context of current clinical practice and other relevant NICE guidance the guideline developers can address these objections.

Respondent	Response to proposal	Details	Comment from Technology Appraisals
British Cardiac Intervention Society / British Cardiovascular Society (continued)		Further detailed reasons for our opinion on the use of bivalirudin in primary PCI for STEMI were provided to NICE in a letter from the then president of BCIS, Dr Mark de Belder, in October 2011. I attach a copy of this letter but will summarise the points as follows: • The guidance leads to contradictions with other TAs as explained above • The guidance was issued without going through the ACD process and BCIS missed the deadline for submitting views on the FAD. • The guidance issued was based on one RCT which demonstrated equal efficacy but lower bleeding rates than the comparator regimen of heparin plus GP. This trial recruited primarily in the USA and mainland Europe and the use of radial angioplasty which reduces bleeding rates dramatically was only 5%. Radial artery PCI is now the majority practice within the UK so that the trial data are not directly applicable to most UK centres. • The guidance issued was based on one RCT in which the use of upstream heparin was common, a practice used almost never in the UK. It has been demonstrated in data from independent studies that lack of upstream heparin leads to a significant reduction in the efficacy of bivalirudin with inferior outcomes. Again, we feel that the trial data evaluated in the NICE appraisal are not directly applicable to routine UK practice. • The RCT on which the guidance was based demonstrated a significant increase in the occurrence of acute stent thrombosis compared to the control arm of heparin plus GPI. We are very much in favour of bivalirudin as a treatment option for primary PCI in the UK, particularly for those centres who continue to employ femoral artery access with its high level of bleeding complications. We would request that the STEMI GDG reconsider the precise wording of TA230 and insert the phrase ‘as a treatment option’. This minor wording change should not require a wholesale re-appraisal of the evidence. To our knowledge, no significant new evidence on the use of bivalirudin in primary PCI has become available.	

Respondent	Response to proposal	Details	Comment from Technology Appraisals
British Cardiac Intervention Society / British Cardiovascular Society (continued)		Alternatively, the GDG might just cross refer to TA230 and put the use of bivalirudin in context for UK practice alongside regimens which include prasugrel or ticagrelor . We hope that the result of either approach would be to allow BCIS members to choose between the variety of effective anti-coagulant and anti-platelet therapies available for primary PCI according to their professional opinions, budgets and existing local practices but still to be 'compliant' with NICE guidelines. This choice acknowledges the current evidence base which in our opinion contains such uncertainty, that no single treatment option - including the use of bivalirudin with aspirin and clopidogrel - can be recommended above all others for use in the UK.	
Royal College of Physicians	Agree	The RCP wishes to endorse the response submitted by the British Cardiovascular Intervention Society (and already endorsed by the BCS).	Comment noted
Boehringer Ingelheim	Agree	I can confirm that Boehringer Ingelheim has no objection to TA52 being incorporated verbatim into a new Clinical Guideline, on the proviso, as stated, that this preserves the funding direction for TA52. In terms of new evidence informing the guideline, the ongoing STREAM trial, which aims to evaluate the outcome of patients presenting with acute ST-elevation myocardial infarction within 3 hours of symptom onset in either a pre-hospital setting or community hospital emergency room without a PCI facility, is due to complete later this year. The study compares a strategy of early tenecteplase and additional antiplatelet and antithrombin therapy followed by catheterisation within 6-24 hours with timely coronary intervention as appropriate (or by rescue coronary intervention if required) to primary PCI performed according to local standards. This study, whilst exploratory in nature, could provide important new evidence. A link to the publicly available trial details is provided below. http://www.clinicaltrials.gov/ct2/show/NCT00623623	Comments noted

Respondent	Response to proposal	Details	Comment from Technology Appraisals
Royal College of Nursing	No comment	Feedback received from nurses working in this area of health suggest that there are no additional comments to submit in relation to the review proposal for the above appraisal	Comment noted
Lilly UK	Agree	We agree with the decision to move TA52 and TA230 into the clinical guideline on 'the acute management of myocardial infarction with ST-segment-elevation' and the related quality standard on the 'management of acute coronary syndromes including myocardial infarction'. Furthermore, we agree with the proposal that TA52 remain on the static list and that TA230 should be moved to the static list.	Comment noted

No response received from:

<u>Manufacturers/sponsors</u> • Actavis UK (reteplase) • CSL Behring (streptokinase) • The Medicines Company UK (bivalirudin) <u>Patient/carer groups</u> • Action Heart • Afiya Trust • Black Health Agency • Blood Pressure Association • British Cardiac Patients Association • British Hypertension Society • Cardiac Risk in the Young • Counsel and Care	<u>General</u> • Board of Community Health Councils in Wales • British National Formulary • Care Quality Commission • Commissioning Support Appraisals Service • Department of Health, Social Services and Public Safety for Northern Ireland • Healthcare Improvement Scotland • National Association of Primary Care • NHS Alliance • NHS Commercial Medicines Unit • NHS Confederation • Public Health Wales NHS Trust • Scottish Medicines Consortium

• Equalities National Council • Grown Up Congenital Heart Patient's Association • Heart Care Partnership (UK) • HEART UK • Muslim Council of Britain • Muslim Health Network • National Obesity Forum • Network of Sikh Organisations • South Asian Health Foundation • Specialised Healthcare Alliance • Stroke Association • Weight Concern <u>Professional groups</u> • British Association for Nursing in Cardiac Care • British Association for Services to the Elderly • British Association of Emergency Medicine • British Atherosclerosis Society • British Geriatrics Society • British Heart Foundation • British Nuclear Cardiology Society • British Society of Cardiac Radiology • National Heart Forum (UK) • Nurses Hypertension Association • Primary Care Cardiovascular Society • Royal College of General Practitioners • Royal College of Pathologists • Royal Pharmaceutical Society • Royal Society of Medicine • Society for Cardiological Science and Technology [BCS	<u>Possible comparator manufacturers</u> • Actavis UK (aspirin, clopidogrel) • Alliance Pharmaceuticals (aspirin) • Aspar Pharmaceuticals (aspirin) • Bayer (aspirin) • Bristol-Myers Squibb Pharmaceuticals (clopidogrel) • Consilient Health (clopidogrel) • Dexcel-Pharma (aspirin, clopidogrel) • Dr Reddy's Laboratories UK (clopidogrel) • Focus Pharmaceuticals (aspirin) • Galpharm-International (aspirin) • Genus Pharmaceuticals (aspirin) • GlaxoSmithKline (eptifibatide) • Kent Pharmaceuticals (aspirin) • Iroko (tirofiban) • Mylan (aspirin, clopidogrel) • Napp Pharmaceuticals (aspirin) • Pinewood Healthcare (aspirin) • Reckitt Benckiser (aspirin) • Sandoz (aspirin) • Sanofi (aspirin, clopidogrel) • Sinclair Pharma (aspirin) • Teva UK (aspirin, clopidogrel) • The Boots Company (aspirin) • Thornton & Ross (aspirin) • Watson Pharmaceuticals (aspirin, clopidogrel) • Wockhardt UK (aspirin, heparin)

affiliated] • Society of Cardiothoracic Surgeons • United Kingdom Clinical Pharmacy Association • Vascular Society <u>Others</u> • Cornwall and Isles of Scilly PCT Cluster • Department of Health • Hywel Dda Health Board • Welsh Government	<u>Relevant research groups</u> • Antithrombotic Trialists' (ATT) Collaboration • British Society for Cardiovascular Research [BCS affiliated] • Cardiac and Cardiology Research Dept, Barts • Cardiovascular Diseases Specialist Library (CVDSL) • Cardiovascular Research Initiative, University of Oxford • Cochrane Heart Group • Cochrane Hypertension Group • Cochrane Peripheral Vascular Diseases Group • Cochrane Stroke Group • CORDA • European Council for Cardiovascular Research • MRC Clinical Trials Unit • National Heart Research Fund • National Institute for Health Research • Research Institute for the Care of Older People <u>Assessment Group</u> • Assessment Group tbc • National Institute for Health Research Health Technology Assessment Programme <u>Associated Guideline Groups</u> • National Clinical Guideline Centre • National Collaborating Centre for Chronic Conditions <u>Associated Public Health Groups</u> • None

GE paper sign-off: Janet Robertson, Associate Director – Technology Appraisals Programme

Contributors to this paper:

Technical Lead: Helen Tucker

Project Manager: Andrew Kenyon

13 July 2012