NICE National Institute for Health and Care Excellence

NICE guidance

Guidance on the use of glycoprotein IIb/IIIa inhibitors in the treatment of acute coronary syndromes

Technology appraisal guidance
Published: 5 September 2002
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www.nice.org.uk/guidance/ta47

Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

This guidance replaces TA12.

This guidance is partially replaced by CG94.

1 Recommendations

1.1 This recommendation no longer stands.

1.2 This recommendation has been updated and replaced by recommendation 1.3.9 in the NICE guideline on unstable angina and NSTEMI.

1.3 This recommendation has been updated and replaced by recommendation 1.3.9 in the NICE guideline on unstable angina and NSTEMI.

1.4 This recommendation has been updated and replaced by recommendations 1.2.1 and 1.2.2 in the NICE guideline on unstable angina and NSTEMI.

1.5 This recommendation no longer stands.

1.6 This recommendation has been updated and replaced by recommendation 1.3.10 in the NICE guideline on unstable angina and NSTEMI.

1.7 It is recommended that a glycoprotein (GP) IIb/IIIa inhibitor is considered as an adjunct to percutaneous coronary intervention (PCI) for all patients with diabetes undergoing elective PCI, and for those patients undergoing complex procedures (for example, multi-vessel PCI, insertion of multiple stents, vein graft PCI or PCI for bifurcation lesions); currently only abciximab is licensed as an adjunct to PCI. In procedurally uncomplicated, elective PCI, where the risk of adverse sequelae is low, use of a GP IIb/IIIa inhibitor is not recommended unless unexpected immediate complications occur.

1.8 GP IIb/IIIa inhibitors are not currently licensed in the UK for use as an adjunct to thrombolytic therapy in ST-segment-elevation MI.

2 Clinical need and practice

2.1 Coronary heart disease (CHD) is the most common cause of death in the UK. It is a progressive disease. The first presenting symptom is often stable angina (pain in the chest on exertion), which may progress to an acute coronary syndrome (ACS). ACSs encompass a range of symptoms with broadly similar underlying causes. They include ischaemic cardiac chest pain of recent origin in the categories:

- non-ST-segment-elevation ACS, including unstable angina and non-ST-segment-elevation myocardial infarction (NSTEMI)
- myocardial infarction (MI) with ST-segment-elevation (an acute MI, also known as STEMI).

2.2 Unstable angina covers a range of clinical states falling between stable angina and acute MI, including angina at rest lasting more than 20 minutes, increasing angina and angina occurring more than 24 hours after an acute MI.

2.3 NSTEMI (also known as non-Q-wave MI) is the term used when the cardiac markers (troponins and creatine kinase [CK]) are elevated to ranges that indicate that MI has occurred, but a Q-wave does not develop on ECG tracings. This profile is thought to indicate damage to the heart muscle that does not extend through the full thickness of the myocardium. NSTEMI therefore represents a subgroup of patients with non-ST-elevation ACS at high risk of a subsequent event.

2.4 In 1998, the overall prevalence of CHD in England was estimated to be 7.1% in men and 4.6% in women. Prevalence increases with age. It is difficult to estimate the incidence of ACS in England and Wales. The hospital episode statistics for 2000/01 detail 148,000 episodes of angina pectoris in England, with 83,000 of these specified as unstable angina. However, there are variations in the coding of this condition, and it has been suggested that these figures are conservative. Recently, the incidence of unstable angina has been estimated at 226 cases per 100,000 population, which equates to approximately 120,000 cases in England and Wales per annum.

2.5 In 1999, in England and Wales, there were over 115,000 deaths caused by CHD. Although CHD-associated mortality rates are falling by about 4% per year in the UK, this does not reflect a fall in incidence of the disease. In addition, improvements in rates of death from CHD have not been uniform across all social classes; death rates among unskilled men are 3 times greater than those among professional men.

2.6 The main aim in the short-term management of non-ST-segment-elevation ACS is to control pain and prevent progression to full-thickness MI (STEMI) and/or death. The first steps in the management pathway involve bed rest and medical treatment including antiplatelet therapy (aspirin), anticoagulants (heparin and low-molecular-weight heparin [LMWH]), vasodilators (nitrates), calcium-channel blockers and beta-blockers. Revascularisation, when necessary, is by means of PCI, usually with stent implantation, or by CABG.

2.7 Certain patients with unstable angina are at high risk of progression to MI or death. The British Cardiac Society guidelines say that certain circumstances are associated with an increased risk of early adverse outcome, including age above 65 years; comorbidity, especially diabetes; prolonged (more than 15 minutes) cardiac pain at rest; ischaemic ECG ST-segment depression on admission or during symptoms; ECG T-wave inversion (associated with an intermediate risk, lying between that associated with ST-segment depression and normal ECG); evidence of impairment of left ventricular function (either pre-existing or during MI); and elevated C-reactive protein. In addition, those with raised levels of cardiac troponin are considered to be at high risk of an event.

2.8 Despite the use of standard therapy (antiplatelet agents and anticoagulants), the rate of adverse outcomes (such as death, non-fatal re-infarction, refractory angina or readmission for unstable angina) at 6 months after presenting with unstable angina is about 30%.

2.9 In guidance issued in September 2000, NICE recommended the intravenous use of glycoprotein IIb/IIIa (GP IIb/IIIa) inhibitors, in addition to aspirin and low (adjusted) dose unfractionated heparin, for patients with unstable angina at high risk of death or further MI. NICE's guidance recommended intravenous administration of GP IIb/IIIa inhibitors to patients undergoing acute or elective PCI.

3 The technology

3.1 Abciximab (ReoPro)

3.1.1 Abciximab is a monoclonal antibody that targets the GP IIb/IIIa receptor on the surface of platelets.

3.1.2 Abciximab is indicated as an adjunct to aspirin and heparin for the prevention of ischaemic complications in patients undergoing PCI. It is also indicated for the short-term (1 month) reduction of risk of MI in patients who have unstable angina that is not responding to full conventional therapy and who are to undergo PCI. Abciximab is administered intravenously at an initial bolus dose of 250 μg/kg body weight followed by a maintenance dose of 0.125 μg/kg/min (maximum 10 μg/min) over 12 to 36 hours.

3.1.3 As with the other GP IIb/IIIa inhibitors, the side effects of abciximab (including bleeding and thrombocytopenia) are related to its pharmacological effects. For full details of side effects and contraindications, see the Summary of Product Characteristics.

3.1.4 The cost of abciximab is £280 (net) for a 10-mg vial (BNF 43rd edition). For a 70-kg person, the cost per course ranges from £840 to £1,120, depending on the duration of treatment (costs rounded to full vials).

3.2 Eptifibatide (Integrilin)

3.2.1 Eptifibatide is a synthetic cyclic heptapeptide and is one of the small-molecule GP IIb/IIIa inhibitors. It reversibly inhibits platelet aggregation by preventing the binding of fibrinogen and other adhesive ligands to the GP IIb/IIIa receptor.

3.2.2 Eptifibatide is indicated for the prevention of early MI in patients presenting with unstable angina or non-Q-wave MI (NSTEMI) who have had chest pain within the last 24 hours and who have ECG changes and/or elevated cardiac enzymes. It is

administered intravenously at an initial bolus dose of 180 μg/kg followed by a maintenance dose of 2.0 μg/kg/min for up to 72 hours (up to 96 hours if the patient has a PCI during treatment).

3.2.3 As with the other GP IIb/IIIa inhibitors, the side effects of eptifibatide (including bleeding and thrombocytopenia) are related to its pharmacological effects. For full details of side effects and contraindications, see the Summary of Product Characteristics.

3.2.4 The cost of eptifibatide is £15.54 (net) for a 20-mg vial and £48.84 (net) for a 75-mg vial (BNF 43rd edition). For a 70-kg person, the cost per course ranges from £455 to £553, depending on the duration of treatment (costs rounded to full vials).

3.3 Tirofiban (Aggrastat)

3.3.1 Tirofiban is a non-peptidal antagonist of the GP IIb/IIIa receptor and is one of the small-molecule GP IIb/IIIa inhibitors. It prevents fibrinogen from binding to the GP IIb/IIIa receptor, thus blocking platelet aggregation.

3.3.2 Tirofiban is indicated for the prevention of early MI in patients presenting with unstable angina or NSTEMI who have had chest pain within the last 12 hours and who have ECG changes and/or elevated cardiac enzymes. It is administered intravenously at an initial dose of 0.4 μg/kg/min for 30 minutes followed by a maintenance dose of 0.1 μg/kg/min for at least 48 hours, up to a maximum duration of treatment of 108 hours.

3.3.3 As with the other GP IIb/IIIa inhibitors, the side effects of tirofiban (including bleeding and thrombocytopenia) are related to its pharmacological effects. For full details of side effects and contraindications, see the Summary of Product Characteristics.

3.3.4 The cost of tirofiban is £146.11 (net) for a 12.5-mg vial (BNF 43rd edition). For a 70-kg person, the cost per course ranges from £292 to £584, depending on the duration of treatment (costs rounded to full vials).

4 Evidence and interpretation

The appraisal committee considered evidence from a number of sources (see appendix B). Each indication was considered separately.

4.1 Clinical effectiveness

4.1.1 GP IIb/IIIa inhibitors for the medical management of ACSs

4.1.1.1 The assessment group found 1 new study (GUSTO IV), in addition to 4 studies from the previous appraisal that are relevant to this review. All were classified as randomised controlled trials (RCTs) that included patients with unstable angina or NSTEMI, but the definitions of the participants varied between trials. Two studies looked at eptifibatide, 2 at tirofiban and 1 at abciximab; all these studies compared treatment with placebo or no treatment. On the whole, the studies were well conducted. Outcome measures included death, MI, need for revascularisation and adverse events associated with use of the trial drugs. Differences between trials precluded pooling results in the assessment report.

4.1.1.2 In nearly all studies involving the small-molecule GP IIb/IIIa inhibitors (eptifibatide and tirofiban), the rates of death and MI were reduced in the treatment groups compared with the comparator group; however, the difference was not always statistically significant. In all of the trials, the risk of bleeding was greater in the groups receiving a GP IIb/IIIa inhibitor than in the comparator group, but the difference was not always statistically significant.

4.1.1.3 In the GUSTO-IV trial of abciximab, the results demonstrated neither benefit nor trends of benefit in the primary outcomes of death and MI at 30 days.

4.1.1.4 The assessment group concluded that the effects of GP IIb/IIIa inhibitors were small compared with those of other interventions in ACS, for example aspirin. Subgroup analyses showed that GP IIb/IIIa inhibitors may be particularly effective in troponin-positive patients. A recently published meta-analysis seen by the committee (the Boersma study) analysed the data for various subgroups and suggested that, in those not routinely scheduled for early PCI, the rate of cardiac

complications is reduced following the administration of GP IIb/IIIa inhibitors.

4.1.1.5 The submissions for this appraisal from consultees (manufacturers/sponsors and professional and patient/carer groups) contained no clinical evidence on the use of GP IIb/IIIa inhibitors for the medical management of ACS that had not already been included in the assessment report.

4.1.1.6 The clinical experts were asked about the evidence for medical management in those not going on to have a PCI during GP IIb/IIIa inhibitor administration, which is frequently the scenario in current UK practice. They stated that current evidence-based good practice is to investigate, by means of coronary angiography, with a view to early revascularisation, all of those patients presenting with ACS deemed to be at high enough risk to merit a GP IIb/IIIa inhibitor.

4.1.1.7 They were also asked to comment on the importance of various risk factors used to identify high-risk ACS patients. They considered that an elevated troponin result often confirms the high-risk status of an individual, but that increased troponin should not be thought of as the only indicator of high risk and that other clinical factors have to be taken into account.

4.1.2 GP IIb/IIIa inhibitors as an adjunct to PCI

4.1.2.1 The assessment group found 5 new trials (PRICE, ADMIRAL, TACTICS-TIMI, TARGET and ESPRIT), in addition to 12 studies from the previous appraisal that are relevant to this review. Fourteen trials compared treatment with placebo or no treatment, 10 of which involved abciximab, 3 involved eptifibatide and 1 involved tirofiban. There were 2 head-to-head trials, 1 of abciximab and eptifibatide and 1 of abciximab and tirofiban. One further trial compared invasive and conservative treatment, with all participants receiving tirofiban. The definition of participants both within and between trials was broad, from patients undergoing elective PCI to those who had acute PCI after MI. All trials were classified as RCTs, and many of them were large (with at least 1,000 participants). Outcomes measured included death, non-fatal MI, the need for PCI or CABG after the current procedure, and adverse events.

4.1.2.2 Again, the results of the trials were not pooled for the assessment report because of heterogeneity, which included differences between studies in the inclusion criteria for patients undergoing the procedure. Only 1 trial showed the use of a GP IIb/IIIa inhibitor to be associated with a significant reduction in the mortality rate at 30 days; another trial showed significant reduction in the mortality rate at 6 months. The use of a GP IIb/IIIa inhibitor was associated with a reduction in the rate of revascularisation at 30 days and at 6 months in studies in which this was measured, but the difference was statistically significant in 1 trial only.

4.1.2.3 However, with composite outcomes (usually a combination of death, subsequent MI and revascularisation), the great majority of trials showed a statistically significant benefit of treatment with a GP IIb/IIIa inhibitor. There were more minor and major bleeds in the treatment groups in all studies, but the increased rates were not always statistically significant. There was little evidence of benefit for subgroups.

4.1.2.4 The only new data submitted on the use of GP IIb/IIIa inhibitors during PCI were longer-term data from 2 trials (ESPRIT and EPIC), some re-analysis of the existing data, and data from a recent UK audit presented by the British Cardiac Society and Royal College of Physicians (London).

4.1.2.5 The clinical experts were asked to comment on the use of GP IIb/IIIa inhibitors as an adjunct during elective PCI. Their view was that elective single-vessel PCI in a low-risk patient carries a very small absolute risk of complications. Consequently, the use of GP IIb/IIIa inhibitors in such low-risk patients was generally considered unlikely to confer any clinically significant additional benefit; GP IIb/IIIa inhibitors should only be used in these circumstances if unexpected complications occur. Conversely, the use of GP IIb/IIIa inhibitors as an adjunct to PCI was considered beneficial in patients with evidence of recent ACS, in patients with diabetes and in patients undergoing potentially complex PCI, which might include multivessel disease, the use of multiple stents, PCI of a vein graft or PCI of bifurcation lesions.

4.2 Cost effectiveness

4.2.1 GP IIb/IIIa inhibitors for the medical management of ACSs

4.2.1.1 The assessment group found no additional cost-effectiveness studies beyond the 7 included in the previous appraisal of GP IIb/IIIa inhibitors. None of these studies were UK-based. Since management of ACS in the UK differs from that in other developed countries, particularly in regard to the rate of PCI, the results were not considered to be applicable to the UK. Economic models for tirofiban and eptifibatide were submitted by the manufacturers for the original appraisal.

4.2.1.2 The eptifibatide manufacturer's model was based on a prospective economic evaluation conducted as part of the PURSUIT trial. Based on the subgroup of patients from Western Europe (12% of the total patients), the cost per life-year gained for eptifibatide was estimated as £8,179 to £11,079. Although lifetime survival duration was modelled, no extrapolation of costs over the patients' lifetime was attempted and it is not clear how this would impact on the results.

4.2.1.3 The tirofiban manufacturer's model reported that 22% of the cost of tirofiban is offset by savings due to the reduction in events. The lack of a standardised outcome measure makes it difficult to interpret these results in relation to other treatments. The absolute reduction in event rates associated with tirofiban was not adjusted for UK-specific baseline-event rates.

4.2.2 Use as an adjunct to PCI

4.2.2.1 A further 6 economic studies in the literature were identified in addition to the 17 studies included in the original appraisal, but none of these fully reflects current UK practice and the long-term costs and consequences. The original appraisal also considered the manufacturer's submission for abciximab.

4.2.2.2 In the manufacturer's model for abciximab, for patients undergoing urgent and elective PCIs in a UK setting, estimates of cost per quality-adjusted life year (QALY) ranged from £6,941 to £9,053 based on the EPILOG trial and from £3,949 to £5,151 based on the EPISTENT trial. These estimates must be interpreted with

caution for the following reasons: the baseline risk of events is different in the UK from that in the trials; the assumption that patients surviving the first year will live for a further 15 years ignores variability of prognosis; and it may not be valid to assume that costs do not differ between treatment options over a period of 2 to 15 years.

4.2.3 Assessment group model

4.2.3.1 The assessment group developed a UK-specific model to look at the optimal use and timing of use of GP IIb/IIIa inhibitors in ACS patients. The model estimated health outcomes in terms of QALYs and had a lifetime time horizon. Four treatment strategies for GP IIb/IIIa inhibitors were compared:

- a GP IIb/IIIa inhibitor used as part of initial management, with treatment begun immediately in all ACS patients at the time they were identified
- a GP IIb/IIIa inhibitor started only after making a decision to carry out PCI
- a GP IIb/IIIa inhibitor used as an adjunct to PCI, started up to 1 hour before the procedure
- no use of GP IIb/IIIa inhibitors.

An additional analysis looked at initial management in high-risk ACS patients only (defined as those with at least 1 of 3 factors: age over 70 years, diabetes, ST-depression). Initially, baseline event rates were calculated based on PRAIS-UK/Leeds audit data. Since PCI rates here may be lower than in current practice, an alternative analysis using the Boersma meta-analysis was performed. The model applied relative risks from all available trials and from the Boersma data. All analyses showed that use of GP IIb/IIIa inhibitors in initial management was the preferred strategy. Depending on the assumptions used, estimates of cost per QALY ranged from £4,605 to £11,671. However, the most cost-effective option was initial medical management in the subgroup of high-risk patients only, with cost per QALY estimated at £3,966. The additional benefit of use in all patients compared to use in high-risk patients alone was gained at a cost per QALY of £91,000. When using GP IIb/IIIa inhibitors as an adjunct to PCI was compared with not

using them, the base-case cost per QALY was £25,811; this was reduced to £11,160 if baseline event rates based on Boersma data were applied.

4.2.3.2 In summary, the assessment report model, which is the closest representation of current UK practice available, indicates that the most cost-effective strategy is for GP IIb/IIIa inhibitors to be used as part of the initial medical management of high-risk ACS patients, irrespective of whether angiography with a view to PCI is performed. Although early angiography with a view to PCI is considered to be of benefit in the initial management of high-risk ACS patients, this was not assessed in the model and is not within the scope of the present guidance. The model suggests that the cost effectiveness of GP IIb/IIIa inhibitors is not dependent on whether a PCI is performed; therefore their administration does not need to be delayed until a decision is made to carry out PCI. The use of GP IIb/IIIa inhibitors as an adjunct during PCI only is also less cost effective than their use in initial medical management.

4.3 Consideration of the evidence

4.3.1 The committee considered the evidence available and the viewpoints expressed by the experts on the current management of ACS patients in the UK. It was emphasised that this appraisal related solely to the use of the GP IIb/IIIa inhibitors in the management of ACS, and that it did not extend to the role of PCI or the management of ACS in general.

4.3.2 Historically, PCI rates have been lower in the UK than in the countries where the majority of the published trials of the GP IIb/IIIa inhibitors in ACS have been carried out. The committee took this into account when considering the validity of these trials in relation to current UK practice, together with evidence from the experts suggesting that PCI rates in the UK are now rising by approximately 20% per annum.

4.3.3 The committee considered that the assessment group model provided the best estimates of cost effectiveness for the UK and, on the balance of clinical and cost effectiveness, the committee concluded that use of GP IIb/IIIa inhibitors for initial medical management in high-risk patients was the preferred treatment strategy.

4.3.4 The current licensed indications for the GP IIb/IIIa inhibitors are for use with aspirin and unfractionated heparin. However, the committee recognised that LMWH is used widely in the management of ACS in place of unfractionated heparin, and was aware of the ongoing trials using GP IIb/IIIa inhibitors in conjunction with LMWH.

4.3.5 If GP IIb/IIIa inhibitors are to be used as part of medical management in high-risk patients, the committee thought that it was important that treatment should be initiated as soon as possible. This proves problematic if raised troponin alone is used to identify high-risk status, as the earliest that raised troponin levels can be accurately detected is 6 to 12 hours after the onset of chest pain. The committee considered that, in the presence of sufficient high-risk factors, GP IIb/IIIa inhibitor treatment should be initiated without delaying to confirm high-risk status with a positive cardiac troponin test.

4.3.6 The committee considered that those ACS patients undergoing PCI should be treated with a GP IIb/IIIa inhibitor. In situations where this is not covered by initial medical management, the committee thought that the administration of a GP IIb/IIIa inhibitor would still be appropriate. No clinical trial evidence is available on a strategy that involves a second administration of a GP IIb/IIIa inhibitor (that is, after initial medical management) for a delayed PCI.

4.3.7 At the same time, the committee considered that, for clinically stable patients without diabetes who are undergoing procedurally uncomplicated, routine, elective single-vessel PCI, GP IIb/IIIa inhibitors may not be necessary and therefore should not be recommended for routine use unless unexpected immediate complications occur. The low risk of adverse events during such PCI procedures is demonstrated by UK audit data submitted by the British Cardiac Society and Royal College of Physicians (London).

5 Recommendations for further research

5.1 All of the trials currently available looked at the GP IIb/IIIa inhibitors in conjunction with heparin, in line with their licensed indications. There is an ongoing trial (A-Z trial) looking at the use of tirofiban in conjunction with LMWH; INTERACT, another ongoing trial, is looking at a combination of eptifibatide with a LMWH (enoxaparin). As LMWH is widely used instead of standard heparin, the results of these trials are awaited with interest.

5.2 The effects of GP IIb/IIIa inhibitors in current UK practice should be investigated in carefully designed research to assess their benefits in non-ST-segment-elevation ACS in patients who are not scheduled for PCI.

5.3 Research should be carried out to investigate the efficacy of GP IIb/IIIa inhibitors in subgroups such as women. A recently published meta-analysis of patient-level data has suggested that GP IIb/IIIa inhibitors may have no benefit in the medical management of ACS in women.

5.4 The results of the CURE trial may lead to a consideration of the use of clopidogrel for the management of patients with ACS. Research to establish the relative roles of the GP IIb/IIIa inhibitors and clopidogrel in the short-term management of patients with ACS will be necessary.

5.5 Research is needed to establish the statistical relationship between clinical risk factors and troponin levels, so as to assess the value added by the troponin result in the determination of risk level.

6 Implications for the NHS

6.1 Replacement of the September 2000 guidance with this revised guidance is not anticipated to increase costs to the NHS. Fewer patients undergoing elective PCI will receive GP IIb/IIIa inhibitors, which may result in some cost savings. Under the previous guidance it was assumed that a positive troponin test would be used to identify high risk and that therefore approximately one-third of people admitted with ACS would receive a GP IIb/IIIa inhibitor. The prevalence of the risk factors described in 1.4 among people admitted with ACS is unknown, but assuming a similar proportion will be identified as being at high risk as would have been identified using the troponin result, the impact of this section of the guidance remains unchanged.

6.2 The British Cardiovascular Intervention Society audit recorded 30,916 PCIs in NHS centres during 2000. However, since there are only limited data as to the case-mix of patients undergoing these procedures estimation of budget impact cannot be made.

7 Implementation and audit

7.1 All clinicians who treat people with an ACS should review their current policies and practice in line with the guidance set out in section 1.

7.2 Local guidelines or care pathways, particularly those on the management of patients with unstable angina or MI, should incorporate the guidance in section 1.

7.3 To measure compliance locally with the guidance, the following criteria could be used. Further details of suggestions for audit are presented in appendix D.

7.4 The following groups of patients receive an intravenous small-molecule GP IIb/IIIa inhibitor (eptifibatide or tirofiban) as part of their initial medical management (together with aspirin and unfractionated heparin):

- patients with unstable angina who are at high risk of subsequent MI or death
- patients with NSTEMI who are at high risk of subsequent MI or death.

7.5 Patients who are at high risk and for whom PCI is recommended but delayed beyond the initial medical management phase receive a GP IIb/IIIa inhibitor (abciximab) as an adjunct to PCI.

7.6 A GP IIb/IIIa inhibitor (abciximab) is considered as an adjunct to PCI for all patients with diabetes who are undergoing elective PCI or for those patients undergoing complex procedures.

7.7 A GP IIb/IIIa inhibitor is not used for patients who are undergoing procedurally uncomplicated, elective single-vessel PCI, unless unexpected immediate complications occur.

7.8 Local clinical audits on the care of patients with ACS also could include criteria on other aspects of care referred to in the National Service Framework for Coronary Heart Disease.

Appendix A: Appraisal committee members

The appraisal committee is a standing advisory committee of NICE. Its members are appointed for a 3-year term. The appraisal committee meets three times a month except in December, when there are no meetings. The committee membership is split into three branches, with the chair, vice-chair and a number of other members between them attending meetings of all branches. Each branch considers its own list of technologies and ongoing topics are not moved between the branches.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations interests, are posted on the NICE website.

The following is a list of the committee members who took part in the discussions for this appraisal.

Dr Jane Adam
Radiologist, St George's Hospital, London

Professor R L Akehurst
Dean, School of Health Related Research, Sheffield University

Dr Sunil Angris
General Practitioner, Waterhouses Medical Practice

Professor David Barnett (Chair)
Professor of Clinical Pharmacology, University of Leicester

Professor Sir Colin Berry
Professor of Morbid Anatomy, St Bartholomew's and Royal London's School of Medicine

Dr Sheila Bird

MRC Biostatistics Unit, Cambridge

Professor Carol Black
Consultant Physician, Royal Free Hospital & UCL, London

Professor John Brazier
Health Economist, University of Sheffield

Professor Martin Buxton
Director of Health Economics Research Group, Brunel University

Professor Mike Campbell
Statistician, Institute of General Practice & Primary Care, Sheffield

Dr Karl Claxton
Health Economist, University of York

Professor Sarah Cowley
Professor of Community Practice Development, Kings College, London

Professor Jack Dowie
Health Economist, London School of Hygiene & Tropical Medicine, London

Mr Chris Evennett
Chief Executive, Mid-Hampshire Primary Care Trust

Dr Paul Ewings
Statistician, Taunton & Somerset NHS Trust

Professor Terry Feest
Clinical Director and Consultant Nephrologist, Richard Bright Renal Unit, and Chairman of the UK Renal Registry

Professor Gary A Ford
Professor of Pharmacology of Old Age/ Consultant Physician,Wolfson Unit of Clinical Pharmacology, University of Newcastle

Mrs Sue Gallagher

Chief Executive, Merton, Sutton and Wandsworth Health Authority

Dr Trevor Gibbs
Head, Global Clinical Safety & Pharmacovigilance, GlaxoSmithKline

Sally Gooch
Director of Nursing, Mid-Essex Hospital Services Trust

Mr John Goulston
Director of Finance, The Royal Free Hampstead NHS Trust

Professor Trisha Greenhalgh
Professor of Primary Health Care, University College London

Miss Linda Hands
Consultant Vascular Surgeon, John Radcliffe Hospital, Oxford

Professor Philip Home
Professor of Diabetes Medicine, University of Newcastle

Dr Terry John
General Practitioner, The Firs, London

Dr Diane Ketley
Research into Practice Programme Leader, NHS Modernisation Agency

Dr Mayur Lakhani
General Practitioner, Highgate Surgery, Leicester, and Lecturer, University of Leicester

Ruth Lesirge
Lay Representative; Director, Mental Health Foundation

Dr George Levvy
Lay Representative; Chief Executive, Motor Neurone Disease Association

Dr Gill Morgan
CEO, North & East Devon Health Authority

Professor Miranda Mugford
Health Economist, University of East Anglia

Mr M Mughal
Consultant Surgeon, Lancashire Teaching Hospitals NHS Trust

Mr James Partridge
Lay Representative; Chief Executive, Changing Faces

Siân Richards
General Manager, Cardiff Local Health Group

Professor Philip Routledge
Professor of Clinical Pharmacology, University of Wales

Dr Rhiannon Rowsell
Pharmaceutical Physician, AstraZeneca UK Ltd

Dr Stephen Saltissi
Consultant Cardiologist, Royal Liverpool University Hospital

Professor Andrew Stevens (Vice-Chairman)
Professor of Public Health, University of Birmingham

Professor Ray Tallis
Consultant Physician, Hope Hospital, Salford

Dr Cathryn Thomas
General Practitioner, and Senior Lecturer, Department of Primary Care and General Practice, University of Birmingham

Professor Mary Watkins
Head of Institute of Health Studies, University of Plymouth

Dr Norman Waugh
Public Health Consultant, University of Southampton

Appendix B: Sources of evidence considered by the committee

The following documentation and opinion were made available to the Committee:

- Assessment report prepared by NHS Centre for Reviews and Dissemination and Centre for Health Economics:
  - A Systematic Review Update of the Clinical Effectiveness and Cost Effectiveness of Glycoprotein IIb/IIIa Antagonists and A Cost-effectiveness Model Comparing Alternative Management Strategies for the Use of Glycoprotein IIb/IIIa Antagonists in Non-ST Elevation Acute Coronary Syndromes
- Manufacturer/sponsor submissions from:
  - Lilly
  - Schering Plough
  - MSD
- Professional/specialist group submissions from:
  - British Cardiac Society and Royal College of Physicians (joint submission)
  - Royal College of General Practitioners
  - Department of Health and the Welsh Assembly Government
- Patient/carer group submissions from:
  - British Heart Foundation
- Expert perspective:
  - Dr J McLenachan, Dept of Cardiology, Leeds General Infirmary
  - Dr Charles Knight, Cardiology Dept, King George Hospital.

Appendix C: The use of glycoprotein IIb/IIIa inhibitors in the treatment of acute coronary syndromes (review of existing guidance)

A summary of this guidance for patients and carers can be found on our website.

Appendix D: Detail on criteria for audit of the use of glycoprotein IIb/IIIa inhibitors in the treatment of acute coronary syndromes

Possible objectives for the audit

An audit on the appropriateness of the use of GP IIb/IIIa inhibitors could be carried out to ensure the following.

- Small-molecule GP IIb/IIIa inhibitors are provided as part of initial medical management for patients with unstable angina or with NSTEMI who are at high risk of subsequent MI or death.
- A GP IIb/IIIa inhibitor (abciximab) is provided as an adjunct for patients at high risk for whom PCI is recommended but delayed beyond the initial medical management phase.
- A GP IIb/IIIa inhibitor (abciximab) is considered as an adjunct to PCI for all patients with diabetes who are undergoing elective PCI or for those patients undergoing complex procedures.
- A GP IIb/IIIa inhibitor (abciximab) is not provided for patients who are undergoing procedurally uncomplicated, elective PCI.

Possible patients to be included in the audit

An audit on the first objective above could be carried out on all patients presenting with unstable angina or NSTEMI over a suitable time period given the total number of patients with these conditions treated in 6 months or 1 year. If clinical coding is reliable, the patients can be identified through clinical or procedure codes. If clinical coding for these conditions is not entirely reliable, it may be necessary to retrieve cases of patients who are coded as unstable angina and those coded as myocardial infarction and screen these cases to find patients with NSTEMI.

An audit on the other objectives could be carried out using all patients booked and on the waiting list for PCI over a suitable time period given the total number of PCIs carried out in 6 months or 1 year.

Table 1 Measures that can be used as a basis for the audit

Criterion	Standard	Exception	Definition of terms
A patient in any one of the following groups receives a GP IIb/IIIa inhibitor: • the patient has unstable angina and is at high risk • the patient has NSTEMI and is at high risk	100% of patients with unstable angina or NSTEMI who are at high risk	None	Clinicians will have to agree locally how the initial medical management phase is identified for audit purposes. High risk is of subsequent MI or death as determined by clinician judgement based on risk factors such as: • clinical history (including age, previous MI, previous PCI or CABG) • clinical signs, including continuing pain despite initial treatment • clinical investigations such as ECG changes, particularly dynamic or unstable patterns indicating myocardial ischaemia, haemodynamic changes and raised cardiac troponin level, if available at the appropriate time. Clinicians will have to agree locally on how high risk is documented for audit purposes.

In this approach, the audit involves finding the patients in the audit group who are at high risk and determining if all those patients had a GP IIb/IIIa inhibitor.

Another way to audit appropriateness of the use of GP IIb/IIIa inhibitors in initial medical management is first to find patients in the audit group who have had small-molecule GP IIb/IIIa inhibitors in the initial medical management phase, then to screen those cases to see if the patient was at high risk.

The measures that could be used in an audit of appropriateness of the use of a GP IIb/IIIa

inhibitor (abciximab) as an adjunct to PCI are as set out below.

Table 2 Measures on the appropriateness of GP IIb/IIIa inhibitor as adjunct to PCI

Criterion	Standard	Exception	Definition of terms
A GP IIb/IIIa inhibitor (abciximab) is provided for the patient who is at high risk and is recommended for PCI but the PCI is delayed beyond the initial medical management phase	100% of patients who are at high risk and are scheduled for a PCI but the PCI is delayed beyond the initial medical management phase	None	See above for a definition of high risk
A GP IIb/IIIa inhibitor (abciximab) is considered for the patient who has diabetes and is undergoing an elective PCI	100% of patients who have diabetes and are undergoing an elective PCI	None	Clinicians will have to agree locally on what constitutes evidence that the treatment was considered for audit purposes
A GP IIb/IIIa inhibitor (abciximab) is considered for the patient who is undergoing a complex procedure	100% of patients who are undergoing a complex procedure	None	Examples of complex procedures = multi-vessel PCI, insertion of multiple stents, vein graft PCI, PCI for bifurcation lesions Clinicians will have to agree locally on what constitutes evidence that the treatment was considered for audit purposes.

Criterion	Standard	Exception	Definition of terms
A GP IIb/IIIa inhibitor (abciximab) is not provided for a patient who is undergoing a procedurally uncomplicated, routine elective PCI	100% of patients who are undergoing an uncomplicated routine elective PCI	An unexpected immediate complication occurs	–

Another way to audit the appropriateness of the use of a GP IIb/IIIa inhibitor (abciximab) as an adjunct to PCI is to screen all patients scheduled for or who have undergone PCI to find out whether, if a GP IIb/IIIa inhibitor (abciximab) was administered, the patient met the criteria listed in the first 3 measures above.

Calculation of compliance with the measure

Compliance with each measure described in the table is calculated as follows:

Numerator divided by the denominator, multiplied by 100.

Numerator: Number of patients whose care is consistent with the criterion plus the number of patients who meet any exception.

Denominator: Number of patients to whom the measure applies.

Clinicians should review the findings of measurement, identify if practice can be improved, agree on a plan to achieve any desired improvement and repeat the measurement of actual practice to confirm that the desired improvement is being achieved.

Update information

March 2010: This guidance was partially updated by the NICE guideline on unstable angina and NSTEMI.

Minor changes since publication

March 2014: Minor maintenance.

March 2012: Minor maintenance.

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