

Bivalirudin for the treatment of ST-segment-elevation myocardial infarction

Technology appraisal guidance

Published: 27 July 2011

www.nice.org.uk/guidance/ta230

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Contents

1 Guidance	4
2 The technology	5
3 The manufacturer's submission.....	6
Clinical effectiveness.....	6
Cost effectiveness	8
Evidence Review Group comments	10
4 Consideration of the evidence	13
Clinical effectiveness.....	13
Cost effectiveness	15
Summary of Appraisal Committee's key conclusions	18
5 Implementation.....	22
6 Related NICE guidance.....	23
Published	23
Under development	23
7 Review of guidance	24
Appendix A: Appraisal Committee members, and NICE project team	25
A Appraisal Committee members	25
B NICE project team	26
Appendix B: Sources of evidence considered by the Committee	27
About this guidance.....	30

1 Guidance

- 1.1 Bivalirudin in combination with aspirin and clopidogrel is recommended for the treatment of adults with ST-segment-elevation myocardial infarction undergoing primary percutaneous coronary intervention.

2 The technology

- 2.1 Bivalirudin (Angiox, The Medicines Company) has a marketing authorisation 'as an anticoagulant in adult patients undergoing percutaneous coronary intervention (PCI), including patients with ST-segment-elevation myocardial infarction (STEMI) undergoing primary PCI'. This indication is an extension of the original indication and was approved in November 2009. The summary of product characteristics (SPC) states that bivalirudin should be administered with aspirin and clopidogrel.
- 2.2 According to the SPC, a very common adverse event associated with bivalirudin treatment is bleeding, which can occur anywhere in the body. Common adverse events are thrombosis (blood clots) and bleeding and bruising at the puncture site (after PCI). Uncommon adverse events are allergic reactions such as hives (nettle rash), itching all over the body and tightness of the chest. For full details of side effects and contraindications, see the SPC.
- 2.3 Bivalirudin is administered by injection or infusion. It is available in vials containing 250 mg powder for reconstitution and dilution before injection or infusion. The recommended dose of bivalirudin for patients undergoing PCI is an intravenous bolus of 0.75 mg/kg body weight followed immediately by an intravenous infusion at a rate of 1.75 mg/kg body weight/hour for at least the duration of the procedure. The infusion may be continued for up to 4 hours after PCI according to clinical need. After cessation of the infusion at 1.75 mg/kg/hour, a reduced dose infusion of 0.25 mg/kg/hour may be continued for 4–12 hours as clinically necessary. Assuming one 250 mg vial is used per patient, the acquisition cost of treatment with bivalirudin is £310.00 (British national formulary [BNF] edition 61]), excluding VAT. Costs may vary in different settings because of negotiated procurement discounts.

3 The manufacturer's submission

The Appraisal Committee (appendix A) considered evidence submitted by the manufacturer of bivalirudin and a review of this submission by the Evidence Review Group (ERG; appendix B).

3.1 The manufacturer's decision problem compared bivalirudin in combination with aspirin and clopidogrel against a strategy of heparin with glycoprotein inhibitor in combination with aspirin and clopidogrel. The population was adults with ST-segment-elevation myocardial infarction intended for primary PCI.

Clinical effectiveness

3.2 The main evidence for the clinical effectiveness of bivalirudin was from one prospective, dual-arm, single-blind, randomised multicentre study. The HORIZONS-AMI trial recruited 3602 patients with STEMI intended for a primary PCI and compared a strategy of bivalirudin with one using heparin plus glycoprotein IIb/IIIa inhibitors. Both treatment arms received aspirin and clopidogrel. The trial is ongoing and has at least 3 years of follow-up data available at this time.

3.3 Patients in the bivalirudin treatment group (n = 1800) received a 0.75 mg/kg intravenous bolus of bivalirudin followed by a 1.75 mg/kg/hour infusion that was continued uninterrupted until at least the end of the PCI. An optional post-procedural dose of 0.25 mg/kg/hour was recommended for up to 4 hours after the procedure; 6% (105/1749) of patients received this. A median of one vial (mean = 1.23 vials) of bivalirudin was used per patient (non-integer numbers of bivalirudin and glycoprotein IIb/IIIa inhibitor vials were increased to the next integer to cover wastage at patient level). Patients in the heparin with glycoprotein IIb/IIIa inhibitor treatment group (n = 1802) received 60 IU/kg heparin as recommended by the European Society of Cardiology guidelines for the management of patients with STEMI undergoing primary PCI. A glycoprotein IIb/IIIa inhibitor (either eptifibatid or abciximab) was given in accordance with its summary of product characteristics.

3.4 The ages of the patients were similar across the treatment groups, with slightly more older patients in the heparin with glycoprotein IIb/IIIa inhibitor group. The mean patient age was 61 years in both treatment groups. Slightly more than 75% of patients were men and more than 90% were white. The study was

conducted at 123 sites in 11 countries; 57% of patients were enrolled in Europe and approximately 3% in the UK. Of the recruited population, 19 left the study because they withdrew consent and 28 were lost to follow-up.

- 3.5 There were two primary outcomes: a composite of major adverse cardiovascular events and major bleeding. Secondary outcomes were the components of major adverse cardiovascular events: death (all-cause mortality and cardiac mortality), reinfarction, target vessel revascularisation for ischaemia, and stroke. The rate of stent thrombosis was also assessed. Analyses were conducted on the intention-to-treat population and outcomes were presented for 30 days and for 1 year after PCI.
- 3.6 For the primary outcome of major adverse cardiovascular events, bivalirudin was not inferior to heparin plus glycoprotein IIb/IIIa inhibitor at 30 days and 1 year. In both treatment groups around 5.5% of patients had a major adverse cardiovascular event after 30 days and about 12% after 1 year. For the primary outcome of major bleeding, there was a statistically significant difference ($p = 0.0001$) between the treatment groups at 30 days and at 1 year. At 30 days, major bleeding occurred in 5.1% of patients in the bivalirudin group and 8.8% of patients in the heparin plus glycoprotein IIb/IIIa inhibitor (comparator) group ($p < 0.0001$). At 1 year, major bleeding occurred in 5.8% of patients in the bivalirudin group and 9.2% of patients in the comparator group ($p < 0.0001$).
- 3.7 For the secondary outcomes of all-cause mortality and cardiac mortality, there were statistically significant differences between treatment with bivalirudin and treatment with heparin plus glycoprotein IIb/IIIa inhibitor. After 1 year of follow-up, all-cause mortality was 3.5% in the bivalirudin group and 4.8% in the comparator group ($p = 0.037$). The 1-year results for cardiac mortality were 2.1% for bivalirudin and 3.8% for comparator ($p = 0.005$). For the intention-to-treat population, 3-year all-cause mortality was significantly lower ($p = 0.03$) for bivalirudin (5.9%) than for the comparator (7.7%).
- 3.8 The proportion of patients who experienced a reinfarction was similar between the treatment groups, as was the proportion experiencing a stroke, and the differences were non-significant. A slightly higher percentage of patients in the bivalirudin group had a target vessel revascularisation than in the heparin plus glycoprotein IIb/IIIa inhibitor group (7.2% compared with 5.9% at 1 year), but this difference was not statistically significant.

- 3.9 The overall rate of any stent thrombosis at 30 days and at 1 year was identical in the bivalirudin and the heparin plus glycoprotein IIb/IIIa inhibitor groups. However, more stent thrombosis events occurred in the bivalirudin group within the first 24 hours of PCI.
- 3.10 Investigators reported comparable rates of adverse events between the treatment groups, with a trend towards fewer events in the bivalirudin group and significantly reduced rates of drug-related adverse events ($p < 0.0001$). Significantly fewer thrombocytopenia events occurred in the bivalirudin group (1.4%) than in the heparin plus glycoprotein IIb/IIIa inhibitor group (3.9%; $p < 0.0001$).
- 3.11 Subgroup analyses were presented for all-cause mortality and for major bleeding. For all-cause mortality, the results for bivalirudin were more favourable for most subgroups that were analysed, but differences were not statistically significant. Treatment with bivalirudin was associated with fewer incidents of major bleeding than treatment with heparin plus glycoprotein IIb/IIIa inhibitor.
- 3.12 In the HORIZONS-AMI trial, radial arterial access was used for 5.9% (214/3597) of patients overall, whereas brachial or femoral access was used for most patients. In clinical practice in England and Wales a higher level of radial access is expected. Because of the small numbers of patients undergoing a primary PCI with radial arterial access, the manufacturer was not able to carry out a statistically meaningful direct comparison of radial arterial access and other routes of access. Bivalirudin was associated with a statistically significant reduction in non-access site (organ) bleeding, with a relative risk of 0.684 (95% confidence interval 0.507 to 0.922) compared with heparin plus glycoprotein IIb/IIIa inhibitor.

Cost effectiveness

- 3.13 The manufacturer submitted an economic analysis that employed an economic model based primarily on the analysis of patient-level data from the HORIZONS-AMI trial. The model has two parts. The first part is a decision-tree structure that covers the initial reperfusion to the end of a specified follow-up period (1 year in the base case). The tree splits into branches to allow for different events to occur: no relevant complications; minor bleed; major bleed;

ischaemic stroke; myocardial infarction; repeat revascularisation; or death. The tree is coupled with a two-state (alive/dead) Markov model to account for subsequent survival over a 39-year horizon using an annual cycle length.

- 3.14 The model is primarily affected by the differences in all-cause mortality between the two treatments observed in the HORIZONS-AMI trial.
- 3.15 Absolute and relative clinical event risks and most resource use parameters were derived from the raw data of the HORIZONS-AMI intention-to-treat population. The relative risks of treatment with bivalirudin compared with heparin plus a glycoprotein IIb/IIIa inhibitor for major bleed, minor bleed, ischaemic stroke, repeat myocardial infarction, repeat revascularisation and death were 0.643, 0.536, 1.057, 0.817, 1.124 and 0.710, respectively. Average life expectancy assumed in the model was 11.26 years. Radial access use of 42.5% was assumed.
- 3.16 Costs of bivalirudin treatment were based on the costs of initial angiography, initial revascularisation and hospital care, anticoagulant medications, management of treatment-related adverse events and long-term follow-up. Unit costs for interventional procedures and associated treatment costs were based on NHS reference costs. Medication usage was based on usage in the HORIZONS-AMI trial. Treatment with the most expensive glycoprotein IIb/IIIa inhibitor (abciximab) was assumed in more than 70% of cases in which glycoprotein IIb/IIIa inhibitor was administered. The cost of heparin treatment was considered insignificant and was omitted from the model. The treatment cost per patient with bivalirudin was £412 compared with £573 for heparin plus glycoprotein IIb/IIIa inhibitor.
- 3.17 Two utility values were used in the model for the period after the initial STEMI event: a value of 0.683 was applied in the first year only and 0.718 was applied for each subsequent year of life. The utility values were obtained from a review of the literature. Costs and health outcomes were discounted at 3.5%.
- 3.18 In the base-case analysis the bivalirudin strategy dominated the heparin plus glycoprotein IIb/IIIa inhibitor strategy because it was cheaper and more effective, with total costs of £12,843 and £13,110, and total QALYs of 6.256 and 6.166, respectively. The manufacturer's deterministic sensitivity analysis showed that the results of the model were robust to a number of parameters,

including changes in the relative risks of death and major bleed in the bivalirudin strategy, life expectancy, and type of glycoprotein IIb/IIIa inhibitor used.

- 3.19 Probabilistic sensitivity analysis presented for the base-case 1-year analysis showed that the bivalirudin strategy was dominant (that is, it was cost-saving and showed a QALY gain) in 9924 (99.2%) of 10,000 ICER results at the £20,000 per QALY threshold.
- 3.20 When the manufacturer presented an 'extreme case scenario' combining several unfavourable assumptions (only eptifibatid but no abciximab use; 100% radial arterial access; no difference in length of initial hospital stay), the ICER was £4106 per QALY gained (with a difference in cost of £367 and a difference in QALYs of 0.089). In all other scenarios, the bivalirudin strategy remained dominant.

Evidence Review Group comments

- 3.21 The ERG noted that there is a lack of comparison of bivalirudin with heparin alone, but the use of heparin alone is not common UK practice. The ERG considered that the manufacturer's submission provided a thorough account of the only available RCT.
- 3.22 The ERG noted that the RCT reported data on the licensed dose of bivalirudin in patients undergoing PCI for STEMI. The RCT differed from standard UK practice in that pre-procedural heparin was used for most patients. Within the bivalirudin group, patients treated with pre-procedural heparin had a lower rate of major adverse cardiovascular events than those who did not receive pre-procedural heparin. This pattern was not seen in the comparator group. However, there was no significant interaction between treatment group and pre-procedural heparin ($p = 0.1060$). The ERG noted that it is unclear how the RCT results would be reflected in practice, given the lack of pre-procedural heparin in standard UK practice. The RCT also differed from standard UK practice in using predominantly femoral rather than radial arterial access. The ERG thought that because access site bleeding is less common with radial than femoral arterial access, the benefit seen in reduced bleeding from bivalirudin is likely to be lower in practice than in the RCT.
- 3.23 Overall the ERG considered that the model structure employed by the

manufacturer addresses the scope of the decision problem. The choice of intervention and comparator was appropriate. The ERG noted that the model applies the same relative risk of events with bivalirudin treatment to all patients in the bivalirudin group, regardless of whether they had undergone a primary PCI. However, this assumption did not alter the conclusions from the model.

- 3.24 The ERG noted that the decision tree part of the model treats clinical events as being mutually exclusive, although in reality they are not. For example, some patients could experience both a bleed and a stroke during the initial period after STEMI. The ERG noted that the same utility values are applied to both treatment strategies, such that any difference in health-related quality of life in the model is driven by differences in survival between the treatment groups. Utility decrements arising from complications following reperfusion were not included in the base-case analysis. However, the ERG noted that only negative health effects associated with repeat revascularisation would have an unfavourable impact on the cost effectiveness of bivalirudin.
- 3.25 The ERG identified some minor issues and discrepancies on costs in the model, but none of these had any significant impact on the results of the model.
- 3.26 The ERG was satisfied that the results of the manufacturer's model, which suggest that a bivalirudin-based intervention dominates heparin plus glycoprotein IIb/IIIa inhibitor, were robust to sensitivity analyses. Bivalirudin remained dominant across most sensitivity analyses and in cases in which it was more effective and more expensive than heparin plus glycoprotein IIb/IIIa inhibitor, the ICER for bivalirudin remained below £5000 per QALY gained.
- 3.27 The ERG conducted exploratory analyses to check that the manufacturer's model was robust. This included sensitivity analysis concerning the long-term Markov model to assess the impact of uncertainty around longer-term outcomes for patients after reperfusion. In this analysis the ERG found that the structure of the manufacturer's model and the use of a Markov component means that provided use of bivalirudin is associated with an improved survival rate and lower cost at 1 year, it will always dominate heparin plus glycoprotein IIb/IIIa inhibitor over longer time horizons.
- 3.28 The ERG investigated the following two issues:

- the impact of assuming 2 vials of bivalirudin per patient instead of 1.23
- the impact of using prasugrel in the comparator group rather than clopidogrel.

- 3.29 The ERG found that when the assumption of mean vial use was changed from 1.23 vials to 2 vials per patient, bivalirudin remained the dominant strategy.
- 3.30 The ERG stated that for investigating the impact of using prasugrel in the comparator arm rather than clopidogrel, there are no data directly comparing bivalirudin plus clopidogrel, with heparin plus glycoprotein IIb/IIIa inhibitor plus prasugrel. The ERG also found that there is a lack of data for treatment with heparin plus glycoprotein IIb/IIIa inhibitor plus prasugrel. There are two ongoing trials of bivalirudin plus prasugrel. The first is comparing bivalirudin plus prasugrel with clopidogrel plus heparin plus abciximab. The second trial is comparing bivalirudin plus prasugrel with clopidogrel plus heparin.
- 3.31 The ERG referred to details contained within the manufacturer's submission for NICE technology appraisal 182 on prasugrel for the treatment of acute coronary syndromes with PCI, which showed that prasugrel results in an additional per patient drug cost of £162 compared with clopidogrel. Costs of hospitalisation in each group were estimated to be similar. The ERG found that if this cost difference was applied to the heparin plus glycoprotein IIb/IIIa inhibitor group in the model, bivalirudin (given with clopidogrel) would remain cost-saving. However, evidence relating to the relative impact of bivalirudin plus clopidogrel versus prasugrel plus heparin and glycoprotein IIb/IIIa inhibitor is not available.
- 3.32 Full details of all the evidence are in the manufacturer's submission and the ERG report, which are available from www.nice.org.uk/guidance/TA230

4 Consideration of the evidence

- 4.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of bivalirudin, having considered evidence on the nature of ST-segment-elevation myocardial infarction (STEMI) and primary percutaneous coronary intervention (PCI) and the value placed on the benefits of bivalirudin by people with the condition, those who represent them, and clinical specialists. It also took into account the effective use of NHS resources.
- 4.2 The Committee considered the nature of the condition, and noted evidence submitted and presented by the patient experts and clinical specialists on the clinical signs and symptoms associated with STEMI. The Committee heard that bivalirudin is already in use in the UK and that both patients and clinicians are in favour of its continued use. It was noted that bivalirudin is easier to use than abciximab because the solution is easier to prepare and administer. The patient expert stressed the importance of reducing major bleeding, which was thought to be an important benefit of bivalirudin. Compared with anticoagulants, bivalirudin may require less monitoring and therefore be more convenient for patients.

Clinical effectiveness

- 4.3 The Committee discussed the evidence for the clinical effectiveness of bivalirudin in combination with aspirin and clopidogrel. It agreed that the results of the single but large HORIZONS-AMI trial (both the primary outcome of major bleeding, and the secondary outcomes of all-cause mortality and cardiac mortality) showed statistically significant advantages for treatment with bivalirudin over treatment with heparin plus glycoprotein IIb/IIIa inhibitor. In particular it noted that all-cause mortality was 1.3% and 1.8% lower in the bivalirudin group than in the comparator group after 1 and 3 years of follow-up, respectively.
- 4.4 The Committee discussed whether similar outcomes to those in the HORIZONS-AMI trial can be expected for patients seen in UK clinical practice. The Committee heard from the clinical specialists that the trial had some limitations: it only compared bivalirudin with heparin and glycoprotein IIb/IIIa inhibitors, not with heparin alone; in the UK, more people have PCI via the radial access site than in the trial; and a substantial proportion of the trial population

received pre-procedural heparin, which is not standard UK practice.

- 4.5 The Committee heard how the use of the radial access site rather than femoral access reduces the incidence of access site bleeding. Radial access is more common in UK practice than in the trial, and hence this could reduce the benefit of reduced access site bleeding with bivalirudin shown in the trial. However, in the trial bivalirudin was also shown to reduce bleeding not related to the access site in comparison with glycoprotein IIb/IIIa inhibitor plus heparin. The Committee accepted that similar outcomes for bleeding not related to access site could be expected in UK clinical practice as in the trial.
- 4.6 The Committee discussed the omission of a comparison against heparin alone in the manufacturer's submission. The clinical specialists stated that there is a question around the necessity to include a glycoprotein IIb/IIIa inhibitor with heparin, because there is some evidence to support the use of heparin alone from the BRAVE-3 study. However, the clinical specialists stated that clinicians still feel that this question is largely unanswered. Treatment with heparin alone is not standard practice in the UK. The Committee was satisfied that it was not necessary to compare bivalirudin against treatment with heparin alone.
- 4.7 The Committee discussed the use of bivalirudin in combination with aspirin and prasugrel as opposed to aspirin and clopidogrel. The clinical experts stated a prasugrel/bivalirudin combination was likely to be better than a clopidogrel/bivalirudin combination because prasugrel reduces stent thrombosis. This was considered particularly important because the bivalirudin group in the trial had a higher incidence of stent thrombosis within the first 24 hours of PCI than the comparator group. The manufacturer, however, explained that when the trials for bivalirudin were designed, and at the time of the first licence application for bivalirudin, prasugrel had not received a marketing authorisation. For this reason, bivalirudin has only been studied with aspirin and clopidogrel, and therefore the marketing authorisation is specifically in combination with these two drugs. The Committee was satisfied that treatment with bivalirudin in combination with aspirin and prasugrel is outside the marketing authorisation for bivalirudin and therefore beyond the remit of this appraisal.
- 4.8 The Committee explored the reasons why in the bivalirudin group, the rates of major adverse cardiovascular events and stent thrombosis were lower in

patients treated with pre-procedural heparin. The clinical specialists explained that it is hard to understand clinically why taking pre-procedural heparin would reduce the rate of major adverse cardiovascular events. They suggested that the population who received pre-procedural heparin may be different from those who did not, and it is this difference that may have affected the rate of major adverse cardiovascular events. The Committee heard from the ERG that there was no interaction between pre-procedural heparin and the major adverse cardiovascular events outcome. The clinical specialists also explained that it is not common practice in the UK to administer pre-procedural heparin, and anecdotally this has not reduced the effectiveness of bivalirudin in clinical practice. The Committee was satisfied that differences in the use of pre-procedural heparin between the trial and UK clinical practice would not significantly alter the favourable outcomes for bivalirudin.

- 4.9 The Committee considered whether there were any subgroups of patients who would be expected to benefit from treatment with bivalirudin more than other groups. It heard from the clinical specialists that theoretically it might be possible to reserve bivalirudin for those who are at the greatest risk of bleeding, but that in reality the same patients would be at a high risk of other symptoms and may not be a discrete subgroup for the purposes of targeting treatment. The Committee was persuaded that no subgroups could be selected on the basis of the greatest potential to benefit from bivalirudin.
- 4.10 The Committee also considered other limitations of the trial. It noted that there was only a single trial and that it was an open-label design with some risk of bias, but agreed that the results suggested an advantage for bivalirudin. The Committee concluded that there was sufficient evidence to demonstrate that bivalirudin was more clinically effective than glycoprotein IIb/IIIa inhibitor plus heparin, leading to lower rates of major bleeds and mortality.

Cost effectiveness

- 4.11 The Committee discussed the manufacturer's economic model in which the main factor affecting cost effectiveness is the reduced mortality risk with bivalirudin treatment compared with treatment with glycoprotein IIb/IIIa inhibitor plus heparin. It noted that in the base case, treatment with bivalirudin was both more effective and less expensive than treatment with a glycoprotein IIb/IIIa inhibitor plus heparin. This finding appeared robust in the face of both

deterministic and probabilistic sensitivity analyses.

- 4.12 The Committee discussed the robustness of the manufacturer's model. First the Committee discussed the two-stage structure of the model: an initial stage, in which clinical events could occur, followed by a stage representing the rest of the lifetime. The manufacturer presented one model in which the first stage is 1 year, and another model in which the first stage is 3 years. The Committee was satisfied that the results from the 3-year model were consistent with those from the 1-year model. Second, it questioned the appropriateness of mutually exclusive events within the first stage of the model and suggested that this was an oversimplification. The manufacturer explained that there were no common combinations of events which could have been modelled. The Committee noted that the ERG's rebuilding of the model found no discrepancies. The Committee was satisfied with the approach taken by the manufacturer in its model design.
- 4.13 The Committee then discussed key input assumptions used in the model, concerning firstly vial use and, secondly, choice of glycoprotein IIb/IIIa inhibitor in the comparator group, and thirdly radial arterial access. With regards to vial use, it heard from the clinical specialists that treatment with bivalirudin would take place at the time of PCI, and that usually not more than one vial would be used. The mean use of 1.23 vials from the trial was used for calculating cost of treatment. The Committee questioned whether vials could be split and heard from the clinical specialists that if more than 1 vial were needed, a second vial would be used and any extra discarded. Sensitivity analysis was conducted by the ERG on the effect of including 2 vials instead of 1.23 vials in the model, but did not lead to any changes in the results. The Committee was satisfied with the way that vial use was incorporated into the economic model.
- 4.14 The Committee considered the assumptions around the choice of glycoprotein IIb/IIIa inhibitor used in the manufacturer's model. It noted that abciximab, which is the most costly glycoprotein IIb/IIIa inhibitor, was assumed to be used in 73% of people, tirofiban in 19% and eptifibatide, which is the least costly glycoprotein IIb/IIIa inhibitor, in only 8.1%. The Committee heard from the clinical specialists that this was largely because abciximab has been the favoured glycoprotein IIb/IIIa inhibitor for many years, and some clinicians are so familiar with its use that they are reluctant to change to eptifibatide or tirofiban. The Committee noted that 100% use of eptifibatide in the manufacturer's sensitivity analysis had a small impact on the ICER, with the

ICER for bivalirudin rising to £1764 per QALY gained. The Committee accepted that 100% eptifibatide use was an extreme position and was satisfied that the high usage of abciximab in the model had a limited impact on the cost effectiveness of bivalirudin.

- 4.15 The Committee considered the assumptions around radial arterial access site in the model. In the base-case analysis, radial arterial access was assumed in 42.5% of cases, in line with UK practice. A sensitivity analysis from the manufacturer which increased the usage to 100% led to no changes in the results, with bivalirudin remaining the dominant treatment option. The Committee was satisfied that the model results were robust to changes in access site.
- 4.16 The Committee discussed the results of the combined sensitivity analysis, in which 100% eptifibatide use had been combined with the assumptions of 100% radial arterial access and equal length of hospital stay in those treated with bivalirudin and those treated with glycoprotein IIb/IIIa inhibitors. In this analysis, which was considered by the manufacturer to be the most unfavourable scenario for bivalirudin, the ICER increased to £4106 per QALY gained. The Committee accepted that this unfavourable position was clinically unrealistic, but noted that the ICER produced with this analysis was still well within the range normally considered to be a cost-effective use of NHS resources.
- 4.17 The Committee concluded the discussion by noting the robustness of the manufacturer's base case, in which treatment with bivalirudin dominated treatment with a glycoprotein IIb/IIIa inhibitor plus heparin (that is, was less costly and more effective) and that the results of the model are robust to the various sensitivity analyses. The Committee concluded that the model is associated with a very low degree of decision uncertainty and that bivalirudin should be recommended for the treatment of adults with STEMI undergoing PCI.
- 4.18 No equalities issues were raised at any point in the appraisal.

Summary of Appraisal Committee's key conclusions

TA230	Appraisal title: Bivalirudin for the treatment of ST-segment-elevation myocardial infarction	Section
Key conclusion		
Bivalirudin in combination with aspirin and clopidogrel is recommended for the treatment of adults with ST-segment-elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PCI).		1.1
Current practice		
Clinical need of patients, including the availability of alternative treatments	Bivalirudin is already in use in the UK and both patients and clinicians are in favour of its continued use. Bivalirudin is easier to use than abciximab (a glycoprotein IIb/IIIa inhibitor) because the solution is easier to prepare and administer. The patient expert stressed the importance of reducing major bleeding, which was thought to be an important benefit of bivalirudin. Compared with anticoagulants, bivalirudin may require less monitoring and therefore be more convenient for patients.	4.2
The technology		
Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	The primary outcome of major bleeding and the secondary outcomes of all-cause mortality and cardiac mortality showed statistically significant advantages for treatment with bivalirudin over treatment with heparin plus glycoprotein IIb/IIIa inhibitor. In particular, all-cause mortality was 1.3% and 1.8% lower in the bivalirudin group than in the comparator group after 1 and 3 years of follow-up, respectively.	4.3
What is the position of the treatment in the pathway of care for the condition?	Bivalirudin is used as an anticoagulant in adult patients with STEMI undergoing primary PCI.	2.1

Adverse effects	The bivalirudin group had a higher incidence of stent thrombosis within the first 24 hours of PCI than the comparator group	4.7
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	A single trial (HORIZONS-AMI) formed the evidence base. It was an open-label trial with some risk of bias. However, the Committee concluded that there was sufficient evidence to demonstrate that bivalirudin was more clinically effective than glycoprotein IIb/IIIa inhibitor plus heparin.	4.10
Relevance to general clinical practice in the NHS	<p>In the UK, more people have PCI via the radial access site than in the trial. The use of the radial access site, compared with femoral access, reduces the incidence of access site bleeding. Hence the reduced access site bleeding observed with bivalirudin in the trial may be attenuated in UK practice. The Committee accepted that similar rates of non-access site bleeding could be expected in UK clinical practice as in the trial.</p> <p>In the trial a substantial number of patients were treated with pre-procedural heparin but this is not common practice in the UK. The Committee was satisfied that differences in the use of pre-procedural heparin between the trial and UK clinical practice would not significantly alter the favourable outcomes for bivalirudin.</p>	4.4 4.5 4.8
Uncertainties generated by the evidence	The Committee discussed the use of bivalirudin in combination with aspirin and prasugrel as opposed to aspirin and clopidogrel. It was satisfied that this treatment combination is outside the marketing authorisation for bivalirudin and therefore beyond the remit of this appraisal.	4.7
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	The Committee was persuaded that no subgroups could be selected on the basis of the greatest potential to benefit from bivalirudin.	4.9

<p>Estimate of the size of the clinical effectiveness including strength of supporting evidence</p>	<p>The primary outcome of major bleeding and the secondary outcomes of all-cause mortality and cardiac mortality showed statistically significant advantages for treatment with bivalirudin over treatment with heparin plus glycoprotein IIb/IIIa inhibitor. In particular, all-cause mortality was 1.3% and 1.8% lower in the bivalirudin group than in the comparator group after 1 and 3 years of follow-up, respectively.</p>	<p>4.3</p>
<p>Evidence for cost effectiveness</p>		
<p>Availability and nature of evidence</p>	<p>The manufacturer submitted an economic analysis that employed an economic model based primarily on the analysis of patient-level data from the HORIZONS-AMI trial.</p>	<p>3.13</p>
<p>Uncertainties around and plausibility of assumptions and inputs in the economic model</p>	<p>The Committee considered that the results from the model were associated with a very low degree of decision uncertainty.</p>	<p>4.17</p>
<p>Incorporation of health-related quality-of-life benefits and utility values Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?</p>	<p>There were no issues raised about health-related quality-of-life values that were thought to be relevant. No health-related benefits were identified that were not included in the economic model.</p>	

Are there specific groups of people for whom the technology is particularly cost effective?	The Committee was persuaded that no subgroups could be selected on the basis of the greatest potential to benefit from bivalirudin.	4.9
What are the key drivers of cost effectiveness?	The main factor affecting cost effectiveness in the model is the reduced mortality risk with bivalirudin treatment compared with treatment with glycoprotein IIb/IIIa inhibitor plus heparin.	4.11
Most likely cost-effectiveness estimate (given as an ICER)	In the base case, treatment with bivalirudin dominated the comparator in that it was both more effective and less expensive than treatment with a glycoprotein IIb/IIIa inhibitor plus heparin.	4.17
Additional factors taken into account		
Patient access schemes (PPRS)	No patient access schemes were submitted.	
End-of-life considerations	End-of-life considerations were not discussed.	
Equalities considerations and social value judgements	No equalities issues were raised at any point in the appraisal.	4.18

5 Implementation

5.1 The Secretary of State and the Welsh Assembly Minister for Health and Social Services have issued directions to the NHS in England and Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends use of a drug or treatment, or other technology, the NHS must usually provide funding and resources for it within 3 months of the guidance being published. If the Department of Health issues a variation to the 3-month funding direction, details will be available on the NICE website. When there is no NICE technology appraisal guidance on a drug, treatment or other technology, decisions on funding should be made locally.

5.2 NICE has developed tools to help organisations put this guidance into practice (listed below). These are available on our website (www.nice.org.uk/guidance/TA230).

- Costing template and report to estimate the national and local savings and costs associated with implementation.
- Audit support for monitoring local practice.

6 Related NICE guidance

Published

- Off-pump coronary artery bypass. NICE interventional procedure guidance 377 (2011). Available from www.nice.org.uk/guidance/IPG377
- Unstable angina and NSTEMI. NICE clinical guideline 94 (2010). Available from www.nice.org.uk/guidance/CG94
- Prasugrel for the treatment of acute coronary syndromes with percutaneous coronary intervention. NICE technology appraisal guidance 182 (2009). Available from www.nice.org.uk/guidance/TA182
- Drug-eluting stents for the treatment of coronary artery disease. NICE technology appraisal guidance 152 (2008). Available from www.nice.org.uk/guidance/TA152
- MI: secondary prevention. NICE clinical guideline 48 (2007). Available from www.nice.org.uk/guidance/CG48
- Balloon angioplasty with or without stenting for coarctation or recoarctation of aorta in adults and children. NICE interventional procedure guidance 74 (2004). Available from www.nice.org.uk/guidance/IPG74
- Coronary imaging: myocardial perfusion scintigraphy for the diagnosis and management of angina and myocardial infarction. NICE technology appraisal guidance 73 (2003). Available from www.nice.org.uk/guidance/TA73
- Guidance on the use of coronary artery stents. NICE technology appraisal guidance 71 (2003). Available from www.nice.org.uk/guidance/TA71

Under development

NICE is developing the following guidance (details available from www.nice.org.uk):

- [Ticagrelor for the treatment of acute coronary syndromes \(ACS\)](#). NICE technology appraisal. Publication date to be confirmed.

7 Review of guidance

- 7.1 The guidance on this technology will be considered for review in July 2014. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Andrew Dillon

Chief Executive

July 2011

Appendix A: Appraisal Committee members, and NICE project team

A Appraisal Committee members

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are four Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

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 of interests, are posted on the NICE website.

Dr Kathryn Abel Reader and Consultant Psychiatrist/Director of Centre for Women's Mental Health, University of Manchester

Dr Daniele Bryden Consultant in Intensive Care Medicine and Anaesthesia, Sheffield Teaching Hospitals NHS Trust

David Chandler Lay member

Dr Mary Cooke Lecturer, School of Nursing, Midwifery and Social Work, University of Manchester

Richard Devereaux-Phillips Director, Public Policy and Advocacy NW Europe, BD, Oxford

Professor Rachel A Elliott Lord Trent Professor of Medicines and Health, University of Nottingham

Dr Alan Haycox Reader in Health Economics, University of Liverpool Management School

Professor Cathy Jackson Professor of Primary Care Medicine, University of St Andrews

Professor Gary McVeigh Professor of Cardiovascular Medicine, Queens University Belfast and Consultant Physician, Belfast City Hospital

Dr Eugene Milne Deputy Regional Director of Public Health, North East Strategic Health Authority, Newcastle upon Tyne

Ruth Oliver-Williams Head of Nursing/Quality Improvement Lead Surgical Services, Royal Derby Hospital

Professor Katherine Payne Professor of Health Economics, University of Manchester

Dr Danielle Preedy Lay member

Ellen Rule Programme Director, NHS Bristol

Dr Peter Selby Consultant Physician, Central Manchester University Hospitals NHS Foundation Trust

Dr Surinder Sethi Consultant in Public Health Medicine, North West Specialised Services Commissioning Team, Warrington

Professor Andrew Stevens Chair of Appraisal Committee C, Professor of Public Health, University of Birmingham

Professor Paul Trueman Professor of Health Economics, Brunel University, London

Dr Judith Wardle Lay member

B NICE project team

Each technology appraisal is assigned to a team consisting of one or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Dr Helen Starkie Technical Lead

Joanne Holden Technical Adviser

Lori Farrar Project Manager

Appendix B: Sources of evidence considered by the Committee

A The Evidence Review Group (ERG) report for this appraisal was prepared by School of Health and Related Research (ScHARR):

- Simpson EL, Fitzgerald P, Evans P, et al. Bivalirudin for the treatment of ST-segment elevation myocardial infarction. March 2011

B The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope. Organisations listed in I were also invited to make written submissions. Organisations listed in II gave their expert views on bivalirudin for the treatment of adults with ST-segment elevation myocardial infarction undergoing percutaneous coronary intervention by providing a written statement to the Committee. Organisations listed in I, II and III have the opportunity to appeal against the final appraisal determination.

I Manufacturer/sponsor

- The Medicines Company

II Professional/specialist and patient/carer groups:

- Heart Care Partnership UK
- HEART UK
- British Association for Nursing in Cardiac Care
- British Cardiovascular Intervention Society (BCIS)
- British Cardiovascular Society
- British Heart Foundation
- Primary Care Cardiovascular Society Royal College of Nursing
- Royal College of Physicians

III Other consultees:

- Department of Health

- Welsh Assembly Government

IV Commentator organisations (did not provide written evidence and without the right of appeal):

- British National Formulary
- Commissioning Support Appraisals Service
- Department of Health, Social Services and Public Safety for Northern Ireland
- Healthcare Improvement Scotland
- Eli Lilly
- GlaxoSmithKline
- Merck Sharp & Dohme
- Sanofi Aventis
- National Institute for Health Research Health Technology Assessment Programme
- School of Health & Related Research Sheffield (ScHARR)

C The following individuals were selected from clinical specialist and patient expert nominations from the non-manufacturer/sponsor consultees and commentators. They gave their expert personal view on Bivalirudin for the treatment of ST-segment elevation myocardial infarction by providing oral evidence to the Committee.

- Dr Daniel Blackman, Consultant cardiologist, nominated by British Cardiovascular Intervention Society – clinical specialist
- Dr Tim Kinnaird, Consultant Interventional Cardiologist, nominated by Welsh Assembly Government – clinical specialist
- Valentino Oriolo, Acute Coronary Syndromes Advanced Nurse Practitioner, nominated by British Association for Nursing in Cardiovascular Care - clinical specialist
- John Miller, nominated by Heart Care Partnership UK – patient expert

D Representatives from the following manufacturer/sponsor attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- The Medicines Company

About this guidance

NICE technology appraisal guidance is about the use of new and existing medicines and treatments in the NHS in England and Wales.

This guidance was developed using the NICE [single technology appraisal](#) process.

We have produced a [summary of this guidance for patients and carers](#). Tools to help you put the guidance into practice and information about the evidence it is based on are also [available](#).

Your responsibility

This guidance represents the views of NICE and was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to avoid unlawful discrimination and to have regard to promoting equality of opportunity. Nothing in this guidance should be interpreted in a way which would be inconsistent with compliance with those duties.

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