NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technology Appraisals and Guidance Information Services

Static List Review (SLR)

Title and TA publication number of static topic:	**TA47; Guidance on the use of glycoprotein IIb/IIIa inhibitors in the treatment of acute coronary syndromes**
Final decision:	The guidance will remain on the 'static guidance list'.

1. Publication date:	September 2002
2. Date added to static list:	March 2010
3. Date the last searches were run:	February 2010
4. Current guidance:	1.7 It is recommended that a GP IIb/IIIa inhibitor is considered as an adjunct to 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.
5. Research recommendations from original guidance:	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. Current cost of technology/ technologies:	ReoPro® (Lilly) PoM Injection, abciximab 2 mg/mL, net price 5-mL vial = £250.24 Source: BNF November 2015 Integrilin® (GSK) PoM Injection, eptifibatide 2 mg/mL, net price 10-mL (20-mg) vial = £13.61 Infusion, eptifibatide 750 micrograms/mL, net price 100-mL (75-mg) vial = £42.79 Source: BNF November 2015 Aggrastat® (Correvio) PoM Concentrate for intravenous infusion, tirofiban (as hydrochloride) 250 micrograms/mL. For dilution before use, net price 50-mL (12.5-mg) vial = £146.11 Electrolytes Na^+ <0.5 mmol/mL Intravenous infusion, tirofiban (as hydrochloride) 50 micrograms/mL, net price 250-mL *Intravia*® bag = £160.72 Electrolytes Na^+ <0.5 mmol/mL Source: BNF November 2015
7. Cost information from the TA (if available):	3.1.4 The cost of abciximab is £280.00 (net) for a 10-mg vial (*British National Formulary,* 43rd edition). For a 70-kg person, the cost per course ranges from £840 to £1120, depending on the duration of treatment (costs rounded to full vials).

	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 (British National Formulary, 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). 3.3.4 The cost of tirofiban is £146.11 (net) for a 12.5-mg vial (*British National Formulary,* 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).
8. Alternative company(ies):	Beacon Pharmaceuticals Tirofiban 50 micrograms/ml solution for infusion Source: electronic Medicines Compendium (eMC)
9. Changes to the original indication:	No changes to the original indications. ReoPro is indicated in adults as an adjunct to heparin and acetylsalicylic acid for: • Percutaneous Coronary Intervention The prevention of ischaemic cardiac complications in patients undergoing percutaneous coronary intervention (balloon angioplasty, atherectomy, and stent). (See section 5.1.) • Unstable Angina The short-term (1-month) reduction of the risk of myocardial infarction, in patients with unstable angina, not responding to full conventional therapy who have been scheduled for percutaneous coronary intervention.

	Source: Reopro 2mg/ml solution for injection or infusion (eMC) INTEGRILIN is intended for use with acetylsalicylic acid and unfractionated heparin. INTEGRILIN is indicated for the prevention of early myocardial infarction in adults presenting with unstable angina or non-Q-wave myocardial infarction, with the last episode of chest pain occurring within 24 hours and with electrocardiogram (ECG) changes and/or elevated cardiac enzymes. Patients most likely to benefit from INTEGRILIN treatment are those at high risk of developing myocardial infarction within the first 3-4 days after onset of acute angina symptoms including for instance those that are likely to undergo an early PTCA (Percutaneous Transluminal Coronary Angioplasty) (see section 5.1). Source: INTEGRILIN 0.75 mg/ml solution for infusion (eMC) and INTEGRILIN 2 mg/ml solution for injection (eMC) Aggrastat is indicated for the prevention of early myocardial infarction in adult patients presenting with acute coronary syndromes without ST elevation (NSTE-ACS) with the last episode of chest pain occurring within 12 hours and with ECG changes and/or elevated cardiac enzymes. Patients most likely to benefit from Aggrastat treatment are those at high risk of developing myocardial infarction within the first 3-4 days after onset of acute angina symptoms including for instance those that are likely to undergo an early percutaneous coronary intervention (PCI). Aggrastat is also indicated for the reduction of major cardiovascular events in patients with acute myocardial infarction (STEMI) intended for

	primary PCI (see sections 4.2 and 5.1). Aggrastat is intended for use with acetylsalicylic acid (ASA) and unfractionated heparin. Source: AGGRASTAT®*(250 micrograms/ml) concentrate for solution for infusion (eMC) and AGGRASTAT®*(50 micrograms/ml) solution for infusion (eMC)
10. New relevant trials:	Trial NCT01475552: Tailored Antiplatelet Therapy During Percutaneous Coronary Intervention in Patients With Diabetes Mellitus. Phase 4, enrolment: 130. Study completed: October 2011. Trial NCT00712101: Abciximab i.v. Versus i.c. in ST-elevation Myocardial Infarction. Phase 3, enrolment: 1912. Study completed: April 2011. Trial NCT00373451: Randomized Comparison of Abciximab Plus Heparin With Bivalirudin in Acute Coronary Syndrome. Phase 4, enrolment: 1721. Study completed: July 2011. Trial NCT00440895: A Randomized Trial of Early Discharge After Trans-radial Stenting of Coronary Arteries in Acute MI and Rescue-PCI. Phase 4, enrolment: 74. Study completed: May 2013. Trial NCT01433627: Minimizing Adverse Haemorrhagic Events by TRansradial Access Site and Systemic Implementation of angioX. Phase 3, estimated enrolment: 7200. Estimated study completion date: December 2015.

	Trial NCT01076764: Effect of Otamixaban Versus Unfractionated Heparin + Eptifibatide in Patients With Unstable Angina/Non ST Elevation Myocardial Infarction Undergoing Early Invasive Strategy. Phase 3, enrolment: 13220. Study completed: May 2013. Trial NCT00638976: INSTANT: INtegrilin Plus STenting to Avoid Myocardial Necrosis Trial. Phase 3, enrolment: 91. Study completed: May 2010. Trial NCT01863134: Clinical Effects of Eptifibatide Administration in High Risk Patients Presenting With Non-ST Segment Elevation Acute Coronary Syndrome (NSTE-ACS) Requiring Urgent Coronary Artery Bypass Graft Surgery in Short- and Long-Term Follow-up. Phase 4, enrolment: 140. Study completed: December 2010. Trial has Results available. Trial NCT02054000: Intracoronary Tirofiban on No-Reflow Phenomena. Phase 4, enrolment: 162. Study completed: December 2013. Trial NCT02294994: Efficacy and Safety of Different Dose of Tirofiban in Interventional Treatment of Complex Coronary Artery Disease. Phase 4, estimated enrolment: 1000. Estimated study completion date: December 2016. Trial NCT01498003: Tirofiban in Stenting for Long Coronary Lesion. Phase 4, enrolment: 748. Study completed: June 2014. Trial NCT01336348: Facilitation Through Aggrastat By drOpping or Shortening Infusion Line in Patients With ST-segment Elevation Myocardial Infarction Compared to or on

	Top of PRasugrel Loading dOse. Phase 3, enrolment: 100. Study completed: June 2012. Trial NCT02131220: Effects of Intracoronary Prourokinase on the Coronary Flow During Primary Percutaneous Coronary Intervention for Acute Myocardial Infarction. Phase 4, estimated enrolment: 360. Estimated study completion date: September 2017. Trial NCT01696110: BivaliRudin in Acute Myocardial Infarction vs Glycoprotein IIb/IIIa and Heparin: a Randomised Controlled Trial. Phase 4, enrolment: 2194. Study completed: July 2014. Trial NCT02592694: Intracoronary Cocktail Injection Combined With Thrombus Aspiration in STEMI Patients Treated With Primary Angioplasty. Phase 4, estimated enrolment: 1000. Estimated study completion date: October 2017. Trial NCT02592720: Cocktail Injection Improves Outcomes of FFR Guided PCI. Phase 4, estimated enrolment: 500. Estimated study completion date: October 2017.
11. Relevant NICE guidance (published or in progress):	Myocardial infarction (acute): Early rule out using high-sensitivity troponin tests (Elecsys Troponin T high-sensitive, ARCHITECT STAT High Sensitive Troponin-I and AccuTnI+3 assays) (2014) NICE diagnostic assessment guidance 15. Acute coronary syndromes in adults (2014) NICE quality standard 68. NICE support for commissioning for acute coronary syndromes (including myocardial

	infarction) (2014) NICE support for commissioning SFCQS68. Myocardial infarction: cardiac rehabilitation and prevention of further MI (2013) NICE guideline CG172. Myocardial infarction with ST-segment elevation: acute management (2013) NICE guideline CG167. Cardiac rehabilitation services (2013) NICE commissioning guides 40. Bivalirudin for the treatment of ST-segment-elevation myocardial infarction (2011) NICE technology appraisal guidance 230. Unstable angina and NSTEMI: early management (2010) NICE guideline CG94. Guidance on the use of coronary artery stents (2003) NICE technology appraisal guidance 71. Guidance on the use of drugs for early thrombolysis in the treatment of acute myocardial infarction (2002) NICE technology appraisal guidance 52.

	Chest pain of recent onset: Assessment and diagnosis of recent onset chest pain or discomfort of suspected cardiac origin. NICE guideline. Publication date to be confirmed. Chest pain of recent onset (standing committee A update). NICE guideline. Publication expected July 2016.
12. Relevant safety issues:	None identified.
13. Any other additional relevant information or comments:	None.
14. Technical Lead comments and recommendation:	Since the publication of NICE technology appraisal guidance 47, the marketing authorisations for each of the technologies have not changed. Additionally no relevant safety issues have been identified, or has NICE published any new guidance appraising glycoprotein IIb/IIIa inhibitors for the treatment of acute coronary syndromes. The list price of the technologies has either remained the same (tirofiban) or reduced (abciximab, eptifibatide) since the publication of NICE technology appraisal guidance 47. Recommendation 1.7 of NICE technology appraisal guidance 47 recommends that “a glycoprotein 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)”. This guidance also highlights that only abciximab has a marketing authorisation as an adjunct to PCI.

	Several of the completed trials identified by NICE's Information Services team included a broad patient population in those that assessing glycoprotein IIb/IIIa inhibitors as an adjunct to PCI, which is consistent with the original evidence base included in the technology appraisal. In NICE technology appraisal guidance 47, the Assessment Group estimated that the ICER for using glycoprotein IIb/IIIa inhibitors in all patients compared with high-risk patients alone (defined as those with at least one of three factors: age > 70 years, diabetes, ST depression) was £91,000 per QALY gained. The Appraisal Committee also considered that, "for clinically stable patients without diabetes who are undergoing procedurally uncomplicated, routine, elective single-vessel PCI, glycoprotein IIb/IIIa inhibitors may not be necessary and therefore should not be recommended for routine use unless unexpected immediate complications occur." Given that the company has not indicated that they are seeking a broader recommendation for 1.7, it suggests that the new clinical evidence and change in price for abciximab is unlikely to result in a clinical- and cost-effective use of NHS resources for those without diabetes. Therefore, there is no new evidence to suggest that recommendation 1.7 is no longer robust. Recommendation 1.8 of NICE technology appraisal guidance 47 states that "GP IIb/IIIa inhibitors are not currently licensed in the UK for use as an adjunct to thrombolytic therapy in ST-segment-elevation MI." The companies have not contacted NICE to suggest that they are seeking an extension to the marketing authorisation for their technology. NICE has also not received any direction from the Department of Health to make recommendations for glycoprotein IIb/IIIa inhibitors outside of the terms of its marketing authorisation and therefore recommendation 1.8 remains robust. It should be acknowledged that the searches undertaken by NICE's Information Services team identified several ongoing trials for tirofiban in Chinese populations that

	may include some people relevant to recommendations 1.7 and 1.8 of NICE technology appraisal guidance 47. However, the results of these trials were either unpublished or not currently analysed (given their ongoing status), and consequently their relevance to the potential for extending tirofiban's European marketing authorisation is unclear. Overall, no new evidence, changes to the marketing authorisation and scheduled updates to relevant NICE clinical guidelines have been identified that would impact recommendations 1.7 and 1.8 of NICE technology appraisal guidance 47. It is therefore appropriate for the guidance to remain on the 'static guidance list'.

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Appendix 1 – explanation of options

Options	Consequence	Selected – 'Yes/No'
The guidance will remain on the 'static guidance list'	The guidance will remain in place, in its current form, unless NICE becomes aware of substantive information which would make it reconsider. Literature searches are carried out every 5 years to check whether any of the Appraisals on the static list should be flagged for review.	**Yes**
The decision to review the guidance will be deferred to specify date or trial	NICE will consider whether a review is necessary at the specified date. NICE will actively monitor the evidence available to ascertain when a consideration of a review is more suitable.	No
A full consideration of a review will be carried out through the Review Proposal Process	There is evidence that could warrant a review of the guidance. NICE will schedule a consideration of a review, including a consultation with relevant consultees and commentators.	No
The guidance will be withdrawn	The guidance is no longer relevant and an update of the existing recommendations would not add value to the NHS. NICE will schedule a consideration of a review, including a consultation with relevant consultees and commentators.	No
The guidance should be updated in an on-going clinical guideline.	Responsibility for the updating the technology appraisal passes to the NICE Clinical Guidelines programme. Once the guideline is published the technology appraisal will be	No

	withdrawn. NICE will schedule a consideration of a review, including a consultation with relevant consultees and commentators.	