NICE appraisals and cardiology: glycoprotein IIb/IIIa inhibitors and acute coronary syndromes

The National Institute for Clinical Excellence (NICE) was set up in 1999, with the aim of creating an independent body to evaluate and recommend therapies for NHS patients. NICE examines research evidence, assesses effectiveness (likely effects on patients in the community) and takes into account efficiency (cost effectiveness) before making recommendations.

NICE produces Technical Appraisal Guidance documents, which are the result of a lengthy appraisal. Each appraisal has a committee with members from the medical and nursing community as well as health economists and lay representatives. The committee seeks evidence from the pharmaceutical and device companies, professional bodies, the Department of Health and experts in the field under consideration.

NICE updated the guidance on glycoprotein IIb/IIIa (GPIIb/IIIa) inhibitors in acute coronary syndromes in September 2002 (NICE, 2002) – the original was published in 2000. GPIIb/IIIa inhibitors are potent antiplatelet agents that inhibit platelet aggregation. They reduce recurrent ischaemia, myocardial infarction (MI) and cardiac death in patients with non-ST elevation acute coronary syndromes (non-ST ACS). There are currently three GPIIb/IIIa inhibitors licensed for use in the UK: tirofiban and eptifibatide are 'small molecules' with a relatively short duration of action; abciximab is a chimeric antibody with more persistent antiplatelet activity.

WHAT DID NICE SAY?

NICE recommends use of GPIIb/IIIa inhibitors during the early hospital phase of admission in high-risk patients with non-ST ACS. The risk factors quoted are age, dynamic ST depression, pulmonary oedema, haemodynamic instability, ventricular arrhythmias and elevated cardiac troponin levels. NICE guidance suggests that GPIIb/IIIa inhibitors should be administered to patients as soon as they are identified as being high risk, even if this is before troponin results are known. NICE estimates the cost of the recommendations as around £17 million, based on a predicted 115 000 admissions per year.

THE EVIDENCE

GPIIb/IIIa inhibitors are of benefit when administered in the early hospital phase of non-ST ACS. Boersma et al's (2002) meta-analysis of six trials, which randomized a total of 31 402 patients with non-ST ACS to receive GPIIb/IIIa inhibitors or placebo, found that the 30-day rate of death or MI was 10.8% for the treatment group compared to 11.8% for placebo (odds ratio = 0.91; 95% confidence interval (CI) = 0.84–0.98).

MANAGEMENT STRATEGY OF PATIENTS WITH NON-ST ACS

Two large trials, the Fragmin and Fast Revascularisation during InStability in Coronay artery disease (FRISC II) (1999) and TACTICS Thrombolysis in Myocardial Infarction 18 (TACTICS TIMI 18) (Cannon et al, 2001), compared an early invasive strategy (early angiography followed by revascularization where appropriate) to an early conservative strategy (initial medical stabilization followed by angiography in the presence of spontaneous or inducible ischaemia) in the management of patients with non-ST ACS. These trials found an early invasive approach to be superior. The risk of death and MI at up to 6 months was reduced in FRISC II by 22% (9.4% *vs* 12.1%, risk ratio (RR) = 0.78, 95% CI = 0.62–0.98) and in TACTICS TIMI 18 by 26% (7.3% *vs* 9.5%, RR = 0.74, 95% CI = 0.54–1.00).

These benefits appear to be of greater magnitude than the risk reduction from GPIIb/IIIa inhibitors and current data suggest that the benefits are still present at up to 2 years. The main group of patients that benefit from an invasive strategy are those with elevated levels of troponin or ST segment depression, i.e. high-risk patients.

An invasive approach to high-risk patients is supported by national and international guidelines but has not yet been assessed by NICE. Despite this it seems reasonable that if patients are sufficiently high risk to warrant treatment with a GPIIb/IIIa inhibitor then they should also undergo angiography with a view to early revascularization.

DO GPIIB/IIIA INHIBITORS WORK IN ALL PATIENTS WITH NON-ST ACS?

Glycoprotein inhibitors are an established adjunctive treatment during percutaneous coronary intervention (PCI), they significantly reduce major periprocedural cardiac events. In the Boersma et al (2002) meta-analysis the benefit of GPIIb/IIIa inhibitors appeared to be confined to patients who underwent revascularization, the 30-day rates of death or MI for patients who underwent PCI within 5 days were 11.8% *vs* 14.5%, odds ratio = 0.77 (95% CI = 0.64–0.92). The event rates of patients who did not undergo revascularization at up to 30 days were 8.4% and 8.8% accordingly; odds ratio = 0.95 (95% CI = 0.86–1.05), i.e. they did not benefit. The European Society of Cardiology recommends that in the early hospital phase GPIIb/IIIa inhibitor therapy is confined to troponin-positive patients who are scheduled for early revascularization (Bertrand et al, 2002).

BENEFIT IS LINKED TO TIMING AND FREQUENCY OF PCI

Further insights about the benefits of GPIIb/IIIa inhibitors in non-ST ACS

patients can be gleaned from subgroup analysis of the Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) trial (1998). This was the largest trial of GPIIb/IIIa inhibitors in non-ST ACS (n=10 948) and randomized patients to a 3-day infusion of eptifibatide or placebo. The benefit of eptifibatide to non-ST ACS patients who underwent PCI was time dependent and confined to procedures performed within 3 days of admission, i.e. during study drug infusion (Ronner et al, 2002).

Univariate analysis of the trial found the benefit of eptifibatide was confined to North America; in Western Europe no significant benefit was seen (PURSUIT Trial Investigators, 1998). Akkerhuis et al (2000) explained this mainly by differences in the rate and timing of PCI. In North America PCI was performed more often during the initial hospital stay than in Western Europe (35% *vs* 25%), and more procedures were performed within 3 days of randomization (25% *vs* 7%), i.e. during study drug infusion. The benefit of eptifibatide in patients who underwent PCI within 3 days was similar in both regions.

PLACE IN UK CLINICAL PRACTICE

GPIIb/IIIa inhibitors are not a cure for ACS but part of a complex treatment process. As outlined above they are especially useful in conjunction with early PCI, analogous perhaps to prophylactic antibiotics during surgery.

In the UK rates of PCI in the management of non-ST ACS patients are low and procedures are performed late – a recent audit of the authors' practice showed that PCI was performed at a median of 16 days after admission. The trial data are therefore less applicable to UK patients and the benefit of treating UK patients in the early hospital phase is likely to be lower than in the trials. The NICE guidance still recommends, however, that GPIIb/IIIa inhibitors should be given to high-risk non-ST ACS patients even if angiography is unlikely to take place. It also recommends that GPIIb/IIIa inhibitors are used during PCI in cases with recent ACS. Strict adherence to the guidance would result in many patients receiving these drugs twice.

It may make more sense in the UK, where revascularization within 3 days is unlikely, to restrict the use of GPIIb/IIIa inhibitors in the early hospital phase to very high-risk patients with refractory symptoms or those expected to undergo early PCI. Most high-risk patients who will undergo PCI will do so later on and GPIIb/IIIa inhibitors can be deferred until the time of the intervention, rather than being given twice.

ARE THESE RECOMMENDATIONS BEING IMPLEMENTED?

Published data describing the use of GPIIb/IIIa inhibitors in UK practice are scanty. In a recent audit of patients transferred for angiography to the authors' centre, only 11 out of 130 (8.5%) high-risk patients (troponin positive non-ST ACS or post-infarct unstable angina) had been treated with GPIIb/IIIa inhibitors at the referring hospital. Of the patients who went on to have a PCI, 68% received adjunctive GPIIb/IIIa treatment, including 9 of the 11 patients who received treatment at the referring hospital. Data from a recent audit of 34 patients transferred to Kings College Hospital were similar: 18% received GPIIb/IIIa inhibitors before transfer (Creagh-Brown et al, 2003).

WHAT CAN NICE DO TO HELP?

We feel that guidance would be more helpful to clinicians if NICE took an integrated approach to non-ST ACS. If NICE recommendations were expanded to include the role and timing of PCI, the maximum treatment benefit could be obtained and duplication of treatment avoided. This is concordant with a parliamentary committee recommendation that NICE should think bigger; instead of focusing on a class of drugs it should shift its emphasis towards treating specific conditions (Burke, 2002). HM

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KEY POINTS

- Glycoprotein IIb/IIIa inhibitors are beneficial in patients with high risk non-ST elevation acute coronary syndromes.
- The benefit of glycoprotein IIb/IIIa inhibitors is related to percutaneous coronary intervention (PCI) and is time dependent.
- If patients are high risk they should receive glycoprotein IIb/IIIa inhibitors and be considered for early angiography.
- National guidance on the role and timing of PCI in patients with non-ST elevation acute coronary syndromes is welcome.