# Bivalirudin in acute coronary syndromes: one step forwards, one step backwards?

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## Background

Across the UK, there are wide variations in the strategies used to manage patients presenting with acute coronary syndromes (ACS). Not withstanding local availability of and access to coronary angiography and revascularisation, the optimal approach both in terms of pharmacotherapy and timing of coronary angiography/revascularisation is by no means clear for patients presenting with or without ST-segment elevation (STEMI and NSTEMI, respectively) on their initial electrocardiogram (ECG).

## An invasive approach in ACS patients

For patients presenting with STEMI, many cardiologists favour the concept of immediate mechanical reperfusion by primary percutaneous coronary intervention (PPCI). This approach is now established in Europe, where PPCI has become the principal modality for STEMI treatment following several impressive trials and a recent overview confirming benefit over the alternative strategy, thrombolytic therapy.[1] Although PPCI is growing in popularity in the UK, it is only practised on a true '24/7' basis by less than 20% of UK centres, and provides only approximately 2% of total UK percutaneous coronary intervention (PCI) activity.[2] By far the majority of STEMI cases in the UK still receive thrombolytic therapy, increasingly with fibrin-specific agents[3] and often delivered before arrival in hospital. Comparisons between pre-hospital thrombolysis and PPCI will be studied in the forthcoming Rescue Angioplasty versus Conservative Therapy or Repeat Thrombolysis Trial (REACT-2) study, but data from the Comparison of Angioplasty and Prehospital Thrombolysis in Acute Myocardial infarction (CAPTIM) study suggest that these approaches may be comparable, certainly in the early stages of STEMI.[4] Furthermore, patients not achieving adequate reperfusion by ECG criteria after thrombolysis should be offered 'rescue' PCI on the basis of the findings in the REACT study.[5] Therefore, intuitively, regardless of ECG success of thrombolytic therapy (which may remove thrombus but not an underlying atherosclerotic lesion), angiography as a risk-stratifying tool would seem sensible, and indeed is enjoying widespread UK uptake in STEMI patients, even after successful thrombolysis.

For patients presenting with NSTEMI, the situation is no clearer. Despite large-scale US- and UK-based trials advocating the benefits of an aggressive approach with early coronary angiography and revascularisation,[6,7] the most up-to-date study encompassing current therapies suggests no clear advantage for a universally-invasive strategy.[8] In the UK, the National Service Framework for Coronary Heart Disease[9] has allowed enhanced access to coronary angiography and, with rising targets for revascularisation, has encouraged cardiologists to pursue an invasive approach in NSTEMI patients, much in line with guidance from the European Society of Cardiology and the American College of Cardiology/American Heart Association.[10,11]

## Optimal pharmacotherapy for PCI in ACS patients

### Glycoprotein IIb/IIIa antagonists

Adjunctive glycoprotein IIb/IIIa antagonist (GPIIb/IIIa) therapy during PCI has been proven to influence patient outcomes,[12,13] and became 'gold-standard' treatment in the setting of ACS patients undergoing PCI in the UK following guidance from the National Institute for Health and Clinical Excellence.[14] Universal uptake of such a strategy has been limited by cost constraints and concerns over increased bleeding risk. Such concerns have been substantiated by the finding that bleeding after PCI independently predicts future mortality.[15] This guidance, nevertheless, has achieved high penetration for groups perceived to be at high risk, notably

patients with complex or multi-vessel disease and insulin-treated diabetics.

### Bivalirudin

Recent uptake of the thrombin-specific anticoagulant bivalirudin in PCI has been backed up by accumulating evidence across a range of patient subgroups, including both stable and unstable coronary syndromes. In a low- to moderate-risk patient group, the Randomised Evaluation in PCI Linking Angiomax to Reduced Clinical Events-2 (REPLACE-2) study confirmed equivalent anti-ischaemic efficacy with low GPIIb/IIIa bailout rates for bivalirudin compared with heparin plus routine GPIIb/IIIa therapy, and a lower incidence of bleeding complications.[16] In PPCI for patients presenting with STEMI, preliminary data suggest outcomes with bivalirudin are comparable to those achieved in historical PPCI trials utilising adjunctive GPIIb/IIIa therapy, but with a lower risk of bleeding complications.[17,18] The Harmonising Outcomes with Revascularisation and Stents (HORIZONS-AMI) trial will further address this question but bivalirudin's use in this setting has already been adopted by some UK centres.[19]

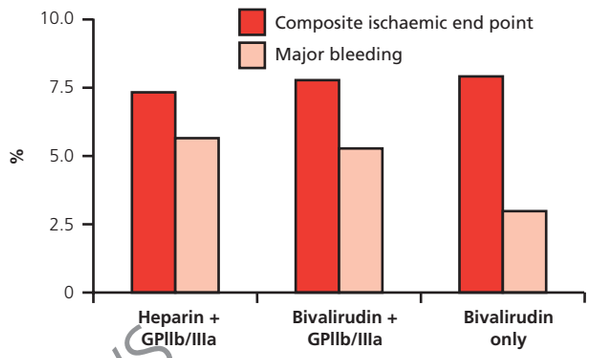
### Clopidogrel

Routine use of the thienopyridine ADP receptor antagonist clopidogrel has become standard practice in PCI, although the duration of treatment after successful PCI remains a subject of debate. In an essentially low-risk patient cohort undergoing elective PCI, the Intracoronary Stenting and Antithrombotic Regimen-Rapid Early Action for Coronary Treatment (ISAR-REACT) study[20] demonstrated no benefit for GPIIb/IIIa therapy when patients were preloaded with high-dose (600 mg) clopidogrel. This throws the applicability of the REPLACE-2 results into some doubt for public healthcare systems such as the NHS, where cost and cost-effectiveness are driving practice: if outcomes following clopidogrel preloading are equivalent to those after GPIIb/IIIa therapy, the potential attractiveness of bivalirudin as a heparin plus GPIIb/IIIa substitute in such stable patients becomes questionable. A *post-hoc* analysis of REPLACE-2 does show enhanced benefit when clopidogrel preloading was given to patients receiving bivalirudin but the dose administered was only 300 mg rather than the 600 mg given in ISAR-REACT.[21]

## One step forwards, one step backwards?

Two further trials, both presented at the American College of Cardiology 55th Annual Scientific Session in Atlanta, US, this year, have further informed the debate over optimal antithrombotic strategy in PCI following ACS. The first of these, Acute Catheterisation and Urgent Intervention Triage Strategy Trial (ACUITY), randomised 13,819 patients presenting with moderate- to high-risk NSTEMI/ACS to receive heparin or enoxaparin plus GPIIb/IIIa, bivalirudin alone or bivalirudin plus GPIIb/IIIa, before early (< 72 hours) angiography and revascularisation.[22] ACUITY confirmed similar rates of ischaemic events (recorded as a composite of death, myocardial infarction [MI] or revascularisation within 30 days) in all groups, thereby highlighting the potential utility of bivalirudin as monotherapy in this setting, and the apparent lack of additive benefit when combined with GPIIb/IIIa. Again in this study, there were fewer bleeding events in the bivalirudin alone arm (figure 1).

**Figure 1.** Summary of results from ACUITY. Equivalent composite end point of death/MI/revascularisation at 30 days with improved bleeding outcomes for bivalirudin therapy alone




**Key:** MI = myocardial infarction; GP IIb/IIIa = glycoprotein IIb/IIIa inhibition

Adapted from Stone GW *et al.*[22]

Controversially, bivalirudin was administered upstream at admission rather than during PCI, and there was an additional potentially confusing and confounding subrandomisation regarding timing of GPIIb/IIIa administration, which may yet alter the final analysis of the study when published. It should also be pointed out that only approximately 60% of the overall population received clopidogrel acutely. These caveats aside, the study does fit with previously published findings and confirms bivalirudin's potential utility in NSTEMI enhanced by its reduced likelihood of bleeding events.

The second study was the much-anticipated ISAR-REACT2 trial, essentially repeating the previous ISAR-REACT study of randomisation to high-dose clopidogrel pre-treatment versus the GPIIb/IIIa abciximab in PCI,[20] but this time in NSTEMI (n=2,022) rather than elective patients.[23] As in ISAR-REACT, there was no difference in bleeding complications but there was an overall benefit in terms of the composite of death, MI or urgent target vessel revascularisation at 30 days, driven entirely by the benefit seen in the troponin-positive group

(composite event rate for placebo *vs*. abciximab in troponin-negative patients 4.6% *vs.* 4.6%; p=NS; in troponin-positive patients 18.3% *vs.* 13.1%; p=0.02). This finding supports GPIIb/IIIa use in PCI for troponin-positive ACS, as suggested by NICE guidance in the UK four years ago.

These studies ask as many questions as they might provide answers: whilst not directly comparable, the ischaemic event rate at 30 days in both studies was similar. However, the issue of high-dose clopidogrel preloading with respect to bivalirudin versus GPIIb/IIIa therapy remains unclear, as does the relative efficacy (given the subrandomisation) of bivalirudin versus GPIIb/IIIa in PCI for ACS patients in the acute setting.

## Bivalirudin: a new niche?

For the majority of the UK not served by PPCI, many centres have developed an aggressive approach to routine early coronary angiography and revascularisation following STEMI or NSTEMI. It is this patient group to whom the NICE guidance on GPIIb/IIIa treatment applies, and it is also the group likely to be at highest bleeding risk, having already received substantial antiplatelet, anticoagulant and, in some cases, fibrinolytic therapy. Whilst most trials have examined either PPCI or very early PCI in ACS patients (e.g. median 21 hours in ACUITY), the situation in the UK is rather different, with patients historically having to endure lengthy in-hospital waits of up to several weeks before transfer for angiography/PCI. Like many District General Hospitals that have set up 'offsite' PCI to combat this issue, we have found that revascularisation in this group of patients now makes up over 50% of our PCI workload. We have also found that out-of-hours calls regarding these patients after PCI were more likely to be for bleeding than ischaemic complications, despite our GPIIb/IIIa usage, like many UK centres, hovering just above 50% (West NEJ, Khan ZI, Chamberlain-Webber R. Unpublished observations, 2005–6).

In order to better provide improved peri-PCI anticoagulation to all patients whilst minimising bleeding risk, and for reasons of financial expediency (in terms of direct and indirect costs), from June 2005 we elected to treat all troponin-positive patients undergoing PCI with bivalirudin as primary anticoagulant as an alternative to the more costly heparin plus GPIIb/IIIa combination. Anti-ischaemic efficacy of this strategy was based on the REPLACE-2 data suggesting comparable outcomes and less bleeding; analysis of this study shows that some ACS patients were included in the dataset – and, indeed, in some respects, given the length of time such patients sometimes have to wait in the current NHS climate, some might view the timing of PCI in ACS patients in the UK as semi-elective rather than acute.

Preliminary data relating to our experience (table 1) suggest high rates of procedural success with acceptable 'bailout' rates to GPIIb/IIIa and a low incidence of bleeding complications, despite a high-risk population. In drug cost alone, this change in strategy has saved around £100,000 in the first year, not withstanding the savings potentially made from early mobilisation/discharge and limited access site complications. Further analysis and follow-up of these patients will provide further insights into bivalirudin's utility in this setting.

**Table 1.** Preliminary patient data for bivalirudin utilisation in PCI for ACS patients in Gloucestershire, June 2005-June 2006. Data are provided as number (%) or median (range) as appropriate

| **Patient demographics** | **n=193** |
|---|---|
| Age (years) | 64 |
| Male sex | 151 (78%) |
| Diabetes mellitus | 27 (14%) |
| Heart failure (LVEF<40%) | 29 (15%) |
| Multivessel disease | 80 (42%) |
| Recent major surgery (<1 week) | 2 (1%) |
| Severe thrombocytopenia (platelet count <50) | 1 (0.5%) |
| **Intervention details** | |
| Admission to PCI time (days) | 5 (2-25) |
| Target lesions | 280 |
| Target lesions/patient | 1 (1-4) |
| ACC type C lesions | 143 (51%) |
| Adjunctive GPIIb/IIIa usage | 11 (6%) |
| **Outcomes** | |
| In-hospital death | 1 (0.5%) |
| In-hospital MI | 1 (0.5%) |
| TIMI major bleeding | 1 (0.5%) |
| TIMI minor bleeding | 0 (0%) |
| Next-day discharge | 178 (92%) |

**Key:** PCI = percutaneous coronary intervention; ACS = acute coronary syndromes; LVEF = left ventricular ejection fraction; ACC = American College of Cardiology; GP IIb/IIIa = glycoprotein IIb/IIIa inhibition; MI = myocardial infarction; TIMI = thrombolysis in myocardial infarction

## Conclusions

Approaches to the overall triage and management of ACS patients, whether STEMI or NSTEMI, remain heterogeneous in the UK. Given the nature of optimal evidence-based pharmacotherapies in such patients, bleeding risk will by necessity be high and when it occurs, betokens poor future outcomes. Whilst bivalirudin offers potential advantages for PCI following ACS in terms of reduced cost and bleeding risk, this is currently an untested strategy and our local experience can only be regarded as anecdotal until further follow-up of our cohort confirms similar reductions in ischaemic events to those hitherto demonstrated by the heparin/GPIIb/IIIa combination.

Nevertheless, it is unlikely, given the peculiarities, inherent delays and rapidly-changing status of current ACS management in the UK, that any trial will be specifically designed to address this area.

The forthcoming HORIZONS-AMI study will answer whether bivalirudin has a future role in STEMI, and further analysis of the ACUITY trial may give more insight into its use in NSTEMI patients. Data currently available from the ACUITY trial suggest that bivalirudin should indeed have a place in the management of PCI in ACS patients, but this should be tempered by the findings in ISAR-REACT-2 that GPIIb/IIIa may still have a key role in high-risk, troponin-positive ACS patients undergoing PCI regardless of clopidogrel pre-treatment.

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**Conflict of interest**

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