Which antithrombotic to use during PCI?

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This editorial refers to ‘Safety and effectiveness of bivalirudin in routine care of patients undergoing percutaneous coronary intervention’, by J.A. Rassen† on page 561 and ‘Bivalirudin vs. unfractionated heparin during percutaneous coronary interventions in patients with stable and unstable angina pectoris: 1-year results of the ISAR-REACT 3 trial†, by S. Schulz et al. on page 582.

With >2 million percutaneous coronary intervention (PCI) procedures performed worldwide annually, the optimal choice of antithrombotic therapy during PCI is of critical importance. There are three main choices for antithrombotic therapy during PCI: (i) heparin alone; (ii) heparin + glycoprotein (GP) IIb IIIa inhibitor; or (iii) bivalirudin.

The use of heparin during PCI is based upon a clinical rationale that PCI is intensively thrombogenic and an anticoagulant would be essential to avoid high rates of thrombotic occlusion of the coronary artery. As the only intravenous anticoagulant available a few decades ago, heparin quickly became standard practice and so until very recently there have been no trials comparing heparin vs. placebo. A recent placebo-controlled trial of heparin (70–100 U/kg, n = 700) in patients with chronic coronary artery disease undergoing elective PCI and receiving dual antiplatelet therapy demonstrated increased overall bleeding (rates of 1.7% heparin vs. 0% placebo, P = 0.048) with no difference in major bleeding (0 vs. 0) with heparin and no significant difference in the composite of death, myocardial infarction (MI), or urgent lesion revascularization (3.7% heparin vs. 2.0% placebo, odds ratio (OR) 1.92; 95% confidence interval (CI) 0.76–4.88, P = 0.17). Further trials of the value of heparin are needed in elective PCI, and at the minimum suggest that lower doses of heparin may be just as effective with less bleeding compared with standard or high dose heparin during PCI.

In a large number of trials, GP IIb IIIa inhibitors have been evaluated vs. placebo in patients receiving heparin and aspirin undergoing PCI. A meta-analysis of 21 trials (n = 23 941) comparing heparin + GP IIb IIIa inhibitor vs. heparin alone showed that GP IIb IIIa inhibitors reduced death at 30 days (0.8% vs. 1.2%, OR 0.72; 95% CI 0.56–0.94), reduced MI events (4.5% vs. 6.5%, OR 0.63; 95% CI 0.54–0.74), but there was a trend for increased major bleeding (4.2% vs. 2.9%, OR 1.29; 95% CI 0.98–1.68) and thrombocytopenia (2.5% vs. 1.7%, OR 1.41; 95% CI 1.10–1.81) (Figure 1). However, many of the studies included did not recommend the use of thienopyridines, and so many have questioned the applicability to current practice. Specifically, the ISAR REACT (n = 2159) study demonstrated that patients undergoing elective PCI pre-treated with 600 mg of clopidogrel, heparin (140 U/kg) vs. heparin (70 U/kg) + abciximab had similar ischaemic outcomes and bleeding. In contrast, the ISAR REACT 2 (n = 2022) study demonstrated in patients with acute coronary syndromes (ACS) undergoing PCI pre-treated with 600 mg of clopidogrel that heparin (70 U/kg) + abciximab vs. heparin monotherapy (140 U/kg) reduced death or MI [relative risk (RR) 0.75; 95% CI 0.57–0.97] without increasing major bleeding (RR 1.00; 95% CI 0.50–2.08). The benefit was mainly observed in patients with an elevated troponin (18.3% vs. 13.1%, RR 0.71; 95% CI 0.54–0.95) and not in those without an elevation (4.6% vs. 4.6%, RR 0.99; 95% CI 0.56–1.76), and this was the rationale for the inclusion of only biomarker-negative patients in the subsequent ISAR REACT 3 trial. These trials support the concept that GP IIb IIIa inhibitors may be less likely to be beneficial in patients undergoing elective PCI or in troponin-negative ACS patients already receiving aspirin, high doses of clopidogrel, and heparin.

The third option for an antithrombotic during PCI is bivalirudin which was specifically tested in the ISAR REACT 3 trial. This trial randomized 4570 biomarker-negative patients undergoing PCI pre-treated with 600 mg of clopidogrel to (i) bivalirudin monotherapy or (ii) heparin monotherapy (140 U/kg). The initial publication compared that reported with heparin, bivalirudin led to a 44% reduction in major bleeding (3.1% vs. 4.6%, RR 0.66; 95% CI 0.49–0.90), with no difference in net clinical benefit (death, MI, urgent target vessel revascularization, or major bleeding; 8.3% vs. 8.7%, RR 0.94; 95% CI 0.77–1.15). The follow-up at 1 year demonstrates no difference in the composite of death, MI, or target vessel revascularization (17.1% vs. 17.5%, RR 0.98; 95% CI 0.86–1.13) or of death or MI (7.7% vs. 6.7%, RR 1.15; 95% CI 0.99–1.30). The benefit was mainly observed in patients with an elevated troponin (18.3% vs. 13.1%, RR 0.71; 95% CI 0.54–0.95) and not in those without an elevation (4.6% vs. 4.6%, RR 0.99; 95% CI 0.56–1.76), and this was the rationale for the inclusion of only biomarker-negative patients in the subsequent ISAR REACT 3 trial. These trials support the concept that GP IIb IIIa inhibitors may be less likely to be beneficial in patients undergoing elective PCI or in troponin-negative ACS patients already receiving aspirin, high doses of clopidogrel, and heparin.

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A limitation of this trial is that heparin doses used (140 U/kg) were much higher than doses recommended by current guidelines (70–100 U/kg with heparin monotherapy). Further, observational data from a pooled analysis of randomized trials in the stent era suggest that lower doses of weight-adjusted heparin during PCI may be associated with lower rates of bleeding and similar efficacy in preventing ischaemic events, a hypothesis that would benefit from direct randomized trials. If true, would bivalirudin still reduce bleeding compared with guideline-recommended doses of heparin monotherapy during PCI?

There have now been six trials of bivalirudin vs. heparin in those with PCI or ACS undergoing an invasive strategy with >24 000 patients. The only other trial to compare heparin monotherapy with bivalirudin monotherapy is the Bivalirudin Angioplasty Trial (BAT) trial which did not utilize stents or thienopyridines, but used infusions of heparin for 18–24 h after the procedure, an approach not applicable to current practice. In the REPLACE 1 trial, the use of GP IIb IIIa inhibitors was at the discretion of the operator, and 70% of patients in both bivalirudin and heparin groups received GP IIb IIIa inhibitors. This study reported similar rates of the composite of death, MI, or revascularization (5.6% vs. 6.9%, OR 0.81; 95% CI 0.49–1.33) and major bleeding (2.1% vs. 2.7%, OR 0.77; 95% CI 0.35–1.70). The other three bivalirudin trials compared bivalirudin with heparin + a GP IIb IIIa inhibitor (Figure 1).

To put the ISAR REACT 3 study in perspective, we performed a meta-analysis of the randomized trials comparing bivalirudin with heparin (trials which routinely used heparin infusions post-PCI were excluded) which confirms the lower rate of major bleeding (5.8% vs. 8.1%, OR 0.69; 95% CI 0.63–0.77, P < 0.001) with bivalirudin. There is a trend towards lower mortality (2.5% vs. 2.8%, OR 0.88; 95% CI 0.75–1.03) but higher reinfarction (6.7% vs. 6.2%, OR 1.09; 95% CI 0.98–1.21) with bivalirudin compared with heparin. The overall data are inconclusive as to whether a difference in mortality or MI exists between bivalirudin and heparin during PCI, but are clear that bivalirudin compared with either heparin + a GP IIb IIIa inhibitor or high-dose heparin monotherapy (140 U/kg) reduces bleeding.

The report of Rassen et al. uses observational analyses to assess the impact of bivalirudin on outcomes from a large administrative database. Observational analyses lack randomization and so to account for selection biases between those who received vs. those who did not receive bivalirudin, the authors could use various methods of adjustment including multivariate analyses, a propensity scoring method, or an instrumental variable method. Standard multivariate analyses are not known to adjust reliably for all important differences. Propensity scoring uses observable
measures that correlate with treatment to adjust for differences, whereas instrumental variable analysis utilizes an instrumental variable that is correlated with treatment but not outcome to account for unmeasured factors. However, disadvantages include (i) difficulties in choice of an appropriate instrument and (ii) ‘weak’ instruments that explain little of the variation and do not control for treatment selection bias. Rassen et al. report on an analysis from a large observational study of the PREMIER administrative registry and compared the outcomes of those undergoing PCI who received bivalirudin vs. heparin + GP IIb IIIa inhibitor or those only receiving heparin. The authors used (i) a Cox proportional hazard model adjusting for baseline characteristics and (ii) an instrumental variable analysis utilizing an instrument to identify a hospital’s preference for using bivalirudin. They reported that bivalirudin was associated with a 33% reduction in blood transfusion [hazard ratio (HR) 0.67; 95% CI 0.61–0.73] adjusting for baseline variables with a Cox proportional hazard model but only a trend when utilizing the instrumental variable analysis (HR 0.72; 95% CI 0.72–0.47). They also reported a 49% reduction in mortality with bivalirudin which was consistent with both methods of analysis (Cox proportional hazard model, HR 0.51; 95% CI 0.44–0.60 and instrumental variable analysis, HR 0.51; 95% CI 0.34–0.78). While the benefit of bivalirudin, in terms of bleeding, that was observed is consistent with the randomized trials, the large mortality reduction (larger than the effect on bleeding) is not plausible. These observations suggest that despite the use of complex statistical methods, residual confounding is virtually impossible to ‘adjust’ for fully using any of the known methods, and so the results of such analyses can be quite untrustworthy. Much larger randomized trials than those conducted to date are needed to determine if bivalirudin can reduce mortality and infarction in patients undergoing PCI. Observational databases and their analyses are not adequate substitutes.

**Implications for practice**

In troponin-positive, high risk non-ST segment elevation ACS, bivalirudin reduces bleeding compared with heparin + GP IIb IIIa inhibitor but their relative impact on death and MI is unclear. In lower risk (e.g. biomarker-negative or stable angina) patients undergoing PCI, heparin monotherapy at guideline-recommended doses (e.g. 70–100 U/kg as a bolus) still remains a reasonable option because of its low cost and widespread clinical experience. Future randomized trials are specifically needed to compare bivalirudin with guideline-recommended (or lower) doses of heparin monotherapy during PCI, especially in patients receiving aspirin, clopidogrel, or another potent antiplatelet agent.

**Conflict of interest.** SSJ. has received honoraria from GlaxoS­smithKline. S.Y. has received honoraria and grant support from Sanofi Aventis, GSK, AZ, Boehringer Ingelheim, and BMS (all companies that manufacture antithrombotic drugs).

**References**


