Balancing the risks of stent thrombosis and major bleeding during primary percutaneous coronary intervention

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This editorial refers to ‘Bivalirudin is superior to heparins alone with bailout GPIIb/IIIa Inhibitors in patients with ST-segment elevation myocardial infarction transported emergently for primary percutaneous coronary intervention: a pre-specified analysis from the EUROMAX trial†, by U. Zeymer et al., on page 2460.

Two feared peri-procedural complications of primary percutaneous coronary intervention (PCI) are stent thrombosis (ST) and major bleeding. Although rare, ST is associated with high rates of myocardial infarction and death. Potent antithrombotic therapy around the time of PCI markedly reduces the risk of ST, but increases bleeding hazard (Figure 1). Historically, the anticoagulant of choice for PCI has been unfractionated heparin (UFH). Glycoprotein inhibitors (GPI) added to heparin significantly reduce peri-procedural ischaemic complications, but increase major bleeding and the need for transfusions. There has been a consistent association between major bleeding and increased mortality. In PCI for elective indications and across the spectrum of acute coronary syndrome (ACS), the direct thrombin inhibitor bivalirudin is non-inferior to heparin plus GPI with respect to overall ischaemic complications, but significantly decreases major bleeding.

In this issue of European Heart Journal, an important pre-specified analysis by Zeymer et al. uses the European Ambulance Acute Coronary Syndrome Angiography (EUROMAX) study population to compare patients receiving bivalirudin with patients receiving heparins [UFH or low-molecular weight heparin (LMWH)] with routine GPI use (defined as initiation before or during coronary angiography) and patients receiving heparins with only bailout GPI use (defined as initiation after the start of PCI). This study expands on the original EUROMAX findings by reporting a significant difference in the composite primary endpoint of death or major bleeding that favours bivalirudin over heparins with routine GPI use and heparins with bailout GPI use (5.1 vs. 7.6 and 9.8%, respectively; $P = 0.03$ and $P = 0.006$). There was no difference in the outcome of death by any cause when comparing bivalirudin (2.9%) against heparins with routine GPI use (2.3%, $P = 0.44$) and against heparins with bailout GPI use (4.1%, $P = 0.23$). The favourable primary outcome observed in the study population was driven by a decrease in major bleeding with bivalirudin (2.6%) compared against heparins with routine GPI use ($5.9\%, P = 0.0007$) and against heparins with bailout GPI use (6.3%, $P = 0.0005$). The benefits observed with bivalirudin regarding the study primary endpoint [odds ratio (OR) 0.53, 95% confidence interval (CI) 0.33–0.87] and major bleeding (OR 0.44, 95% CI 0.24–0.82) persisted even after adjustment for differences in baseline variables. With regard to ST, the bivalirudin cohort experienced an increased rate of 1.6%, compared with 0.6% ($P = 0.09$) for the heparins with routine GPI and 0.4% ($P = 0.09$) for the heparins with bailout GPI use.

The largest trials comparing bivalirudin monotherapy and heparins with or without GPI use in patients with ST-segment elevation (STE) ACS undergoing primary PCI are the Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) and EUROMAX trials. In HORIZONS-AMI, bivalirudin was compared with UFH plus GPI in 3602 patients with STE-ACS. Bivalirudin monotherapy compared with heparin plus GPI was associated with decreased cardiac death (1.8% vs. 2.9%, respectively; $P = 0.03$) in the setting of decreased non-coronary artery bypass graft-related major bleeding (4.9% vs. 8.3%, respectively; $P < 0.001$) and decreased blood transfusion (2.1 vs. 3.5%, respectively; $P = 0.09$). However, increased ST in the bivalirudin group compared with the heparin plus GPI cohort (acute ST 1.3% vs. 0.3%, respectively; $P < 0.001$) was also found. EUROMAX compared pre-hospital initiation of bivalirudin vs. UFH or LMWH with optional GPI use in 2198 patients presenting with STE-ACS. In efforts to attenuate the increased rate of ST noted in HORIZONS-AMI, the EUROMAX protocol called for continuation of a low-dose bivalirudin infusion (0.25 mg/kg/h) or the higher PCI dose (1.75 mg/kg/h) for at least 4 h post-PCI. EUROMAX reaffirmed that bivalirudin compared with control was associated with reduced major bleeding (2.6% vs. 6.0%, respectively; $P < 0.001$) and decreased blood transfusion (2.1 vs. 2.9% respectively).
3.9%, respectively; \( P = 0.02 \)). Once again, however, an increase in definite ST with bivalirudin was seen (1.6 vs. 0.5%, respectively; \( P = 0.02 \)). No significant difference in mortality was observed in EUROMAX.5

This well-crafted, though post-randomization, analysis of EUROMAX by Zeymer et al. is timely, especially in light of the recently presented findings from the How Effective are Antithrombotic Therapies in Primary PCI (HEAT-PPCI) trial and the pre-specified pooled data analysis from the HORIZONS-AMI and EUROMAX trials at the 2014 meeting of the American College of Cardiology (ACC) clinical trial sessions. Initial findings from the single-centre HEAT-PPCI trial reported a reduced rate of major adverse cardiac events and ST in 1812 STE-ACS patients treated with heparin monotherapy compared with bivalirudin monotherapy, with no difference in major bleeding.6 In contrast to these findings, analysis of 5800 patients from the multicentre HORIZONS-AMI and EUROMAX trials found bivalirudin to be associated with a decreased risk of major bleeding and also cardiac death, despite bivalirudin causing an increased risk of ST.7 All three trials were open label, which is a limitation, though less likely to affect ‘hard’ endpoints such as cardiac death. It is important to note that both HEAT-PPCI and the pooled analysis of the HORIZONS-AMI and EUROMAX trials have yet to be published in a peer-reviewed journal, and any conclusions stemming from these large, well-conducted studies should be considered preliminary.

The present study by Zeymer and colleagues reaffirms the superiority of bivalirudin in mitigating clinically relevant bleeding events in the setting of primary PCI.8–10 As noted in the prior Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events (REPLACE)-2 and Acute Catheterization and Urgent Intervention Triage strategY (ACUTIY) trials, the favourable bleeding profile observed with bivalirudin over heparin plus GPI goes beyond the primary PCI setting.8,10 Recent registry data extend those findings. The Evaluation of Drug-Eluting Stents and Ischemic Events (EVENT) registry analysed either bivalirudin or UFH monotherapy in 1036 patients with non-ST-segment elevation ACS (NSTE-ACS) and 2062 patients undergoing elective PCI. Compared with UFH, bivalirudin was again found to be associated with lower composite bleeding rates in both NSTE-ACS (difference = 3.3%, \( P = 0.01 \)) and elective PCI cohorts (difference = 1.8%, \( P = 0.01 \)). Compared with UFH monotherapy, there was no increase in ST in the bivalirudin NSTE-ACS or elective PCI cohorts.11

In the STE-ACS setting of both HORIZONS-AMI and EUROMAX, the favourable bleeding profile of bivalirudin was marred with increased rates of ST during the first 24 h following stent implantation. The present analysis by Zeymer et al. also finds increased ST with bivalirudin compared with heparins with routine GPI use and also heparins with bailout GPI use. The aetiology of this higher rate of acute ST observed with bivalirudin following primary PCI in STE-ACS is not well understood. Current hypotheses include the short half-life of bivalirudin in the setting of discontinuation at the end of primary PCI procedures of relatively short duration in the contemporary era, such that the total exposure to bivalirudin is relatively low and insufficient for the highly thrombotic milieu of STE-ACS. Supporting this theory is an additional subgroup analysis from EUROMAX presented at ACC 2014, which suggests that continuing the higher PCI dose of bivalirudin for 4 h post-PCI may eliminate the
increased risk of acute ST, with no increased risk of major bleeding compared with the cohorts receiving heparins with and without GPI use.13 These findings are also considered preliminary and need to be tested further prospectively.

Both prasugrel and ticagrelor have been shown to reduce early ST compared with clopidogrel. In the setting of ACS, impaired absorption and variation of pharmacokinetic response may limit drug bioavailability and thus delay effective systemic action of oral P2Y12 inhibitors. A potential candidate to fill this void is cangrelor, a fast-acting, potent, intravenous, direct platelet adenosine diphosphate P2Y12 inhibitor. In the Clinical Trial Comparing Cangrelor to Clopidogrel Standard of Care Therapy in Subjects Who Require Percutaneous Coronary Intervention (CHAMPION PHOENIX), cangrelor was compared with clopidogrel in 11 145 patients undergoing PCI and found to reduce the rate of ischaemic events, including intraprocedural ST (OR 0.65; \( P = 0.04 \)) and ST at 48 h (OR 0.62; \( P = 0.001 \)), with no increase in severe bleeding or transfusions.13,14 A conceivable benefit with cangrelor use potentially relevant to bivalirudin is supported by the pre-specified pooled analysis of the CHAMPION program (PCI, PLATFORM, and PHOENIX) involving 24 910 patients, which found cangrelor compared with clopidogrel to be associated with a reduction in acute ST (OR 0.48; \( P = 0.03 \)).15 Preliminary analysis of the bivalirudin subgroup from CHAMPION PHOENIX supports the suggestion that the combination with cangrelor has a favourable risk–benefit profile.16 Thus, cangrelor, if approved, may be of particular utility with bivalirudin in primary PCI to reduce the risk of acute ST without increasing the risk of transfusions. The cost-effectiveness of such a strategy, however, still needs to be evaluated.

In summary, this insightful analysis of the EUROMAX trial supports the role of bivalirudin as having a superior bleeding profile among currently used regimens in primary PCI. Nevertheless, the reduced bleeding at the expense of increased acute ST will continue to spur debate about the optimal antithrombotic approach. Further studies are warranted to determine whether continuing bivalirudin at the PCI dose for 4 h after the procedure eliminates the ST risk while preserving the bleeding benefit. The potential complementary effects of newer agents such as cangrelor with bivalirudin, in combination with bleeding-reduction strategies such as radial artery access, may maximize protection from peri-procedural ischaemic events while mitigating peri-procedural bleeding in the setting of primary PCI.

Conflict of interest: Deepak L. Bhatt discloses the following relationships: Advisory Board, Elsevier Practice Update Cardiology, Medscape Cardiology, Regado Biosciences; Board of Directors, Boston VA Research Institute, Society of Cardiovascular Patient Care; Chair, American Heart Association Get With The Guidelines Steering Committee; Data Monitoring Committees, Duke Clinical Research Institute, Harvard Clinical Research Institute, Mayo Clinic, and Population Health Research Institute; Honoraria, American College of Cardiology (Editor, Clinical Trials, CardioSource), Belvoir Publications (Editor in Chief, Harvard Heart Letter), Duke Clinical Research Institute (clinical trial steering committees), Harvard Clinical Research Institute (clinical trial steering committee), HMP Communications (Editor in Chief, Journal of Invasive Cardiology); Population Health Research Institute (clinical trial steering committee), Slack Publications (Chief Medical Editor, Cardiology Today’s Intervention), WebMD (CME steering committee); other, Clinical Cardiology (Associate Editor); Journal of the American College of Cardiology (Section Editor, Pharmacology); research grants, Amarin, AstraZeneca, Bristol-Myers Squibb, Eisai, Ethicon, Medtronic, Roche, Sanofi Aventis, The Medicines Company [who make bivalirudin] (for his role as co-Chair of the CHAMPION trials of cangrelor); and unfunded research, FlowCo, P2X Pharma, Takeda. Antonio Gutierrez has no disclosures.

References
