Improving outcomes with bivalirudin in primary percutaneous coronary intervention

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Online publish-ahead-of-print 28 May 2014

This editorial refers to ‘Prasugrel plus bivalirudin vs. clopidogrel plus heparin in patients with ST-segment elevation myocardial infarction†, by S. Schulz et al., on page 2282

Optimal pharmacotherapy is essential to realize the best outcomes in patients undergoing primary percutaneous coronary intervention (PCI) for ST-segment elevation myocardial infarction (STEMI). In this regard, effectively restoring reperfusion and maintaining the patency of the infarct artery after stenting requires a balance between the haemorrhagic risks and the ischaemic benefits of anti-coagulant and antiplatelet agents. Over the last three decades, as the principal device used for primary PCI has evolved from balloon angioplasty to bare metal stents to drug-eluting stents, parallel advances have occurred in antithrombotic and antiplatelet regimens, from unfractionated heparin (UFH) alone, to UFH plus a glycoprotein IIb/IIIa inhibitor (GPI), to bivalirudin with provisional (bailout) GPI use, and from ticlopidine and clopidogrel to prasugrel and ticagrelor (on a background of aspirin). Given the time, complexity, and costs of performing appropriately powered randomized trials, clinical practice has progressed faster than the evidence base required to inform optimal drug and device usage for all possible drug and device permutations.

Unfractionated heparin, a heterogeneous mixture of polysaccharides of varying chain lengths, while familiar and inexpensive, has numerous shortcomings,1 which become most clinically apparent in acute coronary syndromes (ACS). Unfractionated heparin has an indirect mechanism of action (binding to and activation of antithrombin III, the amount of which varies in disease states) and has limited activity against clot-bound thrombin. Non-specific protein and cellular binding of UFH results in variable biological activity and can result in heparin-induced thrombocytopenia and thrombosis. Moreover, UFH binds to the glycoprotein IIb/IIIa receptor, thereby paradoxically activating platelets.5 Kastrati and colleagues elegantly demonstrated that, despite pre-treatment with aspirin and clopidogrel, myocardial infarction rates in non-STEMI are substantially reduced after PCI with abciximab.2 Meta-analysis of eight randomized trials in 3949 patients with STEMI undergoing PCI demonstrated that the addition of abciximab to UFH reduced the 30 day odds of re-infarction by 37% (P < 0.001) and the 6–12 month odds of mortality by 28% (P = 0.01).3 In the largest such study, CADILLAC, 30 day stent thrombosis was also reduced with abciximab plus UFH vs. UFH alone (P = 0.01).4 These benefits more than offset the increased rates of bleeding and thrombocytopenia that may occur with GPI.5 As such, aspirin, clopidogrel, and UFH plus GPI became the preferred regimen to support primary PCI in STEMI, used in >90% of patients in the USA and in the majority of patients in Europe.6,7

This regimen remained the standard for more than a decade until challenged by the direct thrombin inhibitor bivalirudin, a rapidly reversible agent (half-life 25 min), which overcomes many of the limitations of UFH. Specifically, bivalirudin does not require antithrombin III for activation, is able to inhibit fibrin-bound thrombin, has predictable biological activity and dosing, does not cause thrombocytopenia or activate platelets, and indeed, blocks both collagen- and thrombin-induced platelet activation.6 A series of multicentre randomized PCI trials across the spectrum of coronary artery disease has demonstrated that in comparison to UFH plus GPI, bivalirudin with provisional GPI use results in similar rates of composite ischaemic events, with 40–50% reductions in major bleeding and thrombocytopenia.8–12 The EuroMax trial confirmed that the bleeding benefits of bivalirudin are present in patients treated with radial as well as femoral access,13 which is not surprising given that the majority of major bleeding events after PCI in ACS are not access site related.13 Moreover, in the largest randomized primary PCI trial to date, anticoagulation with bivalirudin in comparison to UFH plus GPI resulted in reduced cardiac and all-cause mortality at 30 days,11 benefits which were sustained to 3 years,14 reflecting both haematological and non-hematological benefits of bivalirudin.15 As a result, in many countries bivalirudin has supplanted UFH plus GPI as the preferred regimen to support primary PCI in STEMI.

How can the results with bivalirudin be improved further? One glaring deficiency of bivalirudin monotherapy in primary PCI during STEMI (which has not been observed in other settings) was first noted in the HORIZONS-AMI trial, and subsequently confirmed in EuroMax; stent thrombosis, occurring within the first 4 h after the
patients were recruited, resulting in 51% was terminated prematurely for slow enrolment after only 548 clopidogrel in 1240 primary PCI patients. Unfortunately, the trial events) with bivalirudin plus prasugrel in comparison to UFH plus ADP antagonist prasugrel is capable of improving outcomes with bivalirudin anticoagulation during primary PCI for STEMI.17 The first randomized trial to examine whether the potent oral ADP receptor inhibition and/or residual thrombin activity after discontinuation of bivalirudin. Although not outweighing the benefits of bivalirudin in terms of reduced major bleeding, thrombocytopenia, and mortality, and while rarely fatal when occurring in this closely observed setting, any increase in stent thrombosis is clearly an undesirable event that warrants preventative efforts.

Reported in this issue of the European Heart Journal, BRAVE-4 is the first randomized trial to examine whether the potent oral ADP antagonist prasugrel is capable of improving outcomes with bivalirudin anticoagulation during primary PCI for STEMI.17 The trial was powered to demonstrate a 40% reduction in net adverse clinical events (NACE; a composite of adverse ischaemic and bleeding events) with bivalirudin plus prasugrel in comparison to UFH plus clopidogrel in 1240 primary PCI patients. Unfortunately, the trial was terminated prematurely for slow enrolment after only 548 patients were recruited, resulted in 51% post hoc power. Only 93% of patients had a confirmed myocardial infarction, further reducing power. Not surprisingly, no significant differences in NACE were observed between the two groups [15.6 vs. 14.5%; relative risk (95% confidence interval), 1.07 (0.70–1.64)], consistent with bivalirudin plus prasugrel ranging from 30% better to 64% worse for this endpoint, with 95% confidence.

BRAVE-4 raises several important trial design issues. First, in comparison to clopidogrel, prasugrel would be expected to increase non-coronary artery bypass graft-related bleeding; a primary NACE endpoint would therefore mask its expected benefits in reducing stent thrombosis and re-infarction.18 Ideally, pharmacotherapy trials should be powered for separate efficacy (ischaemic events) and safety endpoints (bleeding) to be able to discriminate the relative merits of this expected trade-off. However, because of difficulty in accurately detecting and adjudicating re-infarction in the peri-PCI period, 48 h composite ischaemic event rates are paradoxically lower after STEMI than in other clinical settings,19 which necessitates a trial size of thousands of randomized patients to examine composite ischaemia (even more for stent thrombosis). We can thus draw little inference from the composite ischaemic event rates in BRAVE-4 [4.8% with bivalirudin plus prasugrel vs. 5.5% with UFH plus clopidogrel; relative risk (95% confidence interval), 0.89 (0.40–1.96)], consistent with bivalirudin plus prasugrel ranging from 60% better to 96% worse.

Second, the control arm in BRAVE-4 did not include the routine use of a GPI, which while on the surface may appear to be a step backward, is less costly and not uncommon practice outside the USA. Indeed, other than ISAR-REACT-3, which did show reduced major bleeding with bivalirudin in comparison to UFH alone in troponin-negative PCI patients,9 there is a paucity of randomized trial data comparing bivalirudin with UFH monotherapy, although large-scale registries and meta-analyses also suggest that bivalirudin reduces bleeding and mortality in comparison to UFH alone.20–22 However, in the large-scale, multicentre EuroMax trial, bailout GPI were required in 25.4% of UFH-treated PCI patients, suggesting an unacceptable incidence of refractory thrombotic complications when primary PCI in STEMI is performed with UFH alone.12 In BRAVE-4, bailout GPI were required in 6.1% of UFH plus clopidogrel patients vs. 3.0% with bivalirudin plus prasugrel (P = 0.07). Most importantly, omitting GPI from the UFH control arm would be expected to lower bleeding rates in comparison to UFH alone, further complicating interpretation of a NACE endpoint. The similar bleeding rates with bivalirudin plus prasugrel compared with UFH plus clopidogrel in BRAVE-4 does suggest that adding prasugrel to bivalirudin has diminished some of the safety benefit of bivalirudin plus clopidogrel in comparison to UFH plus clopidogrel, although caution in interpretation is again required given the wide confidence intervals. Lastly, isolated
haematoms (used in the HORIZONS-AMI and BRAVE-4 principal bleeding endpoints) should no longer be considered an important yardstick of safety because they have no long-term consequences. 23

Third, and perhaps most importantly, both prasugrel and ticagrelor have delayed absorption in STEMI, not reaching peak pharmacodynamic efficacy for 4–6 h. 24, 25 Both agents have been shown to reduce stent thrombosis in comparison to clopidogrel in ACS and STEMI, but not within the first 24 h (Figure 1). 18, 26 In BRAVE-4, no insights can be drawn from the three vs four stent thrombosis events in the bivalirudin plus prasugrel and UFH plus clopidogrel arms, respectively. In contrast, the investigational potent intravenous ADP-antagonist cangrelor, which achieves peak pharmacodynamic effect within minutes, has been demonstrated to reduce intra-procedural and acute stent thrombosis post-PCI, without increasing major bleeding. 27 Cangrelor would thus likely be the preferred synergistic partner for bivalirudin, subsequently transitioning to a potent oral agent. In addition to cangrelor, an alternative approach to reduce acute stent thrombosis might be a several hour bivalirudin potent oral agent. In addition to cangrelor, an alternative approach to reduce acute stent thrombosis might be a several hour bivalirudin infusion without increasing bleeding, which warrants further study. 27

Along with system improvements and advances in interventional devices and technique, bivalirudin antiocoagulation during primary PCI has substantially improved clinical outcomes in STEMI, resulting in high event-free survival rates, which are difficult to enhance further. BRAVE-4 is noteworthy not only as the first clinical trial to attempt to fine-tune the benefits of bivalirudin during primary PCI, but also in demonstrating the challenges that all such studies will face regarding adequate sample size and feasibility. Nonetheless, given the substantial morbidity and mortality that STEMI entails, these efforts are not only justified but are essential to improve outcomes further for high-risk patients with ACS.

Conflict of interest: within the last 36 months G. W. Stone has served as a consultant to Abbott Vascular, Boston Scientific, Medtronic, The Medicines Company, Daiichi Sankyo, Eli Lilly, Bristol-Meyers-Squibb, and Astra Zeneca.

References

A 67-year-old female was admitted to our hospital exhibiting chest pain and dyspnea that occurred immediately after an exercise-induced syncope. A priori the clinical symptoms, ECG (Panel A), and myocardial biomarkers were indicative for an acute coronary syndrome (troponin I: 7.35 ng/mL). Coronary angiogram ruled out both coronary artery disease and coronary vasospasm. Surprisingly, however, an abnormal origin of the left main coronary artery (LMCA, arrowheads), arising from the right coronary sinus, sharing a common ostium with the RCA, became apparent (Panel B1, Supplementary material online, Video S1). Left ventricular (LV) angiogram (Panel B2, and Supplementary material online, Video S2) and magnetic resonance imaging (MRI; Supplementary material online, Video S3) demonstrated apical ballooning and basal hyper-contractility (Panel C), ejection fraction (EF) of 40%. Magnetic resonance imaging further uncovered an apical LV thrombus (Panel C, *) and showed no myocardial late gadolinium enhancement. Computed tomography unravelled the course of the LMCA, sharing an ostium with the RCA, running between the posteriorly aorta (Ao) and anteriorly pulmonary trunk (PT) (Panels D1 and D2). Complete normalization of LV function (EF 60%) was documented 2 weeks after admission, confirmed by MRI. Owing to the well-known severe prognosis of this coronary anomaly, exhibiting an increased risk for sudden cardiac death, coronary artery bypass grafting was successfully performed. Global myocardial ischaemia by exercise-induced mechanical compression of the LMCA along its course between the PT and ascending Ao might be a hazardous, ‘non-idiopathic’ cause of tako-tsubo cardiomyopathy other than stress-induced, catecholamine mediated coronary vasospasm.

Supplementary material is available at European Heart Journal online.