Kardiologia Polska 2018; 76, 4: 711–712; DOI: 10.5603/KP.2018.0074 ISSN 0022–9032

EDITORIAL

Bivalirudin bewilderment

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Percutaneous coronary intervention (PCI) with drug-eluting stents (DES) provides effective revascularisation for many patients with coronary artery disease (CAD) [1]. Appropriate procedural anticoagulation is essential to ensure successful PCI and optimal clinical outcomes. Although unfractionated heparin was the dominant periprocedural anticoagulant for a long time [2], other agents, including low-molecular weight heparins [3], and more recently bivalirudin [4, 5], have been trialed as alternatives. In several studies comparing bivalirudin with heparin plus a glycoprotein (GP) IIb/IIIa inhibitor, the former standard of care, the direct thrombin inhibitor bivalirudin, demonstrated a reduced risk of bleeding and an overall favourable profile including reduced cardiovascular mortality [5, 6]. However, these promising findings were hindered by an increased risk of thrombotic events, particularly acute stent thrombosis with bivalirudin [4, 5, 7]. Subsequent studies used more potent adjunct antithrombotic regimens to address this concern, but resulted in attenuation of the bleeding advantage of bivalirudin [8]. In addition, the practice of PCI has evolved since these studies. For example, radial access now predominates at some centres, and is associated with a lower rate of access site-related bleeding compared to femoral access (but similar rates of non-access site bleeding).

The controversy over the optimal antithrombin agent to use during PCI across the spectrum of patients undergoing PCI has persisted, with several recent systematic reviews and meta-analyses published [6, 9]. In this issue of the journal, Grajek et al. [10] report an updated systematic review and meta-analysis of clinical trials of bivalirudin versus heparin for periprocedural anticoagulation in patients undergoing PCI, which most notably differs from prior efforts by incorporating results from the large-scale MATRIX trial [11]. The authors assessed net adverse clinical events (NACE; ischaemic or bleeding events), which occurred in 9.8% of patients receiving bivalirudin and 11.9% of patients receiving heparin ($p = 0.008$). However, the improvement in NACE was driven by decreased major bleeding in patients receiving bivalirudin; the rates of major adverse cardiovascular events were comparable in the two groups. The present study also showed an increased risk of acute stent thrombosis and myocardial infarction with bivalirudin, similar to prior analyses. Of note, however, several of the randomised trials were prematurely stopped for slow-enrollment or loss of funding, which reduces the confidence in the available results [8] BRAVE-4 was also a hybrid randomised trial in which the combination of bivalirudin and prasugrel were compared to heparin and clopidogrel, confounding clear interpretation of the antithrombin effect [8]. In addition, the investigators did not include earlier trials such as TIMI-8, PROBI-VIRI, and ARNO, some of which had suggested a favourable profile for bivalirudin [6, 12], or the recently published large-scale VALIDATE-SWEDEHEART trial [13].

These limitations notwithstanding, the current systematic review and the results of VALIDATE-SWEDEHEART suggest that the use of more potent adjunct antithrombotic regimens (including $P2Y_{12}$ inhibition with ticagrelor or prasugrel) has mitigated the risk for stent thrombosis with bivalirudin, at the cost of reducing its bleeding advantage, especially in patients undergoing radial access. Importantly, however, the signal for increased stent thrombosis with bivalirudin has been largely confined to patients with ST-elevation myocardial infarction (STEMI). Given its short half-life, the stent thrombosis risk of bivalirudin is potentiated with its abrupt bivalirudin discontinuation post-PCI, especially if oral $P2Y_{12}$ inhibitors have not yet had time to become effective given delayed gastric absorption in STEMI. To obviate this risk, a post-PCI bivalirudin infusion has been studied. Several trials (BRIGHT, EUROMAX and MATRIX) have demonstrated that a 3–4 hour post-PCI bivalirudin infusion at the PCI does eliminates the excessive acute thrombosis risk of bivalirudin without increasing bleeding, whereas an infusion at a lower dose is ineffective [7, 11, 14]. Unfortunately this high-dose post-PCI bivalirudin

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infusion strategy was not individually considered in the current meta-analysis.

A panoply of diverse options must be considered when selecting the optimal antithrombotic agent and regimen to minimise both ischaemic events and haemorrhagic complications in patients undergoing PCI, including the clinical presentation (stable ischaemic heart disease vs. non-STEMI vs. STEMI), the patient's ischaemic and bleeding risk profile, the platelet reactivity of older vs. newer, more potent $P2Y_{12}$ inhibitors (including intravenous cangrelor), radial vs. femoral access, routine vs. bailout use of GP IIb/IIIa inhibitors, heparin dose, heparin pre-treatment, bivalirudin post-PCI infusion and dosing, and others — literally resulting in hundreds of possible scenarios that require nuanced consideration. Aggregate effect meta-analyses are unable to provide sufficient discrimination to evaluate each situation. Conversely, individual patient data pooled analyses may be able to identify the optimal peri-procedural antithrombotic regimen across the spectrum of patients undergoing PCI. Such a collaborative analysis is currently being performed by the principal investigators from all the major trials and may provide much needed clarity to guide selection of the safest and most effective antithrombin and antiplatelet regimens in varying patient subsets along the continuum of risk [6, 15].

Conflict of interest: *Dr. Bikdeli is supported by the National Heart, Lung, and Blood Institute, National Institutes of Health, through grant number T32 HL007854. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. No other relevant disclosures.*

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