JACC: CARDIOVASCULAR INTERVENTIONS
VOL. 9, NO. 13, 2016

ISSN 1936-8798/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jcin.2016.05.038

EDITORIAL COMMENT

Bivalirudin in Current Practice

Melius Abundare Quam Deficere?*

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The optimal antithrombotic therapy for preventing ischemic complications while limiting bleeding risk in patients with acute coronary syndrome (ACS) who are undergoing primary percutaneous coronary intervention (pPCI) remains an area of great controversy (1). The quest for an ideal parenteral anticoagulant agent able to replace unfractionated heparin (UFH) has remained an ongoing topic for investigation since the 1990s. Bivalirudin was compared with UFH first in experimental models and then in patients with coronary artery disease (CAD). During this long-lasting journey, contrasting evidence has been accumulated on bivalirudin efficacy and safety profile compared with UFH. After initial promising findings in the early 1990s, HAS/BAS (Hirulog/Bivalirudin Angioplasty Study) published in 1995 (conducted in 1993 to 1994) showed that bivalirudin (bolus of 1.0 mg/kg followed by infusion of 2.5 mg/kg/h for 4 h, then 0.2 mg/kg/h for 14 to 20 h) had similar efficacy but lower bleeding risk than high and prolonged regimen of UFH (bolus of 175 U/kg followed by infusion of 15 U/kg/h for 18 to 24 h). However, the sponsor interpreted these findings as insufficient to warrant further investment, which led to terminate further clinical studies with bivalirudin, including the ongoing TIMI-8 (Thrombolysis In Myocardial Infarction-8) trial. Bivalirudin was then acquired by The Medicines Company, which profoundly invested in a new era of clinical studies. A meta-analysis of randomized trials by Kong et al. (2) in 1999 suggested that bivalirudin was as effective as UFH but safer in patients with CAD. The results of HAS/BAS study were also reanalyzed updating the primary endpoint definition and modifying its time point, which generated new evidence suggesting that bivalirudin was superior for both efficacy and safety at 7 and 90 days (3). Multiple trials were then conducted with bivalirudin at a revised bolus and post-bolus infusion regimen in patients with Non-ST-segment elevation-acute coronary syndrome (NSTE-ACS), ST-segment elevation myocardial infarction (STEMI), or both (Online Table 1) against various comparator arms (UFH with or without glycoprotein IIb/IIIa inhibitors [GPI] and on top of various oral $P2Y_{12}$ inhibitors), which resulted in a large body of evidence for bivalirudin in PCI patients.

Across studies and regimens, bivalirudin has consistently shown to mitigate the bleeding risk (4). This benefit has been observed against all possible comparator arms, including UFH plus routine use of GPI, UFH plus liberal or restricted use of GPI and UFH alone. Importantly, not only access site bleeding was attenuated by bivalirudin but also those not access site-related, which are at least as frequent in ACS patients and most likely more detrimental on prognosis.

Yet, in STEMI patients undergoing pPCI, all major studies so far conducted have identified a sizable risk of acute stent thrombosis (ST) across all compactors, including UFH+GPI, UFH±GPI, or UFH alone (4). This observation fueled an ongoing debate on the value of this anticoagulant option in current practice, where, despite growing awareness on the importance of bleeding on patient outcomes, the avoidance of ST remains the number 1 *obsession* by all interventionists.

To mitigate that risk, 2 studies have protocol mandated and 1 study randomly allocated bivalirudin patients to continue the treatment well after PCI.

*Editorials published in *JACC: Cardiovascular Interventions* reflect the views of the authors and do not necessarily represent the views of *JACC: Cardiovascular Interventions* or the American College of Cardiology.

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JACC: CARDIOVASCULAR INTERVENTIONS VOL. 9, NO. 13, 2016
JULY 11, 2016:1321–3

Results were mixed as in only 1 of the 3 trials no excess of ST risk was observed in patients receiving post-intervention bivalirudin infusion. Yet, focusing on the post-PCI bivalirudin regimen, results are apparently concordant in suggesting that only a full PCI regimen after intervention can mitigate that risk excess to null.

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In this issue of *JACC: Cardiovascular Interventions*, Shah et al. (5) should be commended for the completion of a traditional and network meta-analysis, apparently restricted to patients with STEMI undergoing pPCI, with a specific focus to acute ST. This analysis is timely and provides additional evidence that the effects of anti-thrombotic drugs are largely regimen-dependent. Bivalirudin was unsurprisingly associated to a significantly higher risk of acute ST (4). Yet, the new finding is that a post-pPCI infusion at full dose (Biv-Full) (1.75 mg/kg/h) abolished that risk as compared with the low-dose (Biv-Low) (0.25 mg/kg/h) or no infusion as well as with UFH. Notably, the significant benefit of bivalirudin over UFH in terms of reduction of major bleeding persisted in studies using the post-pPCI Biv-Full treatment strategy.

These results are potentially practice changing and largely consistent with the updated recommendations for use of bivalirudin in the United States.

However, there are numerous limitations to this analysis, which should raise caution.

Shah et al. (5) aimed at restricting the analysis to pPCI patients. Yet, they included a sizable proportion of NSTE-ACS patients. Although the inclusion of all MATRIX (Minimizing Adverse Hemorrhagic Events by Transradial Access Site and Systemic Implementation of Angiox) study patients (i.e., including 3,203 [44%] NSTE-ACS) was acknowledged, Shah et al. (5) did not clarify to the readers that 269 NSTE-ACS patients also included in BRIGHT (Bivalirudin in Acute Myocardial Infarction vs Heparin and GPI Plus Heparin Trial) were pooled due to unavailability of individual patient data. This may have diluted the relative and absolute risks of ST in bivalirudin-treated patients.

The main limitation to this analysis however is its largely nonrandomized and unadjusted nature.

Network meta-analyses are very powerful and increasingly accepted tools to enhance study power and artificially create comparator arm(s) levering on the relative risk reductions observed within randomized arms. Yet, its use for observational findings may amplify the biases known to occur when treatment is not randomly allocated.

The MATRIX trial remains today the only study where patients treated with bivalirudin were randomized to receive post-PCI infusion or no infusion of bivalirudin (6). Hence, the data comparing post-PCI versus no post-PCI bivalirudin infusion (Biv-No) are largely indirect since HORIZONS-AMI (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction) and HEAT-PPCI (How Effective Are Antithrombotic Therapies in Primary Percutaneous Coronary Intervention) studies provided only data on Biv-No strategy, whereas BRIGHT and EUROMAX (European Ambulance Acute Coronary Syndrome Angiography Trial) provided only data on Biv-Full. Even more worrisome is the comparison between low versus full post-PCI regimen.

No study so far has randomized the post-PCI bivalirudin regimen. A full bivalirudin regimen was protocol mandated in BRIGHT, whereas both the EUROMAX and MATRIX studies left post-PCI regimens to the discretion of the treating physicians, which was consistent with current and previous European or North American bivalirudin label, respectively.

Consequently, the Biv-Full population is a mixture of patients derived from BRIGHT, EUROMAX, and MATRIX studies, whereas Biv-Low is a smaller population that was derived exclusively from the EUROMAX and MATRIX trials. In both trials, the 2 populations were imbalanced in number with a majority of patients receiving Biv-Low rather than Biv-Full (63% vs. 37% in MATRIX and 77.5% vs. 22.5% in EUROMAX, respectively). Operators have probably applied a clinical selection in using a regimen over the other, administering Biv-Low to patients with higher bleeding risk whereas Biv-Full to those at increased risk of acute ST.

Additionally, the heterogeneity in the duration of post-PCI infusion should be considered as further potential source of bias. In EUROMAX, bivalirudin had to be prolonged per protocol for at least 4 h after PCI and overall the median duration was 268 min (interquartile range [IQR]: 250 to 292 min). In BRIGHT, the protocol stated that Biv-Full was at least 30 min, but maximum 4 h and that a supplementary infusion at low dose (0.2 mg/kg/h) was allowed up to 20 h at operator's discretion. All patients received a post-PCI infusion of Biv-Full for a median duration of 180 min (IQR: 148 to 240) but 115 patients (15.6%) thereafter also received the optional 0.2 mg/kg/h dose for a median duration of 400 min (IQR: 375 to 410 min). Finally, MATRIX patients assigned to post-PCI infusion were to receive Biv-Full for up to 4 h or Biv-Low for at least 6 h and, overall the average durations were 264 ± 209.8 min and 433 ± 248 min, respectively.

Hence, these results would need prospective validation. Currently, the SWEDEHEART (Bivalirudin vs Heparin in NSTEMI and STEMI in Patients on Modern Antiplatelet Therapy in SWEDEHEART A Multicenter, Prospective, Randomized Controlled Clinical Trial Based on the SWEDEHEART Platform; NCT02311231) trial is ongoing. Although it will contribute to the evidence in the long-lasting journey of bivalirudin versus UFH comparison, the protocol mandates the use of post-PCI bivalirudin at full regimen only.

Should bivalirudin be used from now on in STEMI patients with post-PCI full dose infusion? An individual patient meta-analysis is planned which shall at least try to adjust for measurable and measured confounders given the largely non-randomized nature of this comparison. Whether prolonging bivalirudin at full PCI regimen after PCI mitigates ST while not increasing bleeding risks remains to be ascertained.

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KEY WORDS anticoagulation, bivalirudin, heparin, percutaneous coronary intervention, post-procedural dosage

APPENDIX For a supplemental table, please see the online version of the article.