

EDITORIAL VIEWPOINT

Choice of Optimal Anticoagulant to Support Primary PCI

Out With the New, In With the Old*

Sanjay Kaul, MD



“The past is never dead. It’s not even past.”

— William Faulkner, *Requiem for a Nun* (1)

Bivalirudin, a direct thrombin inhibitor, is indicated as monotherapy in patients with unstable angina undergoing percutaneous transluminal coronary angioplasty (PTCA) (2). Bivalirudin with provisional use of a glycoprotein IIb/IIIa inhibitor (GPI) is indicated as an anticoagulant in patients undergoing percutaneous coronary intervention (PCI) (2). Although not specifically approved for patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary PCI (PPCI), it is widely used to reduce periprocedural ischemic complications. Until recently, bivalirudin monotherapy was endorsed by the guidelines as a Class I, Level of Evidence (LOE): B recommendation, and supported in preference to unfractionated heparin (UFH) and a GPI (Class IIa, LOE: B) in patients at high risk of bleeding (3). These recommendations were primarily driven by results of the landmark HORIZONS-AMI (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction) trial, conducted nearly a decade ago (4). Clinical practice has since evolved, mainly characterized by less frequent GPI use, more frequent use of new and potent P2Y₁₂ inhibitors, more frequent radial-artery PCI access, and, in some regions, pre-hospital initiation of

treatment (5). Accordingly, 4 additional trials evaluated bivalirudin’s role in PPCI (5–8), yielding mixed results and igniting a firestorm of controversy regarding the optimal anticoagulant to support PPCI.

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In this issue of the *Journal*, Stone et al. (9) present the 30-day pooled results of 2 multicenter, prospective, open-label randomized, controlled trials of bivalirudin during PPCI, HORIZONS-AMI and EUROMAX (European Ambulance Acute Coronary Syndrome [ACS] Angiography Trial). The authors conclude that “despite evolution in PCI practice, technique and adjunct pharmacology, anticoagulation during PPCI with bivalirudin compared to heparin ± GPI reduces the 30-day rates of cardiac mortality, major and minor bleeding, thrombocytopenia, and transfusions, at the cost of an increase in acute stent thrombosis. These results support use of bivalirudin for anticoagulation of STEMI patients undergoing PPCI, independent of vascular access site, choice of P2Y₁₂ inhibitor, and timing of drug initiation and discontinuation” (9). Are these conclusions justified? To address this question, several key issues merit consideration.

First, a particular strength of this report is the availability of patient-level data for each study. From a regulatory perspective, patient-level data permit evaluation of each study’s quality and eligibility for inclusion in a meta-analysis, allowing confirmation of study outcomes, particularly time-to-event outcomes, and facilitating evaluation of the consistency of treatment effects across important subgroups. The LOE from a meta-analysis based solely on study-level summary data, either prospective or retrospective, is generally considered lower (10). Other essential dimensions of evidence derived from a meta-analysis relevant for regulatory decision making are

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From the Division of Cardiology, Cedars-Sinai Medical Center, Los Angeles, California; and the David Geffen School of Medicine at UCLA, Los Angeles, California. Dr. Kaul is a consultant to The Medicines Company, manufacturer of bivalirudin; and has been reimbursed for consulting services on cangrelor, a short-acting intravenous investigational antiplatelet inhibitor.

TABLE Hierarchy of Evidence for Meta-analysis or Pooled Analysis*	
Evidentiary Standard	Pooled analysis of HORIZONS-AMI and EUROMAX
Prospectively planned (pre-specification minimizes potential for bias)	No (pre-specified in the EUROMAX protocol, but results of HORIZONS-AMI known in advance)
Lack of heterogeneity to justify pooling	Statistical: yes Clinical: no (substantial clinical heterogeneity between the trials)
Exclusion of hypothesis-generating study	No
Patient-level data (allows for time to event analysis and robust inferences)	Yes
Multiplicity adjustment (allows for protection against inflation of Type I error)	No (the likelihood of a 'false-positive' error not ruled out for 30-day cardiac mortality)
Strength of evidence <ul style="list-style-type: none"> Statistically persuasive p value (<0.001) Probability that meta-analytic finding is due to chance Rigorous assessment of other plausible explanations 	<ul style="list-style-type: none"> Weak evidence against the null for cardiac mortality ($p = 0.03$) and stent thrombosis (0.04). Statistically persuasive evidence for hemorrhagic and hematologic endpoints favoring bivalirudin ($p < 0.001$) Probability that reduced pooled cardiac mortality is due to chance not ruled out Rigorous assessment of other plausible explanations not apparent
Biological and clinical plausibility of the findings	No plausible explanation for reduced cardiac mortality discernible
*Adapted from reference #10.	

summarized in [Table 1](#), which is adapted from the White Paper which came out of the Public Meeting on Meta-Analyses of Randomized Controlled Clinical Trials for the Evaluation of Risk to Support Regulatory Decisions (10). The investigators state that the EUROMAX protocol pre-specified the pooled analysis. However, HORIZONS-AMI results were known, so it is not strictly a prospective pooled analysis needed to minimize potential bias (10). The authors justify pooling due to a lack of statistical heterogeneity, a necessary but not sufficient criterion for pooling. One could argue that given the substantial clinical heterogeneity across trials, which the investigators appropriately and carefully detail in [Table 1](#) of their report, they are not poolable. Furthermore, it is not clear what new or unique insights are offered by the pooled results that cannot be inferred a priori from the individual trial results. The clearest findings from the 2 trials are that bivalirudin increases the risk of acute stent thrombosis while reducing bleeding complications. Because the EUROMAX study did not show a reduction, it is much less certain whether there is a true mortality reduction with bivalirudin. Similarly, EUROMAX did not replicate the reduction in Thrombolysis In Myocardial Infarction (TIMI) major bleeding (prognostically more important, but less frequent than protocol-defined major bleeding) observed in

HORIZONS-AMI, presumably due to EUROMAX's lack of pre-randomization heparin therapy and increased use of radial access (5). Thus, although EUROMAX failed to provide the confirmatory evidence required to support a regulatory claim (11), pooling results can yield misleading inferences of consistent treatment effects (reduction in cardiac mortality and TIMI major bleeding) across the 2 trials.

Second, unconventional use of a composite efficacy (ischemic) and safety (bleeding) outcome, net adverse cardiac events (NACE), biased the results of both trials in favor of bivalirudin. Although combining efficacy and safety into a composite outcome might be desirable to inflate the event rate and enhance trial feasibility, it is often misleading because relatively ineffective, but safer drugs can appear as good as or better than effective drugs, as in the unsubstantiated claims of bivalirudin's superiority over heparin (2). This was previously illustrated in the REPLACE-2 (Randomized Evaluation of PCI Linking Angiomax to Reduced Clinical Events 2) (12) and ACUTY (Acute Catheterization and Urgent Intervention Triage Strategy) (13) trials, where the difference in major bleeding events (risk reduction of 43% and 47%, respectively, in favor of bivalirudin) exceeded the difference in MIs (13% and 9% respective risk increases), resulting in the NACE quadruple composite endpoint favoring bivalirudin. Accordingly, the U.S. Food and Drug Administration, in direct challenge to the investigators' interpretation, did not allow a claim of statistical noninferiority for the triple ischemic endpoint (2). Also, both ACUTY and HORIZONS-AMI were confounded by asymmetrical GPI use (routine, selective, or bailout), and pre-randomization heparin therapy (63% to 64% in the former study and 65.6% in the latter study). Heparin pretreatment could have contributed to the anti-coagulation effect in the bivalirudin treatment arms, making efficacy attributable solely to bivalirudin difficult to determine. For example, in 615 patients in HORIZONS-AMI in whom bivalirudin was not preceded by heparin pretreatment, the risk of major adverse cardiac events numerically increased (relative risk: 1.39; 95% confidence interval [CI]: 0.85 to 2.28) compared with a numerical decrease in those receiving pretreatment heparin (relative risk: 0.81; 95% CI: 0.58 to 1.14; p for interaction = 0.08) (4). Similarly, asymmetrical GPI use could have contributed to the increased bleeding risk in the heparin treatment arms, biasing the results to favor bivalirudin.

Third, a major source of controversy is the choice of comparator in the bivalirudin trials. It has been argued that heparin monotherapy is inappropriate

for STEMI on the basis of pooled analysis of 8 randomized trials demonstrating reduced death and reinfarction by the addition of abciximab to heparin during PPCI (14). Thus, randomizing patients to the heparin monotherapy arm would have been “unethical.” Although ethical justifications to exclude treatment choices should ideally be based on unequivocal evidence of harm, this was clearly not the case, as GPI use during PPCI was not strongly endorsed by the 2004 STEMI guidelines that preceded HORIZONS-AMI enrollment (15). The Guidelines Writing Committee believed that starting treatment with abciximab as early as possible in patients undergoing PPCI was reasonable, but, given the size and limitations of the available dataset, assigned a Class IIa, LOE: B recommendation. Data on tirofiban and eptifibatide in PPCI were far more limited than for abciximab, resulting in a lower grade recommendation (Class IIb, LOE: B) (15). A strong argument for heparin monotherapy could be indirectly derived from the results of the ACUTY trial. The addition of GPI to bivalirudin did not provide any incremental ischemic benefit, but nullified the bleeding advantage of bivalirudin monotherapy (13). The choice of heparin monotherapy (with bailout GPI) was recently vindicated in the HEAT-PPCI (How Effective Are Antithrombotic Therapies in Primary Percutaneous Coronary Intervention) trial, which demonstrated reduced risk of thrombotic complications without increased bleeding risk compared with bivalirudin therapy (6). HEAT-PPCI has been heavily scrutinized and criticized, with questions raised against its ethics, the reliability of single-center trial results, the reduced duration of post-procedure bivalirudin therapy to offset the risk of acute stent thrombosis, and the inadequate degree of anticoagulation achieved with bivalirudin. The study investigators and editorialists offered reasonable and convincing rebuttals (16,17), prompting the most recent guidelines to downgrade the bivalirudin recommendation to Class IIa, LOE: A while retaining treatment with UFH as a Class I, LOE: C recommendation (18). Questions persist, especially in light of the recently reported confirmation of the results of the earlier 2 trials by the unpublished BRIGHT (Bivalirudin Versus Heparin Monotherapy and Glycoprotein IIb/IIIa Plus Heparin for Patients With AMI Undergoing Coronary Stenting) trial (8). Finally, in the BRAVE-4 (Bavarian Reperfusion Alternatives Evaluation -4) trial, neither the composite of ischemic complications nor bleeding was favorably affected by prasugrel plus bivalirudin compared with clopidogrel plus UFH (7). However, in view of premature termination of BRAVE-4 due to slow recruitment, the results must be interpreted with caution.

Fourth, much has been made of the observed reduction in cardiac mortality in favor of bivalirudin in the HORIZONS-AMI trial, with some arguing this finding alone as the *raison d’être* for using bivalirudin during PPCI. Bivalirudin treatment resulted in a significant reduction in cardiac mortality, present by 30 days (1.8% vs. 2.9%, hazard ratio [HR]: 0.62, 95% CI: 0.40 to 0.95; $p = 0.03$) (4) and increasing over 3 years (2.9% vs. 5.1%; HR: 0.56, 95% CI: 0.40 to 0.80; $p = 0.001$) (19). However, its reliability is questionable; it was not a pre-specified endpoint and therefore not adequately powered for comparison. The p value was marginal with a wide CI. The strength of evidence is often summarized using a Bayes factor, a measure of how well 2 competing hypotheses (the null and the alternate) predict the data (20). The p value of 0.03 for cardiac mortality translates into a minimal Bayes factor of 0.088, meaning the evidence supports the null hypothesis approximately one-eleventh as strongly as the alternative, reducing the null probability from 50% pretrial to 8% post-trial, and a more skeptical, albeit plausible, null probability of 75% pre-trial to 21% post-trial, not strong evidence against the null. The p value was not adjusted for multiple comparisons, inflating the possibility of type I error for the 30-day endpoint (less likely for the 3-year endpoint given the statistically persuasive $p = 0.001$). The precise mechanisms linking bivalirudin to mortality reduction have not been elucidated and were not accounted for by the prevention of bleeding, thrombocytopenia, or reinfarction (all reduced at 3 years) (21).

Furthermore, 2 mechanisms by which bivalirudin could potentially yield a mortality benefit, biomarker-determined or magnetic resonance imaging-determined infarct size or left ventricular ejection fraction, were no different (21). Lack of replication in other studies (5,6,13) further challenges the reliability of the HORIZONS-AMI mortality findings. The play of chance cannot be eliminated on the basis of the totality of the evidence (lack of pre-specification, replication, and control of type I error, all of which are required to support regulatory claims). Given the seriousness of the outcome, some have argued that the mortality reduction cannot be ignored. Probabilistic estimates are insensitive to the seriousness of outcome events, especially if unexpected; the unexpected mortality benefit observed in HORIZONS-AMI is as likely as any nonfatal, non-serious outcome to be due to chance. A registration trial supporting mortality reduction would require tens of thousands of patients enrolled in a prospective, well-designed, adequately controlled and powered trial. Thus, the significant reduction in cardiac

mortality in this pooled analysis does not appear reliable. Accordingly, its use as an argument to inform guideline recommendations and guide clinical practice is unwarranted.

Where do we go from here? Although the evidentiary landscape in support of antithrombotic treatment choices during PPCI has been enriched by the bivalirudin trials, recent data question the role of bivalirudin. It costs nearly 400-fold more than heparin, with no discernible efficacy or substantial safety advantage. Some have appropriately recalibrated their opinions and changed practice in alignment with the evidence, whereas others

doggedly maintain the status quo. Arguably, a new, carefully designed trial is required to cut the Gordian knot and adjudicate the uncertainties. Until then, like fine wine that never goes out of fashion, it is time for out with the new (bivalirudin), in with the old (heparin monotherapy with bailout GPI).

REPRINT REQUESTS AND CORRESPONDENCE TO: Dr. Sanjay Kaul, Cedars-Sinai Medical Center, Division of Cardiology, 8635 West Third Street, #790W, Los Angeles, California 90048. E-mail: sanjay.kaul@cshs.org.

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