Commentary

Risk guided use of the direct thrombin inhibitor bivalirudin: insights from recent trials and analyses

William B. Hillegass, Gregory S. Bradford

Heart South Cardiovascular Group, Brookwood Shelby Baptist Medical Center, Department of Biostatistics, University of Alabama at Birmingham, Alabaster and Birmingham, Alabama, USA

Correspondence to: William B. Hillegass, MD, MPH. 13 Brush Creek Farms, Columbiana AL 35051, USA. Email: hillegas@uab.edu.

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During percutaneous coronary intervention, dual antiplatelet therapy with aspirin and a $P2Y_{12}$ receptor antagonist are combined with one of three major strategies for antithrombotic therapy: heparins, bivalirudin, or heparin with an intravenous IIb/IIIa platelet receptor antagonist. Economic constraints in the United States are increasingly driving the choice between these therapies.

Heparin has negligible acquisition cost of approximately $4 to $10 USD for a percutaneous coronary intervention (PCI). Bivalirudin, now as a generic, costs approximately $400 to $600 USD per PCI without a post-procedural infusion. If a three to four hour post-procedural infusion is included the cost increases to $900 to $1,200 USD, similar to the previous branded cost without post-procedure infusion. Glycoprotein IIb/IIIa receptor antagonists have an acquisition cost of approximately $600–$900 USD per PCI.

Historically, demonstration of superior outcomes and/or incremental cost-effectiveness would prompt broad adoption of a higher acquisition cost therapy. With multiple randomized trials demonstrating superiority of routine IIb/IIIa therapy to heparin alone in the plain old balloon angioplasty and early stent era, IIb/IIIa use was widely embraced from 1994 to 2003 (1,2). IIb/IIIa agents became the standard of care in eligible acute coronary syndrome patients undergoing PCI. Shelved despite promising early results in the Bivalirudin Angioplasty Trial, the direct thrombin inhibited bivalirudin resurfaced (3). Unlike heparins indirectly inhibiting soluble thrombin, bivalirudin also inhibits clot bound thrombin. Activated thrombin is a potent *in vivo* platelet agonist. More complete thrombin inhibition with bivalirudin might obviate the need for final common pathway platelet aggregation inhibition with glycoprotein IIb/IIIa agents; and their inherent bleeding risk. Testing this hypothesis, bivalirudin use eclipsed routine IIb/IIIa therapy from 2005 to 2014 when the Bivalirudin and Provisional Glycoprotein IIb/IIIa Blockade compared with Heparin and Planned Glycoprotein IIb/IIIa Blockade during Percutaneous Coronary Intervention (REPLACE-2), Bivalirudin for Patients with Acute Coronary Syndromes (ACUITY), and Bivalirudin during Primary PCI in Acute Myocardial Infarction (HORIZONS-AMI) trials demonstrated similar ischemic outcomes with less bleeding (4-6).

With acquisition cost similar to IIb/IIIa agents, branded bivalirudin's cost was a largely irrelevant factor. Multiple studies documented high morbidity and cost associated with in-hospital bleeding events, implying hospital cost-savings with bivalirudin. Nonetheless bivalirudin's acquisition cost became a highly visible budget line item as hospitals faced increasing economic pressure to remain solvent.

Meanwhile, stent miniaturization compatible with 5 and 6 French catheter delivery systems reduced vascular access bleeding. Better stent designs improved outcomes. Oral $P2Y_{12}$ agents and their use improved. Reliable and better outcomes allowed *ad hoc* PCI at the time of diagnostic angiography obviating separate procedures. Adoption of the radial approach substantially reduced vascular access bleeding and thus procedural bleeding rates. With routine heparin administration in the diagnostic angiography radial "cocktail," operators questioned the necessity and safety of switching or "stacking" antithrombins when proceeding to PCI.

While HORIZON-AMI and Bivalirudin Started during Emergency Transport for Primary PCI (EUROMAX) both showed better overall early and late outcomes in STEMI patients with bivalirudin compared to heparin with

routine IIb/IIIa use, acute (<24 hours) stent thrombosis was incrementally 1% higher with bivalirudin (7-9).

Coupled with intense economic pressure to lower cost, all of these factors created uncertainty as to the incremental benefit of bivalirudin over heparin in contemporary practice. In 2008, the Bivalirudin versus Unfractionated Heparin during Percutaneous Coronary Intervention trial (ISAR-REACT 3) randomized 4,570 biomarker negative stable patients with clopidogrel pre-treatment undergoing PCI to bivalirudin versus heparin (10,11). The heparin dose was 140 units/kg bolus. There was no difference in stent thrombosis or ischemic outcomes at 30 days. Major bleeding occurred in 3.1% of the bivalirudin patients versus 4.6% with heparin, [RR= 0.66 (95% CI: 0.49 to 0.90) P=0.008].

But modern studies comparing bivalirudin to heparin with provisional IIb/IIIa use in acute coronary syndrome patients with newer stent designs and the radial approach were lacking until the single-center Unfractionated Heparin versus Bivalirudin in Primary Percutaneous Coronary Intervention (HEAT-PPCI) trial [2014]. HEAT-PPCI found heparin superior to bivalirudin in 1,812 randomized STEMI patients (12). The result was driven by higher acute stent thrombosis events with bivalirudin 2.9% than heparin at 0.9% [RR= 3.26 (95% CI: 1.32 to 8.07) P=0.007]. Definite or probable stent thrombosis was 3.4% with bivalirudin and 0.9% with heparin [RR=3.91 (95% CI: 1.61 to 9.52) P=0.001]. Major bleeding was similar at 3.5% with bivalirudin and 3.1% with heparin with 81% radial access.

Disrupting the conventional wisdom, HEAT-PPCI's findings wrought a range of responses. Extrapolation from HEAT-PPCI seemed reasonable. If heparin was now shown non-inferior to bivalirudin in the STEMI setting with largely radial access, surely heparin would be non-inferior in stable PCI patients with the radial approach. With the pent up economic pressure and uncertainty over bivalirudin's necessity, HEAT-PPCI provided the evidential impetus for many operators and institutions to curtail or eliminate bivalirudin use. Prudence, however, suggests caution at placing complete confidence in even a very well-designed and superbly conducted single center trial. The large, well-designed, single-center Thrombus Aspiration during Primary Percutaneous Coronary Intervention Trial (TAPAS) showed a convincing and plausible mortality benefit of routine aspiration thrombectomy in STEMI PCI (13). Two subsequent large multicenter trials Randomized Trial of Primary PCI with or without Routine Manual Thrombectomy (TOTAL) and The Thrombus Aspiration in ST-Elevation Myocardial Infarction in Scandinavia (TASTE) could not confirm this benefit. In fact the lack of appreciable myocardial or survival benefit with the specter of increased peri-procedural stroke risk has revised guidelines against routine thrombo aspiration (14-16).

On the heels of HEAT-PPCI, the multi-center Bivalirudin *vs*. Heparin With or Without Tirofiban During Primary Percutaneous Coronary Intervention in Acute Myocardial Infarction (BRIGHT) trial randomized 2,194 STEMI patients to heparin, bivalirudin with post-procedural infusion, and heparin with routine IIb/IIIa use with tirofiban (17). The requirement in BRIGHT for a post-procedural bivalirudin infusion arose from a *post-hoc* analysis of EUROMAX. This showed no increased risk of acute stent thrombosis associated with bivalirudin compared to IIb/IIIa therapy with a post-procedural bivalirudin infusion (18). In BRIGHT, bivalirudin was required to be infused at 1.75 mg/kg/hr for at least 30 minutes and no more than four hours post-procedure. Median infusion time was 180 minutes. The heparin monotherapy patients received 100 units/kg IV and additional heparin if the activated clotting time was <225 seconds. Tirofiban was given with 10 mcg/kg bolus and 0.15 mcg/kg/minute infusion continued for 18 to 36 hours post-procedure. The tirofiban group received 60 units/kg of heparin as a bolus. About 78.5% of patients received the radial approach.

Acute stent thrombosis was 0.3% in each treatment group in BRIGHT. Definite or probable stent thrombosis at 1 year was 1.2% with bivalirudin and tirofiban and 1.9% with heparin. Bleeding Academic Research Consortium (BARC) 3 to 5 bleeds occurred in 0.5% with bivalirudin, 1.5% with heparin, and 2.1% with IIb/IIIa at 30 days. Hence, major bleeding was significantly lower for bivalirudin than IIb/IIIa and borderline significant at α=0.05 level compared to heparin. Overall, the composite endpoint of net adverse clinical events was 12.8% with bivalirudin, 16.5% with heparin, and 20.5% with IIb/IIIa significantly favoring bivalirudin compared to heparin with net reduction in events =–3.7% (95% CI: –7.3 to –0.1) and bivalirudin to routine IIb/IIIa –7.8 (–11.6 to –4.0). Heparin was significantly better than routine IIb/IIIa with net event reduction =–4.1% (–8.1 to –0.1).

The multicenter Bivalirudin or Unfractionated Heparin in Acute Coronary Syndromes (MATRIX) study also addressed the comparison of bivalirudin to heparin in STEMI and NSTEMI/acute coronary syndrome (n=7,213) patients (19). STEMI was the indication for PCI in 4,010 of the patients. Patients were randomized to

radial versus femoral access and in 2×2 factorial design to heparin versus bivalirudin. The bivalirudin assigned group was further randomized to post-procedural bivalirudin infusion for up to four hours. All-cause mortality (1.6 *vs.* 2.2%, P=0.045) and BARC 3 to 5 bleeding (1.6 *vs.* 2.3%, P=0.013) were both significantly lower with the radial than femoral approaches. The primary endpoint of net adverse events at 30 days was similar for bivalirudin and heparin at 11.5% and 12.6%, [RR=0.90 (95% CI: 0.79–1.04), P=0.15]. While the primary composite endpoint was not significantly different, bivalirudin had lower all-cause mortality than heparin (1.7% *vs.* 2.3%, P=0.04) and lower BARC 3 to 5 bleeding (1.4% *vs.* 2.5%, P<0.001). The difference in bleeding was driven by non-access related bleeding events. There was no difference in definite or probable stent thrombosis at 1.3% for bivalirudin versus 1.0% with heparin. Among the 3,610 patients, receiving bivalirudin, post-procedural bivalirudin was not significantly better for the composite primary end-point of net adverse events at 11.0% *vs.* 11.9% [RR=0.91, (95% CI: 0.74–1.11), P=0.34]. The post-procedural bivalirudin infusion did not reduce stent thrombosis nor increase bleeding.

The Bivalirudin versus heparin in non-ST and ST-segment elevation myocardial infarction—a registry-based randomized clinical trial in the SWEDEHEART registry (the VALIDATE-SWEDEHEART) trial is beginning enrollment and will randomize 6,000 acute coronary syndromes to heparin versus bivalirudin with largely the radial approach combined with cangrelor, ticagrelor, and prasugrel (20).

Reflecting the importance of the topic, the level of clinical uncertainty, and accumulating studies, at least 16 separate meta-analyses comparing bivalirudin to heparin have been published in peer-reviewed journals indexed by PubMed in the last 3 years (21-36). The results are not entirely consistent but generally reflect less major bleeding with bivalirudin and a higher acute stent thrombosis rate. Efforts to explain the heterogeneity yield that heparin and bivalirudin are generally equivalent in stable patients. In acute coronary syndrome patients, the radial approach reduces the magnitude of the bleeding benefit with bivalirudin. Higher heparin doses increase the relative benefit of bivalirudin.

These landmark randomized trials and meta-analyses estimate population average differences in outcomes with heparin, bivalirudin, and IIb/IIIa therapies across a spectrum of patient presentations. Yet the question remains. How to synthesize this data into rational and cost-conscious decisions in individual patients? The notion that one strategy will be "dominant" from a clinical outcomes, cost, or cost-effectiveness point of view in all patients, settings, and procedures within broad classes is undoubtedly naïve. Now, and in the foreseeable future, therapeutic decisions will have to be highly cost-effective and almost certainly approach cost-neutral. No one source (or even set of sources) provides guidance on a comprehensive strategy to tailor antithrombotic treatment during PCI based on the individual patient's risk and/or the likely cost implications.

A few recent analyses begin to provide a rational framework for targeting bivalirudin use to meaningfully improve outcomes with perhaps at least neutral total health care cost. Severely reduced left ventricular systolic function and/or clinical congestive heart failure (CHF) may be factors predicting particular benefit from bivalirudin. The subset of PCI patients with CHF and/or severe left ventricular dysfunction are at increased risk of thrombotic, ischemic, and bleeding events (37-40). CHF is associated with higher thrombin levels and accelerated formation of resistant fibrin clots (41-43). Yu *et al.* provide a practical and robust model to predict one-year mortality after PCI (44). The model could be readily implemented with an app or a note card stratifying 1-year mortality risk to low <2%, intermediate 2% to 10%, or high >10%. Age, white blood count (inflammation), creatinine, and LVEF<35% are the most predictive. LVEF <35% is the strongest predictor of the factors. From the pooled randomized trial data of bivalirudin versus heparin with IIb/IIIa, a 4.8% (95% CI: 0.5–9.2%) absolute mortality reduction was seen in >10% mortality risk patients when randomly assigned to bivalirudin compared to heparin with routine IIb/IIIa use. This observed mortality benefit is not appreciably diminished after adjusting for bleeding, suggesting additional mechanisms of mortality benefit with potent direct thrombin inhibition.

Furthering this observation from the randomized trials of bivalirudin versus IIb/IIIa therapy, Pinto *et al.* provide an observational analysis in CHF patients comparing bivalirudin to heparin (45). In a propensity adjusted observational analysis from a prospectively collected registry, a large cohort of patients (n=51,262) with a clinical history of congestive heart failure undergoing PCI treated with either bivalirudin or heparin monotherapy are compared. Bivalirudin use was associated with a lower rate of in-hospital death of 3.3% *vs.* 3.8% with heparin, [OR=0.86 (0.79–0.95) P=0.002]. Clinically apparent

bleeding was similar at 10.1% *vs*. 10.5% [OR =0.96 (0.91–1.02) P=0.15] but clinically apparent bleeding requiring transfusion was 2.7% with bivalirudin versus 3.0% with heparin [OR =0.87 (0.79–0.97) P=0.01]. Any transfusion was 8.6% *vs*. 10.0% [OR=0.85 (0.80–0.90) P<0.0001] with bivalirudin versus heparin monotherapy. Mean and median total cost for hospitalization were nearly identical at $27,319 ± $25,940 *vs.* $27,676 ± $26,234 with medians and interquartile ranges for bivalirudin of $19,614, ($13,203–$31,896) versus heparin $19,736, ($13,126–$32,443). These costs reflect branded bivalirudin without post-procedural infusion. With generic bivalirudin, the cost would be lower unless offset by the addition of a post-procedure infusion. While not prospective randomized proof, these analyses suggest that the specific patient group with significant left ventricular systolic dysfunction and/or clinical heart failure may have improved outcomes with bivalirudin including hospital mortality and bleeding at similar total cost to heparin monotherapy.

Another group to consider for targeted bivalirudin therapy would be high bleeding risk patients. The NCDR bleeding prediction score yields predicted bleeding risks ranging from 0.9% to 86% (46). More generally, patients can be classified as low major bleeding risk at <2%, medium from 2% to <6.5%, or >6.5% major bleeding risk. Amin *et al*. estimated the incremental cost of a major bleed at $8,920 USD (95% CI: $5,508 to $12,333) in 2010 US dollars (47). Branded bivalirudin had an acquisition cost of $592 to $813 per vial with the typical patient requiring 2 vials for bolus and intra-procedural infusion. Amin *et al*. identified bivalirudin as meeting conventional standards for incremental cost-effectiveness in patients at >5% bleeding risk (which is 7.9% of patients undergoing PCI). The generic price is approximately $400 per vial. Substituting the generic price of bivalirudin with Amin *et al*.'s other assumptions and estimates, bivalirudin would be cost-neutral assuming a post-procedural infusion in a patient at roughly 20% bleeding risk. Bivalirudin would be cost-neutral assuming no post-procedural infusion in a patient at 10% bleeding risk. Amin *et al*.'s assumption that bivalirudin reduces bleeding risk by 1/3rd compared to heparin is supported by the single most comprehensive observational study (n=501,107) from the National Cardiovascular Data Registry. This NCDR analysis estimates a 3.8% absolute reduction in major bleeding in high predicted bleeding risk patients with bivalirudin (48). Hence, high bleeding risk patients provide a potential opportunity to improve outcomes with targeted bivalirudin therapy while approaching cost neutrality. The clinical conundrum, however, is that the bleeding risk requisite to achieve cost neutrality through bivalirudin's lower bleeding risk is also in the range where most operators would prefer a strategy with a reversal agent, that is, heparin with protamine.

Bivalirudin monotherapy has largely eclipsed routine IIb/IIIa use in randomized trials and contemporary practice. BRIGHT demonstrates that bivalirudin can provide incrementally better overall outcomes than heparin in STEMI patients. A detailed look at MATRIX provides limited encouraging results for bivalirudin. With low probability of a false claim (type I error), some secondary endpoints in MATRIX, including mortality, were significantly improved with bivalirudin compared to heparin. Nonetheless, informally factoring in a requirement for near cost neutrality rather than just traditional outcome superiority, the accumulated data and meta-analyses imply the choice between bivalirudin and heparin is largely a "toss up" for very broad classes of patients. VALIDATE-SWEDEHEART, despite the lack of continued commercial interest to fuel and fund research, will fortunately provide more data to answer the bivalirudin versus heparin questions.

Individual patient tailored antithrombotic therapy during PCI holds the potential for moving beyond these broad classes of patients and population average effects. Individual patient data meta-analyses examining detailed clinical characteristics might yield prediction models to tailor antithrombotic therapy during PCI. For the comparison of bivalirudin to routine IIb/IIIa therapy, Yu *et al*. have done this with REPLACE-2, ACUITY, and HORIZONS. Perhaps similar efforts with combined individual patient data from HEAT-PPCI, BRIGHT, MATRIX, SWEDEHEART, and other bivalirudin versus heparin randomized trials would provide similar useful results for targeting bivalirudin therapy. Based on Yu *et al*. and Pinto *et al*.'s analyses, patients with background CHF or severe left ventricular dysfunction would be an interesting group to evaluate in the context of other individual factors such as age and presentation. The economic implications of tailored therapy could then be modeled and estimated. More generally, the analyses of Yu and Pinto provocatively imply that overall clinical trial results may be inadequate to guide the daily clinical meta-judgment necessary to select optimal antithrombotic therapies for individual patients.

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Footnote

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