JACC: CARDIOVASCULAR INTERVENTIONS
VOL. 8, NO. 1, 2015

ISSN 1936-8798/$36.00
PUBLISHED BY ELSEVIER INC.
http://dx.doi.org/10.1016/j.jcin.2014.10.004

Follow the Data

Bivalirudin (and Not Heparin Alone) During Percutaneous Coronary Intervention Provides the Best Clinical Outcomes

Gregg W. Stone, MD,* Roxana Mehran, MD,† Philippe Gabriel Steg, MD‡§

The only procedural anticoagulant available for several decades after the introduction of percutaneous coronary intervention (PCI) was unfractionated heparin. Unfortunately, heparin has numerous well-known limitations, including variable pharmacokinetics and pharmacodynamics, leading to frequent under-dosing or overdosing; nonspecific protein binding, a consequence of which is heparin-induced thrombocytopenia; and platelet activation, which increases ischemic event rates (1). Over the last 20 years, physicians have searched for alternatives to improve the safety and efficacy of heparin during PCI, and 2 solutions were found: glycoprotein IIb/IIIa inhibitors (GPIs) and bivalirudin.

ENTER GPIs

Heparin activates platelets by binding to the glycoprotein IIb/IIIa receptor, an effect overcome by GPI. More than 20 randomized trials demonstrated that, compared with heparin alone, heparin + GPI during PCI (on a background of aspirin and clopidogrel) reduces recurrent ischemia, myocardial infarction, stent thrombosis, and death (2,3). These benefits were demonstrated in stable coronary artery disease (CAD) and acute coronary syndromes (non-ST-segment elevation myocardial infarction [NSTEMI] and ST-segment elevation myocardial infarction [STEMI]), although at the cost of increased bleeding and thrombocytopenia. Nonetheless, the risk/benefit tradeoff was favorable, and heparin + GPI became utilized in the majority of PCI procedures. Subsequently, the ISAR-REACT-2 (Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment-2) trial showed that in patients pre-loaded with clopidogrel, heparin alone was an acceptable alternative to heparin + GPI in troponin-negative coronary syndromes, but was inferior in troponin-positive non-ST-segment elevation acute coronary syndromes (4). No multicenter trial has ever suggested otherwise.

ENTER BIVALIRUDIN

The safety profile of heparin was further improved by the introduction of the direct thrombin inhibitor bivalirudin, which has highly predictable pharmacokinetics and pharmacodynamics, a short half-life, and intrinsic antiplatelet activity, and does not cause thrombocytopenia (1). In 2 large-scale randomized trials in stable CAD and NSTEMI (ISAR-REACT-3 and BAT [Bivalirudin Angioplasty Trial]), bivalirudin compared with heparin alone reduced major bleeding while effectively suppressing ischemic complications of PCI (5,6). Moreover, in 5 large-scale randomized PCI trials in stable CAD, NSTEMI, and STEMI (REPLACE-2 [Randomised Evaluation of PCI Linking

From the *Columbia University Medical Center and the Cardiovascular Research Foundation, New York, New York; †Mount Sinai Medical Center and the Cardiovascular Research Foundation, New York, New York; ‡Université Paris-Diderot, Sorbonne Paris Cité, INSERM U-1148, DHU FIRE, Hôpital Bichat, Assistance Publique-Hôpitaux de Paris, Paris, France; and the §Institute of Cardiovascular Medicine and Science, National Lung and Heart Institute, Imperial College, Royal Brompton Hospital, London, United Kingdom. Dr. Stone is a past consultant to Boston Scientific and the Eli Lilly-Daiichi Sankyo partnership. Dr. Mehran has received institutional research grants from The Medicines Company, Sanofi-Aventis, Bristol-Myers Squibb, AstraZeneca, and the Eli Lilly-Daiichi Sankyo partnership; and has served as a consultant to Boston Scientific, Abbott Vascular, AstraZeneca, Covidien, Regado Biosciences, Merck, Janssen, Maya Medical, CSL Behring, Claret, and The Medicines Company. Dr. Steg has received research grants from Sanofi and Servier (to INSERM U-1148); has received personal fees, including speaker and consulting fees, from Amarin, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, GlaxoSmithKline, Janssen, Eli Lilly, Medtronic, Merck Sharpe Dohme, Novartis, Orexigen, Otsuka, Pfizer, Roche, The Medicines Company, Sanofi, Servier, and Vivus; and is a stockholder in Aterovax.

Manuscript received October 13, 2014; accepted October 24, 2014.

Angiomax to Reduced Clinical Events-2], ACUITY [Acute Catheterization and Urgent Intervention Triage Strategy], ISAR-REACT-4, HORIZONS-AMI [Harmonizing Outcomes with Revascularization and Stent in Acute Myocardial Infarction], and EUROMAX [European Ambulance Acute Coronary Syndrome Angiography]) (7–11), bivalirudin compared with heparin + GPI reduced major bleeding, transfusions, and thrombocytopenia with comparable rates of major adverse cardiac events (MACE). Although bivalirudin has been associated with an ~1% increase in acute (<24 h) stent thrombosis in STEMI (but not in stable CAD or NSTEMI), in the largest such randomized trial, HORIZONS-AMI (3,602 patients at 123 centers), bivalirudin reduced all-cause mortality compared with heparin + GPI at 30 days, a finding sustained through 3-year follow-up (10,12).

STUDIES IN THE REAL WORLD

The results of these randomized trials have been supported by the outcomes from extremely large real-world registries in which differences in baseline characteristics were accounted for in multivariable and propensity-adjusted analyses. In 127,185 patients undergoing PCI in the Premier Perspective Database, bivalirudin compared with heparin + GPI was associated with lower rates of major bleeding requiring transfusion and in-hospital mortality in both stable and unstable coronary syndromes, including STEMI (13). In a later report of 458,448 patients from this database, bivalirudin was associated with lower rates of bleeding with transfusion and mortality compared with heparin + GPI or heparin alone (14). Among 1,522,935 PCI patients from the National Cardiovascular Data Registry, bivalirudin was associated with markedly reduced rates of bleeding compared with heparin, with or without the use of vascular closure devices (15). Finally, the National Cardiovascular Data Registry also reported that even with radial access, bivalirudin resulted in 21% less bleeding than heparin after PCI, due to fewer nonaccess site bleeds (16). On the basis of these randomized and registry studies, bivalirudin has become the most widely used anticoagulant during PCI in the United States.

THE CURRENT CONTROVERSY

Notwithstanding the last 2 decades of clinical trial and real-world outcomes data, some have recently suggested that heparin alone should be resurrected for anticoagulation during PCI on the basis of a solitary single-center unblinded trial in patients with STEMI (HEAT-PPCI [Unfractionated Heparin Versus Bivalirudin in Primary Percutaneous Coronary Intervention]) (17). It is conceivable that superior drug-eluting stents, improved adjunctive pharmacotherapy (potent $P2Y_{12}$ inhibitors) and radial intervention may have mitigated the limitations of heparin, and the attractiveness of reducing costs is undeniable. However, the results of single-center trials must be carefully examined, given their well-known limitations. Single-center study outcomes may depend on the specific practices of the institution of origin, and are often not generalizable. Effect sizes from single-center trials tend to be overestimated, and such studies lack external controls and validity. Bias is also of potential concern in single-center trials, particularly for open-label studies. Their outcomes must, therefore, be verified in multicenter trials prior to widespread acceptance as high level of evidence (18).

In this regard the HEAT-PPCI results are notable in several ways (17). Although the study was laudable in imposing few exclusion criteria, and for high rates of radial intervention and use of third-generation $P2Y_{12}$ inhibitors, the acute stent thrombosis rate with bivalirudin was 2 to 3 times higher than in any prior study. This difference drove greater 30-day MACE in patients randomized to bivalirudin compared with heparin alone. These outlying results may be explained by an extremely abbreviated duration of bivalirudin treatment due to very rapid door-to-balloon times, coupled with the lack of a post-PCI infusion. In addition, the median activated clotting time (ACT) achieved with bivalirudin in HEAT-PPCI was substantially lower (246 to 251 s) than in any prior trial (e.g., 357 s in HORIZONS-AMI [10]). Conversely, the median ACT in the heparin arm (224 s) was consistent with prior trials. In addition, supplementary bolus doses of bivalirudin were by protocol to be given for an ACT <225 s in the HEAT-PPCI trial. However, additional bivalirudin was administered in only ~12% of patients, about one-half the intended rate based on measured ACTs. Yet, inexplicably, there was no difference in bleeding with bivalirudin.

RECENT MULTICENTER TRIALS

Fortunately, 2 contemporary, large-scale, multicenter, randomized comparisons of bivalirudin versus heparin alone during PCI in STEMI have been performed, each with high rates of radial access. In the EUROMAX trial (2,198 patients at 65 centers), the 30-day primary endpoint of death or major bleeding was lowest with bivalirudin, intermediate with heparin + GPI, and highest with heparin alone (11). Although the use of heparin alone versus heparin + GPI was not randomized, the results were robust in a

pre-specified multivariable analysis (19). Importantly, the marked reduction in bleeding with bivalirudin was observed with both radial and femoral access, and was present despite the fact that the median dose of heparin was 61 U/kg (quartile [Q] 1 to Q3: 56 to 71 U/kg) for patients receiving GPI and 60 U/kg (Q1 to Q3: 53 to 77 U/kg) for patients not receiving GPI, lower doses than that used in HEAT-PPCI (70 UI/kg). In the BRIGHT (Bivalirudin in Acute Myocardial Infarction versus Heparin and GPI plus Heparin Trial), 2,194 patients at 82 centers were randomized 1:1:1 to bivalirudin, heparin alone, or heparin + GPI (20). Bivalirudin resulted in lower 30-day and 1-year rates of bleeding than both heparin regimens, with similar rates of MACE. Moreover, acute stent thrombosis was not increased with bivalirudin in this trial (0.3% in each group), likely due to the routine use of a 4-h post-PCI bivalirudin infusion.

WEIGHING THE EVIDENCE

Although it is daunting to integrate the entirety of evidence from nearly 40 years of studies since Gruentzig's first PCI in 1977, doing so leads to an inescapable conclusion: PCI outcomes have steadily improved with the evolution from balloon angioplasty to bare-metal stents to drug-eluting stents; with advanced imaging and physiologic lesion assessment; and with enhanced adjunctive antiplatelet and antithrombin pharmacotherapies. Over the last 2 decades, the progression from procedural anticoagulation with heparin alone, to heparin + GPI, and now to bivalirudin has resulted in improved net clinical outcomes in patients undergoing PCI across the spectrum of CAD. Pending the results in 2015 of MATRIX (Minimizing Adverse Haemorrhagic Events by TRansradial Access Site and Systemic Implementation of angioX) (21), a large-scale randomized trial, now is not the time to turn back the clock 20 years. Our patients deserve more.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Gregg W. Stone, Columbia University Medical Center, The Cardiovascular Research Foundation, 111 East 59th Street, 11th Floor, New York, New York 10022. E-mail: gs2184@columbia.edu.

REFERENCES

1. Stone GW, Ohman EM. Antithrombin alternatives in STEMI. Lancet 2011;378:643–5.

2. Karvouni E, Katritsis DG, Ioannidis JPA. Intravenous glycoprotein IIb/IIIa receptor antagonists reduce mortality after percutaneous coronary interventions. J Am Coll Cardiol 2003;41:26–32.

3. De Luca G, Suryapranata H, Stone GW, et al. Abciximab as adjunctive therapy to reperfusion in acute ST-segment elevation myocardial infarction: a meta-analysis of randomized trials. JAMA 2005;293:1759–65.

4. Kastrati A, Mehilli J, Neumann FJ, et al. Abciximab in patients with acute coronary syndromes undergoing percutaneous coronary intervention after clopidogrel pretreatment. JAMA 2006;295:1531–8.

5. Bittl JA, Strony J, Brinker JA, et al. Treatment with bivalirudin (Hirulog) as compared with heparin during coronary angioplasty for unstable or post-infarction angina. N Engl J Med 1995;333:764–9.

6. Kastrati A, Neumann FJ, Mehilli J, et al. Bivalirudin versus unfractionated heparin during percutaneous coronary intervention. N Engl J Med 2008;359:688–96.

7. Lincoff AM, Bittl JA, Harrington RA, et al. Bivalirudin and provisional glycoprotein IIb/IIIa blockade compared with heparin and planned glycoprotein IIb/IIIa blockade during percutaneous coronary intervention: REPLACE-2 randomized trial. JAMA 2003;289:853–63.

8. Stone GW, McLaurin BT, Cox DA, et al. Bivalirudin for patients with acute coronary syndromes. N Engl J Med 2006;355:2203–16.

9. Kastrati A, Neumann FJ, Schulz S, et al. Abciximab and heparin versus bivalirudin for non-ST-elevation myocardial infarction. N Engl J Med 2011;365:1980–9.

10. Stone GW, Witzenbichler B, Guagliumi G, et al. Bivalirudin during primary PCI in acute myocardial infarction. N Engl J Med 2008;358:2218–30.

11. Steg PG, van 't Hof A, Hamm CW, et al. Bivalirudin started during emergency transport for primary PCI. N Engl J Med 2013;369:2207–17.

12. Stone GW, Witzenbichler B, Guagliumi G, et al. Heparin plus a glycoprotein IIb/IIIa inhibitor versus bivalirudin monotherapy and paclitaxel-eluting stents versus bare-metal stents in acute myocardial infarction (HORIZONS-AMI): final 3-year results from a multicentre, randomised controlled trial. Lancet 2011;377:2193–204.

13. Rassen JA, Mittleman MA, Glynn RJ, et al. Safety and effectiveness of bivalirudin in routine care of patients undergoing percutaneous coronary intervention. Eur Heart J 2010;31:561–72.

14. Wise GR, Schwartz BP, Dittoe N, et al. Comparative effectiveness analysis of anticoagulant strategies in a large observational database of percutaneous coronary interventions. J Interv Cardiol 2012;25:278–88.

15. Marso SP, Amin AP, House JA, et al. Association between use of bleeding avoidance strategies and risk of periprocedural bleeding among patients undergoing percutaneous coronary intervention. JAMA 2010;303:2156–64.

16. Baklanov DV, Kim S, Marso SP, et al. Comparison of bivalirudin and radial access across a spectrum of preprocedural risk of bleeding in percutaneous coronary intervention: analysis from the national cardiovascular data registry. Circ Cardiovasc Interv 2013;6:347–53.

17. Shahzad A, Kemp I, Mars C, et al. Unfractionated heparin versus bivalirudin in primary percutaneous coronary intervention (HEAT-PPCI): an open-label, single centre, randomised controlled trial. Lancet 2014;384:1849–58.

18. Bellomo R, Warrillow SJ, Reade MC. Why we should be wary of single-center trials. Crit Care Med 2009;37:3114–9.

19. Zeymer U, van't Hof A, Adgey J, et al. Bivalirudin is superior to heparins alone with bailout GP IIb/IIIa inhibitors in patients with ST-segment elevation myocardial infarction transported emergently for primary percutaneous coronary intervention: a pre-specified analysis from the EUROMAX trial. Eur Heart J 2014;35:2460–7.

20. Han Y, for the BRIGHT Investigators. Bivalirudin versus heparin plus tirofiban in patients with AMI undergoing PCI. Available at: http://www.tctmd.com/show.aspx?id=126013. Accessed September 22, 2014.

21. ClinicalTrials.gov. Minimizing Adverse Haemorrhagic Events by TRansradial Access Site and Systemic Implementation of angioX (MATRIX). Available at: http://clinicaltrials.gov/ct2/show/NCT01433627. Accessed November 4, 2014.

KEY WORDS bivalirudin, heparin, coronary artery disease, percutaneous coronary intervention