Bivalirudin Versus Heparin: A Fight Far From Finished?

Efficacy, Safety, and Cost Remain Battlegrounds for the Treatment Of ST-Segment Elevation Myocardial Infarction

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Results of the HORIZONS-AMI trial, reported in 2008 and 2011,[1,2] demonstrated that patients undergoing primary percutaneous coronary interventions (PCIs) who received aspirin, clopidogrel, and the direct thrombin inhibitor bivalirudin had significantly fewer major hemorrhagic complications and lower all-cause mortality than patients who received unfractionated heparin plus a glycoprotein IIb/IIIa inhibitor (GPI). Rates of acute stent thrombosis (occurring in less than four hours) were higher in the bivalirudin arm of the trial.

The treatment arena for ST-segment elevation myocardial infarction (STEMI) has been evolving rapidly since those results were published. Potent $P2Y_{12}$ inhibitors have been approved and accepted into practice, along with administration of medication before patients enter the hospital. Radial artery access for PCI has been supplanting femoral access, with concomitant lower bleeding rates. The more recent EUROMAX trial[3] reflects those changes, and patient-level data from the two trials were pooled in an effort to lend power for assessing procedural anticoagulation for primary PCI with bivalirudin versus heparin with or without a GPI.

That pooled analysis by Gregg W. Stone, MD, and colleagues was published in the *Journal of the American College of Cardiology* (*JACC*) in January 2015.[4] The data show primary PCI with bivalirudin (Angiomax, The Medicines Company) improves 30-day net clinical outcomes, with significant reductions in major bleeding, thrombocytopenia, and transfusions compared with heparin with or without a GPI. Dr. Stone, Director of Cardiovascular Research and Education at Columbia University Medical Center/NewYork–Presbyterian Hospital, concluded: "These results support the use of bivalirudin for anticoagulation of patients with STEMI undergoing primary PCI, independently of vascular access site, choice of $P2Y_{12}$ inhibitor, and timing of drug initiation and discontinuation."

An accompanying editorial by Sanjay Kaul, MD, of the Division of Cardiology at Cedars-Sinai Medical Center in Los Angeles,[5] questioned the findings and methodologies of that analysis, summing up with a pointed comment about bivalirudin: "It costs nearly 400-fold more than heparin, with no discernible efficacy or substantial safety advantage."

The night-and-day contrast of these conclusions encapsulates a strident, years-long debate that has been surging in the interventional cardiology community over the powerful triumvirate of efficacy, safety, and cost. Where are the battle lines?

The two multicenter, international trials—HORIZONS-AMI (Harmonizing Outcomes with RevasculariZatiON and Stents in Acute Myocardial Infarction) and EUROMAX (European Ambulance Acute Coronary Syndrome Angiography)—both enrolled patients with acute STEMI presenting within 12 hours of symptom onset. All patients (3,602 in HORIZONS-AMI, 2,198 in EUROMAX) were treated through a planned primary PCI reperfusion strategy. In HORIZONS-AMI, they were randomized 1:1 to unfractionated heparin (60 IU/kg intravenous [IV] bolus) plus the routine use of a GPI (abciximab [ReoPro, Jannsen] or eptifibatide [Integrilin, Merck]) or bivalirudin (0.75 mg/kg IV bolus, followed by 1.75 mg/kg per hour infusion), with provisional GPI use for refractory intraprocedural thrombotic complications.

Except for cases with specific indications for extended infusion, bivalirudin was discontinued after the procedure. IV heparin was allowed before randomization, and all patients received loading doses of aspirin and 300 mg or 600 mg of clopidogrel (Plavix, Bristol-Myers Squibb/Sanofi). For patients in EUROMAX, the last of whom were randomized in 2013, radial artery access and potent $P2Y_{12}$ inhibitor use were encouraged. Reflecting European practice, adding GPIs to heparin was optional and patients received antithrombotic agents before arriving at the hospital. Both trials had 30-day primary endpoints: major non-CABG (coronary artery bypass grafting) bleeding and NACE (net adverse clinical events) for HORIZONS-AMI, and composite death or non-CABG major bleeding for EUROMAX. Loading or maintenance doses of prasugrel (Effient, Lilly) or ticagrelor (Brilinta, AstraZeneca) were given to 61.7% of patients in EUROMAX and to none in HORIZONS-AMI. Access was via the radial artery in 5.9% of HORIZONS-AMI patients and in 47.0% of EUROMAX patients. HORIZONS-AMI follow-up was three years; EUROMAX follow-up is complete for 30 days and will continue through one year.

Importantly, while bivalirudin dosing with a provisional GPI-use strategy was identical in EUROMAX and HORIZONS-AMI, continued bivalirudin infusion after PCI for up to four hours was allowed in EUROMAX at 0.25 mg/kg per hour or 1.75 mg/kg per hour.

The Pooled Analysis Results

In the pooled analysis, the median patient age was 60.6 years. Drug-eluting stents were used in 91.1% of patients. Among patients assigned to bivalirudin or heparin, 8.8% and 84.8%, respectively, received a GPI. Restoration of blood flow was similar in both groups.

At 30 days, the rate of ischemic major adverse cardiovascular events (MACE)—all-cause mortality, reinfarction, ischemia-driven revascularization, or stroke—was similar between groups at 5.6% for bivalirudin and 5.5% for heparin plus or minus a GPI (relative risk [RR], 1.02; 95% confidence interval [CI], 0.83–1.26; $P = 0.85$). Among the MACE components, cardiac death was lower in the bivalirudin arm (2.0% versus 2.9%; RR, 0.70; 95% CI, 0.50–0.97; $P = 0.03$). Stent thrombosis was higher for bivalirudin (2.1% versus 1.5%; RR, 1.51; 95% CI, 1.01–2.24, $P = 0.04$).

Major non-CABG bleeding was lower with bivalirudin (4.2% versus 7.8%; RR, 0.53; 95% CI, 0.43–0.66; $P < 0.0001$), as were other hemorrhagic and hematological endpoints and NACE

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Table 1 Outcomes in the Pooled HORIZONS-AMI and EUROMAX Study Population at 30 Days[4]

	Bivalirudin (%) (n = 2,889)	Heparin ± GPI (%) (n = 2,911)	Relative Risk (95% CI)	*P* Value
Major bleeding, non-CABG, protocol	120 (4.2)	226 (7.8)	0.53 (0.43–0.66)	< 0.0001
TIMI major bleeding, non-CABG	47 (1.6)	81 (2.8)	0.58 (0.41–0.83)	0.003
TIMI major or minor bleeding, non-CABG	160 (5.5)	281 (9.6)	0.58 (0.48–0.69)	< 0.0001
Blood product transfusion	62 (2.1)	110 (3.8)	0.57 (0.42–0.77)	0.0002
Acquired thrombocytopenia	37 (1.4)	77 (2.9)	0.48 (0.33–0.71)	0.0002
NACE	253 (8.8)	346 (11.9)	0.74 (0.63–0.86)	< 0.0001

CABG = coronary artery bypass grafting; CI = confidence interval; NACE = net adverse clinical events; TIMI = thrombolysis in myocardial infarction

Adapted from *J Am Coll Cardiol* 2015;65(1):27–38.[4]

(Table 1). Reductions in the bivalirudin arm were highly significant across the range of endpoints, including the need for blood product transfusions and acquired thrombocytopenia.

Overall, heterogeneity between the two studies was not observed for any of the major clinical endpoints. Furthermore, tests for differences among a wide array of subgroups (e.g., $P2Y_{12}$ inhibitor type and vascular access site) revealed consistency across the major endpoints.

In the discussion section, the authors speculated on the cause of the absolute increment of approximately 1% in acute stent thrombosis with bivalirudin reported in HORIZONS-AMI compared with heparin plus a GPI. Since it occurs within the first four hours after the abrupt discontinuation of the bivalirudin infusion, plausible factors that stand out include residual thrombin activity (given bivalirudin's 25-minute half-life) and/or insufficient inhibition of adenosine diphosphate-induced platelet aggregation attributable to clopidogrel's slow onset of action and known response variability. Rates of stent thrombosis after 24 hours trended higher in the heparin-plus-GPI arm (0.9% for bivalirudin, 1.2% for heparin plus a GPI, $P = 0.24$), demonstrating a "catch-up" phenomenon after discontinuation of the GPI infusion. Also, 30-day all-cause and cardiac mortality curves favoring bivalirudin diverged further over the three-year follow-up.

A post-hoc analysis suggested that decreased hemorrhagic complications and reduced thrombocytopenia with bivalirudin, along with other nonhematological advantages,[6] may explain bivalirudin's cardiac mortality benefit.

The possibility that a synergy between bivalirudin and prasugrel or ticagrelor would mitigate the relative and absolute increases in stent thrombosis with bivalirudin compared with heparin with or without a GPI was not borne out in EUROMAX findings, probably because these oral agents have a delayed onset of action in STEMI. An investigational intravenous $P2Y_{12}$ inhibitor, cangrelor, which the authors noted is active within minutes and has demonstrated lower intraprocedural and acute stent thrombosis rates in PCI patients with STEMI, might offer a benefit. While bivalirudin patients in EUROMAX did not have a lower acute stent thrombosis risk, only a minority of patients received extended bivalirudin infusions, Dr. Stone pointed out in an email exchange. Death within 30 days, despite the higher acute stent thrombosis rate with bivalirudin, was reported for one patient each in the bivalirudin and heparin-plus-or-minus-GPI groups. The fact that reductions in bleeding with bivalirudin were independent of the much greater use of radial access in EUROMAX suggests that major hemorrhagic complications after PCI are not related to the access site. Two prognostically important factors, thrombocytopenia and nonaccess-site bleeding, may explain bivalirudin's consistently reduced cardiac mortality.

Conflicting Recent Trial Results

The *JACC* study authors noted that the preponderance of clinical trials and analyses have shown reduced bleeding with or without a survival benefit for bivalirudin versus heparin alone, and that early studies of primary PCI in the "clopidogrel era" revealed high infarct artery reocclusion rates with heparin—until GPIs reduced them, but at the cost of elevated bleeding rates.

The authors reviewed divergent results, however, in HEAT-PPCI (How Effective Are Antithrombotic Therapies in Primary Percutaneous Coronary Intervention), a single-center, all-comer trial conducted in Liverpool, United Kingdom. That 2014 study found no benefit for bivalirudin. HEAT-PPCI tested bivalirudin versus unfractionated heparin in 1,829 primary PCI patients with acute STEMI, randomly assigning them to bivalirudin or heparin. Similar proportions of patients received GPIs (12% in the bivalirudin arm, 15% in the heparin arm). The primary efficacy outcome, a composite of all-cause mortality, cerebrovascular accident, reinfarction, or unplanned target lesion revascularization, was reported as 8.7% in the bivalirudin group and 5.7% in the heparin group, an absolute risk difference of 3.0% (RR, 1.52; 95% CI, 1.099–2.13; $P = 0.01$).

The incidence of the primary safety outcome, major bleeding (Bleeding Academic Research Consortium [BARC] 3–5), was 3.5% in the bivalirudin group and 3.1% in the heparin group, for an absolute risk difference of 0.4% (RR, 1.15; 95% CI, 0.70–1.89; $P = 0.59$). Definite or probable stent thrombosis occurred in 3.4% of patients in the bivalirudin group and 0.9% in the heparin group (RR, 3.91; 95% CI, 1.61–9.52; $P = 0.001$).

The HEAT-PPCI authors concluded, "Compared with bivalirudin, heparin reduces the incidence of major adverse ischemic events in the setting of PPCI, with no increase in bleeding complications. Systematic use of heparin rather than bivalirudin would reduce drug costs substantially."

The *JACC* article authors observed that the HEAT-PPCI acute stent thrombosis rate with bivalirudin was substantially higher than that in the multicenter HORIZONS-AMI and EUROMAX trials (2.9% versus 1.3% and 1.1%, respectively).

A possible explanation for the divergent findings in HEAT-PPCI, the *JACC* authors proposed, is that the bivalirudin dose

might have been too low. While the median activated clotting time in HORIZONS-AMI was 322 seconds, in HEAT-PPCI it was only 241 seconds. Also, bleeding in bivalirudin-treated patients may have been increased by bailout GPI use in HEAT-PPCI (13%). Furthermore, the *JACC* authors cautioned that results from single-center trials need confirmation in adequately powered multicenter trials.

BRIGHT (Bivalirudin in Acute Myocardial Infarction Versus Glycoprotein IIb/IIIa and Heparin Undergoing Angioplasty), a multicenter trial including acute myocardial infarction patients at 82 Chinese sites, randomized 735 to bivalirudin, 729 to heparin monotherapy, and 730 to heparin plus the GPI tirofiban (Aggrastat, Medicure). Approximately 78% of PCI procedures were performed transradially, and 99% of patients received drug-eluting stents. The primary endpoint, 30-day NACE, was a composite of major adverse cardiac and cerebrovascular events or BARC bleeding.

BRIGHT trial results were presented at the September 2014 Transcatheter Cardiovascular Therapeutics (TCT) meeting by lead investigator Yaling Han, MD, from General Hospital of Shenyang Military Region in China. NACE incidence was lower in the bivalirudin group compared with the heparin and heparin-plus-tirofiban groups (8.8% versus 13.2% and 17.0%, respectively; $P < 0.001$). The bivalirudin group also had fewer NACE events at one year (12.8% versus 16.5% and 20.5%, respectively; $P < 0.001$). Bivalirudin also reduced major bleeding ($P = 0.04$) and minor bleeding ($P < 0.001$), with similar rates of adverse ischemic events compared to the heparin and heparin-plus-tirofiban groups (Table 2).

Rates of acute stent thrombosis (occurring in less than 24 hours) were not increased with bivalirudin and were identical in the three treatment arms (0.3%). Overall stent thrombosis was low for all groups at 0.6% for bivalirudin, 0.3% for heparin, and 0.3% for heparin plus tirofiban ($P < 0.77$). At the TCT press conference, Dr. Han suggested that the lack of elevation of stent thrombosis with bivalirudin in BRIGHT might be explained by the mandated routine post-PCI bivalirudin infusion.

The HORIZONS-AMI and EUROMAX findings, the authors said, were based on 5,800 patients randomized at 188 international centers, with careful monitoring and adjudication by blinded clinical events committees. Together with BRIGHT, they represent three large-scale multicenter trials consistently demonstrating reduced rates of bleeding and NACE in PCI with bivalirudin compared with heparin alone or with a GPI. While allowing that further data are needed (e.g., longer-term EUROMAX data), and that the cardiac mortality benefit should be interpreted cautiously, the trials support the use of bivalirudin in STEMI for primary PCI.

Table 2 Results of the BRIGHT Trial

	Bivalirudin (%) (n = 735)	Heparin (%) (n = 729)	Heparin + Tirofiban (%) (n = 730)	*P* Value
30-day NACE	8.8	13.2	17.0	< 0.001
One-year NACE	12.8	16.5	20.5	< 0.001
Stent thrombosis	0.6	0.3	0.3	< 0.77
Acute stent thrombosis (< 24 hours)	0.3	0.3	0.3	1.0

NACE = net adverse clinical events

The Editorial Viewpoint

Dr. Kaul's first challenge to Dr. Stone's *JACC* conclusions was to question the justification for pooling data from HORIZONS-AMI and EUROMAX, given the level of clinical heterogeneity across the trials and uncertainty as to any new or unique insights that such pooling could produce that could not already be inferred from the individual trial results. The evident findings from the trials, he said, are that acute thrombosis risk is increased by bivalirudin and that bleeding complications are reduced.

The reductions in mortality and thrombolysis in myocardial infarction (TIMI) bleeding, because they were not apparent in EUROMAX, are open to further question. Pooling disparate results such as these can give rise to misleading inferences that treatment effects are consistent, Dr. Kaul cautioned. Similarly, the unconventional combining of a composite efficacy (ischemic) and safety (bleeding) outcome as NACE can lead to unsubstantiated claims that a relatively ineffective but safer drug (i.e., bivalirudin) may appear better than an effective drug (heparin).

Next, Dr. Kaul pointed to differences in treatment. Asymmetrical GPI use could confound results by increasing bleeding risk for heparin, while the heparin pretreatment given to some patients makes it difficult to attribute efficacy solely to bivalirudin.

Selecting heparin monotherapy as the comparator arm could be viewed as "unethical," Dr. Kaul said, in light of pooled results from eight trials showing that adding a GPI to heparin reduces death and reinfarction. On the other hand, HEAT-PPCI seems to vindicate heparin monotherapy and led to the downgrading of recommendations for bivalirudin to the Class IIa level of evidence (LOE) in guidelines from the American College of Cardiology, American Heart Association, and Society for Cardiovascular Angiography Interventions. The heparin recommendation was kept in the Class I LOE.

Dr. Kaul cited BRAVE-4 (Bavarian Reperfusion Alternatives Evaluation), in which a comparison failed to reveal a benefit for bivalirudin plus prasugrel over clopidogrel plus unfractionated heparin for the composite of ischemic complications or bleeding. Dr. Kaul urged interpretive caution, however, because the trial was terminated prematurely for slow recruitment.

Some experts have argued that the cardiac mortality benefit in HORIZONS-AMI, in and of itself, would justify bivalirudin use, Dr. Kaul said in the *JACC* editorial. That benefit appeared by 30 days post-procedure (1.8% versus 2.9%; HR, 0.62; 95% CI, 0.40–0.95; $P = 0.03$) and increased over three years (2.9% versus 5.1%; HR, 0.56; 95% CI, 0.40–0.80; $P = 0.001$). Dr. Kaul found the strength of that finding to be questionable because it was not prespecified ("and therefore not adequately powered for comparison") and the confidence intervals were wide. His analysis of the Bayes factor, which assesses the strength of evidence, showed a weak null probability of 21%, and the *P* value was not adjusted for multiple comparisons, raising the likelihood of a type I error for the 30-day endpoint. The three-year benefit, he granted, was statistically

persuasive. Importantly, the mechanisms behind a putative mortality reduction with bivalirudin have not been elucidated.

The Cardiac Mortality Benefit

For this last point, Dr. Kaul referred to Dr. Stone's other published research on the HORIZONS-AMI data showing that prevention of bleeding, thrombocytopenia, and reinfarction, all reduced in the three-year analysis, did not adequately account for the mortality benefit. In that study, bivalirudin was still associated with a 43% reduction in three-year cardiac mortality after a fully adjusted multivariable model accounted for major bleeding and other adverse events (adjusted HR, 0.57; 95% CI, 0.39–0.83; $P = 0.003$). Also, being assigned to bivalirudin was strongly associated with reduced cardiac mortality even in patients who did not have any bleeding.

Dr. Kaul further noted that limiting infarct size and preserving left ventricular ejection fraction—two potential mechanisms for cardiac protection—were no different between the bivalirudin and heparin arms of the trial.

Along with the lack of replication of the benefit in subsequent trials, Dr. Kaul found the cardiac mortality evidence to be insufficient to inform guideline recommendations and clinical practice strategies. A carefully designed further trial is needed, he added. His final words: "out with the new (bivalirudin), in with the old (heparin monotherapy with bailout GPI)."

Is the Evidence Mounting?

Tim Henry, MD, is the Director of Cardiology at Cedars-Sinai Heart Institute in Los Angeles, where Sanjay Kaul, MD, has a cardiology practice. Dr. Henry has in the past been on advisory boards for The Medicines Company, bivalirudin's manufacturer, and has received research grants, but he has had no affiliation with the company for the last 12 months. In an extended interview, he noted that he recently debated Dr. Kaul on this issue at Cedars-Sinai's annual *Controversies and Advances in the Treatment of Cardiovascular Disease* course in Los Angeles.

"Now you have a large U.S. trial, a large European trial, and a large Chinese trial—and all show the same thing," Dr. Henry said, "a benefit for bivalirudin related predominantly to a decrease in bleeding. That is the strongest evidence that has been consistent with almost every trial. I don't know why it wasn't true in HEAT. Maybe there's a mortality benefit and there is a potential stent thrombosis problem—which looks to be solvable based on BRIGHT."

Dr. Henry said that the meta-analysis by Stone et al. was well written and that Dr. Kaul had made many fair points in his editorial, especially from a methodological and regulatory perspective. Dr. Henry took issue, however, with Dr. Kaul's objection to the choice of heparin plus a GPI as a comparator, stating that at the time HORIZONS-AMI was designed, the accepted view was that heparin monotherapy was clearly inferior to heparin plus a GPI, the guideline-recommended approach. "People would have objected to a heparin-only arm," he said.

Dr. Henry noted that in his work in Minneapolis, Minnesota, with Allina Health, a nonprofit health care system, an analysis based on electronic medical records from three large PCI centers showed that use of bivalirudin was one of the strongest predictors of decreased bleeding. Dr. Henry was an author of a *Circulation: Cardiovascular Quality and Outcomes* article[7] noting that when participating hospitals adjusted their practice to reserve bivalirudin use for high-bleeding-risk patients and not lower-bleeding-risk patients, overall bleeding decreased, outcomes improved, and costs went down. He noted, as well, that in the large TRANSLATE-ACS registry, bleeding was reduced significantly with bivalirudin. "So both large hospital and multicenter registries also consistently show reduced bleeding." He added, "Knowing the patients' bleeding risk scores is valuable for this decision process—and heparin plus a thienopyridine is a reasonable choice for a patient who is at very low risk for bleeding."

Dr. Henry conceded that Dr. Kaul's reservations about the mortality benefit are reasonable. "I don't think you use this agent because of the mortality benefit," he said, "but you do have three large trials with mortality going in the right direction, probably because of the improvement in bleeding—but we can't say for sure."

Regarding the smaller trials with results less favorable to bivalirudin such as HEAT-PPCI and BRAVE, Dr. Henry said, "With underpowered trials, you can always get inconsistent results. It's kind of in the nature of clinical trials." Dr. Henry observed that the high stent thrombosis rate of almost 3% in HEAT-PPCI stood out. "That's too high. For me it's a red flag." The biggest weakness in the evidence for using bivalirudin is the stent thrombosis issue, he agreed.

The current practice at the Minneapolis Heart Institute's large regional STEMI system is to pretreat with a thienopyridine and give an IV bolus of heparin before PCI. Bivalirudin is then administered in the majority of cases. "They see 500 STEMIs a year, and the incidence of stent thrombosis is less than 1%, close to 0%. The bivalirudin infusion is continued until the bag runs out, ideally for at least two hours."

Cost Is Also on the Table

"If the two cost the same, I don't think there's any doubt that we'd use bivalirudin," Dr. Henry stated. "It has more predictable anticoagulation than heparin, it doesn't activate platelets, and the preponderance of evidence shows that it decreases bleeding—we know that bleeding matters." Bleeding, he continued, can be mitigated by avoiding GPIs and by performing PCI procedures through radial access. Also, stent thrombosis can be reduced with new-generation stents and thienopyridines. "The major downside is cost—and that's a fair and more complicated discussion."

One cost-balancing factor is that adding GPIs to heparin, depending on which GPIs are used, can bring costs close to equivalency. "I really think the evidence strongly shows that GPIs should be used very selectively—based on our institutional data in STEMI, less than 10%," Dr. Henry said. He reserves GPIs for patients who can't take a thienopyridine: for example, a patient who has had an out-of-hospital cardiac arrest and has been intubated. "Bleeding is clearly increased when you add a GPI to heparin—or to bivalirudin," he said. Reduced thrombocytopenia rates with bivalirudin, which are similar to the stent thrombosis rates, are also consequential, Dr. Henry said, because they increase the chances of bleeding, too.

In the recently completed TRANSLATE-ACS registry, Dr. Henry said, bivalirudin usage in STEMI was 40% to 50%, heparin plus a GPI was 25% to 35%, and heparin alone was 15% to 20%.

As Questions Linger, Debate Continues

"The results of HEAT-PPCI have made a dent in the usage of bivalirudin," said Ron Waksman, MD, Associate Director of the Division of Cardiology at the MedStar Washington Hospital Center in Washington, D.C. "The debate on this subject will continue." Dr. Waksman said in an interview that the handful of meta-analyses that have been published examining bivalirudin use in STEMI have all reached the same conclusions: It offers lower bleeding at the price of higher acute stent thrombosis. What remains as a contested issue in the article by Stone et al. is the mortality reduction—which, Dr. Waksman underscored, was one reason that bivalirudin received upgraded guideline recommendations. "But the mechanism was never clearly understood, and it has not been replicated in other trials. Dr. Kaul has rightfully challenged the interpretation of the pooled data analysis." Dr. Waksman also agreed with Dr. Kaul's objection to the use of NACE, which combines efficacy and safety into a single endpoint. "I want to understand these separately," he said.

The use of bleeding-risk scores, Dr. Waksman said, is "theoretical." He observed that "when you have a patient with STEMI, you give right away whatever you are going to give. You don't have time for [calculating a bleeding-risk score], although bleeding risk affects your decision among patients with obvious risk factors such as advanced age or low body mass index."

Bleeding risk, Dr. Waksman said, can be mitigated without increasing stent thrombosis by "tailoring down" anticoagulation. This can be accomplished by avoiding low-molecular-weight heparins that have been shown to cause more bleeding in STEMI patients, for example. "We've asked all of our referring institutions to use unfractionated heparin, not low-molecular-weight heparin," he said. In addition, more selective use of GPIs will reduce bleeding risk, as will abbreviating the duration of their administration. "Once we establish those strategies, which do not increase stent thrombosis, then we should compare them with bivalirudin to see if the bleeding reductions still hold." Guidelines, Dr. Waksman commented, are not fully up to date. "So we have to exercise common sense."

The bleeding reduction with bivalirudin, Dr. Waksman said, "is for real, but we have to see what we can do to reduce the stent thrombosis—that is the challenge. No one has given a good explanation for it. Is it related to flow? Or early termination of bivalirudin? Or that patients were not treated with third-generation antiplatelet therapy early enough? Or maybe they need a very low supplementary dose of heparin? We have to explore these in mechanistic studies." Because the BRIGHT study has not been published yet and because of differences in the population tested (acute MI patients, as opposed to primary PCI patients for STEMI in HORIZONS-AMI and EUROMAX), Dr. Waksman felt that he could not alter his conclusions based on its findings.

"We should use bivalirudin, but find solutions to the stent thrombosis issue. To know that there is still that risk is troubling." Dr. Waksman noted that subsequent to the HEAT-PPCI findings, bivalirudin use in his institution has been reduced from about 90% of cases to 60% to 70%.

Dr. Waksman was emphatic about cost. "Cost should not be the main factor. When it comes to STEMI, and you are talking about saving lives, or saving myocardium, or lowering complications, then the extra cost is mitigated. You should just look at efficacy and safety, but separately."

Dr. Stone, in an interview, concurred on cost. "To look just at the cost of the drug is incredibly simplistic, because we know that bleeding carries major health care costs."

In three economic analyses supplied by Efthymios N. Deliargyris, MD, Global Medical Director at The Medicines Company and an author with Dr. Stone on the *JACC* study, bivalirudin use was cost-effective compared with heparin plus GPIs in PCI treatment of STEMI. In one analysis assessing 278 hospitals, length of stay was lowered by 0.47 days ($P = .03$) and hospital costs were reduced by 14% ($P = .04$).[8] In the second analysis, evaluating 21,316 STEMI PCIs, mean in-hospital costs were $18,640 with bivalirudin compared with $19,967 for heparin plus a GPI.[9] A third analysis, based on HORIZONS-AMI data, found a per-patient cost saving of $1,690 (average procedural cost, $16,872).[10]

Why Bivalirudin May Reduce Mortality

Dr. Stone pointed out that in another recent paper he had examined potential factors contributing to the cardiac mortality reduction reported in HORIZONS-AMI with bivalirudin.[6]

"A fair amount can be attributed to the bleeding reduction. The reduction in thrombocytopenia, however, also comes into play, along with the fact that platelet counts do not drop after you give bivalirudin as they do with heparin and the GPIs," Dr. Stone said. Experimental observations of nonhematological factors—affecting inflammation, microembolization, neutrophil aggregates, and apoptosis—have been reported, but at this stage they remain speculative and are generating hypotheses.

Will MATRIX Answer the Questions?

At the American College of Cardiology annual meeting in March 2015, the first results of the MATRIX trial—Minimizing Adverse Hemorrhagic Events by TRansradial Access Site and Systemic Implementation of angioX—will be presented in a late-breaking clinical trial session. MATRIX is comparing transradial versus transfemoral access interventions and bivalirudin monotherapy versus the current European standard of care, which is unfractionated heparin plus a provisional GPI (abciximab, eptifibatide, or tirofiban). MATRIX has enrolled 7,211 acute coronary syndrome patients intended for an invasive management strategy.

A subrandomization of patients to either prolonged post-intervention bivalirudin infusion (the long bivalirudin arm) or a peri-PCI bivalirudin infusion only (the short bivalirudin arm) will have as its primary measure the net composite outcome of any death, MI, stroke, stent thrombosis, or BARC-defined type 3 and 5 bleeding events within 30 days. In the short bivalirudin arm, the infusion of bivalirudin (given immediately upon enrollment as a bolus of 0.75 mg/kg followed immediately by an infusion of 1.75 mg/kg per hour) is stopped at the completion of PCI, while in the long bivalirudin arm it is reduced to 0.25 mg/kg per hour for at least six hours. An optional higher-dose infusion of 1.75 mg/kg per hour is also permitted for up to four hours in the prolonged infusion arm but prohibited in the short bivalirudin arm.

MATRIX lead investigator Marco Valgimigli, MD, PhD, of The Thoraxcenter at Erasmus Medical Center in Rotterdam, Netherlands, noted in an interview that the numerical excess of subacute stent thrombosis with bivalirudin in HEAT-PPCI was a surprise and was at variance with the HORIZONS-AMI and

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EUROMAX data. "It will be very important to see if in MATRIX that piece of information is confirmed or not," he said. The other endpoint of intense interest for the MATRIX investigation is the mortality benefit, which was seen in HORIZONS-AMI but not in other trials since.

The wait for more definitive answers to some of the questions raised here by experts may not be long. For pharmacists, clinicians, and hospitals trying to balance the critical factors of efficacy, safety, and cost in their choices for agents in STEMI and primary PCI, data emerging from the MATRIX trial may well tip the scales sharply in one direction or another.

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