Factors Affecting Bleeding and Stent Thrombosis in Clinical Trials Comparing Bivalirudin With Heparin During Percutaneous Coronary Intervention

John A. Bittl, MD; Yulei He, PhD; Christopher D. Lang, MD; George D. Dangas, MD, PhD

Background—Patients treated with bivalirudin in randomized clinical trials of percutaneous coronary intervention generally have less bleeding but more acute stent thrombosis (ST) than do patients treated with heparin, but differences have varied among trials.

Methods and Results—We modeled the risk of major hemorrhage and ischemic outcomes 30 days after percutaneous coronary intervention by treatment assignment and the use of adjunctive therapies in 18 randomized clinical trials enrolling 41,871 patients. Overall bivalirudin caused less major bleeding (odds ratio [OR], 0.64; 95% confidence interval [CI], 0.53–0.76), more ST (OR, 1.58; 95% CI, 1.19–2.09), and no difference in mortality (OR, 0.93; 95% CI, 0.77–1.14) than heparin. A risk–benefit analysis identified 19 fewer bleeds and 5 more STs for every 1000 patients treated with bivalirudin in place of heparin. No significant bleeding advantage of bivalirudin over heparin could be identified in randomized clinical trials when transradial access (OR, 0.89; 95% CI, 0.57–1.41) and planned glycoprotein IIb/IIIa inhibitors were used with bivalirudin in the majority of patients (OR, 1.07; 95% CI, 0.87–1.31). The use of prasugrel or ticagrelor eliminated bleeding differences (OR, 0.80; 95% CI, 0.63–1.03) but did not reduce the risk of ST after bivalirudin (OR, 2.20; 95% CI, 1.48–3.27).

Conclusions—Substituting bivalirudin for heparin conferred a tradeoff between bleeding and ST. Transradial access, adjunctive glycoprotein IIb/IIIa inhibitors, and potent P2Y₁₂ inhibitors attenuated the bleeding advantage of bivalirudin over heparin but had no apparent effect on early ST. New approaches to reduce bleeding and ischemic complications during percutaneous coronary intervention warrant further investigation. (Circ Cardiovasc Interv. 2015;8:e002789. DOI: 10.1161/CIRCINTERVENTIONS.115.002789.)

Key Words: bivalirudin ▪ glycoproteins ▪ heparin ▪ percutaneous coronary intervention ▪ platelet aggregation inhibitors

The intravenous anticoagulants bivalirudin and heparin have been compared in several randomized clinical trials (RCTs) of percutaneous coronary intervention (PCI).¹–²¹ Although most RCTs found that the direct thrombin inhibitor bivalirudin conferred a lower risk of major hemorrhage than heparin,²,⁴,⁶,⁸,¹¹,¹⁵,¹⁷,²⁰,²¹ other studies have found that bivalirudin was associated with an increased risk of acute stent thrombosis (ST).⁹,¹³,¹⁸

Several PCI advances affecting both bleeding and ST have emerged in clinical practice and have been incorporated into the RCTs comparing bivalirudin and heparin. Adjunctive antiplatelet therapies such as intravenous platelet glycoprotein inhibitor (GPIs) and potent oral P2Y₁₂ blockers theoretically increase the overall risk of bleeding and might reduce ST. On the contrary, transradial access may reduce access-site bleeding and the overall risk of hemorrhage. The purpose of the current analysis was to quantify the effect of vascular-access selection and newer antithrombotic strategies on the risk of bleeding and ischemic complications associated with bivalirudin or heparin during PCI.

Methods

Aggregate data from 18 RCTs of patients treated with bivalirudin versus heparin during PCI confirming coronary stents in >50% of patients¹–²⁰ comprised the evidence base for the current analysis (Table). Summary data from each trial were abstracted in triplicate and validated against published reports.¹–²⁰ Major hemorrhage, definite or probable ST, and postprocedural myocardial infarction (MI) were defined according to criteria in each trial. The primary outcomes of the analysis were all-cause mortality, major hemorrhage, postprocedural or recurrent MI, definite ST (which was reported in more RCTs than probable ST), and ischemia-driven revascularization within 30 days of PCI. Whenever possible, PCI-enriched data sets were preferred over data sets from the same trials of subjects treated with medical therapy alone.¹
WHAT IS KNOWN

- Major hemorrhage or stent thrombosis (ST) after percutaneous coronary intervention confers a poor prognosis.
- In many randomized controlled trials, the use of bivalirudin in place of heparin during percutaneous coronary intervention has been associated with reduced bleeding but a greater risk of ST.
- New advances in percutaneous coronary intervention practice, such as the use of transradial access and potent antplatelet agents, alter the risk of bleeding and ST after percutaneous coronary intervention.

WHAT THE STUDY ADDS

- The use of transradial access, new potent oral platelet P2Y₁₂ inhibitors prasugrel and ticagrelor, and adjunctive glycoprotein inhibitors with bivalirudin seemed to reduce the bleeding advantage of bivalirudin over heparin in randomized controlled trials.
- The use of the more potent P2Y₁₂ inhibitors prasugrel and ticagrelor did not seem to reduce the risk of ST in patients randomized to bivalirudin.
- Additional research is needed to determine whether the hazard of ST with bivalirudin persists as newer generation drug-eluting stents replace first-generation drug-eluting stents.

Meta-Analysis

Forest plots were created to show the relative differences in the primary end points. A random-effects model was preferred over a fixed-effect model to acknowledge the variations in study design. To emulate the random-effects model with a Bayesian approach, we used a hierarchical meta-analysis containing a noninformative prior defined by a treatment effect of 0.00 with precision of 0.0001 to ensure that the posterior inference would be dominated by the likelihood of the data.

Trial-Specific Therapies

To define the adjunctive therapies that potentially affected the risk of bleeding or ST associated with bivalirudin, we incorporated parameters into a Bayesian conjugate-normal model representing the underlying treatment effect and the following trial-specific factors: use of transradial access, GPIs with bivalirudin, newer P2Y₁₂ inhibitors (prasugrel and ticagrelor), and provisional use of GPIs with heparin. To assess outcomes by trial-specific factors, we first separated RCTs according to the use of newer adjunctive therapies in ≥50% of subjects. For example, we designated older trials using reports ranging from stable ischemic heart disease to ST-segment-elevation MI. Reports from 2013 to 2015 were more likely than earlier reports to incorporate new PCI advances such as transradial access or new oral antplatelet agents (Table).

Event Rates

Mortality

A total of 587 patients died within 30 days of PCI. After the use of bivalirudin, the weighted mortality rate of 2.18% (95% confidence interval [CI], 1.81%–2.66%) was no different when compared with the rate of 2.34% after use of heparin.

The relative differences in mortality rates were likewise similar. A traditional meta-analysis (OR, 0.93; 95% CI, 0.77–1.14) agreed with a Bayesian hierarchical meta-analysis (posterior median: OR, 0.92; 95% Bayesian credible interval [BCI], 0.76–1.16), and both approaches supported the finding of no survival advantage of bivalirudin over heparin at 30 days (Figure 1A).

Major Hemorrhage

A total of 1622 of 41886 patients in the safety arms of the 18 RCTs had major bleeding within 30 days of PCI. The absolute bleeding rate of 3.52% (95% CI, 2.93%–4.15%) for subjects treated with bivalirudin was lower than the rate of 5.39% in patients treated with heparin. This equated to 35 (95% CI, 29–42) of 1000 patients having a major bleed after bivalirudin when compared with 54 having a major bleed after receiving heparin. For every 1000 patients treated with bivalirudin in place of heparin, the absolute difference of 19 (95% CI, 13–26) fewer hemorrhages with bivalirudin corresponded to a number needed to treat of 54 (95% CI, 41–81).

A traditional meta-analysis (OR, 0.64; 95% CI, 0.53–0.76) and a Bayesian hierarchical meta-analysis (OR, 0.64; 95% BCI, 0.52–0.77) both supported the finding of reduced bleeding with bivalirudin when compared with heparin at 30 days (Figure 1B). When the older BAT trial was added to the analysis, a persistent bleeding advantage of bivalirudin over heparin was observed in a random-effects meta-analysis.
(OR, 0.60; 95% CI, 0.50–0.73) and in a Bayesian hierarchical meta-analysis (OR, 0.61; 95% CI, 0.51–0.74).

### Myocardial Infarction

A total of 2309 patients of 41 770 experienced a procedural or recurrent MI within 30 days of PCI in 17 RCTs reporting the outcome.\(^{1–13,15–20}\) A weighted analysis found a borderline higher rate of MI after bivalirudin than after heparin (7.57% [95% CI, 6.99%–8.21%] versus 6.99%; \(P=0.05\)). For every 1000 patients treated with bivalirudin in place of heparin, 76 (95% CI, 70–82) experienced MI after receiving bivalirudin when compared with 70 after receiving heparin.

The traditional meta-analysis (OR, 1.09; 95% CI, 1.00–1.19) and the Bayesian hierarchical meta-analysis (OR, 1.09; 95% BCI, 0.98–1.23) likewise suggested a borderline difference in the risk of MI after bivalirudin in place of heparin (Figure 1C).

### Stent Thrombosis

A total of 319 patients of 31 389 reported in RCTs\(^{8,10,11,13,15–20}\) experienced definite ST within 30 days of PCI. The absolute rate of ST of 1.40% (95% CI, 1.06%–1.84%) for subjects treated with bivalirudin was higher than the rate of 0.90% for patients treated with heparin. This equated to 14 (95% CI, 11–18) of 1000 patients experiencing ST after receiving bivalirudin when compared with 9 having ST after receiving heparin, the difference for which corresponded to a number needed to harm with bivalirudin of 202 (95% CI, 107–624). Similar results were found when the end point of definite or probable ST was used.

Both a traditional meta-analysis (OR, 1.58; 95% CI, 1.19–2.09) and a Bayesian hierarchical meta-analysis (OR, 1.50; 95% BCI, 1.07–2.24) supported the finding of a significantly increased risk of ST at 30 days after bivalirudin when compared with heparin (Figure 1D).

### Revascularization

A total of 778 of 40 913 patients in 17 RCTs\(^{1–13,15–20}\) had ischemia-driven revascularization reported within 30 days of PCI, which was higher after use of bivalirudin than after

### Table. Trial Summaries

<table>
<thead>
<tr>
<th>References</th>
<th>Year of Report</th>
<th>Indication</th>
<th>ACS, %</th>
<th>FU, d</th>
<th>Bivalirudin±GPI</th>
<th>Heparin±GPI</th>
<th>Bivalirudin GPI, %</th>
<th>Heparin GPI, %</th>
<th>New P2Y12, %</th>
<th>Radial, %</th>
<th>Bivalirudin Post PCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CACHET(^1)</td>
<td>2002 E</td>
<td></td>
<td>0</td>
<td>30</td>
<td>Both</td>
<td>Planned</td>
<td>36</td>
<td>100</td>
<td>0</td>
<td>0</td>
<td>None</td>
</tr>
<tr>
<td>CACHET(^1)</td>
<td>2002 E</td>
<td></td>
<td>0</td>
<td>30</td>
<td>Planned</td>
<td>Planned</td>
<td>100</td>
<td>100</td>
<td>0</td>
<td>0</td>
<td>None</td>
</tr>
<tr>
<td>REPLACE 2(^\text{E}^1)</td>
<td>2003 ACS+E</td>
<td></td>
<td>44</td>
<td>30</td>
<td>Provisional</td>
<td>Planned</td>
<td>7</td>
<td>97</td>
<td>0</td>
<td>0</td>
<td>None</td>
</tr>
<tr>
<td>REPLACE 1(^4)</td>
<td>2004 ACS+E</td>
<td></td>
<td>17</td>
<td>30</td>
<td>Provisional</td>
<td>Provisional</td>
<td>71</td>
<td>73</td>
<td>0</td>
<td>0</td>
<td>Optional</td>
</tr>
<tr>
<td>ACUTY(^\text{E}^6)</td>
<td>2006 ACS</td>
<td></td>
<td>100</td>
<td>30</td>
<td>Both</td>
<td>Planned</td>
<td>97</td>
<td>97</td>
<td>0</td>
<td>6</td>
<td>None</td>
</tr>
<tr>
<td>ACUTY(^\text{E}^6)</td>
<td>2006 ACS</td>
<td></td>
<td>100</td>
<td>30</td>
<td>Planned</td>
<td>Planned</td>
<td>53</td>
<td>97</td>
<td>0</td>
<td>6</td>
<td>Optional</td>
</tr>
<tr>
<td>PROTECT TIMI 30(^7)</td>
<td>2006 ACS</td>
<td></td>
<td>100</td>
<td>2</td>
<td>Provisional</td>
<td>Planned</td>
<td>3</td>
<td>9</td>
<td>0</td>
<td>0</td>
<td>Optional</td>
</tr>
<tr>
<td>ISAR-REACT 3(^8)</td>
<td>2008 ACS+E</td>
<td></td>
<td>18</td>
<td>30</td>
<td>None</td>
<td>None</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>None</td>
</tr>
<tr>
<td>HORIZONS-AMI(^9)</td>
<td>2008 STEMI</td>
<td></td>
<td>100</td>
<td>30</td>
<td>Provisional</td>
<td>Planned</td>
<td>8</td>
<td>98</td>
<td>0</td>
<td>0</td>
<td>None</td>
</tr>
<tr>
<td>NAPLES(^10)</td>
<td>2009 ACS+E</td>
<td></td>
<td>12</td>
<td>30</td>
<td>Provisional</td>
<td>Planned</td>
<td>1</td>
<td>100</td>
<td>0</td>
<td>3</td>
<td>None</td>
</tr>
<tr>
<td>ISAR-REACT 4(^11)</td>
<td>2011 NSTEMI</td>
<td></td>
<td>100</td>
<td>30</td>
<td>Provisional</td>
<td>Planned</td>
<td>0</td>
<td>100</td>
<td>1</td>
<td>0</td>
<td>None</td>
</tr>
<tr>
<td>TENACITY(^\text{E}^8)</td>
<td>2011 ACS+E</td>
<td></td>
<td>74</td>
<td>30</td>
<td>Planned</td>
<td>Planned</td>
<td>100</td>
<td>100</td>
<td>0</td>
<td>0</td>
<td>Optional</td>
</tr>
<tr>
<td>ARMYDA-7 BIVALVE(^\text{E}^3)</td>
<td>2012 ACS+E</td>
<td></td>
<td>29</td>
<td>30</td>
<td>Planned</td>
<td>Planned</td>
<td>12</td>
<td>14</td>
<td>49</td>
<td>2</td>
<td>100</td>
</tr>
<tr>
<td>Deshpande et al(^14)</td>
<td>2012 ACS+E</td>
<td></td>
<td>43</td>
<td>30</td>
<td>Planned</td>
<td>Planned</td>
<td>100</td>
<td>100</td>
<td>0</td>
<td>1</td>
<td>None</td>
</tr>
<tr>
<td>EUROMAX(^15)</td>
<td>2013 STEMI</td>
<td></td>
<td>100</td>
<td>30</td>
<td>Both</td>
<td>Planned</td>
<td>12</td>
<td>69</td>
<td>49</td>
<td>47</td>
<td>100</td>
</tr>
<tr>
<td>NAPLES 3(^16)</td>
<td>2014 ACS+E</td>
<td></td>
<td>23</td>
<td>30</td>
<td>Provisional</td>
<td>Provisional</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>None</td>
</tr>
<tr>
<td>BRIGHT(^17)</td>
<td>2014 AMI</td>
<td></td>
<td>100</td>
<td>30</td>
<td>Provisional</td>
<td>Both</td>
<td>4</td>
<td>37</td>
<td>0</td>
<td>78</td>
<td>Optional</td>
</tr>
<tr>
<td>BRIGHT(^17)</td>
<td>2014 AMI</td>
<td></td>
<td>100</td>
<td>30</td>
<td>Provisional</td>
<td>Planned</td>
<td>4</td>
<td>100</td>
<td>0</td>
<td>78</td>
<td>Optional</td>
</tr>
<tr>
<td>HEAT-PPCI(^18)</td>
<td>2014 STEMI</td>
<td></td>
<td>100</td>
<td>28</td>
<td>Provisional</td>
<td>Provisional</td>
<td>13</td>
<td>15</td>
<td>89</td>
<td>81</td>
<td>None</td>
</tr>
<tr>
<td>BRAVE-4(^19)</td>
<td>2014 STEMI</td>
<td></td>
<td>100</td>
<td>30</td>
<td>Provisional</td>
<td>Planned</td>
<td>3</td>
<td>6</td>
<td>5</td>
<td>1</td>
<td>Optional</td>
</tr>
<tr>
<td>MATRIX(^20)</td>
<td>2015 NSTEMI+STEMI</td>
<td></td>
<td>100</td>
<td>30</td>
<td>Provisional</td>
<td>Provisional</td>
<td>5</td>
<td>26</td>
<td>55</td>
<td>47</td>
<td>47</td>
</tr>
</tbody>
</table>

ACS indicates acute coronary syndrome; ACUITY, Acute Catheterization and Urgent Intervention Triage Strategy; AMI, acute myocardial infarction; ARMYDA-7 BIVALVE, Anti-Thrombotic Strategy for Reduction of Myocardial Damage During Angioplasty–Bivalirudin vs Heparin Study; BMS, bare-metal stent; both, planned or provisional; BRAVE, Bavarian Reperfusion Alternatives Evaluation; BRIGHT, Bivalirudin in Acute Myocardial Infarction vs Glycoprotein IIb/IIIa and Heparin: a Randomised Controlled Trial; CACHET, Comparison of Abciximab Complications With Hirulog for Ischemic Events Trial; E, elective; EUROMAX, European Ambulance Acute Coronary Syndrome Angiography; FU, follow-up; GPI, glycoprotein inhibitor; HEAT-PPCI, How Effective are Antithrombotic Therapies in Primary Percutaneous Coronary Intervention; HORIZONS-AMI, Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction; ISAR-REACT, Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment; MATRIX, Minimizing Adverse Hemorrhagic Events by Transradial Access Site and Systemic Implementation of Angiox; NAPLES, Novel Approaches for Preventing or Limiting Events; new P2Y12, prasugrel or ticagrelor administered at the time of coronary intervention; PROTECT TIMI, The Randomized Trial to Evaluate the Relative Protection Against Post-PCI Microvascular Dysfunction and Post-PCI Ischemia Among Anti-Platelet and Anti-Thrombotic Agents–Thrombolysis In Myocardial Infarction; PTCA, percutaneous transluminal coronary angioplasty; REPLACE, Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events; STEMI, ST-segment–elevation myocardial infarction; and TENACITY, Tirofiban Evaluation of Novel Dosing Versus Abciximab With Clopidogrel and Inhibition of Thrombin.
use of heparin (OR, 1.23; 95% CI, 1.01–1.50) and may have reflected the need for second interventions for early ST.

**Analysis of Trial Factors on Bleeding and ST**

**Effect of Transradial Access on Bleeding**

In the trials using transradial access in the majority of subjects, the risk of major hemorrhage was no different after use of bivalirudin when compared with heparin (OR, 0.89; 95% CI, 0.57–1.41). When the transradial trials were combined in a Bayesian conjugate-normal meta-analysis with the 16 trials using transfemoral access in >50% of subjects, the integrated evidence showed overall less bleeding with bivalirudin when compared with heparin (OR, 0.66; 95% BCI, 0.59–0.73). The point estimate was similar, but the 95% BCI was narrower in the conjugate-normal Bayesian analysis than in the Bayesian hierarchical meta-analysis (95% BCI, 0.52–0.77), because the posterior inference borrowed information from the prior distribution in the conjugate-normal analysis and thus conferred greater precision.

**Effect of Planned GPI Use With Bivalirudin on Bleeding**

In the 5 RCTs that used GPs with bivalirudin in >50% of subjects, including the GPI arm of the Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial, the bleeding advantage of bivalirudin over heparin disappeared (OR, 1.07; 95% CI, 0.87–1.31), whereas the integrated analysis representing evidence from all 18 RCTs replicated the previously observed overall bleeding advantage of bivalirudin over heparin (OR, 0.66; 95% BCI, 0.59–0.73).

---

**Figure 1.** Forest plots showing (A) all-cause mortality, (B) major hemorrhage, (C) postprocedural myocardial infarction, and (D) stent thrombosis ≤30 d after treatment with bivalirudin or heparin. ACUITY indicates Acute Catheterization and Urgent Intervention Triage Strategy; ARMYDA-7 BIVALVE, Anti-Thrombotic Strategy for Reduction of Myocardial Damage During Angioplasty–Bivalirudin vs Heparin Study; BRAVE, Bivalirudin in Acute Myocardial Infarction vs Glycoprotein IIb/IIIa Inhibitor; BRIGHT, Bivalirudin in Acute Myocardial Infarction vs Glycoprotein IIb/IIIa and Heparin: a Randomised Controlled Trial; CACHET, Comparison of Abciximab Complications With Hirulog for Ischemic Events Trial; CI, confidence interval; EUROMAX, European Ambulance Acute Coronary Syndrome Angiography; HEART–PCI, How Effective are Anti-thrombotic Therapies in Primary Percutaneous Coronary Intervention; HORIZONS-AMI,Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction; ISAR–REACT, Intraconary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment; MATRIX, Minimizing Adverse Hemorrhagic Events by Transradial Access Site and Systemic Implementation of Angioplasty; NAPLES, Novel Approaches for Preventing or Limiting Events; new P2Y12, prasugrel or ticagrelor administered at the time of coronary intervention; PROTECT TIMI, The Randomized Trial to Evaluate the Relative Protection Against Post-PCI Microvascular Dysfunction and Post-PCI Ischemia Among Anti-Platelet and Anti-Thrombotic Agents—Thrombolysis In Myocardial Infarction; REPLACE, Randomized Evaluation in PCI Linking Angioplasty to Reduced Clinical Events; and TENACITY, Tirofiban Evaluation of Novel Dosing Versus Abciximab With Clopidogrel and Inhibition of Thrombin.
Effect of New Platelet P2Y12 Receptor Inhibitors on Bleeding

In the 3 trials that used prasugrel or ticagrelor in place of clopidogrel in the majority of subjects, the bleeding advantage of bivalirudin was diminished (OR, 0.80; 95% CI, 0.63–1.03; Figure 2C). When the European Ambulance Acute Coronary Syndrome Angiography (EUROMAX) trial was added to the model to reflect use of the new agents in 47% to 62% of subjects, the bleeding advantage of bivalirudin diminished further (OR, 0.95; 95% CI, 0.72–1.25).

Effect of GPI Use and Heparin Dosing on Bleeding

In the 7 trials that compared bivalirudin with heparin and provisional GPIs, a significant bleeding advantage of bivalirudin over heparin monotherapy was seen in both the likelihood (OR, 0.70; 95% CI, 0.58–0.83) and the integrated analysis (OR, 0.66; 95% BCI, 0.59–0.73; Figure 2D). Similarly, in the 7 trials that used low-bolus heparin (≤65 U/kg), a significant bleeding advantage for bivalirudin was seen both in the likelihood (OR, 0.67; 95% CI, 0.59–0.77) and in the integrated analysis (OR, 0.66; 95% BCI, 0.59–0.73).

Effect of Adjunctive Therapies on ST

Because bivalirudin was associated with a significant risk of ST, we sought to identify the adjunctive therapies that might reduce this complication. In the 3 trials that used newer P2Y12 inhibitors in the majority of subjects, we found a persistent increase in the risk of ST with bivalirudin at 30 days (OR, 2.20; 95% BCI, 1.48–3.27). An increased risk of ST with bivalirudin was also seen in the 4 trials enrolling patients with ST-segment–elevation MI (Figure 3B). When we evaluated the role of low-bolus heparin (≤65 U/kg) used in 3 trials that presented results for definite ST, we observed a diminution in the relative risk of definite ST after use of bivalirudin in the likelihood (OR, 1.23; 95% CI, 0.90–1.70) but a persistent risk of ST with bivalirudin in the integrated analysis (OR, 1.50; 95% BCI, 1.19–1.90).
The present analysis suggested that using bivalirudin in place of heparin reduced the risk of bleeding, but increased the risk of ST in the RCTs.1–20 For every 1000 patients treated with bivalirudin in place of heparin, there were 19 (95% CI, 13–26) fewer major hemorrhages and a statistically nonsignificant 1 life saved (95% CI, −3 to +5). This was offset by a significant 5 more STs (95% CI, 2–9) within 30 days and borderline increase of 6 more MIs (95% CI, 0–12) per 1000 treated with bivalirudin in place of heparin.

**Discussion**

The Bayesian meta-analysis presented in this report produced several new findings. First, the use of bivalirudin in place of heparin during PCI entailed a tradeoff between reduced bleeding and increased ST in 18 RCTs and was associated with a borderline increase in MI but no difference in mortality at 30 days. Second, the analysis suggested that several new PCI advances seemed to reduce the bleeding differences between bivalirudin and heparin in the 18 RCTs. The use of transradial access, P2Y12 inhibitors prasugrel and ticagrelor, and adjunctive GPIs with bivalirudin infusion each seemed to mitigate the hemostatic advantage of bivalirudin over heparin. Third, the use of the P2Y13 inhibitors did not seem to mitigate the risk of ST after use of bivalirudin. Several lines of evidence support the findings in the current analysis.

**Transradial Access**

The main finding in our analysis of no bleeding advantage of bivalirudin over heparin during transradial PCI was supported by a subgroup analysis in the Minimizing Adverse Hemorrhagic Events by Transradial Access Site and Systemic Implementation of Angiox (MATRIX) supplement,20 which reported no difference in major bleeding after the use of bivalirudin or heparin in patients undergoing transradial PCI (21/1798 [1.2%] versus 33/1799 [1.8%]; P=0.10). Like a recent observational study,32 the present analysis could not identify the mechanisms responsible for the diminution in the bleeding advantage of bivalirudin over heparin during trans-radial access, but reduced access-site bleeding is a likely explanation. The MATRIX investigators observed that the transradial approach caused less access-site bleeding than did the transfemoral approach (1.6% versus 2.3%; P=0.01).33

**Bleeding and Mortality Rates**

The present analysis failed to show that the use of bivalirudin conferred a mortality advantage over heparin, despite the observation made in Randomized Evaluation of PCI Linking Angiomax to Reduced Clinical Events (REPLACE) 2 and Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) that bleeding more strongly correlated with late mortality than did early ischemic events.3,34 It is possible that survival differences would have emerged with follow-up >30 days or that survival and bleeding events are disconnected35 or connected only in a subset of high-risk cases.

A recent pooled analysis of patients with ST-segment–elevation MI enrolled in HORIZONS-AMI and EUROMAX36 found that bivalirudin compared with heparin with or without GPIs reduced 30-day rates of major bleeding (4.2% versus 7.8%; P<0.0001) and cardiac mortality (2.0% versus 2.9%; P=0.03). Because the 2013 EUROMAX study35 had a higher proportion than the 2008 HORIZONS-AMI study9 of patients undergoing transradial approach (47% versus 6%) or receiving new P2Y13 inhibitors (47% received a loading dose and 62% received maintenance dosing in EUROMAX versus 0% in HORIZONS-AMI), the authors concluded that the bleeding advantage of bivalirudin over heparin was maintained despite improvements in access and pharmacology.36 The present analysis took the comparison of bivalirudin with heparin further by specifically modeling the risk of major hemorrhage and ST after PCI according to treatment assignment and trial-specific therapies across 18 RCTs.

**Newer Antithrombotic Strategies**

The current analysis suggested that the more potent and rapidly acting P2Y13 inhibitors prasugrel and ticagrelor reduced the bleeding advantage of bivalirudin over heparin. The present study also suggested that the use of GPIs with bivalirudin...
reduced its bleeding advantage, consistent with the findings of a large stratified meta-analysis.\textsuperscript{37}

Although the present analysis could not demonstrate that newer P2Y$\textsubscript{12}$ agents reduced the risk of ST in patients randomized to bivalirudin, there is emerging evidence to suggest that the activity of oral antiplatelet agents is affected by several pharmacological and technical factors. Because most cases of ST recorded during the first 30 days occurred during first 48 hours after PCI for ST-segment-elevation MI,\textsuperscript{9,15,16} initial pharmacological decisions become particularly relevant. Before PCI, the use of morphine, either because of its effect on gastric absorption or through a direct pharmacological action, may impair the antiplatelet activity of oral agents.\textsuperscript{38} Continuing an infusion of bivalirudin after PCI has been proposed as a strategy to reduce early ischemic complications, but such an approach did not seem to reduce ST or net adverse clinical events in the MATRIX trial (11.0% and 11.9%; $P=0.34$).\textsuperscript{20}

Stent type may influence the absolute and relative risk of ST. Compared with first-generation drug-eluting stents, newer generation everolimus-eluting stents have been associated with a $\approx50$% reduction in ST.\textsuperscript{39} The present analysis was unable to determine whether the use of everolimus-eluting stents reduced the relative risk of acute or subacute ST with bivalirudin or heparin because newer generation drug-eluting stents were used in $<20$% of patients in the most recent RCTs comparing bivalirudin with heparin.\textsuperscript{17}

Limitations

The current meta-analysis used aggregate data. Individual-level data might have overcome certain limitations and permitted the use of common definitions (eg, bleeding), but heterogeneity among the 18 trials would have likely precluded proper pooling.\textsuperscript{40}

We used a Bayesian approach to tackle several potential sources of heterogeneity in a series of dedicated subanalyses. Although Bayesian approaches can add new insights and protect against the likelihood of a type 1 statistical error,\textsuperscript{40} the findings require confirmation in prospective clinical trials.

Clinical Perspective

Several pharmacological and technical advances have improved the safety and success of PCI. After reports linked post-PCI bleeding with an unfavorable prognosis and supported the hemostatic advantage of bivalirudin over heparin,\textsuperscript{3} interventional practice gradually substituted oral P2Y$\textsubscript{12}$ inhibitors for intravenous GPs, introduced transradial access, and developed biocompatible stent designs. The implementation of these advances has altered the bleeding-thrombosis calculus and should impact the selection of an antiplatelet during PCI. The current analysis has found that heparin did not cause more bleeding than bivalirudin in RCTs when transradial access, newer P2Y$\textsubscript{12}$ agents, or planned GPs were used with bivalirudin. When any of these 3 adjunctive therapies is selected during PCI, it seems reasonable in the absence of an increased bleeding risk in current practice to use heparin in place of bivalirudin to reduce the risk of ST. Additional studies are needed to determine whether alternative pharmacological approaches can reduce ischemic complications without conferring a bleeding penalty, and whether the risk of ST will continue to decline in contemporary practice as new stent designs and adjunctive therapies are introduced.

Disclosures

None.

References


Factors Affecting Bleeding and Stent Thrombosis in Clinical Trials Comparing Bivalirudin With Heparin During Percutaneous Coronary Intervention
John A. Bittl, Yulei He, Christopher D. Lang and George D. Dangas