Comparison of Bivalirudin and Radial Access Across a Spectrum of Preprocedural Risk of Bleeding in Percutaneous Coronary Intervention

Dmitri V. Baklanov, MD; Sunghee Kim, PhD; Steven P. Marso, MD; Sumeet Subherwal, MD; Sunil V. Rao, MD

Background—Bleeding is a common, noncardiac, preventable complication of percutaneous coronary intervention. We compared the relative safety of radial access and bivalirudin in percutaneous coronary intervention.

Methods and Results—From CathPCI Registry, we determined the association between the site of arterial access, bivalirudin, and periprocedural bleeding rates in 501,017 patients. Radial access patients receiving heparin (radial group) were compared with those receiving bivalirudin (radial combination group). Femoral access patients who had bivalirudin and a vascular closure device served as a reference group (femoral group). An inverse probability weighting analysis incorporating propensity scores was used to compare groups. The overall rate of bleeding was 2.59%. It was 2.71% in the femoral group, 2.5% in the radial group, and 1.82% in the radial combination groups (P<0.001). When compared with femoral group, the adjusted odds ratio for bleeding was significantly lower for patients with radial combination group (odds ratio, 0.79; 95% confidence interval, 0.72–0.86), but not for radial group (odds ratio, 0.96; 95% confidence interval, 0.88–1.05), unless patients treated with IIb/IIIa were excluded (radial group-IIb/IIIa odds ratio, 0.84; 95% confidence interval, 0.75–0.94). The number needed to treat to prevent 1 bleeding event with radial combination group was 138, whereas the number needed to treat to prevent 1 bleeding event in high-bleeding risk patients was 68.

Conclusions—in this observational analysis, the combination of bivalirudin and radial access was associated with reduced bleeding event rate. This benefit was present across the entire spectrum of preprocedural risk of bleeding, with or without exposure to IIb/IIIa inhibitors. These data support an adequately powered randomized trial comparing bleeding avoidance strategies. (Circ Cardiovasc Interv. 2013;6:347-353.)

Key Words: bivalirudin ■ hemorrhage ■ percutaneous coronary intervention ■ radial access
WHAT IS KNOWN

- Bleeding is a relatively common, morbid complication of percutaneous coronary intervention.
- Use of bivalirudin and femoral closure devices has been associated with reduced bleeding.
- Radial access lowers the rate of vascular and bleeding complications in percutaneous coronary intervention.
- Radial access is used infrequently in the United States (16.1% of all percutaneous coronary intervention).

WHAT THE STUDY ADDS

- Observational analysis of bleeding avoidance strategies from a broadly representative contemporary CathPCI Registry.
- The combination of radial access and bivalirudin was associated with a significant reduction in postpercutaneous coronary intervention bleeding, as compared with the best practice of femoral access including use of bivalirudin and closure devices.
- In patients with radial access not exposed to IIb/IIIa inhibitors, the benefit of bivalirudin over heparin was still present, but very small.
- Patients at highest bleeding risk were least likely to receive radial access and bivalirudin.

Endpoints and Definitions

The primary end point for this analysis was periprocedural bleeding, defined using the CathPCI Registry definition because the presence of ≥1 of the following within 72 hours of PCI: external bleeding at the access site, hematoma, retroperitoneal hemorrhage, gastrointestinal or genitourinary bleeding, cardiac tamponade (to qualify all of the above bleeding events had to be associated with ≥3 g/dL hemoglobin drop or blood transfusion or intervention/surgery to stop the bleeding); intracranial hemorrhage, nonbypass surgery related blood transfusion among patients with a preprocedure hemoglobin ≥8 g/dL, or an absolute decrease in hemoglobin ≥3 g/dL. From pre-PCI to post-PCI in patients with a preprocedure hemoglobin value ≤16 g/dL. Access site bleeding event was counted if at least 1 of the following was present: external bleeding at the access site, hematoma, or retroperitoneal hemorrhage. All other periprocedural bleeding events were considered nonaccess site bleeds.

Ethical Considerations

This study was approved by the Duke University Medical Center institutional review board and was determined to meet the definition of research not requiring informed consent.

Statistical Analysis

Patients were grouped according to access site used for PCI (radial or femoral) and procedural anticoagulation (bivalirudin or other). Three BAS were considered: radial access (RA), radial access (RAB), and femoral access (FA). The femoral group (FA) was compared to a radial group (RA), radial access (RA), radial access (RAB), radial combination group (RAB), and femoral access (FA)(vascular closure device: femoral group (FA). The femoral group (FA) served as a reference group. Demographic data by group are expressed as median (interquartile range), and compared using Kruskal–Wallis tests for categorical variables and, as a number (%) compared using Pearson χ² tests for categorical variables. Given our large sample size, some P values comparing demographic data between groups were highly significant despite a small magnitude of absolute differences. Therefore, we have discussed only differences that are both clinically and statistically significant. On the basis of individual bleeding risk calculated using the National Cardiovascular Data Registry bleeding risk model, patients were categorized into 3 groups on the basis of their risk for periprocedural bleeding events occurring during hospitalization: low (<1.78%), intermediate (1.78% to 5.08%), and high (>5.08%).

To minimize confounding, an inverse probability weighting analysis incorporating propensity scores was implemented. Propensity scores for each study group representing a distinct BAS were derived using a multinomial regression model. Variables used in the propensity model included demographics (age, sex, women, white race); clinical characteristics (imputed body mass index, heart failure New York Hospital Association class IV); coronary artery disease risk factors (diabetes mellitus, imputed hypertension, imputed dyslipidemia, current/recent smoker, family history of coronary artery disease); coronary artery disease history (prior PCI, prior coronary artery bypass graft surgery, prior MI); other cardiovascular disease history (prior CHF, prior cerebrovascular disease, prior peripheral vascular disease, prior valve surgery, cardiac transplantation); other disease history (prior chronic obstructive pulmonary disease, renal failure); and presenting syndrome (no symptoms, atypical chest pain, stable angina, unstable angina, ST-segment–elevation MI, and non-ST-segment–elevation MI).
Results

Study Sample and Efficacy of BAS

From July 1, 2009, to March 31, 2012, PCI procedures in 1,707,052 patients were reported to CathPCI Registry. After applying the exclusions, 501,017 patients were available for this analysis (Figure 1). Baseline patient characteristics for the entire study sample and by BAS group are shown in the Table. During the study period, FA (with bivalirudin and VCD) was 4x more common in the United States than radial access with or without bivalirudin.

The overall rate of bleeding was 2.59%. Bleeding was reported in 2.71% of patients in the FA group, compared with 2.5% in RA group, and 1.82% in RAB group (P<0.0001). Bleeding rates by BAS and proportions of patients with access (versus nonaccess) site bleeding are presented in Figure 2. Among patients without IIb/IIIa inhibitors, when compared with FA, the adjusted odds ratio (OR) for bleeding was significantly lower for patients with RAB (OR, 0.79; 95% CI, 0.72–0.86) but not for patients with RA alone (OR, 0.96; 95% CI, 0.88–1.05). The association between RAB and reduced risk for bleeding was present across the spectrum of bleeding risk, with the number needed to treat 561 in low-risk patients, 253 in medium risk, and 68 in high-risk patients. The overall number of patients needed to treat to prevent 1 bleeding event with RAB was 138.

Use of BAS by Strata of Bleeding Risk

Among patients with FA, 25.74% were at high risk for bleeding, whereas among patients with RA the proportion of high-risk patients was lower: 24.07%; among patients with RAB it was the lowest: 20.69%, P<0.0001. The proportion of low risk of bleeding patients was 24.56% among patients with FA, 28.06% among patients with RA, and 24.96% in patients with RAB, P<0.0001.

Inverse Probability Weighting and Center-Adjusted Analysis

The effectiveness of inverse probability weighting was assessed in the propensity model. Figure 3 displays the results of inverse probability weighting adjustment for categorical variables (Cramer’s ϕ V plot) and continuous variables (R² plot) for the total cohort and for the low-, intermediate, and high-bleeding risk subsets. After adjustment, each measure was <0.01 for Cramer’s ϕ and was <0.001 for R².

The adjusted odds ratio and corresponding 95% CI for periprocedural bleeding across the spectrum of bleeding risk, as well as number of patients needed to treat to prevent 1 bleeding complication, are presented in Figure 4. Overall, compared with patients in the reference FA group, the adjusted odds ratio (OR) for bleeding was significantly lower for patients with RAB (OR, 0.79; 95% CI, 0.72–0.86) but not for patients with RA alone (OR, 0.96; 95% CI, 0.88–1.05). The association between RAB and reduced risk for bleeding was present across the spectrum of bleeding risk, with the number needed to treat 561 in low-risk patients, 253 in medium risk, and 68 in high-risk patients. The overall number of patients needed to treat to prevent 1 bleeding event with RAB was 138.

Discussion

Using data from a broadly representative contemporary CathPCI Registry, we found that the combination of radial access and bivalirudin anticoagulation is associated with a significant reduction in post-PCI bleeding compared with either radial access alone or the combination of femoral access, bivalirudin, and vascular closure devices. This was true across the entire spectrum of procedural bleeding risk, and our finding that patients at highest bleeding risk were least likely to undergo the radial combination strategy suggests that wider adoption of this approach, particularly in high-risk patients, may significantly improve the safety of PCI.

The findings of this study add considerably to the previously published data on the use of radial access alone and bivalirudin alone for reducing PCI-related bleeding.
Radial access has been associated with reduced rates of bleeding during PCI for acute coronary syndromes, but this is primarily at the access site.7,15,16 A significant proportion of bleeding events in acute coronary syndrome patients also occur remote from the access site, and the radial approach would not be expected to have a significant effect on this type of systemic bleeding. For example, in the largest randomized clinical trial of radial versus femoral approach in patients with both non–ST-segment– and ST-segment–elevation acute coronary syndrome, nonaccess site bleeding accounted for two thirds of the bleeding events.17 Accordingly, there was no difference in the rate

### Table. Baseline Characteristics of the Study Sample

<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall Cohort (n=501,017)</th>
<th>Femoral Access,* Bivalirudin (n=382,792) 76%</th>
<th>Radial Access, Bivalirudin (n=55,188) 11%</th>
<th>Radial Access, Heparin (n=63,037) 13%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age [years]</td>
<td>65 (56, 73)</td>
<td>65 (56, 74)</td>
<td>64 (55, 72)</td>
<td>63 (55, 72)</td>
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<tr>
<td>Men</td>
<td>68.87</td>
<td>68.44</td>
<td>69.81</td>
<td>70.70</td>
</tr>
<tr>
<td>Race: white</td>
<td>88.86</td>
<td>88.83</td>
<td>88.92</td>
<td>89.01</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>29.3 (25.9, 33.6)</td>
<td>29.2 (25.8, 33.4)</td>
<td>29.9 (26.4, 34.8)</td>
<td>29.7 (26.2, 34.4)</td>
</tr>
<tr>
<td>Previous MI</td>
<td>29.15</td>
<td>29.68</td>
<td>28.37</td>
<td>26.62</td>
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<tr>
<td>Previous CHF</td>
<td>10.65</td>
<td>10.85</td>
<td>10.36</td>
<td>9.70</td>
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<td>Previous valve surgery</td>
<td>1.35</td>
<td>1.42</td>
<td>1.12</td>
<td>1.12</td>
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<tr>
<td>Diabetes mellitus</td>
<td>35.89</td>
<td>33.93</td>
<td>36.81</td>
<td>34.82</td>
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<tr>
<td>Cerebrovascular disease</td>
<td>11.18</td>
<td>11.34</td>
<td>10.92</td>
<td>10.44</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>10.62</td>
<td>10.29</td>
<td>12.15</td>
<td>11.13</td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td>13.98</td>
<td>13.89</td>
<td>14.92</td>
<td>13.72</td>
</tr>
<tr>
<td>Hypertension</td>
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<td>82.54</td>
<td>82.85</td>
<td>80.87</td>
</tr>
<tr>
<td>Current/recent smoker</td>
<td>25.36</td>
<td>24.59</td>
<td>27.52</td>
<td>28.18</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>81.34</td>
<td>81.59</td>
<td>81.54</td>
<td>79.66</td>
</tr>
<tr>
<td>Family history of CAD</td>
<td>25.85</td>
<td>25.55</td>
<td>26.91</td>
<td>26.70</td>
</tr>
<tr>
<td>Previous PCI</td>
<td>40.64</td>
<td>41.56</td>
<td>39.28</td>
<td>36.25</td>
</tr>
<tr>
<td>Previous CABG</td>
<td>16.31</td>
<td>18.66</td>
<td>8.93</td>
<td>8.45</td>
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<tr>
<td>Renal dialysis</td>
<td>1.75</td>
<td>1.98</td>
<td>1.00</td>
<td>1.02</td>
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<tr>
<td>Presentation non-STEMI</td>
<td>17.08</td>
<td>16.04</td>
<td>18.77</td>
<td>21.90</td>
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<tr>
<td>Presentation STEMI</td>
<td>9.11</td>
<td>9.41</td>
<td>6.10</td>
<td>9.96</td>
</tr>
<tr>
<td>NYHA class 4</td>
<td>18.88</td>
<td>18.65</td>
<td>19.14</td>
<td>20.07</td>
</tr>
<tr>
<td>EF [%]</td>
<td>55 (50, 60)</td>
<td>55 (50, 60)</td>
<td>57 (50, 60)</td>
<td>55 (50, 60)</td>
</tr>
<tr>
<td>GP IIb/IIIa</td>
<td>12.31</td>
<td>8.53</td>
<td>7.39</td>
<td>39.57</td>
</tr>
<tr>
<td>Low-bleeding risk</td>
<td>25.00</td>
<td>24.56</td>
<td>28.06</td>
<td>24.96</td>
</tr>
<tr>
<td>Medium bleeding risk</td>
<td>50.00</td>
<td>49.69</td>
<td>51.26</td>
<td>50.98</td>
</tr>
<tr>
<td>High-bleeding risk</td>
<td>25.00</td>
<td>25.74</td>
<td>20.69</td>
<td>24.07</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; CABG, coronary artery bypass graft surgery; CAD, coronary artery disease; CHF, congestive heart failure; EF, ejection fraction; GP IIb/IIIa, glycoprotein IIb/IIIa; MI, myocardial infarction; NYHA, New York Hospital Association; PCI, percutaneous coronary intervention; and STEMI, ST-segment–elevation myocardial infarction.

*All femoral access patients had a vascular closure device.

Figure 2. This figure demonstrates the rate of percutaneous coronary intervention–associated bleeding in 501,017 patients grouped by vascular access and anticoagulation. The numbers in columns are numbers of patients with bleeding and % (in parenthesis). VCD indicates vascular closure device.
of noncoronary artery bypass surgery related major bleeding between patients assigned to radial or femoral access. Interestingly, we observed that the use of glycoprotein IIb/IIIa inhibitors and unfractionated heparin was much more common among patients undergoing transradial PCI, which may reflect a sense of false security that the radial approach affords a reduction in total bleeding. Our study showed that when IIb/IIIa inhibitors are used, the risk of bleeding is increased, which is consistent with the prior studies. Radial access has not been shown to reduce nonaccess site bleeding. However, when a subgroup of patients without IIb/IIIa inhibitors was analyzed, radial access alone, and more so in combination with bivalirudin, was associated with reduced bleeding event rate.

The impact of bivalirudin on the incidence of peri-procedural bleeding has been also evaluated in clinical trials and registries, consistently demonstrating lower bleeding risk in all studied clinical scenarios. Adding vascular closure devices to bivalirudin in the femoral access setting is associated with even better safety. For this reason, we elected to exclude patients with femoral access without closure device and nonbivalirudin anticoagulation, compare radial access with the default US State of the Art bleeding avoidance strategy.

Figure 3. This figure demonstrates the effectiveness of inverse probability weighting adjustment. Bleeding risks cohorts: total (A), low (B), intermediate (C), and high (D). The effectiveness of the IPW was evaluated using Cramer’s $\phi$ (V) and $R^2$ and displayed graphically; values closer to zero demonstrate a more balanced cohort. CABG indicates coronary artery bypass graft surgery; CAD, coronary artery disease; CHF, congestive heart failure; IPW, inverse probability weighting; MI, myocardial infarction; NYHA, New York Hospital Association; and PCI, percutaneous coronary intervention.
Consortium Type 2 and 3 bleeding. Fourth, patients without VCDs were excluded from this analysis, but such patients could not examine bleeding by other definitions, including reporting or misclassification of complications. Third, we could not examine bleeding by other definitions, including the Bleeding Academic Research Consortium definition, and bivalirudin and the lowest rate of bleeding, which is particularly pronounced in high-risk patients.

There are some potential limitations to this study. First, as with any other observational study, associations between treatments and outcomes cannot prove causality. A limitation of the adjustment methodology is that there is always a chance of unmeasured confounding. There might be residual factors that are not known or captured by the registry that may bias the results in favor of the femoral or radial access. However, operators and hospital systems in the United States may bias the results in favor of the femoral or radial access. Factors that are not known or captured by the registry that could not examine bleeding by other definitions, including reporting or misclassification of complications. Third, we could not examine bleeding by other definitions, including the Bleeding Academic Research Consortium definition, because particular data elements necessary are not present in the CathPCI Registry. The definition of bleeding used in version 4 of the CathPCI data collection form (used for the present analysis) approximates Bleeding Academic Research Consortium Type 2 and 3 bleeding. Fourth, patients without VCDs were excluded from this analysis, but such patients have been shown to have higher rates of bleeding in the CathPCI Registry, and the association of the radial access with reduced bleeding would likely have been even higher, if compared against those who did not have VCDs.

## Conclusions

In this observational analysis, the combination of bivalirudin and radial access was associated with reduced bleeding, when compared with either radial access alone or the combination of femoral access, vascular closure devices, and bivalirudin. Radial access–bivalirudin combination was used less frequently among patients at highest risk for bleeding. Given the limitations of these observational data, randomized clinical trials are needed to confirm the benefit of radial access combined with bivalirudin. Until these data are available, the wider application of a radial combination strategy, particularly among high-risk patients, may further improve the safety of PCI.

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## Disclosures

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## References


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