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

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.

Key Words: bivalirudin ■ hemorrhage ■ percutaneous coronary intervention ■ radial access

Periprocedural bleeding is a common, yet largely preventable noncardiac complication of percutaneous coronary intervention (PCI) that is associated with early mortality1 and higher costs of care.2 Use of bleeding avoidance strategies (BAS), such as bivalirudin and femoral vascular closure devices (VCDs), has been associated with lower bleeding rates.3 Radial access is another effective BAS that significantly reduces access site bleeding even in the most challenging clinical scenarios.4 Nevertheless, radial access is used infrequently during PCI in the United States.5 For the femoral operator, bivalirudin along with optimized femoral access represents an attractive BAS because it does not have a significant learning curve that is associated with the radial approach. Moreover, the use of bivalirudin reduces both access site and nonaccess site bleeding.6

Given the significant association between radial access and reduction in vascular complications, and the significant association between bivalirudin and reduction in overall major bleeding, combining radial access with bivalirudin may provide an opportunity to achieve the safest PCI outcomes. Prior trials of bivalirudin had limited radial access, and an analysis of the interaction between pharmacological strategies and radial access did not show an advantage of transradial PCI when bivalirudin was used as the procedural anticoagulant.7 The CathPCI Registry is a large, nationally representative contemporary database of PCI procedures that provides an ideal opportunity to explore the relationship among access site, anticoagulation, and patient outcomes. Accordingly, we examined the association between radial access and bivalirudin with periprocedural bleeding rates across a spectrum of patients with varied preprocedural bleeding risk estimates. We hypothesized that the combination of radial access and bivalirudin would be associated with significantly lower bleeding risk compared with the combination of femoral access with bivalirudin and VCD.

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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.

Methods

Data Source and Study Sample

CathPCI Registry is an initiative of the American College of Cardiology Foundation and the Society for Cardiovascular Angiography and Interventions.

Descriptions of the National Cardiovascular Data Registry have been published. Demographic, clinical, procedural, and institutional data elements from diagnostic catheterization and PCI procedures are collected at >1340 participating centers. Data are entered into a centralized database via either a secure Web-based platform or software provided by American College of Cardiology–certified vendors. Data quality assurance includes automatic system validation and reporting of data completeness, random on-site auditing of participating centers, and education and training for site data managers. All data elements and definitions were prospectively defined by a committee of the American College of Cardiology. A comprehensive description of National Cardiovascular Data Registry data elements and definitions is available at https://www.ncdr.com/webncdr/cathpci/home/datacollection.

To describe the BAS, the most contemporary data from CathPCI Registry version 4 (July 2009–March 2012) was analyzed. Only patients who underwent PCI via the radial and femoral artery approach were included in this analysis. For the purposes of this study, we included only patients who underwent transmural PCI with bivalirudin antiocoagulation and VCD, because a previously published study from the CathPCI Registry showed this strategy to be safer than other anticoagulants and manual compression. Exclusion criteria consisted of patients with >1 PCI procedure during a hospitalization (because bleeding events could not reliably be attributed to a specific procedure), incomplete data for calculation of expected bleeding rates, PCI through access of a nonfemoral and nonradial artery (ie, ulnar, brachial), missing VCD data, death in the catheterization laboratory, or unknown data on bleeding events.

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 (−) bivalirudin: radial group (RA), radial access (+) bivalirudin: radial combination group (RAB), and femoral access (+) bivalirudin (+) 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 continuous 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%–5.08%), and high (≥5.08%). Bleeding risk scores were generated for all patients in this study using the following baseline pre-PCI variables (c-index: 0.77): age, sex, body mass index, cerebrovascular disease, peripheral vascular disease, chronic lung disease, prior PCI, diabetes mellitus, renal function, presentation with ST-segment–elevation MI, ejection fraction, use of Iytics before PCI, cardiogenic shock, preprocedure cardiac arrest, PCI status (defined as elective, urgent, emergent, or salvage), subacute stent thrombosis, lesion as defined by the Society for Cardiovascular Angiography and Intervention, lesion location (proximal left anterior descending or left main versus other), preprocedure heart failure New York Hospital Association class IV, preprocedure thrombolysis in MI flow, number of diseased vessels, and preprocedure hemoglobin.

To minimize confounding, an inverse probability weighting analysis incorporating propensity scores was implemented. Propensity scores for 3 study groups 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).

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The effectiveness of the inverse probability weighting (ie, better balance among the patients that received different bleeding avoidance therapies) was evaluated using Cramer's $\phi$ (V) and $R^2$ and displayed graphically; values closer to zero demonstrate a more balanced cohort.\textsuperscript{12,13} The model for bleeding was weighted using the inverse propensity score for getting each BAS and also included insurance status (none, other, Medicaid, Medicare), PCI type (elective, urgent, emergency), hospital region (West, Northeast, Midwest, South), community type (rural, suburban, urban), profit type (government, private, university), and each site's average annual PCI volume. The model was fit using generalized estimating equations to account for the correlation between patients at the same center.

Odds ratios from the outcome model were obtained to estimate the number of patients needed to treat to prevent 1 bleeding event for RA and RAB compared with FA.\textsuperscript{14} Statistical significance was defined as $P<0.05$. All statistical analyses were performed by the Duke Clinical Research Institute using SAS version 9.2 (SAS Institute, Cary, NC).

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.

### 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. 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. Accordingly, there was no difference in 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 periprocedural 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 setting of femoral access 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.
VCDs were excluded from this analysis, but such patients could not examine bleeding by other definitions, including those that are not adjudicated, and thus, there may be underreporting or insufficiently developed clinical protocols. While the present study cannot address these issues directly, it does clearly show an association between the combination of radial access 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 could not 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.

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Nevertheless, the provision of radial access shown by providers early in the learning curve would likely become more evident with more experience in radial procedures. Second, although an auditing program is used to verify data accuracy in the registry, outcomes are not adjudicated, and thus, there may be underreporting 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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