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Comparison of Bivalirudin and Radial Access Across a Spectrum of Preprocedural Risk of Bleeding in PCI: Analysis from the NCDR®

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Abstract

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

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 (RA) were compared with those receiving bivalirudin (RAB). Femoral access patients who had bivalirudin and a vascular closure device (VCD) served as a reference group (FA). 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 FA group, 2.5 % in the RA and 1.82 % in the RAB groups ($P < 0.001$). 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 RA (OR = 0.96, 95% CI = 0.88–1.05), unless patients treated with IIb/IIIa were excluded (RA-IIb/IIIa OR=0.84, 95% CI=0.75–0.94). The number needed to treat (NNT) to prevent one bleeding event with RAB was 138, whereas NNT to prevent one 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.

Keywords

radial access; bivalirudin; bleeding; PCI

Periprocedural bleeding is a common, yet largely preventable noncardiac complication of PCI that is associated with early mortality (1) and higher costs of care (2). Use of bleeding avoidance strategies (BAS), such as bivalirudin and femoral vascular closure devices, has

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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 bleeding avoidance strategy, as 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 non-access 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 between 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.

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 NCDR have been published (8–9). Demographic, clinical, procedural, and institutional data elements from diagnostic catheterization and PCI procedures are collected at more than 1340 participating centers. Data are entered into a centralized database via either a secure Web-based platform or software provided by ACC-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 (10). All data elements and definitions were prospectively defined by a committee of the ACC. A comprehensive description of NCDR data elements and definitions is available at <https://www.ncdr.com/webncdr/cathpci/home/datacollection>.

In order to describe the bleeding avoidance strategies, 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 the present study, we included only patients who underwent transfemoral PCI with bivalirudin anticoagulation and VCD, since a previously published study from the CathPCI registry showed this strategy to be safer than other anticoagulants and manual compression (3). Exclusion criteria consisted of patients with more than 1 PCI procedure during a hospitalization (since 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 endpoint for this analysis was periprocedural bleeding, defined using the CathPCI registry definition as the presence of one or more 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, non-bypass surgery related blood transfusion among patients with a pre-procedure hemoglobin >8 g/dl, or an absolute decrease in hemoglobin ≥ 3 g/dl from pre-PCI to post-PCI in patients with a pre-procedure hemoglobin value ≥ 16 g/dl. Access site bleeding event was counted if at least one 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 bleeding avoidance strategies were considered: radial access(-)bivalirudin – “radial group” (RA), radial access(+) bivalirudin – “radial combination group” (RAB), 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 χ^2 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. Based on individual bleeding risk calculated using the NCDR bleeding risk model (11), patients were categorized into 3 groups based on 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 (BMI), cerebrovascular disease (CVD), peripheral vascular disease (PVD), chronic lung disease (CLD), prior PCI, diabetes mellitus, renal function, presentation with ST-segment elevation myocardial infarction (STEMI), ejection fraction (EF), use of lytics prior to PCI, cardiogenic shock, pre-procedure cardiac arrest, PCI status (defined as elective, urgent, emergent, or salvage), subacute stent thrombosis, lesion risk as defined by the Society for Cardiovascular Angiography and Intervention (SCAI), lesion location (proximal LAD or Left Main vs. other), pre-procedure Heart Failure NYHA Class IV, pre-procedure TIMI flow, number of diseased vessels, and preprocedure hemoglobin.

To minimize confounding, an inverse probability weighting (IPW) analysis incorporating propensity scores was implemented. Propensity scores for three study groups representing a distinct BAS were derived using a multinomial regression model. Variables used in the propensity model included demographics (age, female gender, white race); clinical characteristics (imputed body mass index, heart failure NYHA class IV); coronary artery disease risk factors (diabetes, 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 CVD, prior PVD, 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). The effectiveness of the IPW (i.e. better balance among the patients that received different bleeding avoidance therapies) was evaluated using Cramer's Phi (V) and R-squared and displayed graphically; values closer to zero demonstrate a more balanced cohort (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 (GEEs) 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 (NNT) to prevent 1 bleeding event for RA and RAB compared with FA (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, North Carolina).

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 Cath PCI 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 four times more common in the U.S. 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 ($P < .0001$). Bleeding rates by bleeding avoidance strategy and proportions of patients with access (vs. 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=0.78, 95% CI=0.71–0.86), and for patients with RA (OR=0.84, 95% CI=0.75–0.94). However, when compared with FA without IIb/IIIa inhibitor, the OR for bleeding was significantly higher for patients with RA and IIb/IIIa inhibitor (OR=1.41, 95% CI=1.26–1.58).

There was no difference in in-hospital death (FA 0.27%, RA 0.26%, RAB 0.22%), stroke (FA 0.14%, RA 0.17%, RAB 0.16%) or periprocedural infarction (FA 1.77%, RA 1.73%, RAB 1.66%), $P = \text{NS}$.

Use of Bleeding Avoidance Strategies 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 %, $P < .0001$. 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, $P < .0001$.

Inverse Probability Weighting and Center-Adjusted Analysis

The effectiveness of inverse probability weighting (IPW) was assessed in the propensity model. Figure 3 displays the results of IPW adjustment for categorical variables (Cramer's

Phi V plot) and continuous variables (R-squared plot) for the total cohort and for the low, intermediate and high bleeding risk subsets. After adjustment, each measure was less than 0.01 for Cramer's Phi, and was less than 0.001 for R-squared.

The adjusted odds ratio and corresponding 95% confidence intervals for periprocedural bleeding across the spectrum of bleeding risk, as well as NNT to prevent one 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 NNT of 561 in low risk patients, 253 in medium risk, and 68 in high risk patients. The overall NNT to prevent one 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 suggest 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 (ACS), but this is primarily at the access site (7, 15–16). A significant proportion of bleeding events in ACS 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 vs. femoral approach in patients with both non-ST-segment and ST-segment elevation ACS, non-access site bleeding accounted for two-thirds of the bleeding events (17). Accordingly, there was no difference in the rate of non-CABG 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 non-access 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 (6, 18–23) and registries (3, 24–25), consistently demonstrating lower bleeding risk in all studied clinical scenarios. Adding vascular closure devices to bivalirudin in the setting femoral access is associated with even better safety. For this reason we elected to exclude patients with femoral access without closure device and non-bivalirudin anticoagulation, in order to compare radial access with the default U.S. “state of the art” bleeding avoidance strategy.

A risk-treatment paradox in the use of the vascular closure device – bivarirudin combination has been previously reported (3), and we have found that a similar paradox exists with the

radial-bivalirudin combination strategy. Potential reasons why this paradox exists for radial-bivalirudin combination in clinical practice are multiple. There is a significant learning curve for the radial approach and most diagnostic procedures require use of unfractionated heparin to reduce the risk of radial artery occlusion. Therefore, there may be reluctance to switch from heparin to bivalirudin for ad hoc PCI due to concerns over increasing bleeding risk, incurring higher costs, or insufficiently developed clinical protocols. While the present study cannot address these issues directly, it does clearly show an association between 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 may bias the results in favor of the femoral or radial access. However, operators and hospital systems in the United States are much more familiar with femoral access, and any advantage of the radial access shown by providers early in the learning curve would likely become more evident with more experience in radial procedures. Second, while 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 (26). Third, we could not examine bleeding by other definitions, including the Bleeding Academic Research Consortium (BARC) definition (27), since 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 BARC 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.

Conclusion

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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS LIST

NCDR[®]	National Cardiovascular Data Registry [®]
PCI	Percutaneous Coronary Intervention
BAS	Bleeding Avoidance Strategy
NNT	Number Needed to Treat
BMI	Body Mass Index
CVD	Cerebrovascular Disease
PVD	Peripheral Vascular Disease
STEMI	ST segment Elevation Myocardial Infarction
SCAI	Society for Cardiovascular Angiography or Intervention
NYHA	New York Heart Association
BARC	Bleeding Academic Research Consortium
TIMI	Thrombolysis in Acute Myocardial Infarction
MI	Myocardial Infarction
OR	Odds Ratio
CABG	Coronary Artery Bypass Surgery
ACS	Acute Coronary Syndrome

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What is Known

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

What this Article 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 post-PCI 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

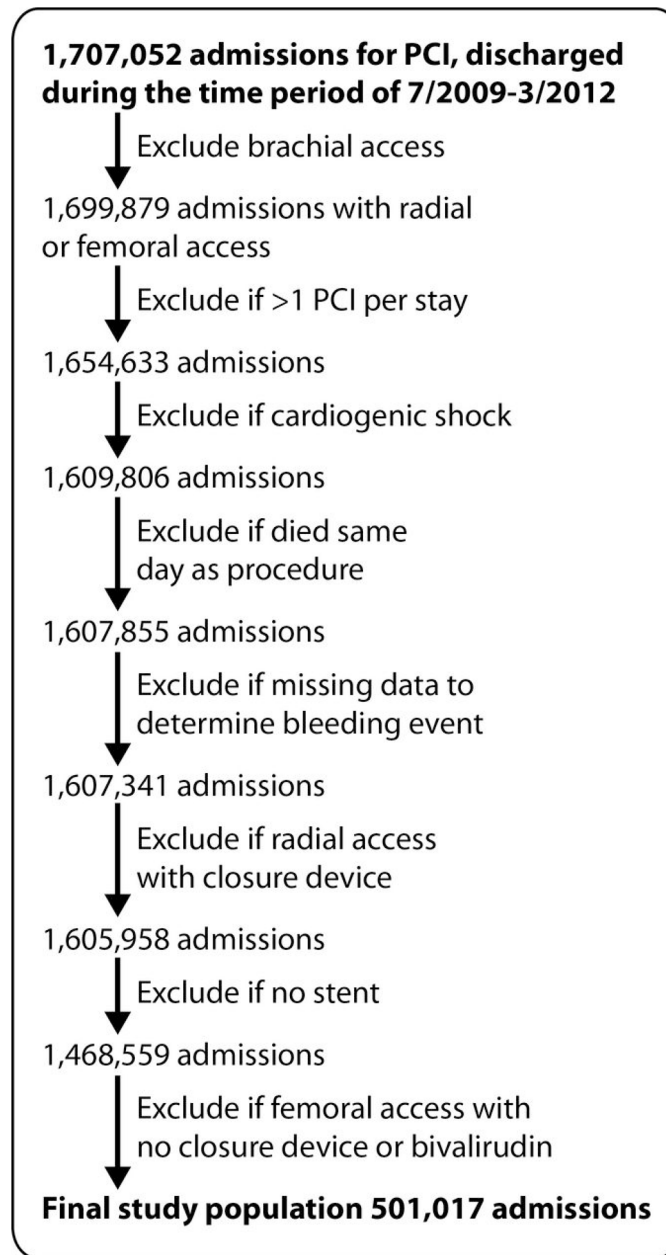


Figure 1. This figure shows the Consort diagram with patient population selection for the study. Abbreviation: PCI – percutaneous coronary intervention.

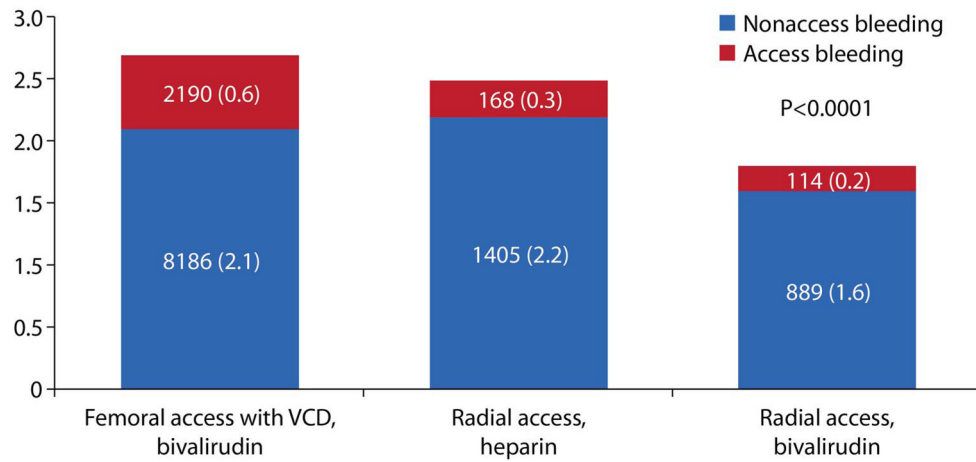
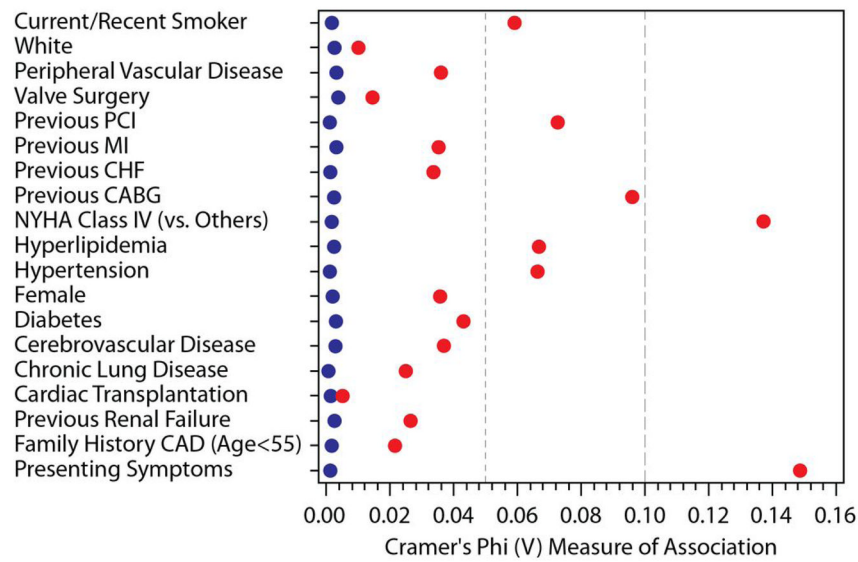


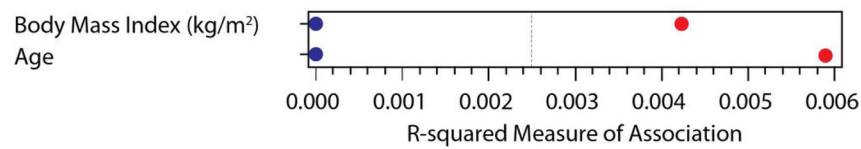
Figure 2.

This figure demonstrates the rate of PCI – 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). Abbreviation: VCD – vascular closure device.

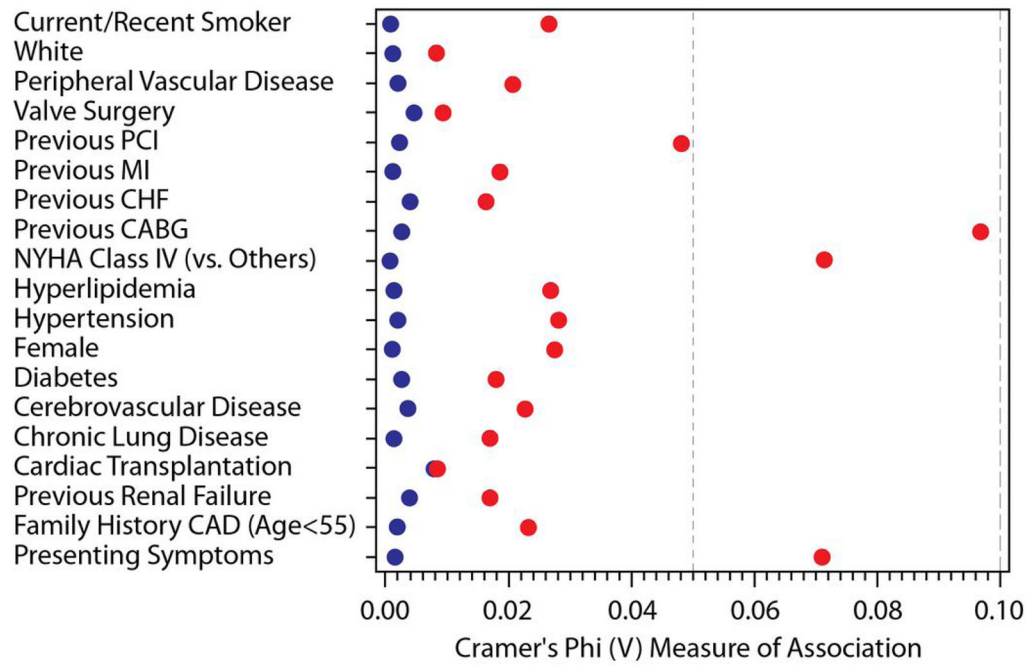
Balance of Categorical Variables Before (●) and After (●) IPW Adjustment



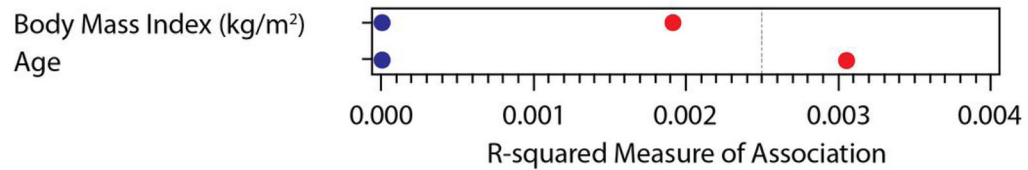
Balance of Continuous Variables Before (●) and After (●) IPW Adjustment



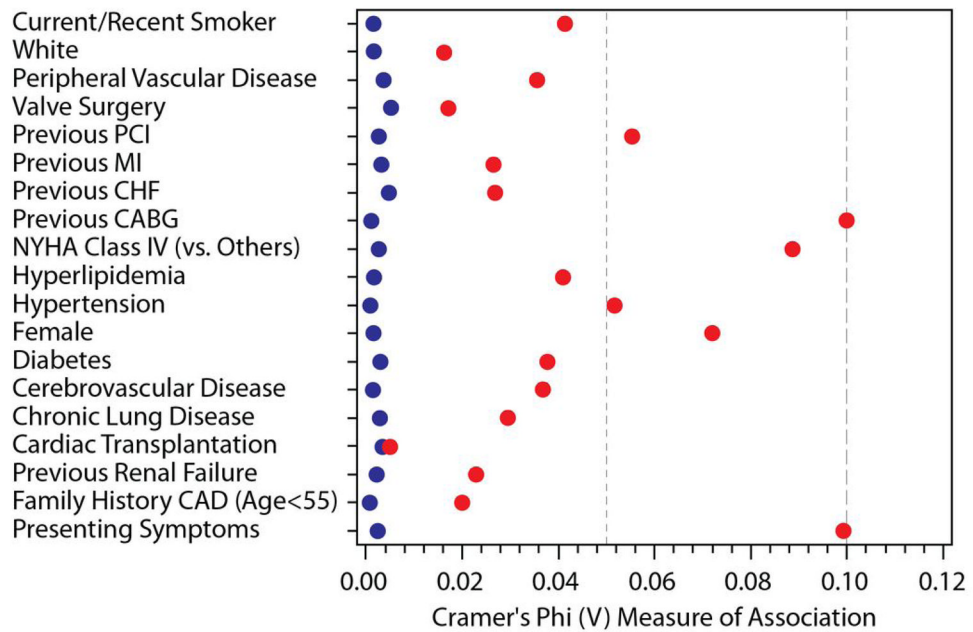
Balance of Categorical Variables Before (●) and After (●) IPW Adjustment



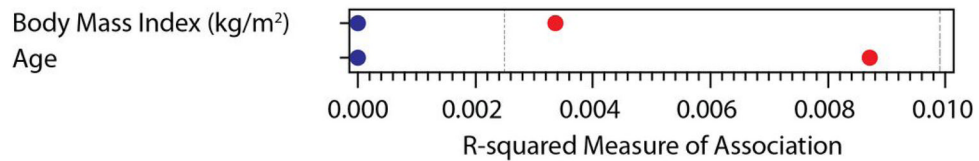
Balance of Continuous Variables Before (●) and After (●) IPW Adjustment



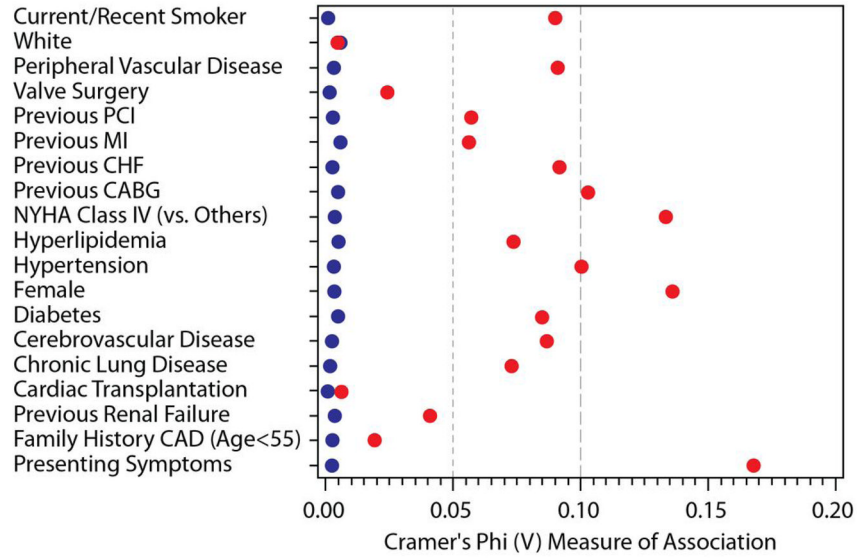
Balance of Categorical Variables Before (●) and After (●) IPW Adjustment



Balance of Continuous Variables Before (●) and After (●) IPW Adjustment



Balance of Categorical Variables Before (●) and After (●) IPW Adjustment



Balance of Continuous Variables Before (●) and After (●) IPW Adjustment

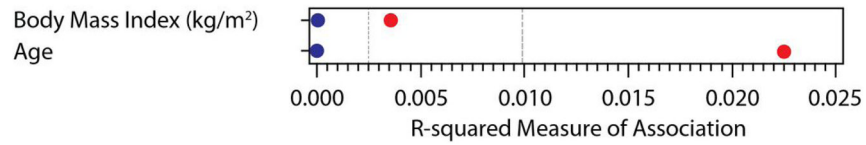


Figure 3. This figure demonstrates the effectiveness of Inverse Probability Weighting adjustment. Bleeding risks cohorts: total – Figure 3A, low – Figure 3B, intermediate – Figure 3C, high – Figure 3D. The effectiveness of the IPW was evaluated using Cramer’s Phi (V) and R-squared and displayed graphically; values closer to zero demonstrate a more balanced cohort. Abbreviations: IPW – inverse probability weighting. PCI – percutaneous coronary intervention. MI – myocardial infarction. CHF – congestive heart failure. NYHA – New York Hospital Association. CAD – coronary artery disease.

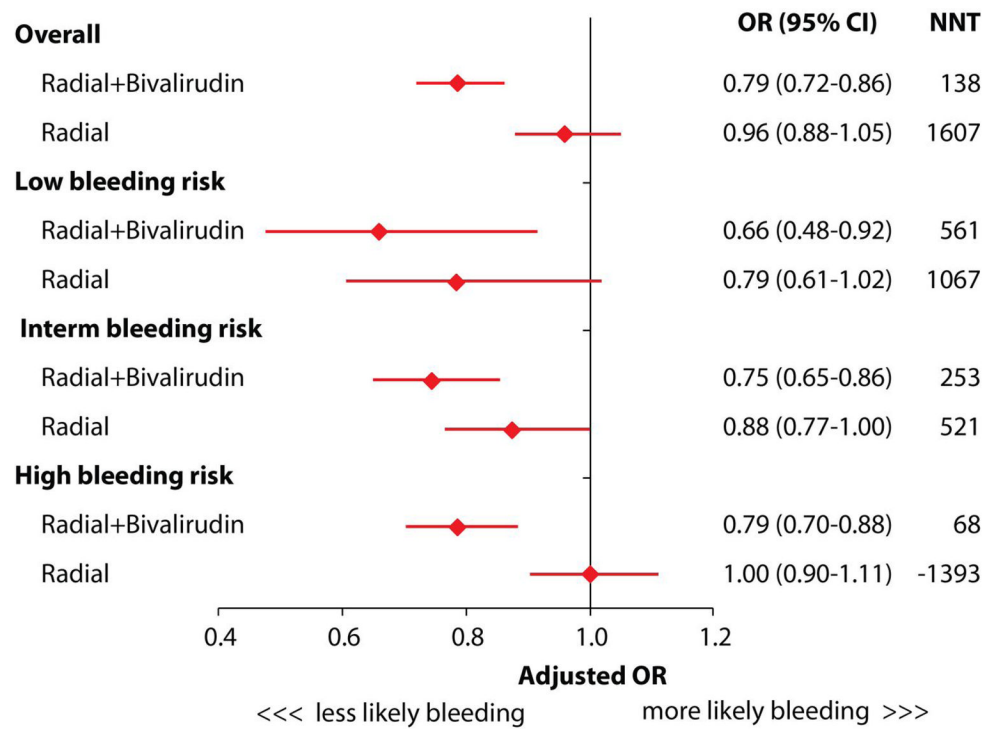


Figure 4. This figure demonstrates the adjusted odds ratios (OR) of bleeding events and Number Needed to Treat (NNT) to prevent one bleeding in PCI. The interaction p-value between BAS and pre-PCI bleeding risk was less than 0.0001.

Table

Baseline characteristics of the study sample

Variable	Overall Cohort (N=501,017) 100%	Femoral access *, bivalirudin (N=382,792) 76%	Radial access, bivalirudin (N=55,188) 11%	Radial access, heparin (N=63,037) 13%
Age	65 (56,73)	65 (56,74)	64 (55,72)	63 (55,72)
Male gender	68.87	68.44	69.81	70.70
Race - white	88.86	88.83	88.92	89.01
BMI (kg/m ²)	29.3 (25.9,33.6)	29.2 (25.8,33.4)	29.9 (26.4,34.8)	29.7 (26.2,34.4)
Previous MI	29.15	29.68	28.37	26.62
Previous CHF	10.65	10.85	10.36	9.70
Previous Valve Surgery	1.35	1.42	1.12	1.12
Diabetes	35.89	33.93	36.81	34.82
Cerebrovascular Disease	11.18	11.34	10.92	10.44
Peripheral Vascular Disease	10.62	10.29	12.15	11.13
Chronic Lung Disease	13.98	13.89	14.92	13.72
Hypertension	82.36	82.54	82.85	80.87
Current/Recent Smoker	25.36	24.59	27.52	28.18
Dyslipidemia	81.34	81.59	81.54	79.66
Family History of CAD	25.85	25.55	26.91	26.70
Previous PCI	40.64	41.56	39.28	36.25
Previous CABG	16.31	18.66	8.93	8.45
Renal Dialysis	1.75	1.98	1.00	1.02
Presentation Non-STEMI	17.08	16.04	18.77	21.90
Presentation STEMI	9.11	9.41	6.10	9.96
NYHA Class 4	18.88	18.65	19.14	20.07
EF	55 (50,60)	55 (50,60)	57 (50,60)	55 (50,60)
GP IIb/IIIa	12.31	8.53	7.39	39.57
Low bleeding risk	25.00	24.56	28.06	24.96
Med bleeding risk	50.00	49.69	51.26	50.98
High bleeding risk	25.00	25.74	20.69	24.07

* All femoral access patients had a vascular closure device. Abbreviations: BMI – body mass index. MI – myocardial infarction. CHF – congestive heart failure. CAD – coronary artery disease. PCI – percutaneous coronary intervention. CABG – coronary artery bypass graft surgery. STEMI – ST segment elevation myocardial infarction. EF – ejection fraction. GP IIb/IIIa – glycoprotein IIb/IIIa.