

CLINICAL RESEARCH

Interventional Cardiology

Pre-Procedural Estimate of Individualized Bleeding Risk Impacts Physicians' Utilization of Bivalirudin During Percutaneous Coronary Intervention

Seshu C. Rao, MD,*† Adnan K. Chhatriwalla, MD,*† Kevin F. Kennedy, MS,‡
Carole J. Decker, RN, PhD,§ Elizabeth Gialde, RN, MSN,* John A. Spertus, MD, MPH,*†
Steven P. Marso, MD*†
Kansas City, Missouri

- Objectives** This study sought to assess whether incorporation of routine bleeding risk estimates affected the utilization of bivalirudin during percutaneous coronary intervention (PCI).
- Background** Bivalirudin use during PCI has been shown to reduce bleeding complications. However, a risk-treatment paradox exists, in which patients at highest risk for bleeding are least likely to receive bivalirudin. Whether routine estimation of individualized bleeding risk can affect physicians' use of bivalirudin is unknown.
- Methods** PCI data from a single health system between 2007 and 2011 were analyzed. Beginning in July 2009, individualized bleeding risk estimates were provided immediately preceding PCI. Using a pre-post design, we compared bivalirudin use before and after this implementation, for patients across 3 strata of bleeding risk (<1%, 1% to 3%, and >3%).
- Results** Data from 6,491 PCI procedures were analyzed. Overall, bivalirudin use increased in the post-implementation period (26.9% vs. 34.2%, $p < 0.001$). Bivalirudin use increased in intermediate (27% to 35%, $p < 0.001$) and high bleeding risk patients (25% to 43%, $p < 0.001$), and decreased in low-risk patients (30% to 25%, $p = 0.014$). During the same period, bleeding complications decreased in intermediate-risk (3.4% to 1.8%, $p = 0.009$) and high-risk (6.9% to 3.7%, $p = 0.005$) patients and remained unchanged in low-risk patients (1.1% to 1.0%, $p = 0.976$).
- Conclusions** There was an increase in bivalirudin use and a lower incidence of bleeding after the incorporation of individualized bleeding risk estimates into clinical practice. This implementation led to a reversal of the risk-treatment paradox, through a rational increase in bivalirudin use in patients at intermediate and high bleeding risk and decreased use in lower-risk patients. (J Am Coll Cardiol 2013;61:1847-52) © 2013 by the American College of Cardiology Foundation

Percutaneous coronary intervention (PCI) is a well-established procedure for the treatment of stable and unstable coronary artery disease, with approximately 600,000 PCI procedures performed annually in the United States alone (1). Although the safety of PCI has improved substantially

over time, post-procedural bleeding remains common (0.2% to 9.1% in various studies) (2-6), with wide center-level variability (7). Furthermore, PCI-related bleeding is associated with increased short- and long-term mortality (2), increased risk of myocardial infarction (2) and stroke (8), prolonged hospital stay, and increased healthcare costs (9). However, patients' bleeding risk can be estimated using a number of available risk prediction models (10,11). For example, the National Cardiovascular Data Registry (NCDR) bleeding risk model (12) can be used to classify patients as having low (<1%), intermediate (1% to 3%), or high bleeding risk (>3%) based on 9 pre-procedural clinical variables.

Bivalirudin use is an established bleeding avoidance strategy and reduces the incidence of major bleeding across a broad spectrum of patients undergoing PCI for stable and

From the *Saint Luke's Mid America Heart Institute, Kansas City, Missouri; †Department of Medicine, University of Missouri-Kansas City, Kansas City, Missouri; ‡Division of Biostatistics, Saint Luke's Mid America Heart Institute, Kansas City, Missouri; and the §University of Missouri-Kansas City School of Nursing, Kansas City, Missouri. Ms. Gialde has received consulting honoraria from Health Outcomes Sciences, LLC. Dr. Spertus has an equity interest in Health Outcomes Sciences, LLC. Dr. Marso has received research grants and consulting fees from The Medicines Company, Novo Nordisk, Abbott Vascular, Amylin Pharmaceuticals, Boston Scientific, Volcano Corporation, and Terumo Medical, which are paid directly to the Saint Luke's Hospital Foundation of Kansas City. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received December 4, 2012; revised manuscript received January 30, 2013, accepted February 14, 2013.

**Abbreviations
and Acronyms****NCDR** = National
Cardiovascular Data
Registry**PCI** = percutaneous
coronary intervention**STEMI** = ST-segment
elevation myocardial
infarction**VCD** = vascular closure
device

unstable coronary artery disease (3,4,13-15). Importantly, the benefit of bivalirudin in terms of bleeding reduction is greatest in patients at highest risk for bleeding (16). However, there exists a "risk-treatment paradox" with respect to the use of bivalirudin, whereby patients who are most likely to benefit from its use (i.e., patients at increased risk for bleeding) are least likely to receive it (16).

In July 2009, our health system prospectively incorporated the NCDR bleeding risk model into the informed consent document for patients undergoing PCI, in an effort to support the more rational use of bivalirudin in patients with the greatest potential to benefit. In this implementation study, we retrospectively compared bivalirudin utilization at 4 centers before and after July 2009, and compared these data to national trends in bivalirudin use during PCI. Bivalirudin use was the primary outcome for this analysis for several reasons. First, bivalirudin is a proven bleeding avoidance strategy, and data supporting other strategies, such as radial PCI and vascular closure devices (VCDs), are less robust (17,18). Second, the benefit of bivalirudin is limited only to bleeding reduction, whereas the benefits of radial PCI and VCDs include early ambulation, improved patient comfort, and improved throughput (18,19). Therefore, the decision to utilize radial PCI and VCDs involves factors other than the bleeding risk alone. Finally, bivalirudin is available for use to nearly all patients undergoing PCI, whereas the use of radial PCI is limited to those operators facile with the technique, and the use of VCDs is dependent on the patient's access site anatomy.

Methods

Approval for this retrospective analysis was obtained from the health system's institutional review board. Data from all PCIs between 2007 and 2011 performed at 4 PCI centers in a single healthcare system were included for analysis. In July 2009, the NCDR bleeding risk model was incorporated into a software platform, ePRISM (Health Outcomes Sciences, LLC, Overland Park, Kansas) (20,21), to generate individualized bleeding risk estimates for all patients undergoing non-emergent coronary angiography and possible PCI. Each patient's demographic and clinical information was entered into the ePRISM application before the procedure, and the individualized bleeding risk estimates were incorporated into the informed consent document. Both the patients and physicians had ready access to this information. The NCDR bleeding risk model has been described previously (12) and incorporates 9 pre-procedural clinical variables: acute coronary syndrome type, cardiogenic shock, sex, prior heart failure, prior PCI, New York Heart Association

functional class IV heart failure, peripheral vascular disease, age, and estimated glomerular filtration rate. The bleeding risk was displayed in the catheterization laboratory, and the laboratory staff was educated to inform the interventional cardiologist of the bleeding risk before PCI. A quarterly assessment of post-PCI bleeding complications was also initiated, and individual operators were provided with their own operator-level data for personal review.

For this analysis, patients were stratified into 3 subgroups according to bleeding risk: low (<1%), intermediate (1% to 3%), and high (>3%), as in prior studies categorizing bleeding risk (16,22). Demographic and clinical variables of the population before and after implementation of prospective risk stratification were compared using the Student *t* test for continuous variables and chi-square or Fisher exact test for categorical variables, as appropriate. Bivalirudin use during PCI was compared before and after July 2009 using a chi-square test. The trend in bivalirudin use across the 3 risk strata before and after incorporation of routine pre-procedural bleeding risk estimates was also compared using a test for trend. To quantify the effect of bleeding risk and bivalirudin use between the 2 time periods, we developed an adjusted logistic regression model predicting bivalirudin use and including an interaction term between bleeding risk and time (before or after July 2009). To identify independent predictors of bivalirudin use, a multivariable logistic regression analysis was performed.

To compare the data from our institution with national trends of bivalirudin use during the same time period, data from the NCDR Cath PCI Registry were analyzed. All patients in the registry from 2007 to 2011 with sufficient data to calculate a bleeding score were included in the analysis. Patients were stratified into low-, intermediate-, and high-risk bleeding strata as outlined in the previous text, and bivalirudin use was compared within strata of bleeding risk, before and after July 2009.

To quantify whether observed changes in care were consistent across operators, we included a 3-way interaction between operator, bleeding risk, and time period for the operators present at our institution in both the pre- and post-implementation periods (9 of 12 total operators). A nonsignificant interaction would signify that a change in the pattern of bivalirudin use is consistent across operators. A median odds ratio was also calculated to evaluate the effect of the operator on the use of bivalirudin (23).

To evaluate the impact of pre-procedural bleeding risk estimation on bleeding, we also assessed the incidence of major bleeding complications before and after July 2009. Major bleeding complications were identified using the CathPCI Registry version 3.0 and 4.0 data collection form definitions. In version 3.0, bleeding was defined as suspected bleeding from any location requiring transfusion, prolonged hospital stay, or a drop in hemoglobin >3.0 g/dl. In version 4.0, a bleeding event was defined as suspected bleeding with transfusion, a drop in hemoglobin of >3.0

g/dl, or a procedural intervention to correct the bleeding event.

All statistical analyses were performed using the statistical analysis software (SAS, version 9.2, SAS Institute, Cary, North Carolina). A two-sided p value <0.05 was used as the criterion for statistical significance.

Results

A total of 6,491 PCI procedures were performed between 2007 and 2011. The baseline demographic and clinical characteristics of patients undergoing PCI before and after the routine incorporation of bleeding risk estimates into clinical practice are presented in Table 1. The mean age of patients undergoing PCI was 64.8 ± 12.4 years, 68% of patients were male, 15% presented with STEMI, and 54% with non-STEMI/unstable angina.

Relationship between bivalirudin use and bleeding risk.

Bleeding risk estimates were introduced into clinical practice in July 2009. As shown in Figure 1A, the use of bivalirudin increased in the post-implementation period (26.9% before July 2009 to 34.2% after July 2009, p < 0.001). Bivalirudin use increased in patients at intermediate (27% to 35%, p < 0.001) and high (25% to 43%, p < 0.001) risk for bleeding, and there was a decrease in bivalirudin utilization in patients at low bleeding risk (30% to 25% p = 0.014). The change in the trend of bivalirudin use across strata of bleeding risk was statistically significant (Fig. 1B).

Relationship between bleeding and bleeding risk. Post-PCI bleeding complications decreased after the introduction of prospective risk stratification (Fig. 2). Bleeding rates in patients at low bleeding risk were similar before and after

July 2009 (1.1% vs. 1.0%, p = 0.976); however, they decreased significantly in intermediate-risk (3.4% to 1.8%, p = 0.009) and high-risk patients (6.9% to 3.7%, p = 0.005).

Patient characteristics associated with bivalirudin use. In the post-implementation time period, only bleeding risk and prior CABG were independent predictors of bivalirudin use, whereas in the pre-implementation time period, smoking status, lack of insurance, hypertension, prior cerebrovascular disease, and history of renal failure were also independent predictors (Table 2). Between 2007 and July 2009, for every 1% increase in bleeding risk, bivalirudin use decreased by 6%, whereas after July 2009, bivalirudin use increased 7% with every 1% increase in bleeding risk. In patients at high bleeding risk, age, history of renal failure, and STEMI were identified as independent predictors of use, and STEMI was the strongest predictor for the lack of bivalirudin use in patients at high risk for bleeding (odds ratio: 0.43, 95% confidence interval: 0.30 to 0.64).

Physician variability. After implementing prospective risk stratification, the pattern of greater bivalirudin use in patients at lower bleeding risk was generally reversed across all interventionalists, and a 3-way interaction between time, operator, and the bleeding risk was not statistically significant (p = 0.31). However, there was substantial variability in bivalirudin use across operators at our institution, even after incorporation of bleeding risk estimates, with the median odds ratio for bivalirudin = 2.77, suggesting that if 2 patients with identical clinical characteristics presented to 2 random interventional cardiologists at our institution, there was, on average, an approximately 3-fold greater

Table 1 Baseline Clinical and Demographic Variables

	Pre-Implementation (n = 3,652)	Post-Implementation (n = 2,839)	p Value
Age, yrs	64.3 ± 12.4	65.5 ± 12.2	<0.001
Female	1,190 (32.6%)	899 (31.7%)	0.432
BMI, kg/m ²	30.0 ± 6.3	29.8 ± 6.3	0.286
Lack of insurance	205 (5.6%)	150 (5.3%)	0.562
GFR	69.8 ± 25.6	78.3 ± 29.2	<0.001
Smoking	1,029 (28.2%)	723 (25.5%)	0.015
Hypertension	2,941 (80.5%)	2,397 (84.4%)	<0.001
Cerebrovascular disease	558 (15.3%)	507 (17.9%)	0.005
Peripheral vascular disease	501 (13.7%)	469 (16.5%)	0.002
Previous PCI	1,575 (43.1%)	1,278 (45.0%)	0.128
Previous CABG	686 (18.8%)	568 (20.0%)	0.216
Previous CHF	392 (10.7%)	430 (15.1%)	<0.001
STEMI	543 (14.9%)	440 (15.5%)	0.483
NSTEMI/UA	1,984 (54.3%)	1,507 (53.1%)	0.319
Bleeding risk			
Low	855 (23.4%)	771 (27.2%)	0.002
Intermediate	1,820 (49.8%)	1,369 (48.2%)	
High	977 (26.8%)	699 (24.6%)	

Values are mean ± SD or n (%).

BMI = body mass index; CABG = coronary artery bypass graft; CHF = congestive heart failure; GFR = glomerular filtration rate; NSTEMI = non-ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction; UA = unstable angina.

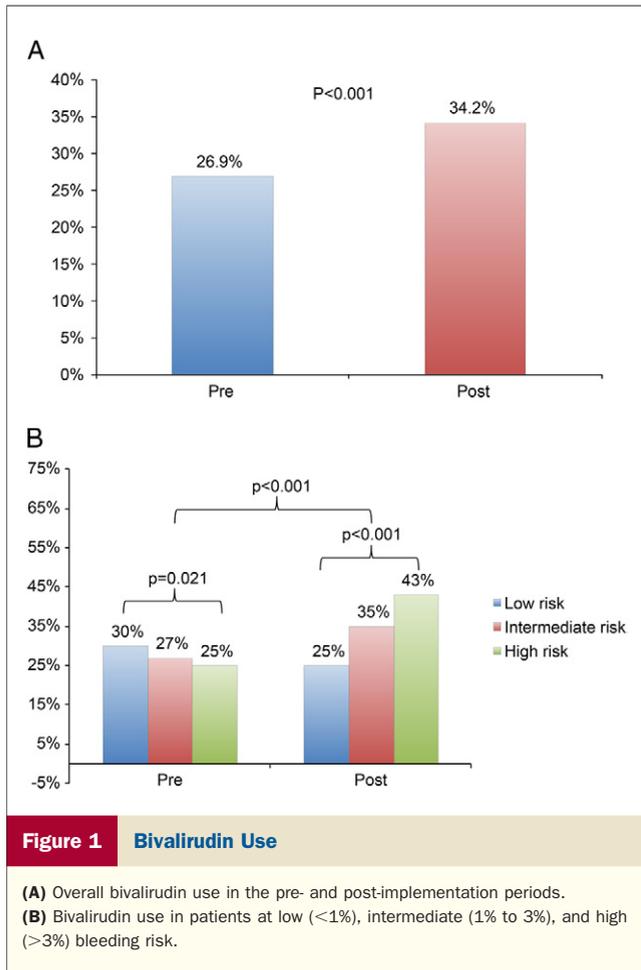


Figure 1 Bivalirudin Use

(A) Overall bivalirudin use in the pre- and post-implementation periods.
(B) Bivalirudin use in patients at low (<1%), intermediate (1% to 3%), and high (>3%) bleeding risk.

probability of receiving bivalirudin with 1 physician as compared with another.

Comparison of bivalirudin use with contemporary controls. There were 1,329,881 PCI procedures reported in the Cath-PCI Registry between 2007 and July 2009, and

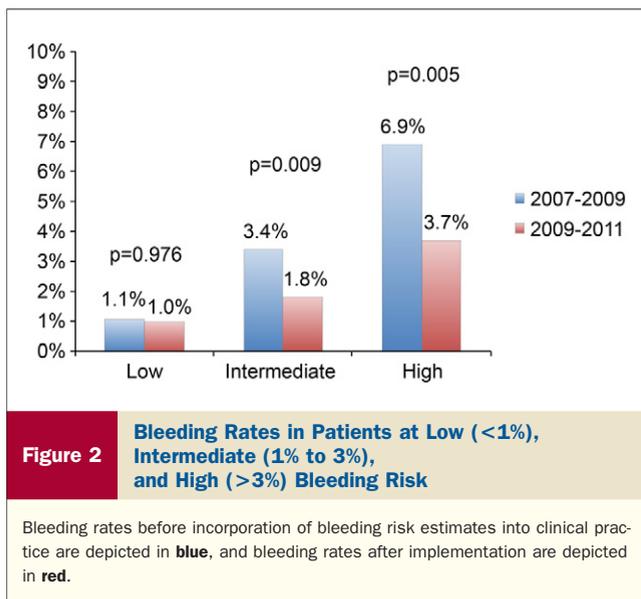


Figure 2 Bleeding Rates in Patients at Low (<1%), Intermediate (1% to 3%), and High (>3%) Bleeding Risk

Bleeding rates before incorporation of bleeding risk estimates into clinical practice are depicted in blue, and bleeding rates after implementation are depicted in red.

Table 2 Independent Predictors of Bivalirudin Use

Pre-Implementation (2007–2009)		Post-Implementation (2009–2011)	
Variable	Odds Ratio (95% CI)	Variable	Odds Ratio (95% CI)
Bleeding risk*	0.94 (0.90–0.97)	Bleeding risk*	1.07 (1.04–1.10)
Hypertension	1.38 (1.12–1.68)	Prior coronary bypass	1.30 (1.07–1.56)
Cerebrovascular disease	1.32 (1.11–1.67)		
Tobacco use	0.77 (0.65–0.92)		
Lack of insurance	0.55 (0.37–0.82)		
Renal failure	0.45 (0.30–0.96)		

*Odds ratio for bleeding risk corresponds to the change in probability in bivalirudin use for every 1% increase in bleeding risk.
CI = confidence interval.

1,471,082 procedures between July 2009 and 2011. The rates of bivalirudin use in the Cath PCI Registry between 2007 and July 2009 were 49%, 45%, and 39% in the low, intermediate, and high bleeding risk strata, respectively (Fig. 3). Bivalirudin use was higher in all 3 strata of bleeding risk in the time period after July 2009, and there was no observed change in the trend to use bivalirudin more often in patients at low risk for bleeding (60%, 56%, and 52% in the low, intermediate, and high bleeding risk strata, respectively), in contrast with the changes in bivalirudin use observed at our institution.

Discussion

The present study demonstrates that the use of prospective bleeding risk estimates at the point of care was associated with increased bivalirudin use in patients at intermediate or high bleeding risk, and decreased use in patients at low risk. This pattern was consistently observed across all operators, although substantial variation in the absolute frequency of bivalirudin use was present at the operator level. Moreover, a comparison with other institutions in the Cath-PCI

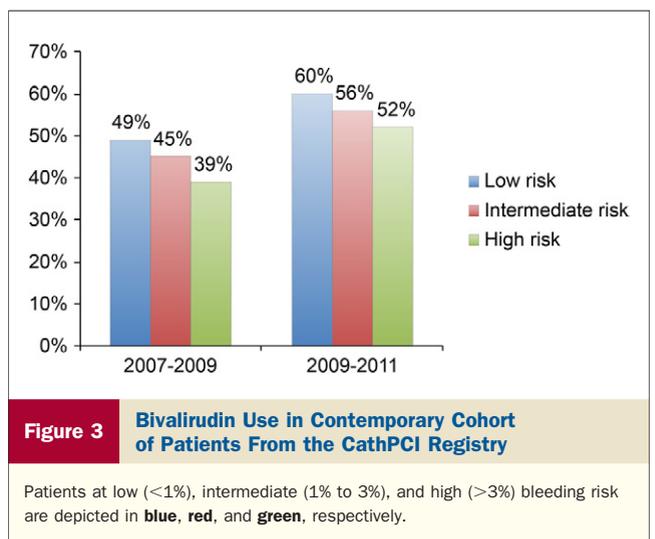


Figure 3 Bivalirudin Use in Contemporary Cohort of Patients From the CathPCI Registry

Patients at low (<1%), intermediate (1% to 3%), and high (>3%) bleeding risk are depicted in blue, red, and green, respectively.

Registry demonstrates that this change in practice was not associated with a similar trend in the change of bivalirudin use nationally. These findings are of great importance because more judicious use of bleeding avoidance strategies such as bivalirudin in the patients most likely to benefit may have a tremendous impact on patient outcomes following PCI.

Bleeding is a common complication of PCI and is associated with increased morbidity and mortality (2,7,8). Because the risk of bleeding is both predictable, and modifiable, bleeding is an ideal target for quality improvement in PCI. Bivalirudin is an accepted alternative to heparin in patients undergoing PCI (24), and has proven efficacy in reducing periprocedural bleeding, with no increased risk of ischemic events (3,4,13–15,25–27). Importantly, the reduction in bleeding with bivalirudin is dependent on patients' underlying bleeding risk. In a propensity-matched study of patients stratified by bleeding risk, the greatest reduction in bleeding with bivalirudin was observed in the highest-risk patients. This was quantified by calculating the number needed to treat to avoid 1 bleeding event, which was only 42 in patients at high bleeding risk, 97 in intermediate-risk patients, and 227 in low-risk patients (16). Furthermore, the cost effectiveness of bivalirudin through bleeding reduction is directly related to patients' underlying bleeding risk. In a prior study at our institution, hospital costs were reduced by \$1,574/patient when bivalirudin was used in high-risk patients and \$461/patient when bivalirudin was used in intermediate-risk patients. However, hospital costs increased by \$705/patient when bivalirudin was used in patients at low risk for bleeding (22).

There was a significant decrease in post-PCI bleeding complications at our institution between 2007 and 2011, driven by an approximately 40% reduction in bleeding in patients at intermediate or high risk for bleeding. Importantly, there was no observed increase in bleeding in low-risk patients, despite a decrease in bivalirudin use. These findings provide evidence to support the increased use of bivalirudin in higher-risk patients and suggest that there is minimal risk associated with decreasing its use in low-risk patients. This is important, because a more rational use of bleeding avoidance strategies, such as bivalirudin use, provides a practical strategy for achieving the aim of improving patient outcomes while lowering costs.

The trends in bivalirudin use at our institution between 2007 and 2011 were not reflective of national PCI trends. We have previously described a risk–treatment paradox, namely that bivalirudin is used most commonly in low-risk and least commonly in higher-risk patients, a pattern that was also present at our institution before the implementation of prospective risk stratification. The changes observed at our institution, without similar changes observed in the rest of the country, suggest that bleeding risk is not intuitive and that prospective risk stratification can support the more rational application of bleeding avoidance strategies in routine clinical practice. Nevertheless, the wide variability in

bivalirudin use across operators at our institution suggests that there is further room for improvement in creating a more consistent healthcare environment that delivers care tailored to patient risks. Supplementing our approach with more standardized protocols based on bleeding risk, feedback reports, and financial incentives might further improve the consistency of care. Ideally, a formal, site-level randomized clinical trial that incorporates prospective risk stratification with additional interventions to improve care consistency and better establish a more systematic approach to bleeding risk management should be considered.

Study limitations. Our findings should be interpreted in the context of the following potential limitations. First, this was a retrospective, single-center study with a pre-/post-implementation study design. However, the changes in practice patterns were abrupt and differed substantially from the rest of the NCDR, which served as a contemporary control to support that the changes in practice at our institution were not attributable to secular trends in care. Second, although the observed reduction in bleeding was temporally associated with the implementation of prospective bleeding risk assessment, causality cannot be concluded. Other changes in care, such as re-education of support staff on best practices for post-PCI sheath care, and the use of smaller sheaths, radial artery access, and vascular closure devices, may have influenced our findings. However, the observed bleeding reductions were greatest in the subgroups of patients at higher bleeding risk in which bivalirudin use increased. This finding supports the notion that prospective risk stratification may have contributed to bleeding reduction in these subgroups. Finally, routine bleeding risk estimates were not estimated for STEMI patients and other patients undergoing emergent PCI procedures. Because patients undergoing emergent procedures are typically at higher risk for bleeding complications, the ability to quickly perform prospective risk stratification in such patients might further increase the rational use of bivalirudin use in this setting, beyond what was observed in this study.

Conclusions

In a single health system, the incorporation of individualized bleeding risk estimates at the point of care led to increased bivalirudin use in patients at intermediate and high bleeding risk, lower use in patients with the least potential to benefit, and reversal of the risk-treatment paradox. During the same time period, a significant decrease in post-PCI bleeding complications was observed in patients at intermediate and high risk for bleeding.

Reprint requests and correspondence: Dr. Adnan K. Chhatriwala, Saint Luke's Mid America Heart Institute, 4300 Wornall Road, Suite 2000, Kansas City, Missouri 64111. E-mail: achhatriwala@saint-lukes.org.

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Key Words: bivalirudin ■ bleeding ■ bleeding risk ■ catheterization ■ PCI.