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ABSTRACT

OBJECTIVE
To examine whether prospective bleeding risk estimates for patients undergoing percutaneous coronary intervention could improve the use of bleeding avoidance strategies and reduce bleeding.

DESIGN
Prospective cohort study comparing the use of bleeding avoidance strategies and bleeding rates before and after implementation of prospective risk stratification for peri-procedural bleeding.

SETTING
Nine hospitals in the United States.

PARTICIPANTS
All patients undergoing percutaneous coronary intervention for indications other than primary reperfusion for ST elevation myocardial infarction.

MAIN OUTCOME MEASURES
Use of bleeding avoidance strategies, including bivalirudin, radial approach, and vascular closure devices, and peri-procedural bleeding rates, stratified by bleeding risk. Observed changes were adjusted for changes observed in a pool of 1135 hospitals without access to pre-procedural risk stratification. Hospital level and physician level variability in use of bleeding avoidance strategies was examined.

RESULTS
In a comparison of 7408 pre-intervention procedures with 3529 post-intervention procedures, use of bleeding avoidance strategies within intervention sites increased with pre-procedural risk stratification (odds ratio 1.81, 95% confidence interval 1.44 to 2.27), particularly among higher risk patients (2.03, 1.58 to 2.61; 1.41, 1.09 to 1.83 in low risk patients, after adjustment for control sites; P for interaction=0.05). Bleeding rates within intervention sites were significantly lower after implementation of risk stratification (1.0% *v* 1.7%; odds ratio 0.56, 0.40 to 0.78; 0.62, 0.44 to 0.87, after adjustment); the reduction in bleeding was greatest in high risk patients. Marked variability in use of bleeding avoidance strategies was observed across sites and physicians, both before and after implementation.

CONCLUSIONS
Prospective provision of individualized bleeding risk estimates was associated with increased use of bleeding avoidance strategies and lower bleeding rates. Marked variability between providers highlights an important opportunity to improve the consistency, safety, and quality of care.

STUDY REGISTRATION
Clinicaltrials.gov NCT01383382.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Bleeding is one of the most common complications of percutaneous coronary intervention (PCI)

Valid models to estimate patients' risks of bleeding have been developed

Bleeding avoidance strategies can reduce bleeding but are paradoxically applied to patients with the lowest risk of bleeding, resulting in inefficient and less effective treatment than could be obtained by preferentially treating higher risk patients

WHAT THIS STUDY ADDS

After provision of patients' individualized estimates of risk before PCI, bleeding avoidance strategies were preferentially increased in those at higher risk of bleeding and the odds of bleeding were reduced by 44%

Marked variability existed in how individual operators treated patients, on the basis of their risk of bleeding, both before and after the provision of patients' bleeding risks

An opportunity exists to improve the consistency of bleeding avoidance management to further improve the safety of PCI

Introduction

Most medical treatments are associated with heterogeneity of benefit; some patients benefit a great deal from treatment, whereas others do not.[1 2] Observational studies show many examples of a "risk-treatment paradox," in which patients at the highest risk (and with the greatest potential to gain from treatment) are treated less often than those at lower risk and with less potential to benefit.[3–10] These practice patterns are not patient centered and are intrinsically inefficient in terms of costs, safety, and outcomes. Developing methods to integrate individualized risk stratification within routine clinical care has the potential to remedy this paradoxical practice pattern by alerting clinicians to each patient's potential benefits from treatment and enabling more patient centered, evidence based, efficient care with safer, better outcomes.[11]

The use of bleeding avoidance strategies at the time of percutaneous coronary intervention is a prototypical example of the risk-treatment paradox. Bleeding is one of the most common non-cardiac complications of percutaneous coronary intervention and is associated with increased mortality, morbidity, and costs.[12–19] It is also modifiable through the use of bleeding avoidance strategies, such as bivalirudin, radial percutaneous coronary

intervention, and, potentially, vascular closure devices.[20–25] Importantly, although the magnitude of bleeding reduction and bleeding related mortality are strongly associated with patients' underlying risk of bleeding,[19 22] bleeding avoidance strategies are paradoxically used most often in patients at low risk of bleeding and least often in those at high risk.[22]

To improve use of bleeding avoidance strategies, and reduce percutaneous coronary intervention related bleeding, we implemented a novel method for prospectively determining and informing physicians of patients' bleeding risks by using a validated risk model developed by the American College of Cardiology's National Cardiovascular Data Registry (NCDR) CathPCI Registry.[26] Patients' personalized risks were calculated with the Patient Risk Information Services Manager (*e*PRISM),[27–29] which was designed to translate multivariable risk models, using each patient's specific clinical risk factors, at the point of care. As a vehicle to translate models to the clinical setting, *e*PRISM was designed to be seamlessly integrated within routine clinical workflow. In the setting of percutaneous coronary intervention, *e*PRISM was used to generate personalized consent forms and replace sites' traditional consent forms, where it has recently been shown to improve patients' experience with care.[30] It also created streamlined decision support tools that could be printed and given to physicians before the percutaneous coronary intervention procedure.

We did a pre/post-implementation study at nine large US percutaneous coronary intervention centers and evaluated changes in use of bleeding avoidance strategies and bleeding outcomes, while correcting for contemporary trends among matched NCDR CathPCI hospitals that did not have access to the *e*PRISM tool. We hypothesized that prospective stratification of bleeding risk could improve the use of bleeding avoidance strategies in higher risk patients and reduce bleeding in patients undergoing percutaneous coronary intervention.

Methods

In this prospective cohort study, individualized bleeding risk estimates were incorporated into the informed consent document for all patients undergoing non-emergent coronary angiography (supplemental figure A) and possible percutaneous coronary intervention at nine US centers (Washington University, Saint Louis, MO; Integris Hospital, Oklahoma, OK; Yale University, New Haven, CT; Henry Ford Hospital, Detroit, MI; Baystate Medical Center, Springfield, MA; The Heart Hospital at Baylor, Plano, TX; Kaiser Hospital, San Francisco, CA; St John's Hospital, Springfield, IL; Mayo Clinic, Rochester, MN). The pre-procedural risk models were generated using the *e*PRISM software platform (Health Outcomes Sciences, Overland Park, KS), which was provided through grant funding to each center. We compared use of bleeding avoidance strategies and bleeding rates before and after implementation of the personalized risk estimates.[28 29] Because the routine process of care was changed at each center to include the new personalized consent forms, randomization of individual patients was not feasible. To overcome the most important bias in pre-/post-intervention comparisons—namely, temporal trends in care that could account for observed changes in treatment and outcomes—we used an additional comparison of non-participating NCDR sites as concurrent controls. This study design (supplemental figure B) was endorsed by two peer reviewed study sections (American Heart Association and the National Heart Lung and Blood Institute), who provided funding for the study.

The implementation of *e*PRISM has been previously described,[27 31] and a rolling enrollment of sites led to staggered start dates between March 24, 2010 and May 5, 2011. Before implementation of the new consent process, a study investigator (JAS) provided didactic education about the bleeding risk model and data on the comparative effectiveness of bleeding avoidance strategies in reducing bleeding. Within one to two months of implementation, an interventional cardiologist (AKC) provided additional information on strategies to reduce bleeding as a function of risk. We considered the period between the start of prospective risk stratification and the interventionalist's visit to be a "break-in" period and excluded it from analysis. We did not provide bleeding avoidance strategy protocols to the sites, and each site was able to implement the tool as fit best within their practice.

Data from all percutaneous coronary interventions performed during the study period were available for analysis through access to each site's CathPCI Registry data. The CathPCI Registry, sponsored by the American College of Cardiology Foundation and the Society for Cardiovascular Angiography and Interventions, collects detailed clinical characteristics, treatments, and outcomes using standardized definitions (www.ncdr.com/webncdr/cathpci/home/datacollection).

The pre-implementation period consisted of the 12 months before implementation of prospective bleeding risk stratification at each site. The post-implementation period consisted of the time period after system activation and a physician site visit for didactic education on the methods and approach to risk stratification. Data collected in the "break-in" period between implementation and the physician site visit were excluded from analysis.

Study population

During the study period, 218 physicians across the nine sites performed 22 066 percutaneous coronary intervention procedures. Patients were excluded from analysis for the following reasons: ST elevation myocardial infarction or other emergent procedures for which insufficient time was available to provide the personalized consent form (n=3895); repeat percutaneous coronary intervention during the same hospital admission for which attribution of which procedure was associated with bleeding is difficult (n=268); procedures of unknown status (emergent or other; n=33); procedures for which the percutaneous coronary intervention operator was not documented (n=274); procedures during

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the "break-in" period between implementation and the physician site visit (n=1470); and procedures in the post-implementation period for which a personalized consent with bleeding risk was not generated (n=3156; for example, a consent had already been signed at a referring institution, administrative error). We excluded an additional 2033 procedures from analysis owing to non-overlapping propensity scores between pre-implementation and post-implementation groups (see below). This resulted in a final study cohort of 10 937 percutaneous coronary intervention procedures (7408 before implementation and 3529 after implementation) performed by 137 physicians.

Bleeding risk estimates

The previously validated CathPCI Registry bleeding risk model incorporates nine pre-procedural clinical variables (age, sex, previous heart failure, glomerular filtration rate, peripheral vascular disease, previous percutaneous coronary intervention, functional status, ST elevation myocardial infarction/non-ST elevation myocardial infarction, and cardiogenic shock; C statistic=0.72).[26] Patients were classified as having low (<1%), moderate (1–3%), or high (>3%) risk of bleeding. We selected these cut-off values a priori on the basis of previous publications.[22] Because the physicians' education components of the intervention encouraged use of bleeding avoidance strategies in patients at moderate or high risk for bleeding, the categorical analyses of bleeding outcomes and changes in bleeding avoidance strategy use are between patients with low and moderate/high risk (<1% *v* ≥1%) for bleeding. We calculated these risk estimates retrospectively for the pre-implementation period by using NCDR data, but they were not available to the physician before percutaneous coronary intervention.

Outcomes

Study outcomes included use of bleeding avoidance strategies and in-hospital, post-procedural bleeding rates. Bleeding avoidance strategies were analyzed individually and by use of any strategy. Use of bivalirudin was considered the most modifiable strategy, as radial approaches are very operator dependent (interventionalists tend to predominantly use or not use this access approach) and the benefits of vascular closure devices to prevent bleeding are controversial.[32] Bleeding events were prospectively collected and defined according to standard NCDR definitions (access site, retroperitoneal, gastrointestinal, genitourinary, or unknown bleeding within 72 hours after percutaneous coronary intervention, associated with a drop in hemoglobin of ≥3 g/dL or requiring transfusion, procedural intervention, or surgery).[26]

Statistical analyses

To account for contemporary trends in use of bleeding avoidance strategies and bleeding incidence, we matched the nine study sites to control hospitals selected from among the 1135 CathPCI Registry sites not participating in this study. Hospitals were matched on annual percutaneous coronary intervention volume, teaching status, and the physicians' average pre-*e*PRISM rate for each outcome. Given the number of outcomes, we could not match intervention sites with controls on the pre-procedural rates of all five outcomes (bleeding, bivalirudin use, closure device use, radial access, and any bleeding avoidance strategy use), so we did separate matches for each outcome. To reduce the effects of measurement error and sampling variation among the specific control hospitals selected, we used full optimal matching to match as many controls as possible to each study site. Between 130 and 178 control hospitals were matched, depending on the outcome. We ensured balance between study and matched control hospitals by calculating standardized differences, which were all less than 10% for each variable within each outcome analysis (supplemental table A).

To adjust for differences in patients' and procedural characteristics before and after *e*PRISM implementation, as well as between study and control sites, we calculated multiple group propensity scores. This enabled us to adjust simultaneously for a myriad of patients' characteristics so that the differences in treatment and outcomes were attributable to the intervention rather than to the types of patients treated in the different time periods. To do this, we constructed a multinomial logistic regression model predicting membership in each of the four "treatment" groups (study *v* control×pre- *v* post-*e*PRISM implementation) on the basis of 31 demographic, clinical, and procedural variables (table 1). From this model, we obtained three propensity scores estimating the probability of membership in each of three groups compared with the reference group of study sites before implementation of *e*PRISM. We assessed covariate balance by comparing propensity adjusted standardized differences between patients in the pre-intervention and post-intervention groups (<10% indicates good balance). Overlap of propensity score distributions among the four groups was good for all scores. We included these scores as covariates in the outcome models.

The primary unit of analysis in this study was the percutaneous coronary intervention physician operator. We used hierarchical logistic regression models to assess the effect of exposure to *e*PRISM on physicians' change in use of bleeding avoidance strategies and the incidence of post-procedural bleeding, corrected for concurrent trends among control hospitals. Models included a fixed effect for study phase (before *v* after *e*PRISM implementation, centered within physician), physician level random intercepts and random effects for study phase, a fixed effect for study versus control hospital groups, a study phase-by-group interaction term, and adjustment for hospital matched sets and the three logit propensity scores. We quantified the effect of *e*PRISM as the relative difference in odds ratio for study phase between study and control hospitals. In addition, among the nine study sites, we evaluated variability in use of bleeding avoidance strategies by physician with median odds ratios, which estimate the relative difference in use between two randomly selected physicians or hospitals for "identical" patients with the same covariates.

Table 1 | Baseline characteristics of patients. Values are numbers (percentages) unless stated otherwise

Characteristic	Standard consent* (n=7408)	Personalized consent (n=3529)	P value
Mean (SD) age, years	65.7 (11.6)	66.2 (11.5)	0.043
Male sex	5158 (69.6)	2504 (71.0)	
Non-white ethnicity	886 (12.0)	409 (11.6)	0.575
No insurance	189 (2.6)	64 (1.8)	0.016
Admission source:			<0.001
Emergency department	1158 (15.6)	360 (10.2)	
Transfer in from another acute care facility	2368 (32.0)	891 (25.2)	
Other	3868 (52.2)	2275 (64.5)	
Mean (SD) body mass index, kg/m^2	30.1 (7.4)	30.3 (8.4)	0.295
Family history of premature coronary artery disease	2377 (32.1)	1089 (30.9)	0.178
Dyslipidemia	6582 (88.8)	3175 (90.0)	0.091
Hypertension	6373 (86.0)	3053 (86.5)	0.492
Diabetes	2679 (36.2)	1265 (35.8)	0.728
Previous myocardial infarction	2643 (35.7)	1346 (38.1)	0.012
Previous PCI	3209 (43.3)	1566 (44.4)	0.286
Previous coronary artery bypass graft	1693 (22.9)	863 (24.5)	0.064
Peripheral arterial disease	988 (13.3)	567 (16.1)	<0.001
Cerebrovascular disease	976 (13.2)	480 (13.6)	0.539
Chronic heart failure	1072 (14.5)	549 (15.6)	0.142
Previous valve surgery/procedure	161 (2.2)	65 (1.8)	0.244
Chronic lung disease	950 (12.8)	511 (14.5)	0.017
On dialysis	207 (2.8)	99 (2.8)	0.974
Mean (SD) glomerular filtration rate, mL/min/1.73 m^2	76.1 (27.4)	75.3 (26.0)	0.147
Mean (SD) pre-procedure hemoglobin, g/dL	13.3 (1.8)	13.4 (1.8)	0.014
Heart failure in previous 2 weeks	632 (8.5)	324 (9.2)	0.278
Cardiomyopathy or left ventricular systolic dysfunction	591 (8.0)	326 (9.2)	0.027
Cardiogenic shock in previous 24 hours	16 (0.2)	6 (0.2)	0.615
Cardiac arrest in previous 24 hours	23 (0.3)	9 (0.3)	0.615
Stress or imaging studies	2956 (39.9)	1618 (45.8)	<0.001
Coronary artery disease presentation:			<0.001
Asymptomatic	817 (11.0)	385 (10.9)	
Symptom unlikely to be ischemic	73 (1.0)	38 (1.1)	
Stable angina	1565 (21.1)	762 (21.6)	
Unstable angina	3083 (41.6)	1633 (46.3)	
NSTEMI	1867 (25.2)	711 (20.1)	
Anginal classification in previous 2 weeks:	(n=7390)	(n=3524)	0.136
No symptoms	871 (11.8)	397 (11.3)	
CCS class I	249 (3.4)	108 (3.1)	
CCS class II	1465 (19.8)	763 (21.7)	
CCS class III	2353 (31.8)	1140 (32.3)	
CCS class IV	2452 (33.2)	1116 (31.7)	
PCI status:			<0.001
Elective	3322 (44.8)	1836 (52.0)	
Urgent	4086 (55.2)	1693 (48.0)	
PCI indication:			<0.001
High risk NSTEMI or unstable angina	4106 (55.4)	1796 (50.9)	
Staged PCI	372 (5.0)	181 (5.1)	
Other	2930 (39.6)	1552 (44.0)	
Bleeding risk:	(n=7143)	(n=3415)	0.760
Low (0 to <0.01)	2237 (31.3)	1047 (30.7)	
Moderate (0.01 to <0.03)	3523 (49.3)	1708 (50.0)	
High (≥0.03)	1383 (19.4)	660 (19.3)	

CCS=Canadian Cardiovascular Society; NSTEMI=non-ST elevation myocardial infarction; PCI=percutaneous coronary intervention.
*Without bleeding risk estimates.
†With individual bleeding risk estimates.

Finally, we repeated the above analyses, augmenting the models with terms for bleeding risk and *e*PRISM-by-risk interactions, to examine whether greater changes in treatment or benefit occurred among higher risk patients. We did separate analyses incorporating bleeding risk as a categorical (low *v* moderate/high) or continuous variable. Among the nine study sites, we derived variability in physicians' use of bleeding avoidance strategies as a function of bleeding risk both before and after implementation of *e*PRISM from the estimated random effects from the model incorporating bleeding risk as a continuous variable. We also repeated these approaches for other anticoagulation and antiplatelet regimens, including unfractionated heparin, low molecular weight heparin, glycoprotein IIb/IIIa inhibitors, and thienopyridine use (both clopidogrel and prasugrel). We also did an exploratory descriptive analysis to assess the effect of pre-procedural risk stratification on in-hospital mortality, as recorded in the NCDR registry, among the intervention sites. We used SAS 9.3 and R version 2.15.0 for all analyses.[33] All hypothesis tests were two tailed and evaluated at a significance level of 0.05.

Results

The mean "break-in" period between implementation of pre-procedural risk stratification and the physician site visit was 2.1 months, and the mean study duration after the physician site visit was 9.4 months (supplemental table B). The final study cohort consisted of 10 937 percutaneous coronary intervention procedures (7408 before implementation and 3529 after implementation) by 137 physicians. Table 1 shows patients' baseline demographic and clinical characteristics. Estimated bleeding risks were similar between the two groups. After propensity adjustment, all patients' and procedural characteristics were well balanced (standardized differences 0–28% before adjustment, 0–7% after; supplemental table A).

Processes of care to mitigate bleeding

To understand the effect of pre-procedural risk stratification on the use of bleeding avoidance strategies, we compared the observed changes at the intervention sites overall, and stratified by bleeding risk, and adjusted these observations for changes in bleeding avoidance strategy use at the control sites. Overall bleeding avoidance strategy use (table 2) increased from 81.4% to 88.7% after implementation (odds ratio 1.81, 95% confidence interval 1.44 to 2.27; P<0.001). The increase was significantly greater in patients at high risk of bleeding (odds ratio 2.03 *v* 1.48 for low risk patients; P=0.05 for interaction). After correction for contemporary trends, the effect of pre-procedural risk stratification on the use of bleeding avoidance strategies was of borderline statistical significance (corrected odds ratio 1.23, 0.98 to 1.56) across all patients but significantly greater in patients at high risk for bleeding (1.41, 1.09 to 1.83; P=0.008). When we examined individual bleeding avoidance strategies, the availability of pre-procedural bleeding risk estimates was associated with similar overall use of bivalirudin (odds ratio 1.18, 0.93 to 1.48) but a change in practice that favored its use in high risk patients (1.36, 1.05 to 1.75) over low risk patients (0.92, 0.69 to 1.24; P value for interaction=0.03). When we adjusted for control hospitals, we found no overall difference in bivalirudin

Table 2 | Bleeding avoidance strategy use and post-percutaneous coronary intervention (PCI) bleeding by bleeding risk and availability of these risks before PCI

	Study hospitals						PRISM effect (corrected for controls)	
	Pre-PRISM rate	Post-PRISM rate	Odds ratio (95% CI)	P value	PRISM×risk interaction P value	Control hospitals—odds ratio (95% CI)	Odds ratio (95% CI)	P value
Outcomes—peri-procedural bleeding								
Post-PCI bleeding:								
Overall	1.7%	1.0%	0.56 (0.40 to 0.78)	<0.001	0.71	0.91 (0.84 to 0.98)	0.62 (0.44 to 0.87)	0.006
Low bleeding risk	0.7%	0.3%	0.46 (0.20 to 1.06)	0.07		0.91 (0.74 to 1.11)	0.51 (0.21 to 1.20)	0.12
Moderate/high bleeding risk	2.1%	1.3%	0.59 (0.41 to 0.85)	0.004		0.90 (0.83 to 0.98)	0.65 (0.45 to 0.94)	0.02
Processes of care—bleeding avoidance strategies								
Any strategy:								
Overall	81.4%	88.7%	1.81 (1.44 to 2.27)	<0.001	0.05	1.46 (1.38 to 1.55)	1.23 (0.98 to 1.56)	0.08
Low bleeding risk	85.9%	90.0%	1.48 (1.08 to 2.04)	0.02		1.50 (1.39 to 1.62)	0.99 (0.71 to 1.37)	0.94
Moderate/high bleeding risk	78.7%	88.3%	2.03 (1.58 to 2.61)	<0.001		1.44 (1.35 to 1.53)	1.41 (1.09 to 1.83)	0.008
Bivalirudin:								
Overall	48.6%	52.6%	1.18 (0.93 to 1.48)	0.17	0.03	1.28 (1.21 to 1.36)	0.92 (0.72 to 1.16)	0.47
Low bleeding risk	51.5%	49.6%	0.92 (0.69 to 1.24)	0.61		1.27 (1.18 to 1.36)	0.73 (0.54 to 0.99)	0.04
Moderate/high bleeding risk	47.9%	55.5%	1.36 (1.05 to 1.75)	0.02		1.29 (1.31 to 1.27)	1.05 (0.81 to 1.37)	0.70
Closure device:								
Overall	31.2%	28.9%	0.90 (0.73 to 1.10)	0.30	0.16	0.94 (0.89 to 0.99)	0.96 (0.77 to 1.18)	0.67
Low bleeding risk	37.4%	33.4%	0.84 (0.64 to 1.10)	0.20		0.90 (0.84 to 0.96)	0.94 (0.71 to 1.24)	0.65
Moderate/high bleeding risk	29.4%	28.6%	0.96 (0.77 to 1.20)	0.73		0.95 (0.89 to 1.00)	1.02 (0.81 to 1.28)	0.88
Radial access*:								
Overall	4.7%	10.7%	2.45 (1.84 to 3.26)	<0.001	0.46	2.26 (2.03 to 2.51)	1.09 (0.80 to 1.47)	0.60
Low bleeding risk	5.6%	14.2%	2.77 (1.90 to 4.02)	<0.001		2.54 (2.22 to 2.91)	1.09 (0.73 to 1.62)	0.68
Moderate/high bleeding risk	4.5%	9.8%	2.32 (1.72 to 3.14)	<0.001		2.36 (2.11 to 2.63)	0.99 (0.72 to 1.36)	0.93

*Among physicians performing at least one radial procedure before implementation of PRISM.

use in high risk patients but decreased use in lower risk patients (odds ratio 0.73, 0.54 to 0.99; P=0.04). We found no significant changes in use of vascular closure devices within intervention sites or between intervention and control sites. Although use of radial access increased within the intervention sites, these changes were similar to those at control sites and did not vary by bleeding risk categories.

Analyses incorporating risk of bleeding as a continuous variable (supplemental figure C) showed significant increases in use of bleeding avoidance strategies after the availability of pre-procedural bleeding risk estimates, although interactions between bleeding avoidance strategy use and bleeding risk were not statistically significant. Other anticoagulation strategies (supplemental table C) also varied after the intervention, including less use of low molecular weight heparin (overall odds ratio 0.62, 0.52 to 0.75; adjusted odds ratio 0.71, 0.59 to 0.86, with no significant interaction by bleeding risk group) and less use of glycoprotein IIb/IIIa inhibitors (0.66, 0.55 to 0.79, with no interaction by bleeding risk group and no difference after adjustment for contemporary practice in control sites: 0.91, 0.75 to 1.10). We observed no significant differences in the use of unfractionated heparin or thienopyridines (either clopidogrel or prasugrel) after pre-procedural risk stratification once we adjusted for changes in hospitals without access to pre-procedural bleeding risk estimates.

Bleeding outcomes

Table 2 summarizes the effect of pre-procedural bleeding risk estimates on bleeding. Bleeding complications decreased from 1.7% to 1.0% after implementation (odds ratio 0.56, 0.40 to 0.78; P<0.001), and this effect persisted after correction for contemporary trends (difference between differences 0.56 *v* 0.91, P<0.001; corrected odds ratio 0.62, 0.44 to 0.87, P=0.006). Bleeding complications decreased significantly at intervention sites, compared with control sites, for patients at high risk of bleeding (odds ratio 0.65, 0.45 to 0.94; P=0.02) but not among patients at low risk of bleeding (0.51, 0.21 to 1.20; P=0.12). Analyses incorporating risk of bleeding as a continuous variable (fig 1) suggested a greater absolute decrease in bleeding rate as bleeding risk increased. In contrast to the beneficial effects of pre-procedural risk stratification on bleeding, we observed no differences in in-hospital mortality among the intervention sites (0.37% pre-*e*PRISM *v* 0.41% post-*e*PRISM; P=0.62).

Hospital and physician variability

Significant hospital and physician level variability in BAS use was present. In the post-implementation period, use of bleeding avoidance strategies ranged from 31% to 98%, bivalirudin use ranged from 1% to 96%, vascular closure device use ranged from 3% to 70%, and radial access ranged from 1% to 51% across hospitals. The effect of pre-procedural bleeding risk estimates on bleeding avoidance strategy use varied widely across hospitals (table 3), with hospital specific odds ratios for the use of any strategy ranging from 0.49 to 2.65 (P=0.006 for differences by hospital), although the effect of *e*PRISM on bleeding avoidance strategy use was greater than 1.0 in seven of nine

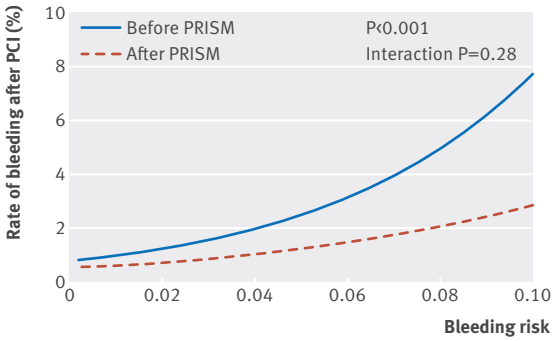

Fig 1 | Unadjusted rates of bleeding before and after *e*PRISM implementation, as a function of bleeding risk. PCI=percutaneous coronary intervention

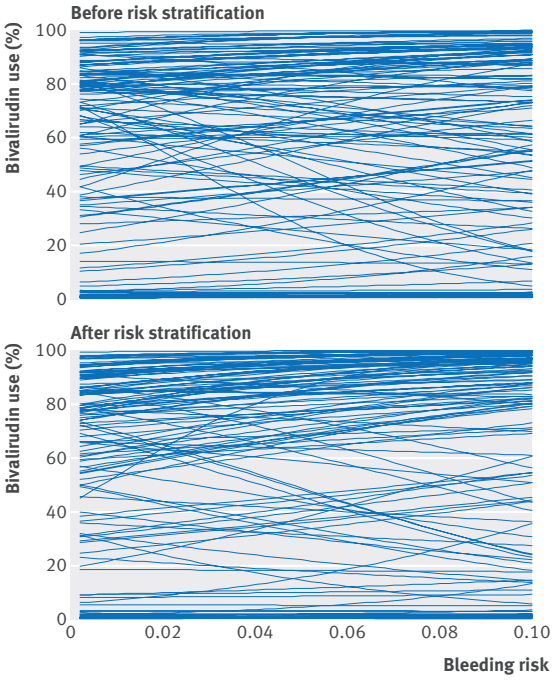

Fig 2 | Individual physicians' variability in use of bivalirudin, as a function of bleeding risk, before and after PRISM. Each line represents a physician in the study

hospitals, suggesting that all but two hospitals increased their use of such strategies after being provided with pre-procedural estimates of patients' bleeding risk. Within hospitals, we also saw substantial variability in bleeding avoidance strategy use by physicians at each hospital (table 4). The median odds ratio for any use of any strategy, after adjustment for between hospital differences, was 4.1 when the personalized consents were used, indicating a fourfold difference in the probability of any bleeding avoidance strategy use between two randomly selected physicians at the same hospital treating patients with identical bleeding risk and other clinical characteristics. We observed similar variation for each individual strategy, with bivalirudin use showing the greatest variability. Figure 2 shows the use of bivalirudin as a function of patients' bleeding risks, before and after pre-procedural risk stratification. This figure emphasizes the wide variability across physicians, even after personalized estimates of bleeding were provided. Some physicians never used bivalirudin, even among the patients at highest risk for bleeding, whereas others used it in all of their high risk patients. Physician level performance for other strategies are shown in supplemental figure D.

Table 3 | Variation in bleeding avoidance strategy (BAS) use and effect of personalized bleeding risk estimates across hospitals

	Range in BAS use		Range in effect of PRISM	
Bleeding avoidance strategy	Pre-PRISM	Post-PRISM	Odds ratios	P value
Any strategy	13–98%	31–98%	0.49–2.65	0.006
Bivalirudin	1–95%	1–96%	0.63–2.20	0.20
Closure device	0.2–80%	3–70%	0.48–18.09	<0.001
Radial access	1–14%	1–51%	0.24–4.02	0.07

Table 4 | Variation in bleeding avoidance strategy use and effect of personalized bleeding risk estimates across physicians

	Median odds ratios across all hospitals		Median odds ratios within hospitals	
Bleeding avoidance strategy	Pre-PRISM	Post-PRISM	Pre-PRISM	Post-PRISM
Any strategy	9.4	7.8	3.7	4.1
Bivalirudin	11.0	11.3	3.7	4.5
Closure device	7.9	6.3	3.5	4.2
Radial access	3.2	3.3	2.8	2.2

Discussion

To our knowledge, this is the first demonstration that precision medicine, delivered through pre-procedural risk stratification, can improve the safety of medical care by supporting tailored treatment in patients at the greatest risk for adverse outcomes. In this before/after study at nine US percutaneous coronary intervention centers, we sought to overcome a well documented risk-treatment paradox in healthcare delivery by prospectively providing personalized estimates of bleeding risk for patients undergoing percutaneous coronary intervention. This intervention was associated with increased use of bleeding avoidance strategies overall, with a greater use in high risk patients (odds ratio 1.41) after adjustment for contemporary trends in bleeding management. The only other change in anticoagulation regimens observed at the intervention sites, compared with control sites, was a lower use of low molecular weight heparins, which have been associated with less bleeding and may have diminished the observed differences in bleeding between intervention and control sites. Most importantly, the overall bleeding rates improved significantly more at the intervention sites after prospective risk stratification than was observed at other matched hospitals participating in the NCDR registry (reduction in odds of bleeding at intervention sites 44% *v* 9% at control sites). These findings extend our previous experience at a single institution to support the generalizability of this approach.[34]

Implications of findings

This study highlights the potential value of risk models to improve care. Although risk adjusted benchmarking of performance can enable hospitals to identify whether they are performing favorably compared with their

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peers, we are unaware of any examples in which these models have been prospectively used to improve medical decision making. In the case of percutaneous coronary intervention related bleeding, the CathPCI Registry data enabled researchers to create a risk model to predict bleeding,[26] determine that bleeding avoidance strategies were preferentially used in patients at the lowest risk and with the least potential to benefit,[22] and prospectively use that model to support more efficient, evidence based medical decision making and safer care. Many additional opportunities exist to update the risk models with emerging risk factors and extend this concept to other medical disciplines.[35]

This study also highlights extraordinary variability in care by both hospitals and physicians within hospitals. For example, the use of bivalirudin varied from 1% to 95% across the nine centers in this study, with an 11-fold difference in the likelihood that two patients with identical characteristics treated by one random physician versus another would be treated with the drug. Even within the same hospital, a fourfold variation in bivalirudin use existed across providers, after adjustment for risk of bleeding and patients' other characteristics. For example, few people would argue that a patient with a very high, 10% risk of bleeding should not be treated with at least one bleeding avoidance strategy. In this study, we found that the likelihood of such a patient receiving any bleeding avoidance strategy ranged from 1% to 100%, depending on which interventionalist performed the procedure. Decreasing such variability in care based on physicians' preferences, rather than patients' benefits, represents an important opportunity to improve quality and outcomes. Given that the provision of prospective, individualized bleeding risk estimates had little effect on the observed variability in care, we believe that future efforts to support more consistent care may require implementation of clear protocols for optimal use of bleeding avoidance strategies as a function of bleeding risk, feedback reports on protocol adherence, and holding physicians accountable for their practice patterns.[36]

Limitations of study

Our findings should be interpreted in the context of several potential limitations. Firstly, this was a non-randomized study with a before/after design. Because we changed the processes of obtaining informed consent, we could not randomize individual patients. A cluster randomized study design would have more definitively compared the effect of pre-procedural risk stratification on care and outcomes. Nevertheless, we were able to leverage the same data collection infrastructure at more than 1100 hospitals to document a significantly greater reduction in bleeding compared with contemporary trends. We were also able to use propensity models to ensure that patients in the pre-intervention phase were similar to those in the post-intervention time period. Secondly, the inclusion of nine sites limits the generalizability of the findings to other institutions. Our findings are also not generalizable to ST elevation myocardial infarction or emergent patients, as these emergency cases were excluded from our study. However, the lessons learnt from this effort, particularly our belief in the importance of having established protocols and feedback, could potentially lead to more successful future implementations.

A third limitation is that the optimal management of anticoagulation and antiplatelet treatment at the time of percutaneous coronary intervention is complex,[37] with both oral (for example, clopidogrel, aspirin) and intravenous (glycoprotein IIb/IIIa) antiplatelet agents and a range of anticoagulants (bivalirudin, unfractionated and low molecular weight heparin) used in various combinations by different operators. We were unable to attribute the reduction in bleeding solely to the observed changes in use of bleeding avoidance strategies. However, this does not detract from the importance of our finding that prospective risk stratification was associated with improved bleeding outcomes for patients undergoing percutaneous coronary intervention, however it was achieved. An additional concern might be the recently announced results of the HEAT PPCI study, in which bivalirudin did not result in less bleeding than heparin alone.[38] We excluded primary percutaneous coronary intervention from our analyses, and our results should not be affected by this new information. A further potential concern is the short time of observation after pre-procedural risk stratification was introduced and that physicians might take a longer time to incorporate such information into their practice patterns, something that would have led to underestimation of the potential benefits of this approach. Finally, the bleeding events were not independently adjudicated, with reliance on the NCDR data collection infrastructure, and we were not able to adjudicate ischemic complications that may have been affected by changes in antithrombotic treatment. We also did not have long term outcomes available, and nor were we able to compare the accuracy of bleeding events in NCDR between our nine centers and the rest of the NCDR. Future work should attempt to assess these outcomes more definitely.

The Institute of Medicine has challenged US healthcare to be more patient centered, evidence based, and efficient, as well as safer.[11] We have previously reported that the enhanced informed consent documents generated by the personalized consents improved patients' experiences with consent to percutaneous coronary intervention.[39] In this study, we have shown that prospective, individualized bleeding risk estimates were associated with more appropriate use of bleeding avoidance strategies and significantly lower bleeding rates. Nevertheless, the variability of care observed in this study suggests an important opportunity to further improve the safety and quality of percutaneous coronary intervention care.

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Contributors: JAS, PGJ, CD, and AKC designed the study. JAS obtained funding. PGJ did the data analysis. JAS, PGJ, and AKC interpreted the

data. JAS drafted the manuscript, and all the other authors critically revised it. JAS is the guarantor.

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Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: this study was funded by grants from the American Heart Association and the National Heart Lung and Blood Institute; JAS owns several patents on the *e*PRISM technology used to deliver the pre-procedural estimates of bleeding and has an economic interest in Health Outcomes Sciences, the company the distributes and supports the *e*PRISM software to hospitals; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: This study was a quality improvement initiative, and patient level informed consent was not required, as all data were stripped of individual patients' identifiers. Each institution's institutional review board approved the protocol, including that of Saint Luke's Hospital.

Transparency declaration: The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Data sharing: Requests for additional data analysis, methods, or code can be directed to the corresponding author at spertusj@umkc.edu, who will make every permissible attempt to accommodate all requests. Participants' consent was not obtained, but the presented data are anonymized and risk of identification is low.

1 Guyatt GH, Sackett DL, Cook DJ. Users' guides to the medical literature. II. How to use an article about therapy or prevention. A. Are the results of the study valid? *JAMA* 1993;270:2598–601.
2 Laupacis A, Sackett DL, Roberts RS. An assessment of clinically useful measures of the consequences of treatment. *N Engl J Med* 1988;318:1728–33.
3 Bhatt DL, Roe MT, Peterson ED, et al. Utilization of early invasive management strategies for high-risk patients with non-ST-segment elevation acute coronary syndromes: results from the CRUSADE Quality Improvement Initiative. *JAMA* 2004;292:2096–104.
4 Brogan GX Jr, Peterson ED, Mulgund J, et al. Treatment disparities in the care of patients with and without diabetes presenting with non-ST-segment elevation acute coronary syndromes. *Diabetes Care* 2006;29:9–14.
5 Lee DS, Tu JV, Juurlink DN, et al. Risk-treatment mismatch in the pharmacotherapy of heart failure. *JAMA* 2005;294:1240–7.
6 Spertus JA, Weiss NS, Every NR, et al, for the Myocardial Infarction Triage and Intervention Project Investigators. The influence of clinical risk factors on the use of angiography and revascularization after acute myocardial infarction. *Arch Intern Med* 1995;155:2309–16.
7 Yan AT, Yan RT, Tan M, et al. Management patterns in relation to risk stratification among patients with non-ST elevation acute coronary syndromes. *Arch Intern Med* 2007;167:1009–16.
8 Pilote L, Miller DP, Califf RM, et al. Determinants of the use of coronary angiography and revascularization after thrombolysis for acute myocardial infarction. *N Engl J Med* 1996;335:1198–205.
9 Spertus JA, Furman MI. Translating evidence into practice: are we neglecting the neediest? *Arch Intern Med* 2007;167:987–8.
10 McAlister FA, Oreopoulos A, Norris CM, et al. Exploring the treatment-risk paradox in coronary disease. *Arch Intern Med* 2007;167:1019–25.
11 Institute of Medicine. Crossing the quality chasm: a new health system for the twenty-first century. National Academy Press, 2001.
12 Dauerman HL, Rao SV, Resnic FS, et al. Bleeding avoidance strategies: consensus and controversy. *J Am Coll Cardiol* 2011;58:1–10.
13 Doyle BJ, Rihal CS, Gastineau DA, et al. Bleeding, blood transfusion, and increased mortality after percutaneous coronary intervention: implications for contemporary practice. *J Am Coll Cardiol* 2009;53:2019–27.
14 Rao SV. Implications of bleeding and blood transfusion in percutaneous coronary intervention. *Rev Cardiovasc Med* 2007;8(suppl 3):S18–26.
15 Ndrepepa G, Berger PB, Mehilli J, et al. Periprocedural bleeding and 1-year outcome after percutaneous coronary interventions: appropriateness of including bleeding as a component of a quadruple end point. *J Am Coll Cardiol* 2008;51:690–7.
16 Feit F, Voeltz MD, Attubato MJ, et al. Predictors and impact of major hemorrhage on mortality following percutaneous coronary intervention from the REPLACE-2 Trial. *Am J Cardiol* 2007;100:1364–9.
17 Cohen DJ, Lincoff AM, Lavelle TA, et al. Economic evaluation of bivalirudin with provisional glycoprotein IIB/IIIA inhibition versus heparin with routine glycoprotein IIB/IIIA inhibition for percutaneous coronary intervention: results from the REPLACE-2 trial. *J Am Coll Cardiol* 2004;44:1792–800.
18 Kinnaird TD, Stabile E, Mintz GS, et al. Incidence, predictors, and prognostic implications of bleeding and blood transfusion following percutaneous coronary interventions. *Am J Cardiol* 2003;92:930–5.
19 Chhatriwalla AK, Amin AP, Kennedy KF, et al. Association between bleeding events and in-hospital mortality after percutaneous coronary intervention. *JAMA* 2013;309:1022–9.
20 Jolly SS, Amlani S, Hamon M, et al. Radial versus femoral access for coronary angiography or intervention and the impact on major bleeding and ischemic events: a systematic review and meta-analysis of randomized trials. *Am Heart J* 2009;157:132–40.
21 Kastrati A, Neumann FJ, Mehilli J, et al. Bivalirudin versus unfractionated heparin during percutaneous coronary intervention. *N Engl J Med* 2008;359:688–96.
22 Marso SP, Amin AP, House JA, et al. Association between use of bleeding avoidance strategies and risk of periprocedural bleeding among patients undergoing percutaneous coronary intervention. *JAMA* 2010;303:2156–64.
23 Sanborn TA, Ebrahimi R, Manoukian SV, et al. Impact of femoral vascular closure devices and antithrombotic therapy on access site bleeding in acute coronary syndromes: the Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial. *Circ Cardiovasc Interv* 2010;3:57–62.
24 Stone GW, McLaurin BT, Cox DA, et al. Bivalirudin for patients with acute coronary syndromes. *N Engl J Med* 2006;355:2203–16.
25 Stone GW, Witzenbichler B, Guagliumi G, et al. Bivalirudin during primary PCI in acute myocardial infarction. *N Engl J Med* 2008;358:2218–30.
26 Mehta SK, Frutkin AD, Lindsey JB, et al. Bleeding in patients undergoing percutaneous coronary intervention: the development of a clinical risk algorithm from the National Cardiovascular Data Registry. *Circ Cardiovasc Interv* 2009;2:222–9.
27 Arnold SV, Decker C, Ahmad H, et al. Converting the informed consent from a perfunctory process to an evidence-based foundation for patient decision making. *Circ Cardiovasc Qual Outcomes* 2008;1:21–8.
28 Soto GE, Jones P, Spertus JA. PRISM™: a web-based framework for deploying predictive clinical models. *Computers in Cardiology* 2004;31:193–6.
29 Soto GE, Spertus JA. EPOCH and ePRISM: a web-based translational framework for bridging outcomes resaerch and clinical practice. *Computers in Cardiology* 2007;34:205–8.
30 Spertus JA, Bach R, Bethea C, et al. Improving the process of informed consent for percutaneous coronary intervention: Patient Outcomes from the Patient Risk Information Services Manager (ePRISM) study. *Am Heart J* 2015;169:234–41.
31 Decker C, Arnold SV, Olabiyi O, et al. Implementing an innovative consent form: the PREDICT experience. *Implement Sci* 2008;3:58.
32 Patel MR, Jneid H, Derdeyn CP, et al. Arteriotomy closure devices for cardiovascular procedures: a scientific statement from the American Heart Association. *Circulation* 2010;122:1882–93.
33 R Project for Statistical Computing. R: a language and environment for statistical computing. R Foundation for Statistical Computing, 2006.
34 Rao SC, Chhatriwalla AK, Kennedy KF, et al. Pre-procedural estimate of individualized bleeding risk impacts physicians' utilization of bivalirudin during percutaneous coronary intervention. *J Am Coll Cardiol* 2013.
35 Mangiacapra F, Patti G, Barbato E, et al. A therapeutic window for platelet reactivity for patients undergoing elective percutaneous coronary intervention: results of the ARMYDA-PROVE (Antiplatelet therapy for Reduction of MYocardial Damage during Angioplasty-Platelet Reactivity for Outcome Validation Effort) study. *JACC Cardiovasc Interv* 2012;5:281–9.
36 James BC, Savitz LA. How Intermountain trimmed health care costs through robust quality improvement efforts. *Health Aff* 2011;30:1185–91.
37 Rao SV, Ohman EM. Anticoagulant therapy for percutaneous coronary intervention. *Circ Cardiovasc Interv* 2010;3:80–8.
38 Shahzad A, Kemp I, Mars C, et al. Unfractionated heparin versus bivalirudin in primary percutaneous coronary intervention (HEAT-PPCI): an open-label, single centre, randomised controlled trial. *Lancet* 2014;384:1849–58.
39 Spertus JA, Gialde E, Chhatriwalla AK, et al. Testing an evidence-based, individualized informed consent form to improve patients' experiences with PCI. *Circulation* 2011;124:2368.