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Assessing the Risks of Bleeding vs Thrombotic Events in Patients at High Bleeding Risk After Coronary Stent Implantation
The ARC–High Bleeding Risk Trade-off Model

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IMPORTANCE Patients who are candidates for percutaneous coronary intervention (PCI) and are at high bleeding risk constitute a therapeutic challenge because they often also face an increased risk of thrombotic complications.

OBJECTIVES To develop and validate models to predict the risks of major bleeding (Bleeding Academic Research Consortium [BARC] types 3 to 5 bleeding) and myocardial infarction (MI) and/or stent thrombosis (ST) for individual patients at high bleeding risk and provide assistance in defining procedural strategy and antithrombotic regimens.

DESIGN, SETTING, AND PARTICIPANTS This prognostic study used individual patient data from 6 studies conducted from July 1, 2009, to September 5, 2017, for 6641 patients at more than 200 centers in Europe, the US, and Asia who underwent PCI and were identified as being at high bleeding risk using the Academic Research Consortium criteria. In 1 year of follow-up (excluding periprocedural events), individual patient risks of MI and/or ST and major bleeding were evaluated using 33 baseline variables. To validate these models, a subgroup of 1458 patients at high bleeding risk from the ONYX ONE trial were analyzed. Statistical analysis was performed from February 1, 2019, to April 30, 2020.

EXPOSURES All patients underwent PCI with bare metal, drug-coated, or drug-eluting stent implants.

MAIN OUTCOMES AND MEASURES Forward, stepwise multivariable proportional hazards models were used to identify highly significant predictors of MI and/or ST and BARC types 3 to 5 bleeding.

RESULTS A total of 6641 patients (4384 men [66.0%]; median age, 77.9 years [interquartile range, 70.0-82.6 years]) were included in this study. Over 365 days, nonperiprocedural MI and/or ST occurred in 350 patients (5.3%), and BARC types 3 to 5 bleeding occurred in 381 patients (5.7%). Eight independent baseline predictors of risk of MI and/or ST and 8 predictors for risk of BARC types 3 to 5 bleeding were identified. Four of these predictors were in both risk models. Both risk models showed moderate discrimination: C statistic = 0.69 for predicting MI and/or ST and 0.68 for predicting BARC types 3 to 5 bleeding. Applying these same models to the validation cohort gave a similar strength of discrimination (C statistic = 0.74 for both MI and/or ST and BARC types 3-5 bleeding). Patients with MI and/or ST had a mortality hazard ratio of 6.1 (95% CI, 4.8-7.7), and those with BARC types 3 to 5 bleeding had a mortality hazard ratio of 3.7 (95% CI, 2.9-4.8) compared with patients free of both events. Taking these data into account, the risk scores facilitate investigation of the individual patient trade-off between these 2 risks: 2931 patients (44.1%) at high bleeding risk in the 6 studies had a greater risk of MI and/or ST than of BARC 3 to 5 bleeding, 1555 patients (23.4%) had a greater risk of BARC 3 to 5 bleeding than of MI and/or ST, and 2155 (32.4%) had a comparable risk of both events.

CONCLUSIONS AND RELEVANCE In a large cohort of patients at high bleeding risk undergoing PCI, 2 prognostic models have been developed to identify individual patients' risk of major coronary thrombotic and bleeding events. In future clinical practice, using an application on a smartphone to evaluate the trade-off between these 2 quantifiable risks for each patient may help clinicians choose the most appropriate revascularization strategy and tailor the duration and intensity of antithrombotic regimens.

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Supplemental content

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Extending the duration and intensity of dual antiplatelet therapy (DAPT) after coronary stenting may be associated with a lower rate of myocardial infarction (MI) and stent thrombosis (ST), but it carries a bleeding risk that may adversely affect mortality.[1] Guidelines therefore recommend adjusting DAPT duration to individual patient needs.[2,3] The decision, however, remains a challenge for clinicians: bleeding and thrombotic events often have common predictors, and adapting treatment according to platelet function testing does not seem to improve outcomes.[4-6] Several scoring systems exist to assess either the thrombotic risk, the bleeding risk, or the balance of bleeding vs thrombotic events at different time points,[7-13] but these scores are best applied to the low- to moderate-risk populations from which they were derived.[14]

Recently, a previously neglected and heterogeneous group of patients at high bleeding risk who are undergoing percutaneous coronary intervention (PCI) has been identified, and a consensus definition has been proposed by the Academic Research Consortium (ARC).[15-21] These patients represent approximately 40% of candidates for PCI in routine clinical practice.[22-24] Bare metal stents have until recently been considered the default approach for such patients because it was believed they safely allowed treatment with DAPT for 1 month only. Two trials have now shown that, together with 1 month of treatment with DAPT, both a polymer-free biolimus A9-coated stent and a durable polymer zotarolimus-eluting stent were safer and more effective than bare metal stents for patients at increased bleeding risk.[15-18] Also, a bioabsorbable, polymer-coated everolimus-eluting stent was shown to be more effective than a bare metal stent with either 1 or 6 months of treatment with DAPT given to patients aged 75 years or older undergoing PCI.[19] For patients at increased bleeding risk treated with 1 month of DAPT In the ONYX ONE trial, a permanent polymer zotarolimus-eluting stent was shown to be noninferior to the biolimus A9-coated stent in terms of safety and effectiveness.[20]

Because both MI and/or ST and major bleeding are frequent in patients at high bleeding risk, the need for optimizing their management appears particularly important. The ability to evaluate both risks for an individual patient at the time of PCI should contribute to defining the safest procedural strategy (eg, choice of stent and complexity of procedure) as well as the intensity and duration of antithrombotic therapy. Using pooled patient-level data from 5 randomized clinical trials and 1 observational registry, we focused on a subset of patients who satisfied ARC high bleeding risk criteria[21] and assessed their 1-year risks of nonperiprocedural MI and/or ST and Bleeding Academic Research Consortium (BARC) types 3 to 5 bleeding after PCI, as well as the mortality risks associated with those 2 events. External validation was obtained from ONYX ONE trial patients.[20]

Key Points

Question How should the balance of bleeding and thrombotic risks for patients who are at high bleeding risk after percutaneous coronary intervention be assessed?

Findings In this prognostic study of 6641 patients at high bleeding risk pooled from 6 studies and followed up for 1 year, 350 patients at high bleeding risk (5%) sustained myocardial infarction (MI) and/or stent thrombosis (ST) and 381 patients (6%) experienced Bleeding Academic Research Consortium types 3 to 5 bleeding. There were 8 predictors for MI and/or ST and 8 for major bleeding, 4 of which predicted both; mortality after MI and/or ST was 1.9 times higher than after major bleeding.

Meaning This study suggests that predicting the absolute and relative risks of bleeding and MI and/or ST at the time of percutaneous coronary intervention may usefully contribute to clinical decision-making for individual patients at high bleeding risk.

Methods

Objective

All patients from 5 randomized clinical trials (CENTURY II [Clinical Evaluation of New Terumo Drug-Eluting Coronary Stent System in the Treatment of Patients With Coronary Artery Disease], ZEUS [Zotarolimus-Eluting Endeavor Sprint Stent in Uncertain DES Candidates], LEADERS FREE, LEADERS FREE II, and SENIOR) and 1 observational registry (PARIS [Patterns of Non-Adherence to Anti-Platelet Regimens in Stented Patients]), conducted from July 1, 2009, to September 5, 2017, in more than 200 centers in Europe, the US, and Asia were evaluated for the present prognostic study (eTable 1 in the Supplement).[15,17,19,25-27] We pooled patients from 3 trials focusing on patients at increased bleeding risk, 2 trials with broader inclusion criteria, and 1 large registry to improve the generalizability of our results. Adapting the criteria to fit the available information, a subset of patients with at least 1 major or 2 minor modified ARC high bleeding risk criteria was defined (eTable 2 in the Supplement).[21] We studied the risks of MI and/or ST and BARC types 3 to 5 bleeding occurring between 48 hours and 1 year after PCI and focused on MI and/or ST and BARC types 3 to 5 bleeding because those events are most likely to be associated with patient characteristics, procedure complexity, choice of stent, and DAPT duration.[11-13] We excluded periprocedural events (≤48 hours from PCI) because of controversy about the clinical relevance of periprocedural MI and the modifiable risk of access site-related bleeding. Also, patients were enrolled only at discharge in the PARIS registry.[27] A list of 33 candidate predictors for either event was the basis for creating multivariable predictors of the risks of MI and/or ST and BARC types 3 to 5 bleeding for each patient (eTable 3 in the Supplement). To assess the discrimination of our models, we compared them with the PARIS and the PRECISE (Predicting Bleeding Complications in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy) DAPT scores in our validation and derivation cohorts.[12,13] Institutional review board approval was not required because this study is a secondary analysis of deidentified data centrally transferred to the London School of Hygiene and Tropical Medicine.

End Points

Myocardial infarction and/or ST was defined as the first occurrence of either a stent-related coronary thrombotic complication (definite or probable ST according to ARC) and/or any MI that was not periprocedural (ie, occurring >48 hours after the index or staged procedure for each of the randomized trials and after patient discharge in the PARIS registry). Myocardial infarction was defined according to each study protocol (ad hoc definition for ZEUS, ARC for CENTURY II, and third universal definition[28] for the other 5 studies), and major bleeding was defined as the first occurrence of BARC type 3, 4, or 5 bleeding for all studies.[28-30] The independent event committee of each study adjudicated all thrombotic or ischemic and bleeding events.

External Validation

For external validation, we analyzed a subgroup of patients who underwent PCI in the ONYX ONE trial and satisfied at least 1 major or 2 minor adapted ARC high bleeding risk criteria.[20,21] We used the same definition of MI and/or ST (third universal definition for MI) and bleeding (BARC types 3 to 5) and excluded events that occurred within 48 hours after the index procedure.[28,30]

Statistical Analysis

Statistical analysis was performed from February 1, 2019, to April 30, 2020. For the 6641 patients at high bleeding risk in the development cohort, 33 candidate predictors were considered for inclusion in risk prediction models for MI and/or ST or BARC types 3 to 5 bleeding. Multivariable models were built using forward stepwise variable selection, with $P < .05$ required for inclusion. For each outcome, forward stepwise variable selection was used to select the set of independent predictors that formed the final multivariable model. The Harrell C statistic was used to assess discrimination. To assess each model's fit, patients were categorized into approximately equal ordered quintiles of risk: observed and model-predicted percentage of patients with the event (BARC types 3-5 bleeding and MI and/or ST) over 1 year were compared. The same 2 risk models were then applied to the validation cohort of 1458 patients with ARC high bleeding risk in the ONYX ONE trial using the same methods to document risk discrimination and model fit. To assess the predictive accuracy of risk models for BARC types 3 to 5 bleeding and MI and/or ST, we applied baseline hazard functions and hazard ratios (HRs) derived in the development cohort to eligible patients from the ONYX ONE trial and calculated the C statistic for each separate event type. A scatterplot was created to document simultaneously each patient's 1-year predicted risks of BARC types 3 to 5 bleeding and MI and/or ST.

The respective associations of BARC types 3 to 5 bleeding and MI and/or ST with mortality were assessed using Cox proportional hazards regression models. These events were fitted as time-updated covariates with death as the outcome variable. We adjusted for baseline variables significantly predictive of mortality risk (eTable 7 in the Supplement). From this model, we could calculate excess mortality hazard associated with BARC types 3 to 5 bleeding and MI and/or ST. The ratio of these excess hazards was used to produce an adjusted mortality-weighted line of equal trade-off on the above-mentioned scatterplot. Whether a patient's risk of MI and/or ST was more or less prognostically important than their BARC types 3 to 5 bleeding risk depended on whether their position on the scatterplot was above (or below) this line of equal trade-off. Analyses were performed using Stata, version 16.0 (StataCorp LLC). All *P* values were from 2-sided tests, and results were deemed statistically significant at $P < .05$.

Results

A total of 12 517 patients from 6 studies were eligible for evaluation (eTable 1 in the Supplement). Based on the adapted ARC high bleeding risk criteria (eTable 2 in the Supplement), 6641 patients satisfied at least 1 major or 2 minor criteria and were thus considered to be at high bleeding risk. **Table 1** shows the baseline and procedural characteristics of the ARC high bleeding risk group.[31] At 365 days, after excluding periprocedural events, 381 patients (5.7%) had BARC types 3 to 5 bleeding, and 350 (5.3%) experienced an MI and/or ST (312 MIs [4.7%] and 104 [1.6%] STs). Sixty patients (0.9%) experienced both types of event during follow-up: 27 patients had BARC types 3 to 5 bleeding after MI and/or ST, 18 patients experienced MI and/or ST after BARC types 3 to 5 bleeding, and 15 experienced both events on the same day. The median delay between both events was 14.5 days (interquartile range, 0.5-76 days). At 1 year after the procedure, 79 patients with BARC types 3 to 5 bleeding (20.7%), 90 patients with MI and/or ST (25.7%), and 16 (26.7%) patients with both events had died. Among 5970 patients who experienced neither event, 357 (6.0%) died. Compared with patients without the event, the HR for death after BARC types 3 to 5 bleeding was 3.7 (95% CI, 2.9-4.8) and after MI and/or ST was 6.1 (95% CI, 4.8-7.7). The ratio of excess mortality was thus (6.1 − 1)/(3.7 − 1) = 1.9 times higher after MI and/or ST than after BARC types 3 to 5 bleeding (**Figure 1**).

Among 5876 patients in the 6 studies who were not ARC high bleeding risk, 73 (1.2%) had BARC types 3 to 5 bleeding, and 146 (2.5%) had MI and/or ST at 365 days (eTable 5 in the Supplement). The risks of BARC types 3 to 5 bleeding and of MI and/or ST both increased with the number of ARC high bleeding risk criteria satisfied; this trend was more marked for BARC types 3 to 5 bleeding (eTable 6 in the Supplement).

Risk Prediction Models

We identified 12 baseline or procedural characteristics associated with either MI and/or ST or BARC types 3 to 5 bleeding (**Table 2**).[31] Anemia (MI and/or ST: HR, 1.50; 95% CI, 1.12-1.99; BARC types 3-5 bleeding: HR, 3.99; 95% CI, 3.06-5.20), kidney insufficiency (MI and/or ST: HR, 1.69; 95% CI, 1.20-2.37; BARC types 3-5 bleeding: HR, 1.43; 95% CI, 1.04-1.96), current smoking (MI and/or ST: HR, 1.48; 95% CI, 1.09-2.01; BARC types 3-5 bleeding: HR, 1.47; 95% CI, 1.08-1.99), and a complex PCI procedure (MI and/or ST: HR, 1.50; 95% CI, 1.21-1.85; BARC types 3-5 bleeding: HR, 1.32; 95% CI, 1.07-1.61) were significantly associated with increased risk of both MI and/or ST and major bleeding. Four variables were associated only with

Table 1. Baseline Characteristics of the Study Population

Characteristic	Patients, No./total No. (%)			
	All (N = 6641)	With BARC types 3-5 bleeding (n = 381)[a]	With MI and/or ST (n = 350)[a]	With neither event (n = 5970)
Baseline characteristics				
Age, median (IQR), y	77.9 (70.0-82.6)	77.9 (70.6-83.0)	78.1 (69.2-82.5)	77.9 (70.0-82.6)
Female	2257/6641 (34.0)	138/381 (36.2)	107/350 (30.6)	2032/5970 (34.0)
Diabetes (requiring treatment with either insulin or oral medication)	2327/6634 (35.1)	146/380 (38.4)	164/350 (46.9)	2048/5964 (34.3)
BMI, median (IQR)	26.6 (24.0-29.9)	26.4 (23.5-30.0)	26.5 (23.8-29.8)	26.6 (24.0-30.0)
History of hypertension	5462/6633 (82.3)	321/381 (84.3)	292/350 (83.4)	4901/5962 (82.2)
Current smoker	697/6596 (10.6)	50/375 (13.3)	49/349 (14.0)	609/5932 (10.3)
Hypercholesterolemia	4272/6593 (64.8)	240/379 (63.3)	225/345 (65.2)	3851/5928 (65.0)
Previous CABG	809/6553 (12.3)	54/379 (14.2)	58/347 (16.7)	706/5887 (12.0)
Previous MI	1558/6527 (23.9)	95/377 (25.2)	132/347 (38.0)	1345/5863 (22.9)
Congestive heart failure	608/4162 (14.6)	57/263 (21.7)	37/220 (16.8)	521/3712 (14.0)
Peripheral artery disease	920/5602 (16.4)	66/347 (19.0)	62/285 (21.8)	804/5024 (16.0)
COPD	554/4947 (11.2)	50/291 (17.2)	35/280 (12.5)	476/4416 (10.8)
STEMI or NSTEMI at presentation	1737/6577 (26.4)	112/377 (29.7)	139/346 (40.2)	1499/5914 (25.3)
Plasma creatinine, median (IQR), mg/DL	0.62 (0.47-0.85)	0.60 (0.43-0.84)	0.59 (0.43-0.78)	0.62 (0.47-0.85)
Hemoglobin, mean (SD), g/L	12.6 (1.9)	11.7 (2.0)	12.2 (1.9)	12.7 (1.8)
ARC high bleeding risk criteria (adapted)[b]				
Aged >75 y	4259/6641 (64.1)	237/381 (62.2)	222/350 (63.4)	3831/5970 (64.2)
Anemia				
Mild	1896/6641 (28.5)	104/381 (27.3)	119/350 (34.0)	1696/5970 (28.4)
Moderate or severe	1239/6641 (18.7)	142/381 (37.3)	87/350 (24.9)	1033/5970 (17.3)
Platelet count <100 000/mm^3	198/6641 (3.0)	10/381 (2.6)	18/350 (5.1)	172/5970 (2.9)
Hospital admission for bleeding in past 12 mo and/or transfusion for anemia during prior 4 wk	185/6641 (2.8)	16/381 (4.2)	11/350 (3.1)	160/5970 (2.7)
Intracranial bleeding or stroke in the previous 12 mo	511/6641 (7.7)	23/381 (6.0)	23/350 (6.6)	468/5970 (7.8)
eGFR, mL/min				
30-59	3171/6641 (47.7)	165/381 (43.3)	174/350 (49.7)	2860/5970 (47.9)
<30	603/6641 (9.1)	56/381 (14.7)	52/350 (14.9)	506/5970 (8.5)
Severe liver disease	57/6641 (0.9)	5/381 (1.3)	3/350 (0.9)	49/5970 (0.8)
Cancer in previous 3 y[c]	579/6641 (8.7)	43/381 (11.3)	30/350 (8.6)	512/5970 (8.6)
Planned major surgery in next 12 mo	655/6641 (9.9)	46/381 (12.1)	37/350 (10.6)	580/5970 (9.7)
Oral anticoagulation planned after PCI	2086/6641 (31.4)	153/381 (40.2)	103/350 (29.4)	1848/5970 (31.0)
Glucocorticoids or NSAIDs planned after PCI	136/6641 (2.0)	15/381 (3.9)	8/350 (2.3)	115/5970 (1.9)
Angiographic and procedural characteristics				
Multivessel disease	3115/6362 (49.0)	194/357 (54.3)	208/343 (60.6)	2749/5720 (48.1)
BMS implanted	2290/6641 (34.5)	133/381 (34.9)	153/350 (43.7)	2029/5970 (34.0)
No. of stents implanted, mean (SD)	1.8 (1.1)	1.9 (1.3)	2.1 (1.4)	1.8 (1.1)
Complex PCI procedure[d]	2289/6641 (34.5)	159/381 (41.7)	159/350 (45.4)	2013/5970 (33.7)
Multivessel procedure	2081/6641 (31.3)	132/381 (34.6)	145/350 (41.4)	1831/5970 (30.7)
Lesion				
Left main	280/6641 (4.2)	29/381 (7.6)	28/350 (8.0)	231/5970 (3.9)
Bifurcation	751/5713 (13.1)	60/351 (17.1)	43/288 (14.9)	659/5128 (12.9)
Saphenous vein	105/6641 (1.6)	9/381 (2.4)	12/350 (3.4)	86/5970 (1.4)

Abbreviations: ARC, Academic Research Consortium; BARC, Bleeding Academic Research Consortium; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); BMS, bare metal stent; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; IQR, interquartile range; MI, myocardial infarction; NSAIDs, nonsteroidal anti-inflammatory drugs; NSTEMI, non–ST-segment elevation MI; PCI, percutaneous coronary intervention; ST, definite or probable stent thrombosis; STEMI, ST-segment elevation MI.

SI conversion factors: To convert creatinine to micromoles per liter, multiply by 88.4; hemoglobin to grams per liter, multiply by 10.0.

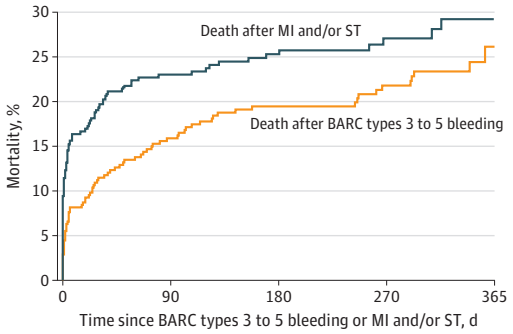
[a] Periprocedural events (≤48 hours) excluded.

[b] Adapted ARC high bleeding risk criteria are in eTable 1 in the Supplement.

[c] Excluding nonmelanoma skin cancer.

[d] As defined by Giustino et al.[31]

Figure 1. One-Year Mortality Associated With Bleeding Academic Research Consortium (BARC) Types 3 to 5 Bleeding and Myocardial Infarction (MI) and/or Stent Thrombosis (ST)



No. at risk

BARC types 3 to 5 bleeding	381	274	215	161
MI and/or ST	350	233	175	106

Patients with MI and/or ST compared with those without had a hazard ratio of death during the 1-year follow-up period of 6.1 (95% CI, 4.8-7.7). Patients with BARC types 3 to 5 bleeding compared with those without had a hazard ratio of death during the 1-year follow-up period of 3.7 (95% CI, 2.9-4.8).

BARC types 3 to 5 bleeding (aged ≥65 years [HR, 1.50; 95% CI, 1.08-2.08]; chronic obstructive pulmonary disease [HR, 1.39; 95% CI, 1.05-1.83]; a composite of cancer, severe liver disease, or planned surgery [HR, 1.63; 95% CI, 1.27-2.09]; and planned oral anticoagulation after PCI [HR, 2.00; 95% CI, 1.62-2.48]). Four variables were significantly associated with MI and/or ST only (prior MI [HR, 1.89; 95% CI, 1.52-2.35], diabetes treated with either insulin or oral medication [HR, 1.56; 95% CI, 1.26-1.93], ST-segment elevation MI or non–ST-segment elevation MI presentation [HR, 1.82; 95% CI, 1.46-2.25], and use of bare metal stents [HR, 1.53; 95% CI, 1.23-1.89]). The 2 models showed moderate discrimination, with C statistics = 0.68 for predicting BARC types 3 to 5 bleeding and 0.69 for predicting MI and/or ST. The distribution of the predicted 1-year risk of BARC types 3 to 5 bleeding and MI and/or ST is shown in eFigure 1 in the Supplement. Because of the well-recognized association of acute coronary syndrome presentation with thrombotic complications and that of oral anticoagulant use with bleeding, we completed sensitivity analyses of our models for those 2 subgroups (eTables 11 and 12 in the Supplement).

A comparison of the observed and predicted rates of BARC types 3 to 5 bleeding and MI and/or ST for patients classified in 5 ordered quintiles of risk showed a good model fit (**Figure 2**A and B). For both BARC types 3 to 5 bleeding and MI and/or ST, patients in the top quintile had more than 5 times the risk of those in the bottom quintile (12.0% [184 of 1531] vs 2.1% [28 of 1325] for BARC types 3-5 bleeding and 11.5% [154 of 1339] vs 1.5% [19 of 1307] for MI and/or ST). The predicted risks of MI and/or ST and major bleeding for every individual patient (6641 in all) are simultaneously plotted in **Figure 3**A. When the adjusted mortality risks of both types of adverse events were taken into account, the line of equal risk trade-off was shifted down. Figure 3B shows that, accounting for the associated mortality, there were 1555 patients (23.4%) with a greater predicted risk of BARC types 3 to 5 bleeding than of MI and/or ST, while 2931 patients (44.1%) had a greater risk of MI and/or ST than of BARC types 3 to 5 bleeding and 2155 patients (32.4%) were in a "white zone" (between the line of equal trade-off and the associated mortality-weighted line) where the risk of both types of events can be considered comparable.

External Validation

We validated our risk trade-off model by applying it to a predefined subset of patients from the ONYX ONE trial who underwent PCI.[20] Of 1996 enrolled patients, 213 were excluded because BARC types 3 to 5 bleeding, MI and/or ST, or death occurred during the first 48 hours after the procedure or because of loss to follow-up. Among the remaining 1783 patients, 1458 satisfied the adapted ARC high bleeding risk criteria and were used for validation. The C statistic of our trade-off model was 0.74 for BARC types 3 to 5 bleeding and 0.74 for MI and/or ST in this validation cohort. Between days 3 and 365, BARC types 3 to 5 bleeding occurred in 58 patients (4.0%) and MI and/or ST occurred in 110 patients (7.5%), respectively lower and higher than in our database of patients at high bleeding risk in 6 studies. Hence, our models tended to overestimate the risk of BARC types 3 to 5 bleeding and underestimate the risk of MI and/or ST in this validation cohort. Both BARC types 3 to 5 bleeding and MI and/or ST showed a marked risk gradient when classifying patients into 5 ordered quintiles (eFigure 2A and B in the Supplement). Again, for both outcomes, patients classified in the top quintile had more than 5 times the risk of those in the bottom quintile (8.1% [27 of 334] vs 1.5% [4 of 261] for BARC types 3-5 bleeding and 17.1% [51 of 299] vs 2.3% [6 of 261] for MI and/or ST).

When applied to our validation cohort, the C statistics for the PARIS score were 0.63 for BARC types 3 to 5 bleeding and 0.64 for MI and/or ST. The C statistic for BARC types 3 to 5 bleeding using PRECISE DAPT (alternative model without the white blood cell count) was 0.68. For the derivation cohort, the comparisons of C statistics are reported in eTable 9 of the Supplement.

Discussion

Our study found that patients at high bleeding risk who experience BARC types 3 to 5 bleeding and MI and/or ST events during the first year after PCI have a marked increased risk of death compared with other patients at high bleeding risk. In addition, the adjusted excess risk almost doubles for MI and/or ST compared with BARC types 3 to 5 bleeding.

Our study also found that, based on multivariable models, it is possible to predict 1-year risks of BARC types 3 to 5 bleeding and MI and/or ST for individual patients who meet criteria for ARC high bleeding risk and compare them (Figure 3A). Each model uses 8 readily available patient and procedural features. This comparison of thrombotic and bleeding risks can be further improved by taking the adjusted mortality risk of both events into account (Figure 1). Three patient groups can be defined (Figure 3B): those with a mortality-weighted bleeding risk higher than their thrombotic risk (23.4%), those with a thrombotic risk higher than their bleed-

Table 2. Multivariate Predictors of BARC Types 3 to 5 Bleeding and MI and/or ST at 365 Days

	BARC types 3-5 bleeding		MI and/or ST	
Predictor	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Aged ≥65 y	1.50 (1.08-2.08)	.01	NA	NA
Diabetes (requiring treatment with either insulin or oral medication)	NA	NA	1.56 (1.26-1.93)	<.001
Prior MI	NA	NA	1.89 (1.52-2.35)	<.001
Liver disease, cancer, or surgery[a]	1.63 (1.27-2.09)	.0001	NA	NA
COPD	1.39 (1.05-1.83)	.02	NA	NA
Current smoker	1.47 (1.08-1.99)	.01	1.48 (1.09-2.01)	.009
NSTEMI or STEMI presentation	NA	NA	1.82 (1.46-2.25)	<.001
Hemoglobin, g/dL				
≥13	1 [Reference]	<.001	1 [Reference]	.005
11-12.9	1.69 (1.30-2.20)		1.27 (0.99-1.63)	
<11	3.99 (3.06-5.20)		1.50 (1.12-1.99)	
eGFR, mL/min				
≥60	1 [Reference]	.02	1 [Reference]	.001
30-59	0.99 (0.79-1.24)		1.30 (1.03-1.66)	
<30	1.43 (1.04-1.96)		1.69 (1.20-2.37)	
Complex procedure[b]	1.32 (1.07-1.61)	.008	1.50 (1.21-1.85)	<.001
Bare metal stent[c]	NA	NA	1.53 (1.23-1.89)	<.001
OAC at discharge	2.00 (1.62-2.48)	<.001	NA	NA
C statistic	0.68	NA	0.69	NA

Abbreviations: ARC, Academic Research Consortium; BARC, Bleeding Academic Research Consortium; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; HR, hazard ratio; MI, myocardial infarction; NA, not applicable; NSTEMI, non–ST-segment elevation MI; OAC, oral anticoagulants; ST, definite or probable stent thrombosis; STEMI, ST-segment elevation MI.

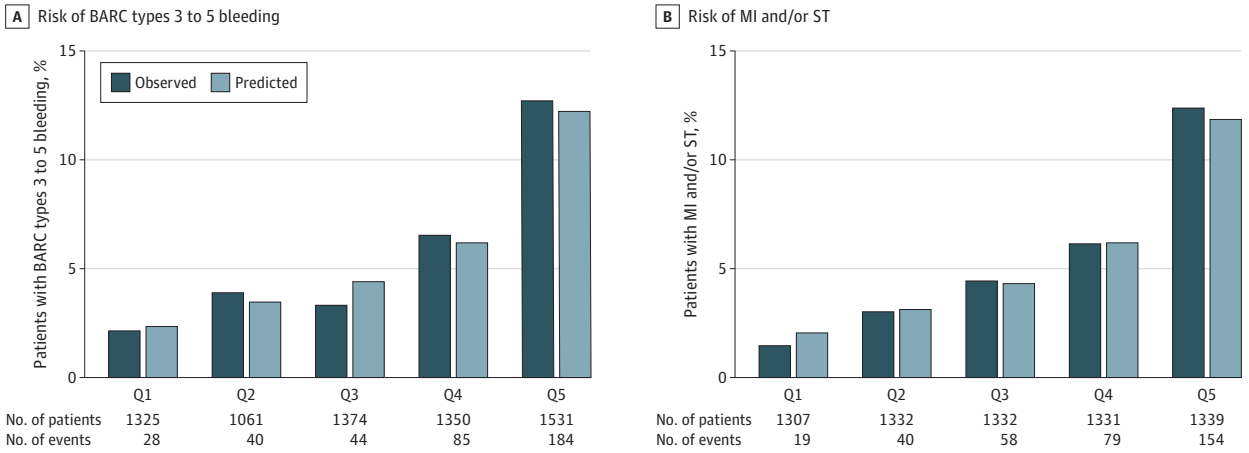
SI conversion factor: To convert hemoglobin to grams per liter, multiply by 10.0.

[a] At least 1 of 3 modified ARC high bleeding risk criteria (cancer, severe liver disease, and planned major surgery; eTable 1 in the Supplement).

[b] As defined by Giustino et al.[31]

[c] Compared with drug-eluting stents or drug-coated stents.

Figure 2. Observed and Predicted Risk of Bleeding Academic Research Consortium (BARC) Types 3 to 5 Bleeding and Myocardial Infarction (MI) and/or Stent Thrombosis (ST) by Risk Strata Quintiles (Q1 to Q5)

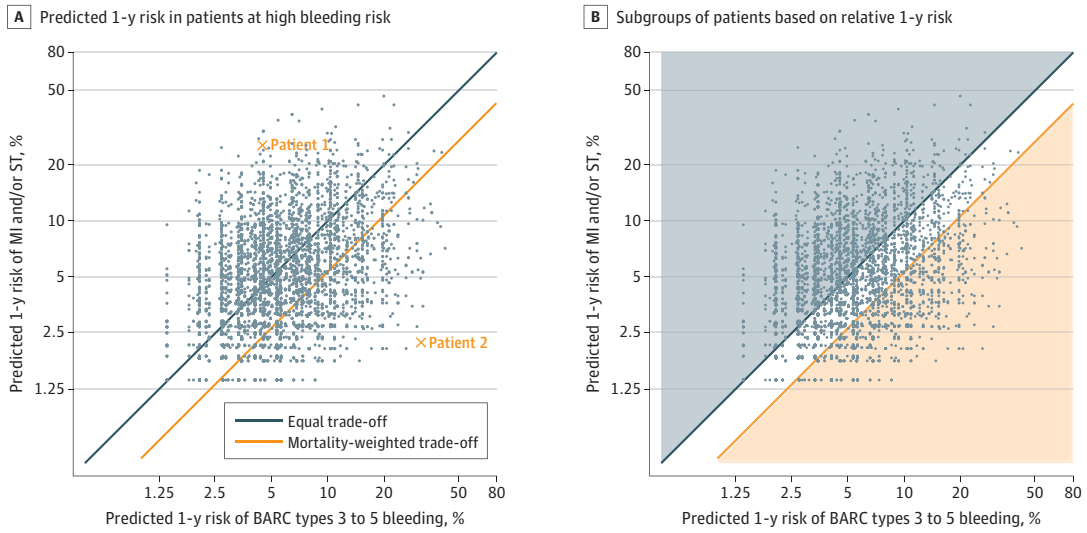


ing risk (44.1%), and those in a "white zone" (32.4%) for whom the risk of bleeding occurring is higher than the risk of MI and/or ST, but the associated mortality is greater for MI and/or ST. A dedicated smartphone application to evaluate the trade-off between these 2 quantifiable risks for use at the bedside is being designed and will be available shortly. Together with a clinical assessment, this information may be of help when considering the indication for PCI, revascularization strategy (eg, vascular access, periprocedural medication, choice of stent, and procedure complexity), and antithrombotic regimen after the procedure for an individual patient.

Our study also found that patients meeting ARC high bleeding risk criteria had more than 4 times greater risk of BARC types 3 to 5 bleeding and more than 2 times greater risk of MI and/or ST than patients not at high bleeding risk. These findings fit with previous reports.[22-24]

External validation was achieved using patients at high bleeding risk from the ONYX ONE trial and showed good discrimination. In both the development and validation cohorts for both MI and/or ST and major bleeding, our model showed that patients in the top quintile of risk have more than 5 times the event rate compared with those in the lowest risk quintile. Patients at high bleeding risk in the ONYX ONE trial had a lower-than-expected risk of bleeding and a higher-than-expected risk of MI and/or ST: the former is potentially associated with differing use of the BARC definitions by clinical

Figure 3. Predicted Risks of Bleeding Academic Research Consortium (BARC) Types 3 to 5 Bleeding and Myocardial Infarction (MI) and/or Stent Thrombosis (ST) for Patients at High Bleeding Risk



A, Plot of predicted 1-year risk of MI and/or ST and BARC types 3 to 5 bleeding (log scales) in patients at high bleeding risk according to the Academic Research Consortium. The equal trade-off line corresponds to the points where the risk of either BARC types 3 to 5 bleeding or MI and/or ST occurrence is the same. The mortality-weighted line takes the associated mortality of both events into account. Two examples are provided. Patient 1 is a 56-year-old woman who presents with a non–ST-elevation MI. Her medical history includes a previous MI 2 years ago, diabetes, active smoking, and osteoporosis treated with long-term ibuprofen. Her hemoglobin level is 12.0 g/dL (to convert to grams per liter, multiply by 10.0) and estimated glomerular filtration rate (eGFR) is 40 mL/min. She was treated with complex percutaneous coronary intervention (4 drug-eluting stents [DES]) and discharged with a regimen of ticagrelor plus aspirin. Patient 2 is a 79-year-old man with atrial fibrillation taking an oral anticoagulant (OAC) who presents with exertional angina. He is an ex-smoker (stopped 2 years ago) with chronic obstructive lung disease and underwent a hemicolectomy for cancer 6 months ago. His hemoglobin level is 10.5 g/dL and eGFR is 70 mL/min. He was treated with percutaneous coronary intervention (single DES to the proximal left anterior descending coronary artery) and discharged with a regimen of clopidogrel and OAC. B, Subgroups of patients based on relative 1-year risk of MI and/or ST and BARC types 3 to 5 bleeding (log scale). The gray zone indicates 2931 of 6641 patients (44.1%) with a greater risk of a thrombotic event (MI and/or ST) than a BARC types 3 to 5 bleeding event. The orange zone indicates 1555 of 6641 patients (23.4%) with a mortality-weighted greater risk associated with a BARC types 3 to 5 event than with a thrombotic event (MI and/or ST). The white zone indicates 2155 patients (32.4%) who can be considered to face a comparable risk of either type of adverse event.

events committees and the latter may be owing to more comprehensive angiographic and biomarker assessment of MI and/or ST in ONYX ONE, leading to more clinical events committee-adjudicated MIs but with a relatively low associated mortality (eTable 8 in the Supplement).[30,32]

Others have reported that bleeding risks were greater than, equal to, or inferior to thrombotic and/or ischemic risks after PCI.[33-36] Although it is possible that the relative mortality risks of MI and/or ST and BARC types 3 to 5 bleeding observed in our series differ from those of patients not at high bleeding risk because of baseline comorbidities, any model for predicting the trade-off between thrombotic and bleeding events is highly dependent on the population studied, the procedures performed, the prescribed DAPT regimen, the event definitions used, the duration of the observation period, and the timing of risk assessment. We specifically considered patients at high bleeding risk, for whom the stakes are high and the issue therefore of particular importance. We decided to exclude periprocedural events from our analysis because there is no consensus regarding the best definition and the prognostic implications of periprocedural MI. Excluding periprocedural events may have tilted the scales toward the MI and/or ST mortality risk in our model because, while periprocedural bleeding has been shown to carry a prognostic risk, small periprocedural MIs are often without clinical significance. Had these events been part of our model, the overall mortality risk associated with MI would probably have appeared lower.[37,38]

The PARIS score[12] was based on 4190 patients undergoing PCI who were enrolled in an all-comers registry at discharge after successful PCI using drug-eluting stents and guideline-recommended DAPT. After 2 years, MI and/or ST occurred in 3.8% of patients and BARC types 3 to 5 bleeding occurred in 3.3% of patients. Using 6 baseline predictors each for BARC types 3 to 5 bleeding and MI and/or ST after discharge, the study concluded that patients with the highest thrombotic risk (16.6% of the entire cohort) might benefit from prolonging DAPT beyond 12 months irrespective of their bleeding risk, whereas those with the lowest thrombotic risk (53.3% of the cohort) would not benefit from prolonged DAPT. Both anemia and need for DAPT plus oral anticoagulation predicted bleeding in the PARIS score, but less markedly than in our own model, and several other PARIS bleeding predictors were not as predictive in our score. For patients meeting ARC high bleeding risk criteria in our validation cohort, the PARIS score performed less well than our own model (BARC types 3-5 bleeding: C statistic, 0.63 vs 0.74; MI and/or ST: C statistic, 0.64 vs 0.74).

The PRECISE-DAPT score[13] pooled data from 14 963 patients in 8 randomized clinical trials, none of whom were

treated with oral anticoagulants. After 1 year, Thrombolysis in Myocardial Infarction minor or major bleeding occurred in 1.3% of patients. The authors identified 5 variables (age, creatinine clearance, hemoglobin, white blood cell count, and previous spontaneous bleeding) that predicted nonperiprocedural bleeding after PCI. Comparing patients randomized to receive short-term (3-6 months) vs long-term (12-24 months) DAPT, the study found that longer DAPT duration significantly increased bleeding in patients at high bleeding risk but not in others. A benefit associated with prolonged DAPT occurred only in the latter group. Three of their bleeding predictors are also included in our model, but their definition, cutoff values, and relative weights differ. For patients meeting ARC high bleeding risk criteria in our validation cohort, the PRECISE-DAPT score (alternative model without the white blood cell count) also performed somewhat less well than our own model (BARC types 3-5 bleeding: C statistic, 0.68 vs 0.74).

This outcome confirms that the population of all patients undergoing PCI differ markedly from those at high bleeding risk. The former generally receive longer courses of DAPT, their thrombotic and bleeding events rates are lower, and several predictors of adverse events, especially bleeding, differ in both quantity and quality from those in our model. Choosing the appropriate score for an individual patient must therefore depend on prior identification of their risk profile.[14] Given the limitations of all trade-off scores, it may also be appropriate to consider the degree by which one risk differs from the other when deciding how much weight to give the result in the clinical decision process. The 2 patient examples in Figure 3A are illustrative of how extreme the trade-off can be for patients who both meet ARC high bleeding risk criteria.

A notable finding in our database of patients at high bleeding risk is the often-overlooked importance of baseline hemoglobin: even mild World Health Organization–defined anemia carries an increased risk of both bleeding and MI and/or ST, while moderate or severe anemia (hemoglobin, <11 g/dL [to convert to grams per liter, multiply by 10.0]) predicts a 4-fold increase in bleeding risk.[39] A meta-analysis of 6 DAPT duration trials of patients at low to moderate bleeding risk suggested that a longer DAPT course is associated with benefits in patients undergoing complex PCI but not in other patients.[31] In our study, complex PCI predicted both MI and/or ST and BARC types 3 to 5 bleeding. Although the increased MI and/or ST risk is consistent with previous findings, the increased bleeding risk may be explained in part by more aggressive and/or prolonged antithrombotic therapy after complex procedures and by a greater need for repeated PCI procedures during follow-up (eTable 10 in the Supplement). Only 0.9% of our patients experienced both BARC types 3 to 5 bleeding and an MI and/or ST event during the 1-year follow-up period. This low incidence is comparable with that reported by others and suggests that the "classic" sequence of bleeding-induced interruption of antithrombotic treatment leading to MI and/or ST is a relatively rare occurrence.[33,40]

Limitations

This study has some limitations. First, we used adapted ARC high bleeding risk criteria rather than using exactly those defined by consensus.[20] This protocol was necessary to fit with available information in the 7 data sets, but the key criteria required no adjustments (eTable 2 in the Supplement). Comparable adjustments were done for other recent series.[22-24] It is likely that our findings would have changed negligibly had full information on true ARC high bleeding risk criteria been available. Second, several infrequent risk factors were not retained among the final multivariate predictors. We attempted to partially compensate for this outcome by using a composite of cancer, severe liver disease, and planned major surgery as a single predictor, but other relatively rare but well-recognized predictors for BARC types 3 to 5 bleeding (thrombocytopenia) or MI and/or ST (saphenous vein target lesion) are absent. Our model is thus intended as a complement to the clinical assessment of an individual patient, not as a standalone approach for assessing bleeding and thrombotic risks. Third, DAPT duration was protocol driven for 4 of the studies[15,17,19,25] and guideline based in 2 studies (eTable 4 in the Supplement).[26,27] Information regarding the risks and benefits associated with different DAPT regimens can therefore not be obtained from our data. Furthermore, no definitive conclusions can be made concerning the potential association of different antithrombotic strategies with the risks of bleeding and thrombotic events or with their respective associated mortality because our model does not provide evidence that modifying treatment would have an association with outcome. Fourth, our modeling was conceived for assessing the MI and/or ST vs bleeding trade-off for patients meeting ARC high bleeding risk criteria at the time of PCI. Our model required the ARC high bleeding risk status to first be defined and is not applicable to all patients undergoing PCI.[21] Also, both risks change over time; hence, our findings are not well suited for reassessing risks during follow-up. Fifth, no information on vascular access site was available in some studies. This factor is unlikely to have been an important predictor, however, since periprocedural events were excluded.

Conclusions

The ARC high bleeding risk criteria identify a subset of patients undergoing PCI with a more than 4-fold increase in BARC types 3 to 5 bleeding risk and doubling of MI and/or ST risk. In a large cohort of patients at high bleeding risk undergoing PCI, 2 prognostic models have been developed and may be used with a handheld smartphone application to identify with moderate discrimination the risks of major coronary thrombotic and bleeding events for individual patients. In future clinical practice, knowledge of the trade-off between these 2 quantifiable risks for each patient may help tailor their optimal management.

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Acquisition, analysis, or interpretation of data: Urban, Gregson, Owen, Mehran, Windecker, Valgimigli, Varenne, Saito, Baber, Chevalier.
Drafting of the manuscript: Urban, Gregson.
Critical revision of the manuscript for important intellectual content: Urban, Owen, Mehran, Windecker, Valgimigli, Varenne, Krucoff, Saito, Baber, Chevalier, Capodanno, Morice, Pocock.
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Supervision: Urban, Mehran, Varenne, Krucoff, Saito, Chevalier, Capodanno, Morice.

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