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ORIGINAL RESEARCH

Factors Related to Major Bleeding After Ticagrelor Therapy: Results from the TICO Trial

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BACKGROUND: There is a lack of data on factors that are related to clinically relevant bleeding after ticagrelor treatment. We investigated the clinical and procedural factors related to major bleeding in patients with acute coronary syndrome treated with ticagrelor after coronary stent implantation.

METHODS AND RESULTS: From the TICO (Ticagrelor Monotherapy After 3 Months in Patients Treated With New Generation Sirolimus-Eluting Stent for Acute Coronary Syndrome) randomized trial, a total of 2660 patients were included for the present study. Patients with major bleeding, defined by TIMI (Thrombolysis in Myocardial Infarction) major or Bleeding Academic Research Consortium type 3 or 5, were compared with those without major bleeding. On the basis of multivariable and receiver operating characteristic curve analyses, weight ≤65 kg, hemoglobin ≤12 g/dL, and estimated glomerular filtration rate <60 mL/min per 1.73 m^2 were associated with an increased risk of major bleeding. In contrast, 3-month aspirin therapy with continued ticagrelor (versus 12-month aspirin and ticagrelor) was associated with a decreased risk of major bleeding. The lower risk of a net adverse clinical event (a composite of TIMI major bleeding and major adverse cardiac and cerebrovascular events) in patients treated with 3-month aspirin therapy reported from the TICO trial remained valid in patients with any of these risk factors (hazard ratio, 0.59; 95% CI, 0.39–0.90; $P_{interaction}$=0.74).

CONCLUSIONS: Low body weight, anemia, and chronic kidney disease were risk factors for major bleeding after ticagrelor therapy. Early aspirin discontinuation had a net clinical benefit among patients with a bleeding risk.

REGISTRATION: URL: https://www.clinicaltrials.gov/. Unique Identifier: NCT02494895.

Key Words: acute coronary syndrome ■ antiplatelet therapy ■ drug-eluting stent

It is reasonable to use ticagrelor in preference to clopidogrel for maintenance P2Y12 inhibitor therapy in patients with acute coronary syndrome (ACS) treated with dual antiplatelet therapy (DAPT) after coronary stent implantation.[1,2] Although ticagrelor reduces ischemic events in these patients, bleeding is a major treatment-related concern. In the PLATO (Platelet Inhibition and Patient Outcomes) trial,[3] ticagrelor (compared with clopidogrel) resulted in fewer ischemic complications but led to more frequent major bleeding events not related to coronary artery bypass grafting. Results from a recent network meta-analysis confirmed increased bleeding with ticagrelor treatment compared with clopidogrel.[4] Given the beneficial effects of this potent P2Y12 inhibitor on ischemia, it is clinically essential to assess the risk of bleeding with ticagrelor therapy.

On the basis of the above, we sought to evaluate the clinical and procedural factors related to clinically

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CLINICAL PERSPECTIVE

What Is New?

- Low body weight, anemia, and chronic kidney disease increase major bleeding risk after ticagrelor therapy.

What Are the Clinical Implications?

- These bleeding factors may be considered for adopting ticagrelor as P2Y12 inhibitor therapy among patients with acute coronary syndrome undergoing drug-eluting stent implantation.

Non-standard Abbreviations and Acronyms

BARC	Bleeding Academic Research Consortium
DAPT	dual antiplatelet therapy
TICO	Ticagrelor Monotherapy After 3 Months in Patients Treated With New Generation Sirolimus-Eluting Stent for Acute Coronary Syndrome
TIMI	Thrombolysis in Myocardial Infarction

relevant bleeding in patients with ACS treated with ticagrelor after coronary stent implantation.

METHODS

The data that support the findings of this study are available from the corresponding author on reasonable request.

Study Population

From the TICO (Ticagrelor Monotherapy After 3 Months in Patients Treated With a New Generation Sirolimus-Eluting Stent for Acute Coronary Syndrome) trial,[5] a total of 2660 patients with ACS treated with ticagrelor were included for the present study. Briefly, the TICO trial was an investigator-initiated, multicenter, randomized, unblinded trial conducted at 38 centers in Korea. It tested whether switching to ticagrelor monotherapy after 3 months of DAPT (3-month aspirin therapy) would reduce net adverse clinical events compared with a ticagrelor-based 12-month DAPT regimen (12-month aspirin therapy) among patients with ACS treated with drug-eluting stents. Patients who underwent successful percutaneous coronary intervention (PCI) with ultrathin bioresorbable polymer sirolimus-eluting stents (Orsiro; Biotronik, Germany) for ACS (ST-segment–elevation myocardial infarction, non–ST-segment–elevation myocardial infarction, or unstable angina) were eligible for enrollment (Table S1). The TICO trial excluded patients at an increased risk of bleeding attributable to following conditions: any hemorrhagic stroke, ischemic stroke or impairment of central nervous system within a year, internal bleeding within 6 weeks, hemoglobin ≤8 g/dL, platelet count $<100\times10^3$/mL, major surgery or traumatic injury resulting in any impairment of physical activity within 3 weeks, need for oral anticoagulation therapy, life expectancy <1 year, or moderate to severe hepatic dysfunction (Table S1). Between August 2015 and October 2018, a total of 3056 patients were randomly assigned to ticagrelor monotherapy after a 3-month DAPT (n=1527) regimen or a ticagrelor-based 12-month DAPT regimen (n=1529). Among these patients, 396 who did not receive the intervention as randomized were excluded from the present study; 251 received other P2Y12 inhibitors, 95 received unspecified aspirin therapy, and 50 received aspirin monotherapy. Therefore, the present analyses were based on the per-protocol cohort in the TICO trial. The detailed protocol and participant schema of the TICO trial were previously described.[5] The study was approved by an institutional review committee, and the subjects gave informed consent.

Procedures

PCI was performed according to standard techniques. The access sites for PCI and the size and length of implanted stents were determined by operators. Before PCI, loading doses of aspirin (300 mg) and ticagrelor (180 mg) were administered. After PCI, a single aspirin dose (100 mg per day) and 2 ticagrelor doses (90 mg per day) were maintained. After 3 months of DAPT, aspirin was discontinued in the patients who were assigned to receive ticagrelor monotherapy after 3 months of DAPT, and aspirin use was continued in patients who were randomized to receive ticagrelor-based DAPT for 12 months. The concomitant use of other antiplatelet agents or anticoagulants was not allowed.

Outcomes and Definitions

Major bleeding was defined according to the TIMI (Thrombolysis in Myocardial Infarction)[6] or the Bleeding Academic Research Consortium (BARC) criteria.[7] The TIMI criteria defined major bleeding as non–coronary artery bypass grafting–related bleeding with intracranial bleeding, hemorrhage with a hemoglobin decrease of at least 5 g/dL, or bleeding that was fatal within 7 days.[6] The major bleeding by BARC criteria was defined as type 3 (clinical, laboratory, and/or imaging evidence of bleeding with specific healthcare provider responses) or type 5 bleeding (bleeding that directly causes death with no other explainable cause).[7] The BARC type 3 category was further classified into 3a, 3b, and 3c, according

to the BARC criteria.[7] On the basis of the TICO trial,[5] a major adverse cardiac and cerebrovascular event was defined as a composite of death, myocardial infarction, stent thrombosis, stroke, and target-vessel revascularization; a net adverse clinical event was defined as a composite of TIMI major bleeding and a major adverse cardiac and cerebrovascular event.

Cardiac death was defined as death attributable to myocardial infarction, cardiac perforation, or pericardial tamponade; arrhythmia or conduction abnormality; stroke within 30 days of the procedure or related to the procedure; death attributable to a procedural complication; or any case of death in which a cardiac cause was not excluded by a clinical event committee.[5] Myocardial infarction after hospital discharge was defined by ischemic symptoms, electrocardiographic changes, or abnormal imaging findings, combined with a creatine kinase myocardial band fraction above the upper normal limit or a troponin T or troponin I level >99th percentile of the upper normal limit.[8] Stent thrombosis was defined as definite or probable stent thrombosis, according to the Academic Research Consortium criteria.[9] Stroke was defined as a fatal acute cerebrovascular event, a neurological deficit lasting >24 hours, or an acute infarction revealed by imaging studies.[10] Target-vessel revascularization was defined as a repeated PCI or bypass surgery of the target vessel with either[1]: symptoms of ischemia or a positive stress test and an angiographic diameter stenosis of >50%; or[2] an angiographic diameter stenosis of >70% without symptoms of ischemia or a positive stress test.[5]

Outcomes were categorized according to predefined criteria by an independent clinical event committee blinded to the treatment assignments and primary results.[5]

Statistical Analysis

Continuous variables are reported as mean±SD and were compared using the Student *t* test. Categorical variables are reported as numbers (percentages) and were compared using the Fisher exact test or the χ^2 test. Hazard ratios (HRs) with 95% CIs were analyzed by Cox regression analysis, including each participating institution as a random effect. Clinically relevant variables or statistically significant variables on univariate analysis were entered into the multivariable model that assessed independent factors for TIMI major bleeding and BARC type 3 or 5 bleeding (Table S2). Given the overfitting of our model, entered variables were as follows: age, women, weight, diabetes mellitus, current smoker, prior stroke (only for BARC bleeding), hemoglobin, thrombocytopenia (platelets <100×10^3/mL) (only for BARC bleeding), chronic kidney disease (estimated glomerular filtration rate <60 mL/min per 1.73 m^2), transradial intervention, and 3-month aspirin therapy. Kaplan-Meier estimates were used to determine the cumulative incidences of study outcomes at 12 months. A total of 110 and 107 patients were censored for TIMI major bleeding and BARC type 3/5 bleeding, respectively, because of the follow-up loss before 12 months or the withdrawal of consent. In this case, the last information available for study was used for the survival analysis. The optimal cutoff values for bleeding-related variables were determined considering the Youden index derived from receiver operating characteristic curve analysis and whether it is suitable for clinical use. Statistical analysis was performed using SAS 9.2 (SAS Institute) or MedCalc (MedCalc Software). All tests were 2 sided, and a $P<0.05$ was considered statistically significant.

RESULTS

Distribution of Major Bleeding

Among 2660 patients treated with ticagrelor, 54 (2.0%) and 97 (3.6%) patients underwent TIMI major bleeding and BARC type 3/5 bleeding, respectively, within 12 months of therapy initiation. There were 39 cases of BARC type 3a, 51 cases of BARC type 3b, 5 cases of BARC type 3c, and 2 cases of BARC type 5 bleeding. Coronary artery bypass grafting was not performed in these patients. Figure 1 represents the frequency of bleeding events. Within 30 days after ticagrelor treatment, 53.7% (29/54) of TIMI major bleeding (Figure 1A) and 47.4% (46/97) of BARC type 3/5 events were recorded (Figure 1B). The periprocedural bleeding occurred in 18.5% (10/54) of TIMI major bleeding (Figure 1A) and 20.6% (20/97) of BARC type 3/5 bleeding (Figure 1B).

Risk Factors for Major Bleeding

Given the heterogeneity of bleeding definitions, patients with TIMI major bleeding were compared with those without; those with BARC type 3/5 bleeding were compared with those without.

Table 1 shows the baseline characteristics of patients with and without TIMI major bleeding. Patients with TIMI major bleeding were older and weighed less than those without. In patients with TIMI major bleeding, the frequencies of women and diabetes mellitus were higher, and the levels of hemoglobin and estimated glomerular filtration rate were lower. Transradial intervention and 3-month aspirin therapy were less frequently administered in patients with TIMI major bleeding. Table 2 shows the baseline characteristics of patients with and without BARC type 3/5 bleeding. Differences among variables were similar to those from TIMI major bleeding, except that the frequency of current smoker was less in patients with BARC type 3/5 bleeding. Table 3 demonstrates independent correlates of major bleeding after ticagrelor therapy. The

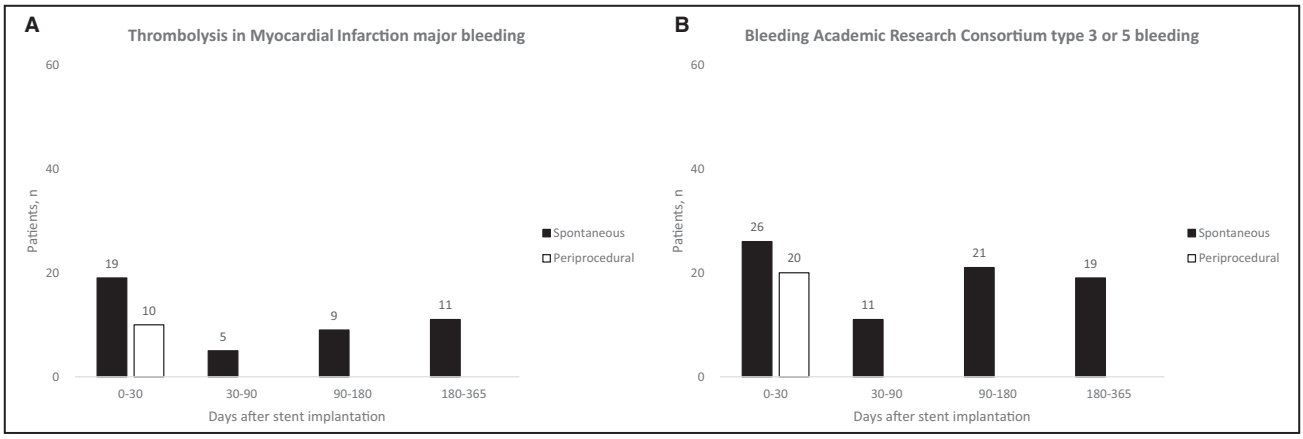

Figure 1. Distribution of major bleeding events.
A, TIMI (Thrombolysis in Myocardial Infarction) major bleeding. **B**, Bleeding Academic Research Consortium type 3 or 5 bleeding.

weight was associated with an increased risk of BARC type 3/5 bleeding. The hemoglobin and estimated glomerular filtration rate <60 mL/min per 1.73 m^2 (chronic kidney disease) were associated with an increased risk of both TIMI major bleeding and BARC type 3/5 bleeding.

On the basis of the receiver operating characteristic curve analyses (Figure S1), ≤65 kg (low body weight) was the optimal cutoff value for body weight to predict both TIMI major bleeding and BARC type 3/5 bleeding (area under the receiver operating characteristic curve [95% CI]: TIMI major bleeding, 0.65 [0.63–0.67]; BARC type 3/5 bleeding, 0.66 [0.64–0.68]). With this threshold, the diagnostic sensitivity and specificity were 66.7% and 60.0%, respectively, for TIMI major bleeding, and 65.6% and 60.4%, respectively, for BARC type 3/5 bleeding. The optimal cutoff value for hemoglobin was ≤12 g/dL (anemia) (area under the receiver operating characteristic curve [95% CI]: TIMI major bleeding, 0.70 [0.68–0.71]; BARC type 3/5 bleeding, 0.65 [0.64–0.67]). With this threshold, the diagnostic sensitivity and specificity were 35.2% and 91.3%, respectively, for TIMI major bleeding, and 30.9% and 91.5%, respectively, for BARC type 3/5 bleeding.

The HR (95% CI) of risk factors for TIMI major bleeding and BARC type3/5 were as follows: low body weight, 3.08 (1.74–5.43) and 2.96 (1.94–4.53), respectively; anemia, 5.72 (3.26–10.04) and 4.91 (3.18–7.58), respectively; and chronic kidney disease, 3.68 (2.14–6.34) and 2.79 (1.84–4.23), respectively. TIMI major bleeding (Figure 2A) and BARC type 3/5 bleeding (Figure 2B) occurred more frequently in proportion to the burden of risk factors.

Effects of Early Aspirin Discontinuation and Transradial Intervention

The 3-month aspirin therapy plus ticagrelor regimen was associated with a decreased risk of major bleeding, compared with the 12-month aspirin plus ticagrelor regimen (Table 3). Baseline characteristics were not different between patients with 3- and 12-month aspirin therapies (Table S3).[5] Table 4 summarizes clinical outcomes at 12 months. The 3-month aspirin therapy resulted in a reduction of net adverse clinical events compared with the 12-month aspirin therapy.[5] This effect of early aspirin discontinuation was consistent in patients with a risk of major bleeding (Table 5).

Transradial access for PCI showed a tendency to be associated with a decreased risk of major bleeding, compared with a transfemoral intervention (Table 3). Although a lower risk of net adverse clinical events was identified in patients administered a transradial intervention (Table 4 and Table 5), baseline characteristics were different between patients with transradial and transfemoral interventions (Table S4). However, the net benefit was still valid even after multivariable adjustments for age, sex, current smoker status, clinical presentation of myocardial infarction, chronic kidney disease, and multivessel disease (HR [95% CI], 0.66 [0.45–0.98]; *P*=0.0385).

Figure 3A (early aspirin discontinuation) and Figure 3B (transradial intervention) represent time-to-event curves for net adverse clinical events in patients at risk of major bleeding.

DISCUSSION

The main findings of this post hoc analysis are as follows: (1) 50% of major bleeding events occurred within 30 days after ticagrelor treatment; (2) low body weight, anemia, and chronic kidney disease were risk factors for major bleeding; (3) net clinical benefits of early aspirin discontinuation, as reported by the TICO trial, were still valid in patients with any of the major bleeding risk factors; and (4) transradial intervention, compared with transfemoral intervention, showed potential benefits on reducing major bleeding and improving net outcomes.

Table 1. Baseline Characteristics, Grouped by TIMI Criteria

Characteristic	TIMI Major Bleeding		*P* Value
	Presence (n=54)	Absence (n=2606)	
Age, y	65.2±9.0	60.5±10.8	0.0013
Women	19 (35.2)	506 (19.4)	0.0040
Weight, kg	63.2±10.0	69.0±11.8	0.0004
Comorbid conditions			
Hypertension	30 (55.6)	1289 (49.5)	0.3754
Diabetes mellitus	24 (44.4)	687 (26.4)	0.0030
Current smoker	17 (31.5)	1009 (38.7)	0.2795
Dyslipidemia	28 (51.9)	1576 (60.5)	0.1998
Prior percutaneous coronary intervention	6 (11.1)	206 (7.9)	0.4397
Prior stroke	3 (5.6)	105 (4.0)	0.4809
Clinical presentation			
Unstable angina	17 (31.5)	762 (29.2)	0.5277
Non–ST-segment–elevation myocardial infarction	21 (38.9)	880 (33.8)	
ST-segment–elevation myocardial infarction	16 (29.6)	964 (37.0)	
Laboratory findings at admission			
White blood count, $\times10^3$/mL	10.1±4.5	9.4±3.5	0.2127
Hemoglobin, g/dL	13.0±2.0	14.3±1.7	<0.0001
Platelets, $\times10^3$/mL	268±146	242±64	0.1945
Estimated glomerular filtration rate, mL/min per 1.73 m^2	61.2±29.7	77.6±23.3	0.0002
<60 mL/min per 1.73 m^2	24 (44.4)	503 (19.3)	<0.0001
Antithrombotic drug before intervention			
Unfractionated heparin	33 (61.1)	1627 (62.4)	0.8427
Low–molecular-weight heparin	6 (11.1)	235 (9.0)	0.6283
Glycoprotein IIb/IIIa inhibitors	2 (3.7)	177 (6.8)	0.5806
Multivessel coronary artery disease	32 (59.3)	1445 (55.4)	0.5770
Percutaneous coronary intervention			
Emergent intervention	15 (27.8)	923 (35.4)	0.2448
Transradial approach	18 (33.3)	1461 (56.1)	0.0009
Multilesion intervention	11 (20.4)	516 (19.8)	0.9172
Multivessel intervention	11 (20.4)	433 (16.6)	0.4639
Treated lesions per patient	1.2±0.5	1.2±0.5	0.8810
Total No. of stents per patient	1.3±0.6	1.4±0.7	0.7376
Total stent length per patient, mm	34±16	35±20	0.6431
3-mo Aspirin therapy	19 (35.2)	1320 (50.7)	0.0244

Data are presented as mean±SD or number (percentage). TIMI indicates Thrombolysis in Myocardial Infarction.

Table 2. Baseline Characteristics, Grouped by BARC Criteria

Characteristic	BARC Type 3 or 5 Bleeding		*P* Value
	Presence (n=97)	Absence (n=2563)	
Age, y	64.5±9.7	60.4±10.8	0.0002
Women	31 (32.0)	494 (19.3)	0.0021
Weight, kg	63.1±9.4	69.1±11.9	<0.0001
Comorbid conditions			
Hypertension	54 (55.7)	1265 (49.4)	0.2221
Diabetes mellitus	36 (37.1)	675 (26.3)	0.0186
Current smoker	27 (27.8)	999 (39.0)	0.0269
Dyslipidemia	51 (52.6)	1553 (60.6)	0.1132
Prior percutaneous coronary intervention	7 (7.2)	205 (8.0)	0.7801
Prior stroke	4 (4.1)	104 (4.1)	1.0000
Clinical presentation			
Unstable angina	28 (28.9)	751 (29.3)	0.8874
Non–ST-segment–elevation myocardial infarction	35 (36.1)	866 (33.8)	
ST-segment–elevation myocardial infarction	34 (35.1)	946 (36.9)	
Laboratory findings at admission			
White blood count, $\times10^3$/mL	10.4±5.3	9.3±3.5	0.0668
Hemoglobin, g/dL	13.3±2.1	14.3±1.7	<0.0001
Platelets, $\times10^3$/mL	260±117	241±64	0.1150
Estimated glomerular filtration rate, mL/min per 1.73 m^2	64.5±25.4	77.7±23.3	<0.0001
<60 mL/min per 1.73 m^2	37 (38.1)	490 (19.1)	<0.0001
Antithrombotic drug before intervention			
Unfractionated heparin	61 (62.9)	1599 (62.4)	0.9207
Low–molecular-weight heparin	8 (8.2)	233 (9.1)	0.7763
Glycoprotein IIb/IIIa inhibitors	7 (7.2)	172 (6.7)	0.8453
Multivessel coronary artery disease	56 (57.7)	1421 (55.4)	0.6561
Percutaneous coronary intervention			
Emergent intervention	34 (35.1)	904 (35.3)	0.9646
Transradial approach	39 (40.2)	1440 (56.2)	0.0019
Multilesion intervention	17 (17.5)	510 (19.9)	0.5649
Multivessel intervention	17 (17.5)	427 (16.7)	0.8224
Treated lesions per patient	1.2±0.4	1.2±0.5	0.4658
Total No. of stents per patient	1.3±0.6	1.4±0.7	0.6136
Total stent length per patient, mm	34±19	35±20	0.7343
3-mo Aspirin therapy	35 (38.0)	1246 (50.0)	0.0251

Data are presented as mean±SD or number (percentage). BARC indicates Bleeding Academic Research Consortium.

The PRECISE-DAPT (PREdicting bleeding Complications In patients undergoing Stent implantation and subsEquent Dual Anti Platelet Therapy) score was designed to evaluate the benefits and risks of different DAPT durations and may be considered at the time of PCI.[1,2] However, the score was based on pooled analysis of 8 randomized trials that were treated with DAPT, largely consisting of aspirin and clopidogrel.[11] Although the PRECISE-DAPT score

Table 3. Correlates of Major Bleeding

Variable	Multivariable Analysis		
	Hazard Ratio	95% CI	*P* Value
TIMI major bleeding			
Age	1.00	0.97–1.03	0.9203
Women	1.07	0.55–2.07	0.8463
Weight per 1-kg increase	0.97	0.94–1.00	0.0675
Diabetes mellitus	1.38	0.77–2.47	0.2817
Hemoglobin per 1-g/dL increase	0.79	0.67–0.93	0.0054
Chronic kidney disease (estimated glomerular filtration rate <60 mL/min per 1.73 m^2)	2.22	1.21–4.09	0.0106
Transradial intervention	0.55	0.30–1.02	0.0560
3-mo Aspirin therapy	0.56	0.32–0.98	0.0428
Bleeding Academic Research Consortium type 3 or 5 bleeding			
Age	1.00	0.98–1.03	0.9473
Women	0.89	0.53–1.50	0.6561
Weight per 1-kg increase	0.96	0.94–0.99	0.0021
Diabetes mellitus	1.17	0.75–1.83	0.4983
Current smoker	0.80	0.49–1.32	0.3775
Prior stroke	0.69	0.25–1.92	0.4817
Hemoglobin per 1-g/dL increase	0.82	0.72–0.94	0.0036
Thrombocytopenia (platelets <100×10^3/mL)	1.10	0.15–8.23	0.9297
Chronic kidney disease (estimated glomerular filtration rate <60 mL/min per 1.73 m^2)	2.02	1.27–3.20	0.0029
Transradial intervention	0.67	0.42–1.06	0.0887
3-mo Aspirin therapy	0.66	0.44–0.99	0.0486

TIMI indicates Thrombolysis in Myocardial Infarction.

was validated in the PLATO trial population, a c-index for out-of-hospital TIMI major or minor bleeding was modest (0.70 in the PLATO trial validation cohort and 0.66 in the BernPCI registry validation cohort).[11] In addition, risk factors related to bleeding were not consistent across studies. In the PLATO trial, increasing age, decreasing creatinine clearance, low admission hemoglobin, female sex, prior gastrointestinal bleeding, glycoprotein IIb/IIIa inhibitor use, and randomization to ticagrelor were associated with non–coronary artery bypass grafting–related major bleeding,[12] whereas age, creatinine clearance, hemoglobin, white blood cell count, and previous spontaneous bleeding were predictors for out-of-hospital bleeding in the PRECISE-DAPT score.[11] Given the above limitations and uncertainties, data on specific bleeding factors directly linked to ticagrelor therapy provide addition information to improve clinical outcomes in patients with ACS undergoing PCI.

Age and female sex were statistically attenuated in the present multivariable analyses, whereas low body weight, anemia, and chronic kidney disease were significant correlates of major bleeding, even after the adjustments. In contrast to clopidogrel and prasugrel, ticagrelor does not require metabolic activation and binds rapidly and reversibly to the P2Y12 receptor.[13] *CYP2C19* and *ABCB1* genotypes do not appear to influence ticagrelor pharmacodynamics.[13] The effects of age and sex on the pharmacokinetics of ticagrelor are modest, and do not require dose adjustment.[13] The other points to be considered are differences in the study population. In the PLATO trial, the median age and body weight were about 62 years and 80 kg, respectively, whereas those were 61 years and 69 kg, respectively, in the present study. Thus, in the present study, fewer elderly patients were included, but patients with low body weight were more represented. Because the TICO trial enrolled patients from Korea, the racial difference

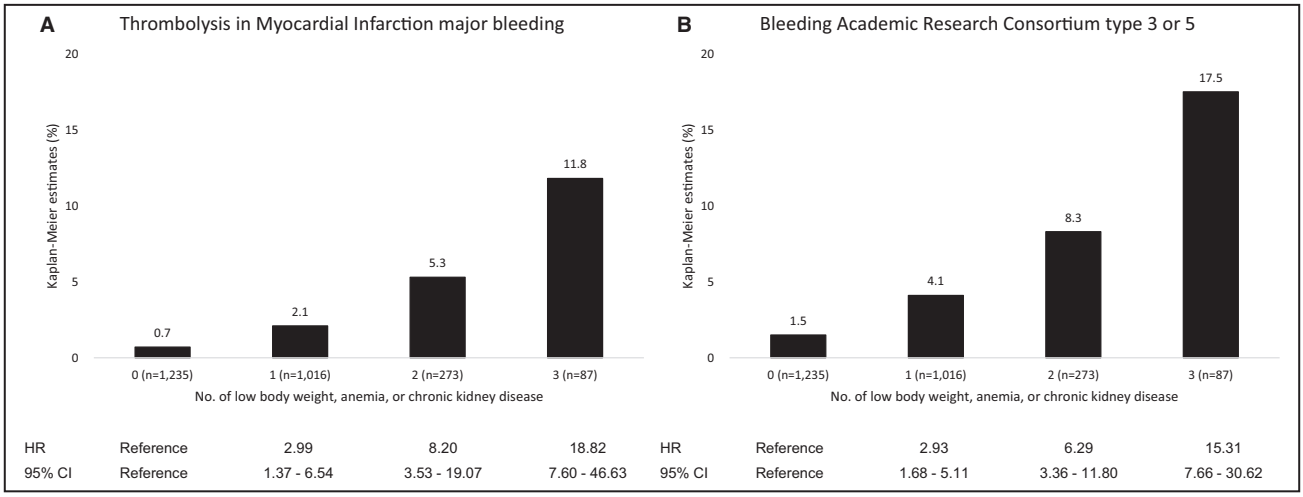

Figure 2. Event rates for major bleeding, at 12-month follow-up.
A, TIMI (Thrombolysis in Myocardial Infarction) major bleeding. **B**, Bleeding Academic Research Consortium type 3 or 5 bleeding. HR indicates hazard ratio.

Table 4. Clinical Outcomes at 12 Months

Outcome	3-mo Aspirin (n=1339)	12-mo Aspirin (n=1321)	Hazard Ratio	95% CI	*P* Value
TIMI major bleeding	19 (1.4)	35 (2.7)	0.53	0.30–0.92	0.0243
BARC type 3 or 5 bleeding	38 (2.9)	59 (4.5)	0.62	0.41–0.93	0.0218
Major adverse cardiac and cerebrovascular event	29 (2.2)	46 (3.5)	0.62	0.39–0.99	0.0450
Death	16 (1.2)	23 (1.8)	0.69	0.36–1.30	0.2520
Cardiac	7	12			
Noncardiac	9	11			
Myocardial infarction	3 (0.2)	9 (0.7)	0.33	0.09–1.22	0.0956
Stent thrombosis	5 (0.4)	4 (0.3)	1.24	0.33–4.60	0.7526
Stroke	7 (0.5)	9 (0.7)	0.77	0.29–2.06	0.5962
Target-vessel revascularization	4 (0.3)	9 (0.7)	0.44	0.14–1.42	0.1704
Net adverse clinical event	47 (3.6)	74 (5.7)	0.62	0.43–0.89	0.0098
Outcome	**Transradial (n=1479)**	**Transfemoral (n=1181)**	**Hazard Ratio**	**95% CI**	***P* Value**
TIMI major bleeding	18 (1.2)	36 (3.1)	0.48	0.27–0.88	0.0168
BARC type 3 or 5 bleeding	39 (2.7)	58 (5.0)	0.60	0.39–0.94	0.0264
Major adverse cardiac and cerebrovascular event	37 (2.5)	38 (3.3)	0.78	0.49–1.22	0.2626
Death	22 (1.5)	17 (1.5)	0.99	0.52–1.88	0.9714
Cardiac	12	7			
Noncardiac	10	10			
Myocardial infarction	6 (0.4)	6 (0.5)	0.80	0.26–2.47	0.6934
Stent thrombosis	6 (0.4)	3 (0.3)	1.59	0.40–6.37	0.5105
Stroke	8 (0.5)	8 (0.7)	0.79	0.30–2.12	0.6397
Target-vessel revascularization	4 (0.3)	9 (0.8)	0.35	0.11–1.15	0.0840
Net adverse clinical event	52 (3.6)	69 (5.9)	0.62	0.43–0.90	0.0120

Data are given as number (percentage), unless otherwise indicated. Percentages are Kaplan-Meier estimates at day 365. BARC indicates Bleeding Academic Research Consortium; and TIMI, Thrombolysis in Myocardial Infarction.

may affect the present results. A recent randomized clinical trial conducted in Korean patients with ACS resulted in the higher incidence of clinically significant bleeding in patients treated with ticagrelor compared with clopidogrel.[14] However, the subgroup analyses from the PLATO trial or the pharmacokinetic findings of ticagrelor were not different according to the ethnicity.[12,13] The low body weight may strengthen the direct antiplatelet effects of ticagrelor, presumably by increasing plasma concentrations of ticagrelor and AR-C124910XX (active metabolite of ticagrelor). Although low body weight was one of the risk factors for bleeding, as per the 2016 American College of Cardiology/American Heart Association guidelines,[1] it was absent in the criteria developed by the Academic Research Consortium for high bleeding risk.[15] The major and minor criteria for high bleeding risk at the time of PCI, defined by the Academic Research Consortium, included anticipated use of long-term oral anticoagulation, chronic kidney disease, anemia, spontaneous bleeding requiring hospitalization or transfusion, thrombocytopenia, chronic bleeding diathesis, liver cirrhosis with portal hypertension, active malignancy, intracranial hemorrhage, ischemic stroke, nondeferrable major surgery on DAPT, recent major surgery or trauma, age ≥75 years, and long-term use of oral nonsteroidal anti-inflammatory drugs or steroids.[15]

Previously, the TWILIGHT (Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention) trial, including high-risk patients who underwent PCI, revealed that ticagrelor monotherapy was associated with a lower incidence of clinically relevant bleeding than was ticagrelor plus aspirin, without an increase in risk of death, myocardial infarction, or stroke.[16] Thus, the present study is in line with the results from the TWILIGHT trial and confirms the effectiveness of early termination of DAPT among patients with ACS with high bleeding risk after coronary stent implantation. However, it is not yet clear whether aspirin or ticagrelor may be discontinued in those patients. Although discontinuation of P2Y12 inhibitor therapy is currently recommended in patients with ACS with stent implantation who are at high risk of bleeding,[1,2] it has been associated with an increased risk of ischemic events in patients with ACS undergoing PCI.[17,18] In addition, results from the landmark analysis of the

Table 5. Clinical Outcomes, Grouped by the Presence of Major Bleeding Risk (Low Body Weight, Anemia, or Chronic Kidney Disease)

Outcome	Presence of Major Bleeding Risk			Absence of Major Bleeding Risk			$P_{interaction}$
	3-mo Aspirin (n=682)	12-mo Aspirin (n=694)	Hazard Ratio (95% CI)	3-mo Aspirin (n=629)	12-mo Aspirin (n=606)	Hazard Ratio (95% CI)	
TIMI major bleeding	17 (2.5)	28 (4.1)	0.65 (0.35–1.19)	2 (0.3)	7 (1.2)	0.28 (0.06–1.32)	0.2868
BARC type 3/5 bleeding	31 (4.6)	47 (6.9)	0.69 (0.44–1.08)	7 (1.1)	11 (1.8)	0.61 (0.24–1.58)	0.7603
MACCE	18 (2.7)	37 (5.4)	0.49 (0.28–0.87)*	9 (1.5)	9 (1.5)	0.97 (0.38–2.43)	0.2231
NACE	34 (5.0)	59 (8.6)	0.59 (0.39–0.90)*	11 (1.8)	15 (2.5)	0.71 (0.32–1.54)	0.7431
Outcome	**Transradial (n=751)**	**Transfemoral (n=625)**	**Hazard ratio (95% CI)**	**Transradial (n=700)**	**Transfemoral (n=535)**	**Hazard ratio (95% CI)**	**$P_{interaction}$**
TIMI major bleeding	15 (2.0)	30 (4.9)	0.54 (0.28–1.05)	3 (0.4)	6 (1.1)	0.38 (0.10–1.52)	0.9311
BARC type 3/5 bleeding	30 (4.1)	48 (7.8)	0.59 (0.36–0.97)*	9 (1.3)	9 (1.7)	0.76 (0.30–1.91)	0.4505
MACCE	25 (3.4)	30 (4.9)	0.69 (0.41–1.18)	11 (1.6)	7 (1.3)	1.20 (0.47–3.09)	0.3228
NACE	38 (5.1)	55 (8.9)	0.60 (0.39–0.92)*	13 (1.9)	13 (2.5)	0.76 (0.35–1.64)	0.4950

Data are given as number (percentage), unless otherwise indicated. Percentages are Kaplan-Meier estimates at day 365. BARC indicates Bleeding Academic Research Consortium; MACCE, major adverse cardiac and cerebrovascular event; NACE, net adverse clinical event; and TIMI, Thrombolysis in Myocardial Infarction.

*$P<0.05$.

GLOBAL LEADERS trial (clinical study comparing 2 forms of antiplatelet therapy after stent implantation) indicate that ischemic events tended to be lower with ticagrelor monotherapy (versus aspirin monotherapy), without an increase of BARC type 3/5 bleeding.[19] Accordingly, ticagrelor monotherapy with early aspirin discontinuation may be considered among patients with ACS with high bleeding risk. Furthermore, given the high incidence of clinically relevant bleeding within 1 month after PCI in the present study, and the efficacy and safety of P2Y12 inhibitor monotherapy, as per previous randomized clinical trials,[5,16,19–21] aspirin-free PCI or ticagrelor monotherapy immediately after PCI may further improve clinical outcomes; these aspects need to be investigated by future studies. Promisingly, a recent pilot study demonstrated the feasibility and safety of aspirin-free prasugrel monotherapy following successful everolimus-eluting stent implantation in selected low-risk patients with stable coronary artery disease.[22] In patients with ACS undergoing invasive management, previous studies confirmed that radial compared with femoral access reduced net adverse clinical events, through a reduction in major bleeding and all-cause mortality.[23,24] In agreement with these studies, the present analyses suggest that this net benefit may be still valid among patients with high bleeding risk for ticagrelor therapy.

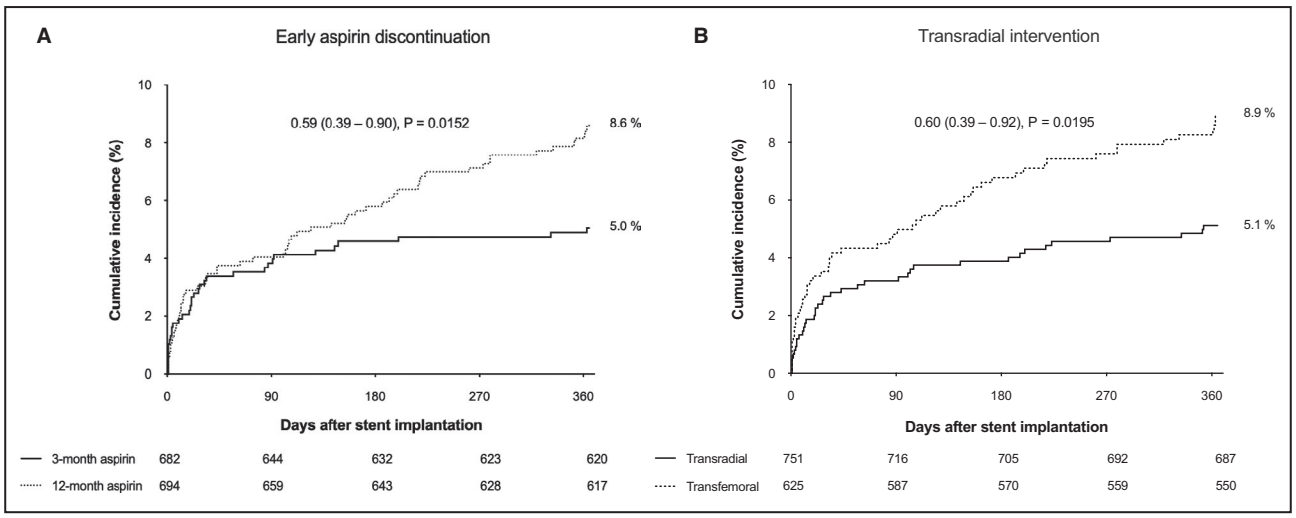

Figure 3. Time-to-event curves for net adverse clinical event in patients with risk of major bleeding. Hazard ratio (95% CI) was noted. **A**, Early aspirin discontinuation. **B**, Transradial intervention.

By interaction analyses in the present study, the treatment effects with early aspirin discontinuation and transradial access were consistent regardless of the presence of major bleeding risk, thus suggesting the possibility of these strategies to all patients with ACS undergoing PCI. However, this approach should be cautious given that current evidence has supported the extended use of DAPT in patients at low bleeding risk by reducing ischemic events without an increase of bleeding complications.[1,2,25] In addition, the radial or femoral access for PCI should be determined, taking into account patients' characteristics, clinical situations, and lesional complexities, as well as the risk of bleeding. Therefore, a dedicated clinical trial is required to figure out the clinical usefulness of the present findings.

Study Limitations

First, the present study should be interpreted considering the limitations of post hoc analyses. Although the major bleeding was defined by TIMI major bleeding or BARC type 3/5 bleeding, the weight showed a borderline significancy on multivariable analysis for TIMI major bleeding. Second, although the presence of prior stroke or thrombocytopenia may potentially increase the risk of major bleeding, it was rarely presented in the present study because the TICO trial excluded patients having these conditions. In addition, unmeasured variables, including peripheral artery disease, may have affected the present findings. Third, the effects of transradial intervention on clinical outcomes should be considered as explorative. Fourth, bleeding factors associated with ticagrelor monotherapy, despite the discontinuation of aspirin, are beyond our analyses, thus requiring further investigations. Fifth, it would be difficult to evaluate ticagrelor-related bleeding factors in the intention-to-treat cohort because not a few patients received other P2Y12 inhibitors or unspecified aspirin therapy. Finally, caution should be used to apply the results of this study to races other than Asians or patients receiving drug-eluting stents other than Orsiro stents.

CONCLUSIONS

Low body weight, anemia, and chronic kidney disease were risk factors for bleeding among patients with ACS treated with ticagrelor after coronary stent implantation. The strategy with early aspirin discontinuation in addition to ticagrelor had a net clinical benefit in patients with a bleeding risk.

ARTICLE INFORMATION

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Disclosures

None.

Supplementary Material

Tables S1–S4
Figure S1

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Supplemental Material

Table S1. Inclusion and exclusion criteria.

Inclusion criteria
1. Age ≥19 years old
2. Patients who received bioresorbable polymer sirolimus-eluting stent implantation to treat acute coronary syndrome
3. Provision of informed consent
Exclusion criteria
1. Age >80 years old
2. Increased risk of bleeding due to:
1) Any prior event of hemorrhagic stroke
2) Ischemic stroke, dementia, or impairment of central nervous system within a year
3) Traumatic brain injury or brain surgery within 6 months
4) Known intracranial tumor
5) Documented or suspected aortic dissection
6) Internal bleeding within 6 weeks
7) Active bleeding or bleeding diathesis
8) Hemoglobin ≤8 g/dL or thrombocytopenia (platelet count $<100\times10^3$/mL)
9) Major surgery or traumatic injury resulting in any impairment of physical activity within 3 weeks
3. Need for oral anticoagulation therapy
4. Current or potential pregnancy
5. Life expectancy <1 year
6. Currently treated with strong CYP3A4 inhibitors
7. Moderate to severe hepatic dysfunction (Child-Pugh class B or C)
8. Increased risk of bradycardia-related symptoms

Table S2. Univariate analysis for major bleeding correlates.

	Hazard ratio	95% CI	P
Thrombolysis in Myocardial Infarction major bleeding			
Age	1.05	1.02 – 1.08	0.0009
Women	2.35	1.34 – 4.13	0.0028
Weight per 1 kg increase	0.95	0.93 – 0.98	0.0002
Hypertension	1.28	0.75 – 2.21	0.3664
Diabetes	2.23	1.30 – 3.83	0.0036
Current smoker	0.68	0.38 – 1.22	0.1983
Dyslipidemia	0.75	0.43 – 1.30	0.3030
Prior percutaneous coronary intervention	1.41	0.60 – 3.32	0.4367
Prior stroke	1.33	0.41 – 4.29	0.6308
Acute myocardial infarction	0.84	0.46 – 1.54	0.5779
Leukocytosis (white blood count >11 $\times 10^3$/mL)	1.56	0.89 – 2.74	0.1235
Hemoglobin per 1 g/dL increase	0.66	0.58 – 0.76	<0.0001
Thrombocytopenia (platelets <100 $\times 10^3$/mL)	4.96	0.67 – 36.58	0.1159
Chronic kidney disease (estimated glomerular filtration rate <60 mL/min/1.73 m^2)	3.67	2.13 – 6.31	<0.0001
Unfractionated heparin	0.84	0.45 – 1.60	0.5998
Low–molecular-weight heparin	1.51	0.58 – 3.93	0.3994
Glycoprotein IIb/IIIa inhibitors	0.65	0.15 – 2.75	0.5529
Emergent intervention	0.62	0.33 – 1.17	0.1384
Transradial intervention	0.48	0.27 – 0.87	0.0157
Multivessel intervention	1.23	0.63 – 2.40	0.5466
3-month aspirin therapy	0.53	0.30 – 0.93	0.0255
Bleeding Academic Research Consortium type 3/5 bleeding			
Age	1.04	1.02 – 1.06	<0.0001
Women	2.04	1.33 – 3.13	0.0012
Weight per 1 kg increase	0.95	0.93 – 0.97	<0.0001
Hypertension	1.29	0.86 – 1.93	0.2251
Diabetes	1.66	1.10 – 2.51	0.0169
Current smoker	0.56	0.36 – 0.87	0.0109
Dyslipidemia	0.75	0.50 – 1.13	0.1669
Prior percutaneous coronary intervention	0.89	0.41 – 1.94	0.7752
Prior stroke	1.01	0.37 – 2.75	0.9894
Acute myocardial infarction	1.04	0.66 – 1.65	0.8632
Leukocytosis (white blood count >11 $\times 10^3$/mL)	1.32	0.86 – 2.02	0.2126
Hemoglobin per 1 g/dL increase	0.71	0.64 – 0.79	<0.0001

Thrombocytopenia (platelets <100 $\times 10^3$/mL)	2.77	0.38 – 20.12	0.3146
Chronic kidney disease (estimated glomerular filtration rate <60 mL/min/1.73 m^2)	2.79	1.84 – 4.23	<0.0001
Unfractionated heparin	0.98	0.60 – 1.61	0.9341
Low–molecular-weight heparin	0.96	0.42 – 2.17	0.9157
Glycoprotein IIb/IIIa inhibitors	1.31	0.58 – 2.98	0.5146
Emergent intervention	0.93	0.60 – 1.45	0.7426
Transradial intervention	0.60	0.39 – 0.94	0.0264
Multivessel intervention	0.99	0.58 – 1.68	0.9678
3-month aspirin therapy	0.62	0.41 – 0.93	0.0218

CI, confidence interval.

Table S3. Baseline characteristics between 3-month and 12-month aspirin therapy.

	3-month aspirin (n=1,339)	12-month aspirin (n=1,321)	P
Age, years	60.3 ± 10.8	60.8 ± 10.8	0.3121
Women	270 (20.2)	255 (19.3)	0.5771
Weight, kg	68.9 ± 11.8	68.9 ± 11.9	0.9634
Comorbid conditions			
Hypertension	649 (48.5)	670 (50.7)	0.2458
Diabetes	355 (26.5)	356 (27.0)	0.7990
Current smoker	507 (37.9)	519 (39.3)	0.4505
Dyslipidemia	810 (60.5)	794 (60.1)	0.8384
Prior percutaneous coronary intervention	108 (8.1)	104 (7.9)	0.8543
Prior stroke	50 (3.7)	58 (4.4)	0.3910
Clinical presentation			0.3035
Unstable angina	377 (28.2)	402 (30.4)	
Non–ST-elevation myocardial infarction	470 (35.1)	431 (32.6)	
ST-elevation myocardial infarction	492 (36.7)	488 (37.0)	
Laboratory findings at admission			
White blood count, $\times 10^3$/mL	9.3 ± 3.6	9.4 ± 3.5	0.5017
Hemoglobin, g/dL	14.3 ± 1.7	14.3 ± 1.8	0.9909
Platelets, $\times 10^3$/mL	240 ± 63	244 ± 70	0.1479
Estimated glomerular filtration rate, mL/min/1.73 m^2	78.2 ± 24.5	76.3 ± 22.6	0.0362
<60 mL/min/1.73 m^2	256 (19.1)	271 (20.5)	0.3664
Antithrombotic drug before intervention			
Unfractionated heparin	820 (61.2)	840 (63.6)	0.2112
Low–molecular-weight heparin	112 (8.4)	129 (9.8)	0.2082
Glycoprotein IIb/IIIa inhibitors	91 (6.8)	88 (6.7)	0.8899
Multivessel coronary artery disease	734 (54.8)	743 (56.3)	0.4586
Percutaneous coronary intervention			
Emergent intervention	469 (35.0)	469 (35.5)	0.7967
Transradial intervention	734 (54.8)	745 (56.4)	0.4123
Multilesion intervention	260 (19.4)	267 (20.2)	0.6072
Multivessel intervention	213 (15.9)	231 (17.5)	0.2748
Treated lesions per patient	1.2 ± 0.5	1.2 ± 0.5	0.5835
Total No. of stents per patient	1.4 ± 0.7	1.4 ± 0.7	0.9874
Total stent length per patient, mm	35 ± 20	35 ± 20	0.7360

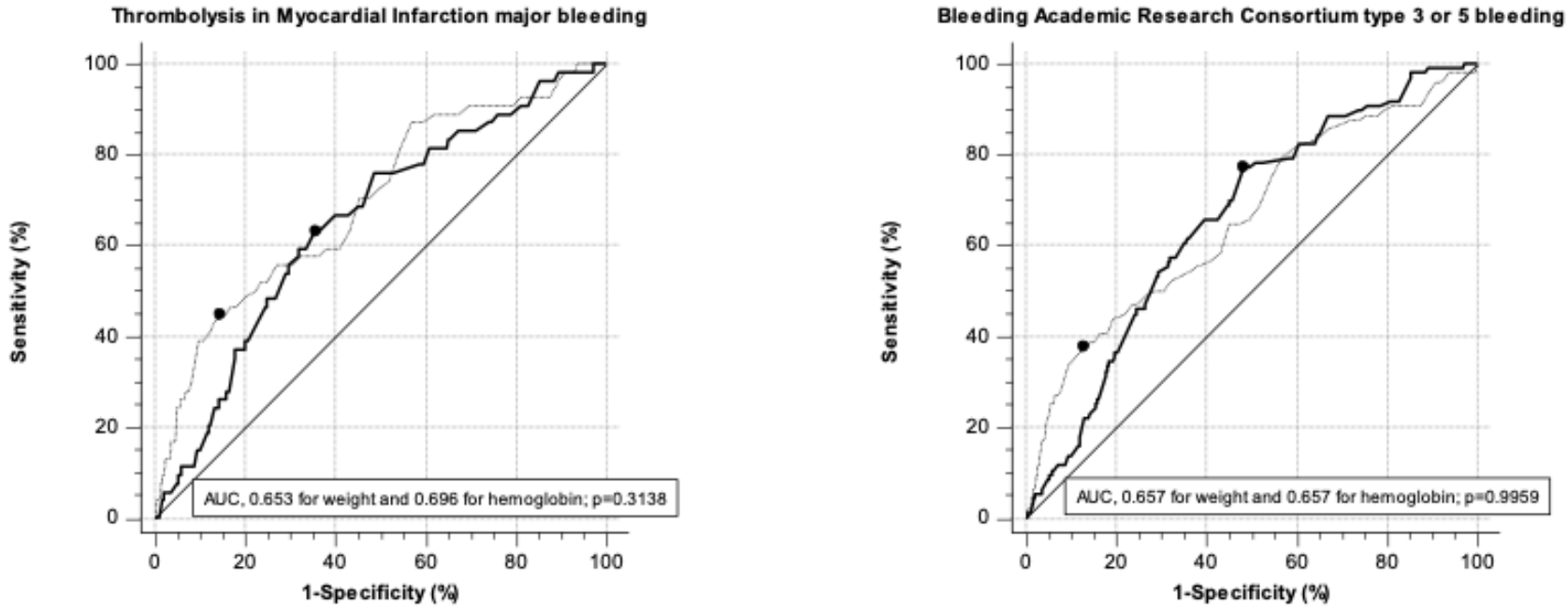
Data are presented as n ± standard deviation or n (percentage).

Table S4. Baseline characteristics between transradial and transfemoral intervention.

	Transradial (n=1,479)	Transfemoral (n=1,181)	P
Age, years	60.8 ± 10.8	60.3 ± 10.7	0.2091
Women	314 (21.2)	211 (17.9)	0.0303
Weight, kg	68.8 ± 12.1	69.0 ± 11.6	0.7811
Comorbid conditions			
Hypertension	740 (50.0)	579 (49.0)	0.6056
Diabetes	394 (26.6)	317 (26.8)	0.9069
Current smoker	533 (36.0)	493 (41.7)	0.0027
Dyslipidemia	884 (59.8)	720 (61.0)	0.5313
Prior percutaneous coronary intervention	120 (8.1)	92 (7.8)	0.7595
Prior stroke	58 (3.9)	50 (4.2)	0.6853
Clinical presentation			<0.0001
Unstable angina	581 (39.3)	198 (16.8)	
Non–ST-elevation myocardial infarction	562 (38.0)	339 (28.7)	
ST-elevation myocardial infarction	336 (22.7)	644 (54.5)	
Laboratory findings at admission			
White blood count, $\times 10^3$/mL	8.8 ± 3.5	10.0 ± 3.5	<0.0001
Hemoglobin, g/dL	14.3 ± 1.7	14.3 ± 1.8	0.7138
Platelets, $\times 10^3$/mL	243 ± 69	241 ± 64	0.3909
Estimated glomerular filtration rate, mL/min/1.73 m^2	78.8 ± 20.8	75.3 ± 26.6	0.0002
<60 mL/min/1.73 m^2	257 (17.4)	270 (22.9)	0.0004
Antithrombotic drug before intervention			
Unfractionated heparin	923 (62.4)	737 (62.4)	0.9990
Low–molecular-weight heparin	113 (7.6)	128 (10.8)	0.0043
Glycoprotein IIb/IIIa inhibitors	95 (6.4)	84 (7.1)	0.4807
Multivessel coronary artery disease	801 (54.2)	676 (57.2)	0.1121
Percutaneous coronary intervention			
Emergent intervention	344 (23.3)	594 (50.3)	<0.0001
Multilesion intervention	282 (19.1)	245 (20.8)	0.2806
Multivessel intervention	247 (16.7)	197 (16.7)	0.9892
Treated lesions per patient	1.2 ± 0.5	1.2 ± 0.5	0.1734
Total No. of stents per patient	1.3 ± 0.6	1.4 ± 0.7	0.0440
Total stent length per patient, mm	34 ± 20	36 ± 20	0.0370
3-month aspirin therapy	734 (49.6)	605 (51.2)	0.4123

Data are presented as n ± standard deviation or n (percentage)

Figure S1. Receiver operating characteristic curve analyses for major bleeding.



Line indicates weight; dotted line, hemoglobin; dot, Youden's index. AUC, area under the curve.