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Bleeding Events Before Coronary Angiography in Patients With Non-ST-Segment Elevation Acute Coronary Syndrome

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ABSTRACT

BACKGROUND Upstream administration of antithrombotic drugs to patients with non–ST-segment elevation acute coronary syndromes before coronary angiography is a common practice despite an incomplete understanding of the risks and benefits.

OBJECTIVES The authors analyzed the incidence of bleeding and ischemic events occurring before angiography and assessed their association with antithrombotic drugs and mortality risk.

METHODS All patients from the ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) trial with planned angiography after enrollment were included. Bleeding events were classified according to the ACUITY scale as major or nonmajor bleeding. Kaplan-Meier and Cox proportional hazards analyses were performed.

RESULTS Of 13,726 patients, 275 (2.0%) bled before angiography, including 52 (0.4%) with major bleeding. Forty-four (0.3%) experienced myocardial infarction. The median time from randomization to coronary angiography was 4.5 h (interquartile ratio [IQR]: 1.7 to 19.7 h) for patients who did not bleed while waiting for angiography and 27.9 h (IQR: 21.9 to 65.6 h) for patients who bled while waiting for angiography ($p < 0.001$). Bleeding events accrued linearly over time, reaching 10.4% at 96 h post-randomization. Independent predictors of bleeding before angiography included age (adjusted hazard ratio [HR]: 1.03 per year of age; 95% confidence interval [CI]: 1.01 to 1.04; $p < 0.001$), renal insufficiency (adjusted HR: 1.48; 95% CI: 1.07 to 2.04; $p = 0.02$), and use of multiple antithrombotic drugs (adjusted HR: 1.33; 95% CI: 1.14 to 1.56; $p < 0.001$). Bleeding before coronary angiography was associated with longer hospitalization (4.8 days [IQR: 3.0 to 8.9 days] vs. 3.0 days [IQR: 1.9 to 5.9 days]; $p < 0.001$). Patients who bled before angiography were more likely to die within 1 year than patients who did not bleed (8.5% vs. 4.1%; $p < 0.001$; adjusted HR: 1.89 (95% CI: 1.23 to 2.90; $p = 0.004$).

CONCLUSIONS Upstream antithrombotic treatment of patients with non–ST-segment elevation acute coronary syndromes awaiting coronary angiography is associated with excess bleeding with mortality implications. Bleeding avoidance strategies before angiogram, including early angiography, may negate the need to prolong upstream antithrombotic treatment and improve the overall risk-benefit balance for these patients. (Acute Catheterization and Urgent Intervention Triage Strategy [ACUITY]; NCT00093158) (J Am Coll Cardiol 2016;68:2608–18) © 2016 by the American College of Cardiology Foundation.

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Upstream (before coronary angiography) administration of antithrombotic drugs to patients with non-ST-segment elevation acute coronary syndrome (NSTEACS) may reduce the risk of ischemic events, but increases the bleeding risk (1–5). Bleeding events occurring during or after percutaneous coronary intervention (PCI) are associated with increased mortality (6–10); however, the incidence, predictors, and impact of bleeding events occurring before angiography on clinical prognosis have not been well-detailed. We report and compare the incidence of bleeding and ischemic events occurring before coronary angiography in the ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) trial, with emphasis on their association with antithrombotic drugs and mortality risk.

SEE PAGE 2619

METHODS

The ACUITY trial design has been reported in detail (11). Briefly, it was a multicenter, prospective, randomized trial of patients with moderate- and high-risk NSTEACS who were managed with an early invasive strategy. Patients were randomly assigned before coronary angiography to heparin (unfractionated or low molecular weight) plus a glycoprotein IIb/IIIa inhibitor (GPI), bivalirudin plus a GPI, or bivalirudin monotherapy with provisional GPI use. Patients assigned to 1 of the GPI arms were further randomized in a 2 × 2 factorial design to upstream GPI initiation or a deferred selective strategy in which GPI was given only in patients with PCI. Angiography was planned for all patients within 72 h of randomization. Depending on coronary anatomy, patients were then treated with PCI, coronary artery bypass grafting, or medical therapy. Dual antiplatelet therapy with aspirin and clopidogrel was strongly recommended for at least 1 year. All patients were anticoagulated during coronary artery bypass grafting with unfractionated heparin, with dosing per standard institutional practice. Detailed information regarding date and time of day was available for: 1) time of randomization; 2) time of coronary angiography; 3) time of initiation of in-hospital treatment with antiplatelet and anticoagulant drugs; and 4) in-hospital bleeding or ischemic events. The study was approved by the institutional review board or ethics committee at each center, and all patients provided written informed consent. All major adverse events were adjudicated by an independent clinical events committee blinded to treatment assignment.

STUDY POPULATION, OBJECTIVES, AND ANGIOGRAPHIC ANALYSIS. Of the 13,819 patients enrolled in ACUITY, 93 were enrolled at the time of or after coronary angiography and were excluded from the present study. The remaining 13,726 constituted the study population (Figure 1A). Our primary objectives were: 1) describe the incidence of bleeding events occurring before coronary angiography; 2) study the unadjusted and adjusted association between the number of antithrombotic drugs administered to the patients and these bleeding events; and 3) study the unadjusted and adjusted association between having a bleeding event before angiography and long-term mortality risk. We performed a sensitivity analysis restricted to patients who had coronary angiography (n = 13,614) (Figure 1B). The same statistical models (i.e., the same covariates) were used in the sensitivity analyses.

DEFINITIONS. Bleeding events were classified as major or nonmajor according to the ACUITY scale. Major bleeding was defined as any intracranial or intraocular bleeding, any overt bleeding associated with a hemoglobin drop ≥3 g/dl, any hemoglobin drop ≥4 g/dl, or any bleeding associated with a blood transfusion. Nonmajor bleeding was defined as any clinically significant overt bleeding that did not meet the criteria for major bleeding. Bleeding was classified as procedure-related or not procedure-related, and the date and time of the bleeding episode was recorded as the time when bleeding started. Recurrent myocardial infarction (MI) was defined as previously described (11). For patients with unstable angina (no biomarker elevation at baseline), MI was defined as any elevation of troponin or creatine kinase-myocardial band isoenzyme (CK-MB) greater than the upper limit of normal. For patients with MI (elevated biomarkers at baseline), MI (i.e., reinfarction) was defined as follows: 1) if the peak troponin or CK-MB had not yet been reached: recurrent chest pain lasting ≥30 min or new electrocardiographic changes consistent with MI and the next troponin or CK-MB measured approximately 8 to 12 h after the event elevated by at least 50% above the previous level; 2) if the troponin or CK-MB was falling or had returned to normal: a new elevation of troponin or CK-MB above the upper limit of normal or a rise by 50% above the previous nadir level if the troponin or CK-MB had not returned to less than the upper limit of normal.

STATISTICAL ANALYSIS. Continuous data are presented as mean ± SD and were compared using the Student *t* test or the Wilcoxon rank sum test, as

ABBREVIATIONS AND ACRONYMS

CI = confidence interval

CK-MB = creatine kinase-myocardial band isoenzyme

GPI = glycoprotein IIb/IIIa inhibitor

GRACE = Global Registry of Acute Coronary Events

HR = hazard ratio

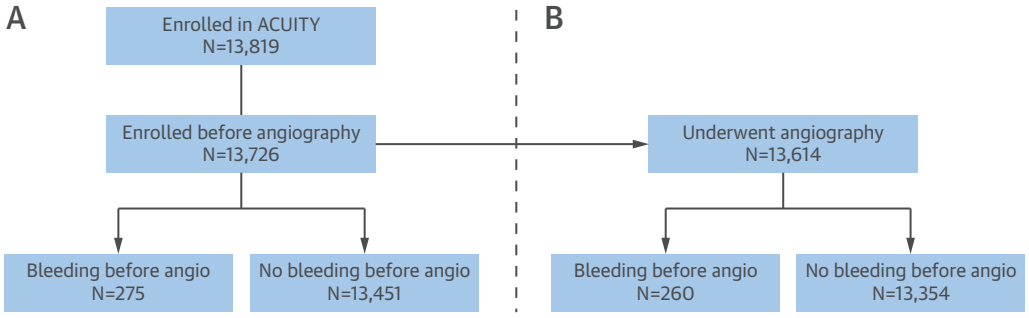
MI = myocardial infarction

NSTEACS = non-ST-segment elevation acute coronary syndrome

PCI = percutaneous coronary intervention

TIMI = Thrombolysis In Myocardial Infarction

FIGURE 1 Study Flow Chart



The study population consisted of 13,726 patients who were enrolled in ACUITY without having undergone coronary angiography **(A)**. We performed sensitivity analyses (repeated all statistical models) for the subgroup of patients who underwent coronary angiography (n = 13,614) **(B)**. Patients who did not undergo angiography either died in the hospital (n = 9) or were discharged without undergoing coronary angiography (n = 103).

appropriate. Categorical variables were compared using the chi-square or the Fisher exact test. We defined the composite endpoint major adverse cardiac events as any all-cause mortality, MI, or unplanned revascularization.

We tested the unadjusted and adjusted association between the risk of bleeding with the number of antithrombotic drugs administered and treatment assignment by univariate and multivariable Cox proportional hazards regression models. We included the following variables in the adjusted models: age, sex, insulin-treated diabetes, current smoking, previous PCI, previous coronary artery bypass graft surgery, weight, renal insufficiency, and biomarker positivity. The time-to-event variable was time in hours from randomization to a bleeding event. Patients were censored at the time of coronary angiography.

We compared the duration of the index hospitalization between patients with and without bleeding by the rank sum test and by multiple regression adjusted for age, sex, current smoking, insulin-treated diabetes, renal insufficiency, and biomarker positivity.

We assessed the association between bleeding before angiography and mortality by unadjusted and adjusted Cox proportional hazards models. Bleeding before coronary angiography was included in the model as a time-varying covariate. The following variables were also included in the adjusted model: age, sex, insulin-treated diabetes, current smoking, previous PCI, previous coronary artery bypass graft surgery, weight, renal insufficiency, and biomarker positivity. A sensitivity analysis was performed using Poisson regression, with the same covariates included. We also fitted an alternative model that also included treatment assignment (i.e., bivalirudin alone, bivalirudin+GPI, or heparin+GPI) in addition to the previously named covariates. Patients were censored at study completion (365 days) or loss to follow-up.

For all multivariable models, we imputed missing values by multiple imputation, under the assumption that data were missing at random. The following variables were included in the imputation model: age, sex, insulin-treated diabetes, current smoking, previous PCI, previous coronary artery bypass graft surgery, weight, treatment assignment (i.e., bivalirudin alone, bivalirudin+GPI, or heparin+GPI), and biomarker positivity. We included the outcome of interest (bleeding or death) as well as a Nelson-Aalen cumulative hazards indicator. We performed statistical analyses using SAS version 9.4 (SAS Institute, Cary, North Carolina). A p value <0.05 was considered statistically significant.

RESULTS

STUDY POPULATION. Of the 13,726 patients included in our analysis, the median time to coronary angiography was 4.7 h (interquartile range [IQR]: 1.7 to 20.2 h). The median time from randomization to coronary angiography was 4.5 h (IQR: 1.7 to 19.7 h) for patients who did not bleed while waiting for angiography and 27.9 h (IQR: 21.9 to 65.6 h) for patients who bled while waiting for angiography ($p < 0.001$). For patients who bled before angiography, the median time to coronary angiography after bleeding was 16.2 h (IQR: 6.3 to 31.5 h). The time from beginning randomized treatment (i.e., receiving first study

TABLE 1 Clinical Characteristics

	Bleeding* (n = 275)	No Pre-angiography Bleeding (n = 13,451)	p Value
Age, yrs	66.75 ± 11.03 (275)	62.50 ± 11.66 (13,451)	<0.0001
Men	64.0 (176/275)	70.1 (9,425/13,451)	0.03
Weight, kg	83.34 ± 17.27 (275)	85.42 ± 18.49 (13,437)	0.06
Diabetes mellitus	29.4 (80/272)	28.0 (3,745/13,363)	0.61
Insulin-treated	9.6 (26/272)	8.6 (1,154/13,363)	0.59
Hypertension	62.8 (172/274)	67.1 (8,987/13,400)	0.13
Hyperlipidemia	56.8 (155/273)	57.2 (7,551/13,195)	0.88
Current smoker	21.6 (59/273)	29.3 (3,868/13,216)	0.006
Previous MI	34.6 (93/269)	31.2 (4,104/13,142)	0.24
Previous PCI	36.3 (99/273)	38.9 (5,186/13,336)	0.38
Previous CABG	23.3 (64/275)	17.8 (2,392/13,425)	0.02
Renal insufficiency	34.1 (90/264)	18.8 (2,371/12,627)	<0.0001
Biomarker positive NSTEACS	62.5 (163/261)	59.4 (7,364/12,406)	0.31
ST-segment deviation ≥ 1 mm	36.4 (100/275)	34.9 (4,692/13,446)	0.61
Biomarker elevation or ST-segment deviation	72.6 (191/263)	72.3 (9,229/12,767)	0.90
TIMI risk score			
Low (0-2)	14.2 (35/247)	15.7 (1,877/11,923)	0.50
Intermediate (3-4)	50.2 (124/247)	54.7 (6,521/11,923)	0.16
High (5-7)	35.6 (88/247)	29.6 (3,525/11,923)	0.04
Platelets, × 1,000	237.64 ± 72.66 (265)	235.49 ± 66.54 (12,682)	0.63
Hemoglobin, g/dl	13.25 ± 2.04 (266)	14.02 ± 1.58 (12,716)	<0.0001
Hematocrit, %	39.25 ± 5.82 (265)	41.22 ± 4.58 (12,615)	<0.0001
WBC, × 1,000,000	8.79 ± 3.39 (261)	8.53 ± 2.97 (12,357)	0.22
Creatinine, mg/dl	1.20 ± 0.77 (264)	1.06 ± 0.59 (12,649)	0.003
Creatinine clearance, ml/min	80.91 ± 69.65 (264)	94.70 ± 139.74 (12,626)	0.002
C-reactive protein, mg/dl	5.07 ± 14.62 (177)	4.29 ± 42.53 (8,201)	0.52
Number of lesions per patient	4.60 ± 2.98 (100)	4.08 ± 2.93 (6,775)	0.08
Time from first study drug to angiography, h	26.65 [19.53, 61.58]	3.65 [1.00, 18.00]	<0.0001
Time from admission to angiography, h	42.67 [24.37, 67.18]	17.86 [5.76, 26.78]	<0.0001
Time from angiography to discharge, h	48.8 [25.5, 120.2]	49.6 [25.5, 120.9]	0.43
Treatment strategy			
PCI	46.9 (129/275)	56.6 (7,616/13,451)	0.001
CABG	11.6 (32/275)	11.2 (1,505/13,451)	0.82
Medical	41.5 (114/275)	32.2 (4,330/13,451)	0.001
1-Vessel coronary artery disease	6.9 (7/101)	18.6 (1,263/6,790)	0.003
2-Vessel coronary artery disease	35.6 (36/101)	27.9 (1,895/6,790)	0.09
3-Vessel coronary artery disease	48.5 (49/101)	44.2 (2,999/6,790)	0.38
Jeopardy score	2.51 ± 2.93 (94)	2.35 ± 2.75 (6,517)	0.56
Ejection fraction, %	61.89 ± 12.71 (58)	64.22 ± 12.17 (4,494)	0.15
Number of PCI vessels per patient	1.20 ± 0.45 (51)	1.17 ± 0.40 (3,607)	0.68
Left anterior descending coronary artery treated	44.2 (57/129)	42.9 (3247/7,565)	0.77
Right coronary artery treated	35.7 (46/129)	34.9 (2,638/7,565)	0.85
Left circumflex artery treated	36.4 (47/129)	36.8 (2,787/7,565)	0.92
Baseline TIMI flow grade			
0/1	10.6 (7/66)	12.5 (598/4,785)	0.64
2	4.5 (3/66)	9.5 (456/4,785)	0.17
3	84.8 (56/66)	78.0 (3731/4,785)	0.18
Final TIMI flow grade			
0/1	1.5 (1/67)	1.4 (66/4,763)	0.61
2	1.5 (1/67)	1.9 (90/4,763)	1.00
3	97.0 (65/67)	96.7 (4,607/4,763)	1.00

Values are mean ± SD (N), % (n/N), or median [first quartile, third quartile]. *Events occurring before coronary angiography. Three patients had both a bleeding event and an MI before angiography. Two of these patients had their bleeding event first, and 1 patient had an MI followed by bleeding. These patients are grouped according the event that occurred first.

CABG = coronary artery bypass grafting; MI = myocardial infarction; NSTEACS = non-ST-segment elevation acute coronary syndromes; PCI = percutaneous coronary intervention; TIMI = Thrombolysis In Myocardial Infarction; WBC = white blood cell.

TABLE 2 Medications

	Bleeding* (n = 275)	No Pre-angiography Bleeding (n = 13,451)	p Value
Antithrombin medications			
Pre-randomization	66.5 (183/275)	64.2 (8,631/13,451)	0.42
Unfractionated heparin	25.5 (70/275)	41.2 (5,539/13,451)	<0.0001
Low-molecular-weight heparin	42.9 (118/275)	25.2 (3,386/13,451)	<0.0001
Post-randomization, pre-angiography			
Bivalirudin	55.6 (153/275)	64.9 (8,736/13,451)	0.001
Unfractionated heparin	16.4 (45/275)	17.2 (2,308/13,451)	0.73
Enoxaparin	27.6 (76/275)	15.9 (2,140/13,451)	<0.0001
Glycoprotein IIb/IIIa inhibitor			
Pre-angiography	63.6 (175/275)	32.8 (4,409/13,451)	<0.0001
During PCI	37.5 (103/275)	38.0 (5,105/13,451)	0.87
Admission			
Aspirin	75.3 (207/275)	69.5 (9,349/13,445)	0.04
Thienopyridines	30.2 (83/275)	24.3 (3,262/13,444)	0.02
Statins	50.5 (139/275)	48.7 (6,548/13,439)	0.55
Beta-blockers	49.8 (137/275)	49.1 (6,603/13,440)	0.82
ACE inhibitors	44.0 (121/275)	42.2 (5,668/13,433)	0.55
Pre-procedure			
Aspirin	75.3 (207/275)	74.6 (10,029/13,445)	0.80
Thienopyridines	43.3 (119/275)	40.4 (5,430/13,445)	0.33
Statins	28.7 (79/275)	28.3 (3,796/13,436)	0.86
Beta-blockers	51.3 (141/275)	50.2 (6,750/13,438)	0.73
ACE inhibitors	29.5 (81/275)	25.9 (3,480/13,432)	0.18
Discharge			
Aspirin	80.4 (217/270)	85.9 (11,069/12,879)	0.009
Thienopyridines	57.4 (155/270)	65.8 (8,474/12,879)	0.004
Aspirin/clopidogrel/ticlopidine	84.4 (228/270)	90.7 (11,686/12,879)	0.0005
30 days			
Aspirin	95.1 (250/263)	92.8 (12,111/13,047)	0.16
Thienopyridines	66.2 (174/263)	68.0 (8,872/13,047)	0.53
Statins	78.7 (207/263)	80.3 (10,482/13,046)	0.51
Beta-blockers	72.2 (190/263)	76.8 (10,014/13,045)	0.09
ACE inhibitors	62.4 (164/263)	59.4 (7,750/13,045)	0.34
1 yr			
Aspirin	84.5 (213/252)	88.1 (11,180/12,689)	0.08
Thienopyridines	44.0 (111/252)	44.4 (5,633/12,686)	0.91
Statins	72.6 (183/252)	77.1 (9,791/12,692)	0.09
Beta blockers	62.3 (157/252)	72.3 (9,171/12,688)	0.0005
ACE inhibitors	60.3 (152/252)	56.7 (7,199/12,688)	0.26

Values are % (n/N). *Events occurring before coronary angiography. Three patients had both a bleeding event and a myocardial infarction before angiography. Two of these patients had their bleeding event first, and 1 patient had a myocardial infarction followed by bleeding. These patients are grouped according to the event that occurred first.

ACE = angiotensin-converting enzyme; other abbreviation as in Table 1.

drug) was 3.65 h (IQR: 1.00 to 18.00 h) for patients who did not bleed while waiting and 26.65 h (IQR: 19.53 to 61.58 h) for patients who bled ($p < 0.001$).

CLINICAL AND PROCEDURAL CHARACTERISTICS. Baseline and procedural characteristics are presented in Table 1. Patients who had a bleeding event while awaiting coronary angiography were older, were more likely to have renal insufficiency, and less likely to be a smoker. Medications used before, during, and after the index hospitalization are presented in Table 2. Patients who bled were more likely to have received low-molecular-weight heparin and less likely to have received bivalirudin than patients who did not bleed before angiography. Patients who experienced a bleeding event before coronary angiography were also more likely to have received an upstream (i.e., before coronary angiography) $P2Y_{12}$ inhibitor and GPI. Patients who bled were less likely to be on aspirin at discharge and at 30-day follow-up, with no difference at 1 year. Independent predictors of longer waiting time for coronary angiography were renal insufficiency (adjusted β: 1.52; 95% confidence interval [CI]: 0.63 to 2.40; $p < 0.001$) and previous CABG (adjusted β: 0.96; 95% CI: 0.14 to 1.79; $p = 0.02$), whereas previous PCI was associated with shorter waiting time (adjusted β: -2.42; 95% CI: -3.05 to -1.77; $p < 0.001$). The same variables predicted longer or shorter waiting time regardless of whether patients who bled before angiography were included (with time to angiography replaced with time to bleed for these patients) or whether the analysis population was restricted to patients who did not bleed before angiography.

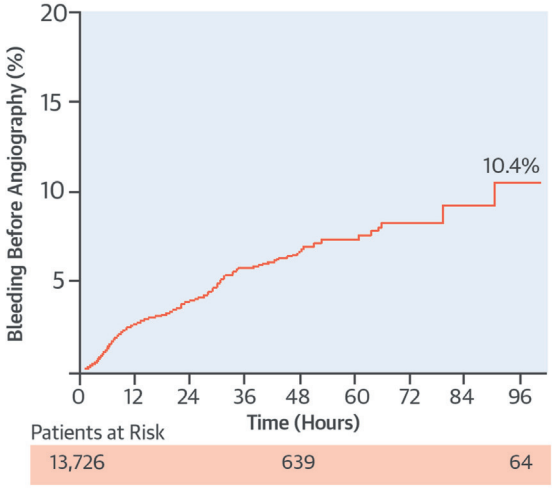
BLEEDING AND MI BEFORE CORONARY ANGIOGRAPHY. Two hundred and seventy-five (2.0%) patients bled (major and nonmajor) between randomization and angiography; 52 (0.4%) of these patients fulfilled the criteria for major bleeding. Forty-four (0.3%) patients had an MI before undergoing coronary angiography. Three patients had both a bleeding event and an MI before undergoing coronary angiography. Two of these patients bled first and subsequently had an MI, whereas 1 had an MI first. Bleeding events accrued linearly over time (i.e., the risk of bleeding was consistent from randomization up to 96 h post-randomization) (Central Illustration). The accrual patterns for major bleeding and MI events were similar (Figures 2A and 2B).

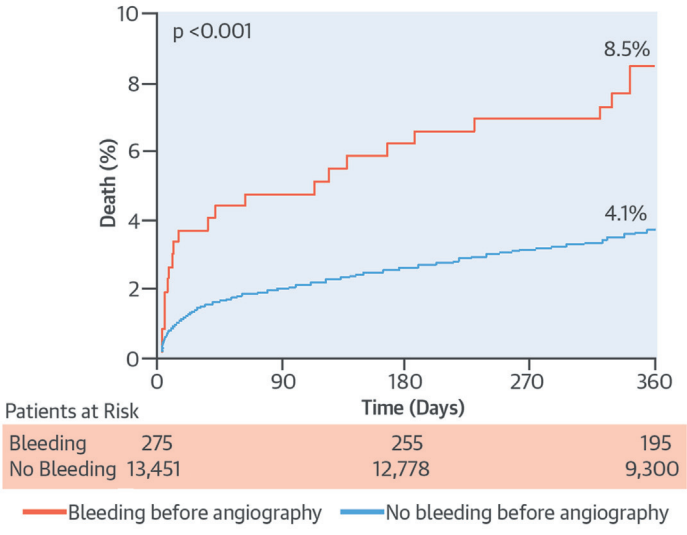
Number of antithrombotic drugs predicted the risk of bleeding before coronary angiography in unadjusted and adjusted analyses (Table 3). The only other independent predictors of bleeding before coronary angiography were age (adjusted hazard ratio [HR]: 1.03 per year of age; 95% CI: 1.01 to 1.04; $p < 0.001$) and renal insufficiency (adjusted HR: 1.48; 95% CI: 1.07 to 2.04; $p = 0.02$). The unadjusted and adjusted effect of treatment assignment on bleeding risk stratified according to whether the patient was randomized to heparin+GPI, bivalirudin+GPI, or bivalirudin alone is presented in Table 4. We also present

CENTRAL ILLUSTRATION **Bleeding Before Coronary Angiography in Patients With Non-ST-Segment Elevation Acute Coronary Syndrome: Bleeding Events and Death**

Independent Predictors of Delayed Angiography
Renal insufficiency
Previous coronary bypass surgery
Independent Predictors of Earlier Angiography
Previous percutaneous coronary intervention

Independent Predictors of Increased Bleeding Risk Before Angiography	Adj. HR (95% CI, p-value)
N of antithrombotic drugs (per drug)	1.33 (1.14-1.56, p <0.001)
Age (per year)	1.03 (1.01-1.04, p <0.001)
Renal insufficiency	1.48 (1.07-2.04, p =0.02)





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Bleeding events accrued linearly over time among patients waiting for coronary angiography, with 1 in 10 having a bleeding event by 96 h. Predictors of delayed or early angiography as well as predictors of increased bleeding risk are listed in the tables. Bleeding before angiography was associated with increased risk of dying.

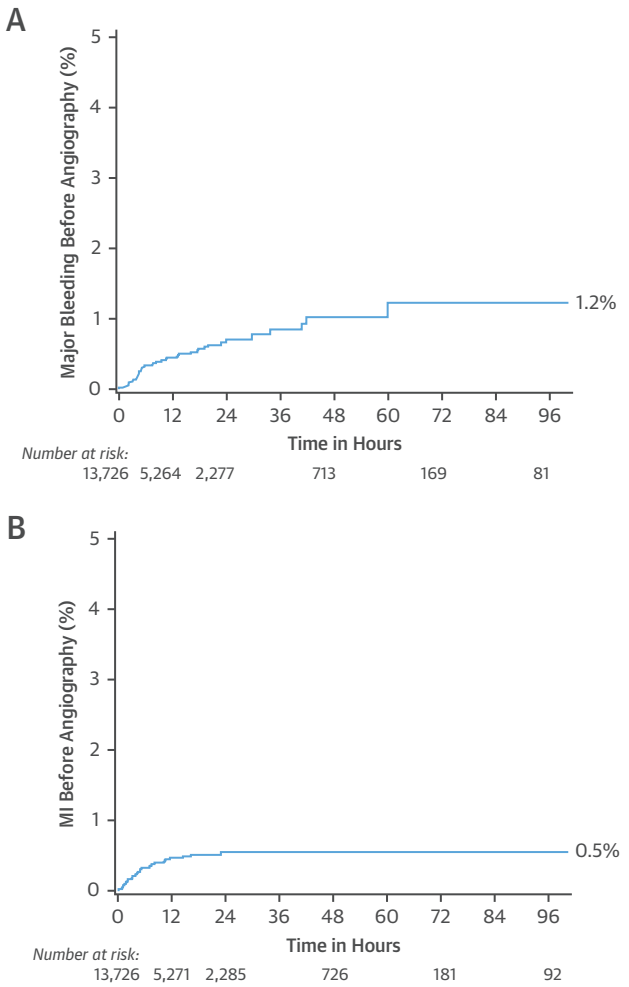
the effect of treatment assignment stratified according to whether patients were randomized to enoxaparin+GPI before angiography, enoxaparin alone before angiography (with provisional GPI during the procedure), unfractionated heparin+GPI before angiography, unfractionated heparin alone before angiography (with provisional GPI during the procedure), bivalirudin+GPI before angiography, or bivalirudin alone before angiography (with or without provisional GPI during the procedure) (Online Table 1, Online Figure 1). Patients with GPI had considerably higher unadjusted and adjusted risk of bleeding before angiography.

Bleeding events, including major bleeds, accrued similarly for patients who were biomarker-positive and/or had ST-segment deviation and patients who had neither (Online Figures 2A and 2B). No statistical interaction was detected between the effects of elevated biomarkers and/or ST-segment deviation and the number of antithrombotic drugs on bleeding (adjusted p interaction = 0.43). On the other hand, patients with elevated biomarkers and/or ST-segment deviation were more likely than patients with neither to have an MI before coronary angiography (Online Figure 2C). Both bleeding events and MI were similar for patients stratified by Thrombolysis In Myocardial Infarction (TIMI) risk score (Online Figures 3A and 3B).

Bleeding before coronary angiography was associated with considerably longer hospitalization (median stay: 4.8 days [IQR: 3.0 to 8.9 days] vs. 3.0 days [IQR: 1.9 to 5.9 days], $p < 0.001$). This was also true in a multiple regression model that adjusted for age, sex, insulin-treated diabetes, smoking, renal insufficiency, and biomarker positivity (adjusted β: 2.06; 95% CI: 1.07 to 3.05; $p < 0.001$).

CLINICAL OUTCOMES. In-hospital, 1-month, and 1-year clinical outcomes are presented in **Table 5**. Patients who bled before coronary angiography were

FIGURE 2 Time to Bleeding and Myocardial Infarction Before Coronary Angiography



(A) Time from enrollment in the trial to major bleeding (event) or coronary angiography (censored). **(B)** Time from enrollment in the trial to myocardial infarction (event) or coronary angiography (censored).

TABLE 3 Unadjusted and Adjusted Associations Between Number of Antithrombotic Drugs and the Risk of Bleeding Before Coronary Angiography

Model	HR* (95% CI)	p Value
Unadjusted	1.31 (1.12–1.53)	0.001
Adjusted	1.33 (1.14–1.56)	<0.001

Number of antithrombotic drugs was included in a Cox proportional hazards model as a time-varying continuous covariate along with the following covariates: Age, sex, insulin-treated diabetes, current smoking, previous percutaneous coronary intervention, previous coronary artery bypass graft surgery, and weight. Time variable was time from randomization to bleeding or coronary angiography (censored). *HR per 1 additional antiplatelet or antithrombotic drug.

CI = confidence interval; HR = hazard ratio.

TABLE 4 Unadjusted and Adjusted Associations Between Treatment Assignment and the Risk of Bleeding Before Coronary Angiography

Model	HR (95% CI)	p Value
Unadjusted		
Bivalirudin+GPI vs. UFH+GPI	1.01 (0.78–1.32)	0.94
Bivalirudin alone vs. UFH+GPI	0.48 (0.35–0.67)	<0.001
Adjusted		
Bivalirudin+GPI vs. UFH+GPI	1.03 (0.79–1.34)	0.84
Bivalirudin alone vs. UFH+GPI	0.48 (0.35–0.66)	<0.001

Treatment assignment was included in a Cox proportional hazards model along with the following covariates: Age, sex, insulin-treated diabetes, current smoking, previous percutaneous coronary intervention, previous coronary artery bypass graft surgery, and weight. Time variable was time from randomization to bleeding or coronary angiography (censored).

GPI = glycoprotein IIb/IIIa inhibitor; UFH = unfractionated heparin.

more likely to die in the hospital. This difference in mortality risk persisted throughout the study period (Table 5, Central Illustration). Bleeding, major bleeding, and MI before angiography were associated with unadjusted HRs for death of 2.4 (95% CI: 1.6 to 3.6; $p < 0.001$), 7.20 (95% CI: 4.06 to 12.75; $p < 0.001$), and 4.77 (95% CI: 2.26 to 10.05; $p < 0.001$). Having a bleeding event before coronary angiography was associated with an increased adjusted HR in multivariable Cox proportional hazards models (Table 6). This was true for analyses of complete case data as well as after multiple imputations (Online Table 2). There were no significant differences between the groups in the incidence of ischemic events.

SENSITIVITY ANALYSIS. Among patients who bled before coronary angiography, 59 (21.5%) also bled intra- or post-procedure. Bleeding before coronary angiography remained significant when other bleeds (intraprocedural or post-procedural) were added to the Cox model as another time-varying covariate (adjusted HR: 1.73; 95% CI: 1.12 to 2.66; $p = 0.013$).

Our findings were consistent when we restricted the study population to patients who underwent coronary angiography. Two hundred and sixty of these 13,614 (1.9%) patients bled before angiography. Forty-four (0.3%) had a major bleed and 42 (0.3%) had an MI before angiography. The number of administered antithrombotic drugs remained independently associated with increased risk of bleeding before angiography (unadjusted HR: 1.18; 95% CI: 1.00 to 1.39; $p = 0.046$; adjusted HR: 1.20; 95% CI: 1.02 to 1.41; $p = 0.028$). Bleeding before angiography was associated with an increased risk of dying also in this cohort (unadjusted HR: 2.04; 95% CI: 1.28 to 3.27; $p = 0.003$; adjusted HR: 1.67; 95% CI: 1.04 to 2.68; $p = 0.032$). In a landmark analysis starting at the time of coronary angiography, bleeding before

angiography was associated with increased risk of dying (Online Figure 4). Last, the risk associated with bleeding before coronary angiography was consistent in a multivariable Poisson regression model adjusted for the same covariates used in the Cox proportional hazards model (Online Table 3).

DISCUSSION

To the best of our knowledge, this is the first study to address the incidence and impact on prognosis of bleeding events among patients with NSTEACS who are awaiting diagnostic coronary angiography and are being treated with antiplatelet and anticoagulant drugs. Using data from 13,726 patients, we demonstrated that: 1) bleeding events were considerably more common than reinfarction while awaiting coronary angiography because of NSTEACS; 2) the risk of bleeding before angiography increases with the number of antithrombotic drugs administered, and was especially high with the use of GPIs; and 3) bleeding while awaiting coronary angiography was associated with increased 1-year mortality.

In the current report, we show that more than 6 times as many patients had a bleeding event than an MI while awaiting coronary angiography. Importantly, bleeding rates were 32 times higher than MI rates among patients without elevated biomarkers or ST-segment deviation. Furthermore, having a bleeding event before coronary angiography was associated with an increased mortality risk and a prolonged hospital stay. These findings imply that a better balance between reducing ischemic risk and exacerbating bleeding risk through a more restrictive antithrombotic use, particularly in patients without objective signs of ischemia, may significantly improve patient prognosis. In this regard, our data support the results reported in the ACCOAST (A Comparison of Prasugrel at the Time of Percutaneous Coronary Intervention Or as Pretreatment at the Time of Diagnosis in Patients with Non-ST-Elevation Myocardial Infarction) trial (5). The ACCOAST trial did not detect any reduction in ischemic events with an upstream strategy of prasugrel, but revealed an increased bleeding risk for these patients compared with patients who received prasugrel at the time of angiography (5).

Contemporary nonrandomized studies have shown that bleeding events that occur after PCI, regardless of whether they occur in-hospital or after discharge, are as dangerous or even more dangerous than ischemic events (6–10). We believe that understanding the prognostic impact of bleeding events that occur before coronary angiography is of particular importance for 2 reasons. First, contrary to the situation post-PCI wherein antithrombotic agents clearly reduce the risk of ischemic events, no randomized trial has convincingly demonstrated any benefit for patients with NSTEACS with upstream potent antithrombotic treatment compared with treatment at the time of coronary angiography (1–4). Second, because the NSTEACS diagnosis is typically not confirmed until coronary angiography is performed, patients who do not have NSTEACS are at risk of unnecessarily receiving antithrombotic therapy if

TABLE 5 In-Hospital, 1-Month, and 1-Year Clinical Outcomes

	Bleeding* (n = 275)	No Pre-Angiography Bleeding (n = 13,451)	p Value
In-hospital			
Major adverse cardiac events	5.5 (15/275)	5.1 (687/13,451)	0.80
Death	2.2 (6/275)	0.6 (87/13,451)	0.01
Cardiac death	2.2 (6/275)	0.6 (80/13,451)	0.008
Myocardial infarction	3.3 (9/275)	4.0 (542/13,451)	0.53
Q-wave	0.4 (1/275)	0.8 (101/13,451)	0.73
Non-Q-wave	2.9 (8/275)	3.3 (441/13,451)	0.73
Unplanned revascularization	1.5 (4/275)	1.1 (143/13,451)	0.54
Target vessel revascularization	0.7 (2/275)	0.6 (82/13451)	0.69
Non-target vessel revascularization	1.1 (3/275)	0.5 (68/13,451)	0.17
Target lesion revascularization	0.7 (2/275)	0.5 (64/13,451)	0.38
Non-CABG-related major bleeding	18.2 (50/275)	3.7 (499/13,451)	<0.0001
Definite/probable stent thrombosis	0.0 (0/275)	0.4 (51/13,451)	0.63
1 month			
Major adverse cardiac events	9.5 (26)	7.7 (1,028)	0.29
Death	4.0 (11)	1.5 (196)	0.0006
Cardiac death	4.0 (11)	1.2 (163)	<0.0001
MI	5.5 (15)	5.2 (689)	0.82
Q-wave	1.5 (4)	1.1 (141)	0.51
Non-Q-wave	4.1 (11)	4.1 (551)	0.93
Unplanned revascularization	3.4 (9)	2.5 (332)	0.38
Target vessel revascularization	1.5 (4)	1.3 (175)	0.81
Nontarget vessel revascularization	1.9 (5)	1.2 (163)	0.35
Target lesion revascularization	1.5 (4)	1.0 (131)	0.42
Non-CABG-related major bleeding	20.5 (56)	4.4 (588)	<0.0001
Definite/probable stent thrombosis	0.7 (2)	0.8 (102)	0.96
1 yr			
Major adverse cardiac events	19.1 (52)	16.5 (2,108)	0.16
Death	8.5 (23)	4.1 (498)	<0.0001
Cardiac death	6.2 (17)	2.4 (298)	<0.0001
MI	6.7 (18)	7.4 (964)	0.71
Q-wave	1.5 (4)	1.5 (195)	0.98
Non-Q-wave	5.2 (14)	6.0 (780)	0.64
Unplanned revascularization	9.6 (25)	9.1 (1,135)	0.63
Target vessel revascularization	5.4 (14)	5.3 (659)	0.83
Nontarget vessel revascularization	4.2 (11)	4.4 (555)	0.98
Target lesion revascularization	5.0 (13)	4.5 (556)	0.57
Definite/probable stent thrombosis	0.7 (2)	1.2 (147)	0.58

Values are % (n/N) or % (n). *Events occurring before coronary angiography. Three patients had both a bleeding event and an MI before angiography. Two of these patients had their bleeding event first, and 1 patient had an MI followed by bleeding. These patients are grouped according the event that occurred first.

Abbreviation as in Table 1.

TABLE 6 Unadjusted and Adjusted Association Between Bleeding Before Coronary Angiography and Death Within 1 Year

Model	HR (95% CI)	p Value
Unadjusted	2.35 (1.55–3.57)	<0.001
Adjusted	1.89 (1.23–2.90)	0.004
Adjusted – alternative*	1.89 (1.23–2.92)	0.004

A binary indicator variable for whether or not the patient bled before coronary angiography was included in a Cox proportional hazards model along with the following covariates: Age, sex, insulin-treated diabetes, current smoking, previous percutaneous coronary intervention, previous coronary artery bypass graft surgery, weight, renal failure, and biomarker positivity. The time variable was time from coronary angiography to death, study completion (censored) or loss to follow-up (censored). *Included, in addition to the previous named covariates, treatment assignment (i.e., bivalirudin alone, bivalirudin+glycoprotein IIb/IIIa inhibitor, or heparin+glycoprotein IIb/IIIa inhibitor).

Abbreviation as in Table 3.

administered before angiography. This is especially true for patients presenting with symptoms compatible with unstable angina but no ST-segment deviation or positive biomarkers. These patients may experience bleeding events without any benefits from a thrombotic point of view. In light of these facts, our study provides a strong argument against administration of potent antithrombotic agents before angiography. This argument is supported by a recent report (12) that demonstrated exceedingly low rates of ischemic events among patients who sought medical attention because of chest pain and who did not have elevated cardiac biomarkers.

This argument is further supported by 3 additional observations. First, the risk of unnecessarily administering antithrombotic drugs to patients who do not have NSTEACS is likely reduced in carefully designed and conducted clinical trials in which vigilant exclusion of patients with contraindications for antithrombotic drugs increases patient safety compared with everyday clinical practice. Second, older patients and patients with severe renal disease are typically excluded from clinical trials, despite representing an important proportion of patients treated in daily practice (13). In the current study, age and renal insufficiency were the only independent variables, aside from number of antithrombotic drugs, associated with increased bleeding risk. Third, clinical trials typically have shorter door-to-balloon times than what is observed in everyday clinical practice, especially when compared with geography where coronary angiography might not be readily available, or the culture of early angiography for NSTEACS is not established (5,14,15). Considering that bleeding risk in our cohort was constant over time, delayed angiography in NSTEACS, especially when multiple antithrombotic drugs are given, increases a patient's cumulative risk of bleeding.

That being said, alternatives exist that may allow us to reduce the bleeding risk for patients with NSTEACS with minimal additive ischemic risk (16). First, earlier coronary angiography can confirm or disprove an NSTEACS diagnosis sooner and help to better risk stratify and individualize intensity of antithrombotic treatment. A recent study (17) showed that ischemic events can be reduced in biomarker positive patients with early angiography. Because no study has demonstrated any convincing benefit with delayed angiography, we argue that angiography, if planned, should be performed promptly in all patients with suspected NSTEACS (18–22). If the initial diagnosis is correct, earlier confirmation of the diagnosis reduces the time the patient is at risk of ischemic events. If the initial diagnosis is disproved, earlier angiography reduces the time the patient is at risk of iatrogenic bleeding. A high-risk patient (defined by currently available risk clinical scores, e.g., the GRACE [Global Registry of Acute Coronary Events] score [23]) benefits from early intervention by reduction in both ischemic risk and bleeding risk (17,19), whereas a lower risk patient would benefit at least in terms of reduced bleeding risk. A strong argument in favor of early coronary angiography is the finding that bleeding events accrued linearly over time in this study (i.e., at a constant rate); hence, a reduction in time to angiography of any magnitude is associated with a proportional reduction in cumulative bleeding risk.

Finally, the cost-effectiveness of an early angiogram in NSTEACS, in terms of reduced length of stay, reduction in number of antithrombotic drugs used, and bleeding complication, is of crucial importance from a health care perspective. Therefore, we argue that there is a strong rationale for performing angiography promptly among all patients with suspected ACS for whom antithrombotic therapy is considered indicated. Our data imply that it could be hazardous to delay angiography for a patient who is treated with multiple antithrombotic drugs. We further argue that GPIs, which were associated with a particularly high risk of bleeding, should not be administered upstream of coronary angiography. If the patient is considered to be at sufficiently high risk of a thrombotic event to require a GPI, to favor coronary angiogram in a timely fashion will decrease the risk of bleeding and decrease the risk of MI.

The recent approval of the novel, very short-acting, reversible $P2Y_{12}$ antagonist cangrelor also provides an attractive alternative to the slower onset oral $P2Y_{12}$ agents. Cangrelor has a rapid onset of action (seconds) and can be administered as an intravenous bolus in the catheterization laboratory at the time of PCI (24–27). This overcomes the

argument that administering $P2Y_{12}$ antagonists upstream of coronary angiography is necessary to achieve sufficient antiplatelet effects at the time of stent delivery. The rapid offset of action of Cangrelor is also advantageous for NSTEACS patients who fulfill criteria for coronary artery bypass surgery because it allows these patients to be operated on sooner than if they had received any of the oral $P2Y_{12}$ agents (28,29). This would translate to shorter hospitalizations and reduced costs but could also be life-saving for unstable patients who require prompt revascularization (30).

STUDY LIMITATIONS. This is a retrospective analysis from a prospective, randomized trial, and the results should be considered hypothesis generating. Patients who are considered a high risk of bleeding by their treating physicians may be less likely to be administered antithrombotic agents. Although we adjusted for known cardiovascular risk factors when assessing the association between number of antithrombotic drugs and bleeding, we cannot rule out residual bias in this regard. However, this would also be expected to bias the results toward a smaller estimated effect of antithrombotic agents on bleeding risk. We did not have access to all components necessary to calculate the GRACE score; therefore, we could not compare bleeding risk for patients with different GRACE scores; however, we detected no difference in bleeding risk when patients were stratified according to TIMI risk score. Last, although major bleeding was clearly defined and adjudicated in the ACUITY trial, nonmajor bleeding was site-reported as any clinically significant bleed and was not adjudicated.

CONCLUSIONS

Bleeding complications commonly occur before coronary angiography in patients with NSTEACS who are treated with contemporary antithrombotic drugs. Patients who bleed before coronary angiography have increased mortality. Bleeding avoidance strategies such as timely and early coronary angiogram, ischemic risk-based antithrombotic therapy approach, and conservative use of upstream oral antiplatelet therapy may improve patient prognosis.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Bleeding increases linearly over time in patients with NSTEACS given antithrombotic drugs before coronary angiography, suggesting that these drugs should be used judiciously in patients awaiting angiography and that earlier angiography could improve the benefit of angiographic interventions in proportion to risk.

TRANSLATIONAL OUTLOOK: Further studies are needed to assess the impact of specific clinical strategies directed at avoiding bleeding complications, including earlier angiography, in patients with NSTEACS.

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KEY WORDS antithrombotic drugs, bleeding, coronary angiography, non-ST-elevation acute coronary syndrome

APPENDIX For supplemental tables and figures, please see the online version of this article.