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Intraprocedural Thrombotic Events During Percutaneous Coronary Intervention in Patients With Non–ST-Segment Elevation Acute Coronary Syndromes Are Associated With Adverse Outcomes

Analysis From the ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) Trial

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Objectives The purpose of this study was to assess the prognostic impact of intraprocedural thrombotic events (IPTE) during percutaneous coronary intervention (PCI).

Background Ischemic complications of PCI are infrequent but prognostically important. How often these events are a consequence of intraprocedural complications is unknown, with only limited data assessing the occurrence and importance of IPTE.

Methods A total of 3,428 patients who underwent PCI for non–ST-segment elevation acute coronary syndrome in the ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) trial underwent detailed frame-by-frame core laboratory angiographic analysis. An IPTE, defined as the development of new or increasing thrombus, abrupt vessel closure, no reflow, slow reflow, or distal embolization at any time during the procedure, occurred in 121 patients (3.5%).

Results Patients with IPTE had higher in-hospital, 30-day, and 1-year major adverse cardiac event rates than patients without IPTE (25.6% vs. 6.3% in-hospital, 30.6% vs. 9.3% at 30 days, and 37.0% vs. 20.5% at 1 year; $p < 0.0001$ for each). An IPTE was strongly associated with Q-wave myocardial infarction and out-of-laboratory definite/probable stent thrombosis (in-hospital 3.3% vs. 0.5%, $p = 0.006$; 30 days 5.8% vs. 1.3%, $p < 0.0001$; and 1 year 6.7% vs. 2.0%, $p = 0.0002$). Unplanned revascularization, target vessel revascularization, and major bleeding not associated with coronary artery bypass graft surgery were also increased among patients with IPTE, as was overall 30-day mortality (3.3% vs. 0.7%, $p = 0.002$). Moreover, IPTE was an independent predictor of 30-day and 1-year composite death/myocardial infarction, stent thrombosis, and major adverse cardiac events.

Conclusions Although infrequent among patients undergoing early PCI for moderate and high-risk non–ST-segment elevation acute coronary syndrome, IPTE was strongly associated with subsequent adverse outcomes including death, myocardial infarction, and stent thrombosis. (J Am Coll Cardiol 2012;59:1745–51) © 2012 by the American College of Cardiology Foundation

Acute ischemic complications in the modern era of percutaneous coronary intervention (PCI) are infrequent, but when they occur, are often severe and affect future prognosis. The ischemic complications of PCI that have garnered most extensive study are periprocedural myocardial infarction (MI) and stent thrombosis. How often these adverse events develop directly as a consequence of intraprocedural complications is unknown, and few studies have assessed the occurrence and importance of intraprocedural thrombotic events (IPTE) such as slow flow, vessel closure, distal embolization, and new thrombus formation (1–4). Indeed, the frequency and implications of IPTE have not previously been

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Abbreviations and Acronyms

ARC = Academic Research Consortium
CABG = coronary artery bypass graft surgery
GPI = glycoprotein IIb/IIIa inhibitor
IPST = intraprocedural stent thrombosis
IPTE = intraprocedural thrombotic events
MACE = major adverse cardiovascular events
MI = myocardial infarction
NSTEACS = non–ST-segment elevation acute coronary syndrome
PCI = percutaneous coronary intervention

reported from a dedicated core laboratory-based angiographic study, in part because such analysis requires detailed assessment of all procedural cineangiographic frames, a time-intensive and expensive process. Moreover, as the standard Academic Research Consortium (ARC) definitions (5) of stent thrombosis exclude intraprocedural events, the frequency and implications of intraprocedural stent thrombosis (IPST) have never been reported.

We, therefore, sought to determine the incidence of IPTE (including IPST), to describe the patient, lesion, and procedural characteristics associated with their occurrence, and to assess their impact on early and late clinical outcomes from the ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) trial, a large-scale contemporary study that investigated different antithrombotic regimens in patients with moderate- and high-risk non–ST-segment elevation acute coronary syndrome (NSTEACS) who were undergoing an early invasive strategy (6).

Methods

The study design, protocol, and primary results of the ACUITY trial have previously been described in detail (6,7). In brief, 13,819 patients were prospectively randomized to 1 of 3 antithrombotic regimens, heparin plus a glycoprotein IIb/IIIa inhibitor (GPI), bivalirudin plus a GPI, or bivalirudin alone. Angiography was performed in all patients within 72 h, followed by triage to PCI, coronary artery bypass graft surgery (CABG), or medical therapy at the discretion of the physician. Aspirin loading was administered before catheterization while clopidogrel was given to all patients before catheterization or within 2 h post-PCI. Aspirin was continued indefinitely and clopidogrel for 1 year after hospital discharge.

A pre-specified angiographic substudy was undertaken in 6,921 consecutive patients from U.S. centers, with all analyses performed at an independent core laboratory (Cardiovascular Research Foundation, New York, New York) by technicians blinded to randomization and clinical outcomes. From this group, PCI was performed in 3,428 patients, who represent the present study cohort. In addition to routine pre- and post-procedural quantitative and qualitative assessment, additional analyses of every cineangiographic frame was performed. Intraprocedural complications were independently assessed for each angiographic run.

An IPTE was defined as the development of new or increasing thrombus, abrupt vessel closure, no reflow or slow reflow, or distal embolization occurring at any time during the procedure. An IPST (a subset of IPTE) was defined as new or increased thrombus within the deployed stent during the PCI procedure. Each complication was assessed relative to the status of the previous frames. Thus, if thrombus was present at baseline but then resolved only to recur later, this was coded as an IPTE. Similarly, thrombus at baseline that qualitatively "grew" in subsequent frames was considered an IPTE. Conversely, baseline thrombus that persisted in size without growing, diminished, or resolved was not considered an IPTE.

The pre-specified primary clinical endpoints of major adverse cardiovascular events (MACE) [death from any cause, MI, or unplanned revascularization for ischemia]), major bleeding (not related to CABG), and net adverse clinical events (MACE or major bleeding) were assessed at hospital discharge, 30 days, and 1 year. Definitions of these endpoints have previously been described in detail, and were adjudicated by an independent clinical events committee blinded to treatment assignment (6). Stent thrombosis was adjudicated by the ARC criteria (5).

Categorical variables were compared using the chi-square test. Continuous variables are expressed as mean ± SD and median (interquartile range), and compared using analysis of variance or Kruskall-Wallis tests, as appropriate based upon the distribution. Univariate analysis was performed to identify factors associated with IPTE, and to determine which of its components were associated with ischemic outcomes. Multivariable analysis by logistic regression was performed to determine independent predictors of IPTE, and whether IPTE was an independent predictor of outcomes at 1 month; Cox models were used for 1-year outcomes. Candidate covariates for multivariable models were selected using stepwise selection and included IPTE event, randomization group, age, sex, medically treated diabetes mellitus, insulin-treated diabetes, hypertension, hyperlipidemia, current smoker, previous MI, previous PCI, previous CABG, renal insufficiency, baseline biomarker elevation (troponin or creatine kinase–myocardial band), baseline ST-segment deviation ≥1 mm, Thrombolysis In Myocardial Infarction (TIMI) risk score, baseline hematocrit, baseline white blood cell count, left ventricular ejection fraction, number of diseased vessels, total extent of disease, time from randomization to study drug, time from study drug to PCI, pre-procedure thienopyridines, and pre-procedure statins. After initial variable selection, models were refitted using a limited number of covariates to prevent model over-fitting and loss of data due to missing data.

Results

Of the 3,428 patients treated with PCI, 121 (3.5%) had an IPTE, including 10 (0.3%) with IPST. The individual components of IPTE are listed in Table 1. There were no

Table 1 Components of Intraprocedural Thrombotic Events (N = 121)

Main branch IPTE	108 (89.3%)
New or worsened thrombus	21 (17.4%)
Abrupt closure	27 (22.3%)
No reflow (new TIMI flow grade 0 or 1)	17 (14.0%)
Slow reflow (new TIMI flow grade 2)	71 (58.7%)
Distal embolization	39 (32.2%)
Side branch IPTE	23 (19.0%)
New or worsened thrombus	9 (7.4%)
Abrupt closure	15 (12.4%)
Distal embolization	6 (5.0%)
IPTE before stent	54 (44.6%)
IPTE after stent	81 (66.9%)
Intraprocedural stent thrombosis	10 (8.3%)

Values are n (%).
IPTE = intraprocedural thrombotic events; TIMI = Thrombolysis In Myocardial Infarction.

significant differences in the rates of IPTE or IPST among the 3 antithrombotic treatment arms of the trial (3.6% with heparin plus GPI, 3.1% with bivalirudin plus GPI, and 4.0% with bivalirudin alone; p = 0.51).

Baseline and procedural characteristics. Patients with IPTE had had a lower prevalence of prior diabetes, hypertension, hyperlipidemia, and previous PCI, but more often had elevated baseline cardiac biomarkers (Tables 2 and 3). There were no significant differences in the pre-procedural administration of antithrombotic therapy and antiplatelet therapy among the IPTE and no-IPTE groups. Procedural GPI use tended to be more frequent among patients with IPTE. Bailout GPI use (permitted in the bivalirudin alone arm) was given more frequently to patients with IPTE (28.9% vs. 7.6% without IPTE, p < 0.0001). Baseline TIMI flow grade and myocardial blush scores were significantly worse in the IPTE group, and patients with subsequent IPTE more frequently had a lesion with angiographically apparent thrombus before PCI. Lesions with an IPTE were longer, had smaller minimum lumen diameter and higher percentage diameter stenosis, but a larger reference vessel diameter.

By multivariable analysis, including clinical characteristics associated with IPTE, absence of prior hyperlipidemia (odds ratio: 0.53 [95% confidence interval (CI): 0.35 to 0.78], p = 0.0014) and baseline cardiac biomarker elevation (odds ratio: 3.20 [95% CI: 1.92 to 5.32], p < 0.0001) were the sole independent correlates of an IPTE.

Clinical outcomes. Patients in whom an IPTE developed had markedly higher in-hospital, 30-day, and 1-year MACE rates than did patients without IPTE (25.6% vs. 6.3% in-hospital, 30.6% vs. 9.3% at 30 days, and 37.0% vs. 20.5% at 1 year, p < 0.0001 for each comparison) (Table 4, Fig. 1). Each of the individual components of IPTE was significantly associated with MACE at 30 days and 1 year (with the exception of no reflow and MACE at 1 year) (Table 5).

Table 2 Baseline Demographic and Patient Characteristics

Demographics	IPTE (n = 121)	No IPTE (n = 3,307)	p Value
Age at randomization, yrs	60.0 (53.0–71.0)	61.0 (53.0–70.0)	0.90
Male	70.2%	70.2%	1.0
Weight, kg	86.0 (74.0–97.6)	87.2 (76.0–100)	0.21
Diabetes mellitus	23.1%	31.8%	0.046
Insulin-requiring diabetes	6.6%	9.0%	0.51
Hypertension	53.7%	70.1%	0.0003
Hyperlipidemia	39.2%	62.7%	<0.0001
Current smoker	36.4%	31.5%	0.27
Previous myocardial infarction	34.2%	34.3%	1.0
Previous percutaneous coronary intervention	33.3%	47.6%	0.002
Previous coronary artery bypass graft surgery	24.8%	21.7%	0.43
Renal insufficiency	13.4%	17.2%	0.37
Baseline cardiac biomarker elevation	83.0%	56.3%	<0.0001
ST-segment deviation ≥1 mm	24.8%	26.0%	0.83
Baseline cardiac biomarker elevation or ST-segment deviation	87.5%	66.0%	<0.0001
TIMI risk score			
Low, 0–2	16.5%	13.0%	0.30
Intermediate, 3–4	58.3%	56.1%	0.69
High, 5–7	25.2%	30.9%	0.23
Admission medications, taken at home			
Aspirin	73.6%	76.0%	0.52
Thienopyridines	24.8%	29.9%	0.27
Statins	34.7%	54.4%	<0.0001
Beta-blockers	44.6%	54.1%	0.04
ACE inhibitors or angiotensin-receptor blockers	30.6%	43.1%	0.007

Values are median (range) or %.
ACE = angiotensin-converting enzyme; other abbreviations as in Table 1.

Table 3 Pre-Percutaneous Coronary Intervention and Procedural Characteristics

Characteristics	IPTE (n = 121)	No IPTE (n = 3,307)	p Value
Time intervals, h			
Admission to randomization	5.71 (1.71–14.43)	6.83 (1.87–16.07)	0.29
Randomization to first study drug	0.70 (0.40–1.08)	0.67 (0.40–1.13)	0.90
First study drug to angiogram	2.05 (0.68–7.97)	2.87 (0.88–13.28)	0.10
First study drug to PCI	2.63 (1.17–8.07)	3.37 (1.32–14.63)	0.10
Antithrombin medications pre-randomization			
Any heparin	75 (62.0%)	2,006 (60.7%)	0.85
Unfractionated heparin	53 (43.8%)	1,392 (42.1%)	0.71
Low molecular weight heparin	29 (24.0%)	704 (21.3%)	0.50
Antiplatelet medications pre-PCI			
Aspirin	120 (99.2%)	3,249 (98.4%)	1.0
Thienopyridine	69 (57.0%)	1,975 (60.0%)	0.51
Glycoprotein IIb/IIIa inhibitor	37 (30.6%)	1,110 (33.6%)	0.56
Target vessel			
Left anterior descending artery	27 (22.3%)	1,338/3,305 (40.5%)	<0.0001
Right coronary artery	45 (37.2%)	1,273/3,305 (38.5%)	0.85
Left circumflex	32 (26.4%)	1,186/3,305 (35.9%)	0.04
Left main artery	0 (0.0%)	1/3,305 (0.0%)	1.0
Saphenous vein graft	22 (18.2%)	43/3,305 (1.3%)	<0.0001
Stents implanted			
Drug-eluting stent	104 (86.0%)	2989 (90.4%)	0.12
Bare-metal stent	31 (25.6%)	534 (16.1%)	0.008
Both drug-eluting and bare-metal stent	14 (11.6%)	216 (6.5%)	0.04
Worst baseline TIMI flow grade, all arteries			
0/1	51 (42.5%)	450 (13.7%)	<0.0001
2	25 (20.8%)	371 (11.3%)	0.003
3	45 (37.5%)	2,484 (75.5%)	<0.0001
Worst baseline myocardial blush grade, all arteries			
0/1	50 (43.5%)	503 (17.1%)	<0.0001
2	21 (18.3%)	510 (17.3%)	0.80
3	46 (40.0%)	1,951 (66.2%)	<0.0001
Baseline visible thrombus	76 (62.8%)	498 (15.1%)	<0.0001
Number of vessels undergoing PCI	1.15 ± 0.36	1.18 ± 0.41	0.32
Number of lesions per vessel	1.19 ± 0.41 (n = 139)	1.15 ± 0.37 (n = 3,907)	0.19
Lesion length, mm	20.84 ± 14.42 (n = 151)	15.65 ± 10.11 (n = 4,358)	<0.0001
Reference vessel diameter, mm	3.01 ± 0.65 (n = 166)	2.77 ± 0.55 (n = 4,479)	<0.0001
Minimum lumen diameter, mm	0.53 ± 0.48 (n = 166)	0.74 ± 0.46 (n = 4,479)	<0.0001
Percentage diameter stenosis, %	82.85 ± 15.07 (n = 166)	73.23 ± 15.59 (n = 4,479)	<0.0001

Values are median (interquartile range), n (%), n/N (%), or mean ± SD.
IPTE = intraprocedural thrombotic events; IQR = interquartile range; PCI = percutaneous coronary intervention.

An IPTE was strongly associated with the development of MI (Table 4). Of note, Q-wave MI was especially common among patients with IPTE (in-hospital 6.6% vs. 0.5%, $p < 0.0001$). Definite or probable stent thrombosis occurring out-of-laboratory was also strikingly higher among patients with IPTE (in-hospital 3.3% vs. 0.5%, $p = 0.006$; 30 days 5.8% vs. 1.3%, $p < 0.0001$; and 1 year 6.7% vs. 2.0%, $p = 0.0002$) (Fig. 1), as was definite stent thrombosis (in-hospital 3.3% vs. 0.4%, $p = 0.002$; 30 days 5.0% vs. 0.8%, $p < 0.0001$; and 1 year 5.9% vs. 1.3%, $p < 0.0001$). Unplanned revascularization and non-CABG major bleeding were also increased in patients with IPTE (Table 4). Overall, 30-day mortality was greater among patients with IPTE (3.3% vs. 0.7%, $p = 0.002$).

By multivariable analysis, the development of IPTE was independently associated with the 30-day and 1-year occurrence of MACE, death, or MI, and ARC definite/probable stent thrombosis (Table 6).

An IPST, although uncommon, was strongly associated with death or MI (in-hospital 50.0% vs. 6.4%; 30 days 50.0% vs. 8.1%; and 1 year 50.0% vs. 12.5%; each $p < 0.0001$), and out-of-laboratory ARC definite stent thrombosis (in-hospital and 30 days 20.4% vs. 0.9%; and 1 year 20.0% vs. 1.4%; each $p < 0.0001$).

Discussion

The principal findings of this analysis from the ACUITY trial are that although IPTE in patients with moderate- and

high-risk NSTEACS treated with early PCI is uncommon, its occurrence is strongly associated with early and late MACE. Each of the individual components of IPTE was associated with adverse ischemic outcomes, and in aggregate, IPTE was a powerful independent predictor of adverse events, including death or MI (especially Q-wave MI), and subsequent (out-of-laboratory) stent thrombosis. Thus, the occurrence of IPTE identifies patients at high risk for subsequent adverse events, warranting preventive and therapeutic strategies.

Table 4 Clinical Outcome According to Intraprocedural Thrombotic Event Occurrence

Outcome	IPTE (n = 121)	No IPTE (n = 3,307)	p Value
In-hospital outcomes			
Net adverse clinical events	33.9% (41)	10.4% (343)	<0.0001
MACE	25.6% (31)	6.3% (209)	<0.0001
Death or myocardial infarction	24.0% (29)	5.9% (195)	<0.0001
Death	0.0% (0)	0.3% (11)	1.0
Myocardial infarction	24.0% (29)	5.7% (189)	<0.0001
Q-wave	6.6% (8)	0.5% (17)	<0.0001
Non–Q-wave	17.4% (21)	5.2% (172)	<0.0001
Unplanned revascularization	5.0% (6)	1.0% (34)	0.003
PCI	2.5% (3)	0.9% (31)	0.12
CABG	2.5% (3)	0.1% (3)	0.0008
Non-CABG major bleeding	12.4% (15)	5.0% (165)	0.001
Definite or probable ST	3.3% (4)	0.5% (17)	0.006
Definite ST	3.3% (4)	0.4% (12)	0.002
1-month outcomes			
Net adverse clinical events	37.2% (45)	13.7% (450)	<0.0001
MACE	30.6% (37)	9.3% (305)	<0.0001
Death or myocardial infarction	28.9% (35)	7.5% (246)	<0.0001
Death	3.3% (4)	0.7% (24)	0.0020
Myocardial infarction	28.1% (34)	7.0% (230)	<0.0001
Q-wave	7.5% (9)	0.9% (30)	<0.0001
Non-Q-wave	20.7% (25)	6.1% (202)	<0.0001
Unplanned revascularization	7.5% (9)	3.4% (112)	0.01
PCI	5.8% (7)	3.2% (105)	0.11
CABG	2.5% (3)	0.3% (11)	<0.0002
Non-CABG major bleeding	12.4% (15)	5.8% (192)	0.002
Definite or probable ST	5.8% (7)	1.3% (43)	<0.0001
Definite ST	5.0% (6)	0.8% (26)	<0.0001
1-yr outcomes			
MACE	37.0% (44)	20.5% (648)	<0.0001
Death or myocardial infarction	33.4% (40)	11.8% (380)	<0.0001
Death	3.3% (4)	2.9% (91)	0.71
Myocardial infarction	32.6% (39)	9.9% (319)	<0.0001
Q-wave	8.5% (10)	1.5% (46)	<0.0001
Non-Q-wave	24.2% (29)	8.6% (276)	<0.0001
Unplanned revascularization	13.0% (15)	13.4% (411)	0.93
PCI	10.6% (12)	12.1% (370)	0.69
CABG	3.4% (4)	1.7% (54)	0.15
Definite or probable ST	6.7% (8)	2.0% (62)	0.0002
Definite ST	5.9% (7)	1.3% (41)	<0.0001

Values are % (n).

CABG = coronary artery bypass graft surgery; MACE = major adverse cardiac event(s); ST = stent thrombosis; other abbreviations as in Tables 1 and 3.

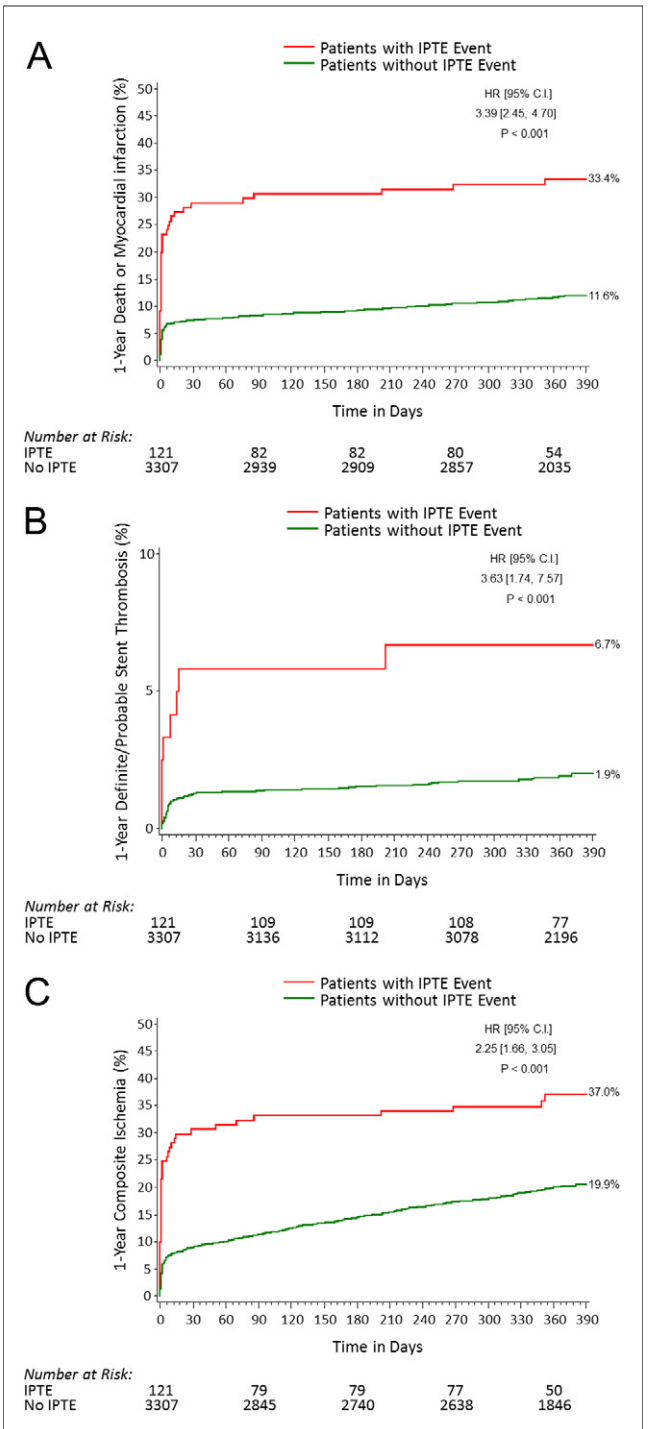

Figure 1 Time-to-Event Curves in Patients With IPTE Versus Patients Without IPTE

(A) Time-to-event curves for 1-year rate of death or reinfarction in patients with intraprocedural thrombotic events (IPTE) **(red line)** versus patients without IPTE **(green line)**. **(B)** Time-to-event curves for 1-year rate of definite or probable stent thrombosis in patients with IPTE **(red line)** versus patients without IPTE **(green line)**. **(C)** Time-to-event curves for 1-year rate of composite ischemia in patients with IPTE **(red line)** versus without IPTE **(green line)**. CI = confidence interval; HR = hazard ratio.

Table 5 Components of IPTE as Predictors of MACE at 1 Month and 1 Year

IPTE Components	1-Month MACE (n = 342)	No 1-Month MACE (n = 3,086)	p Value
All IPTE	10.8% (37)	2.7% (84)	<0.001
Main branch IPTE	9.6% (33)	2.4% (75)	<0.001
New or worsened thrombus	2.3% (8)	0.4% (13)	0.0006
Abrupt closure	2.6% (9)	0.6% (18)	0.0008
No reflow (new TIMI flow grade 0 or 1)	1.5% (5)	0.4% (12)	0.02
Slow reflow (new TIMI flow grade 2)	7.0% (24)	1.5% (47)	<0.0001
Distal embolization	3.8% (13)	0.8% (26)	<0.0001
Side branch IPTE	2.0% (7)	0.5% (16)	0.006
New or worsened thrombus	0.9% (3)	0.2% (6)	0.052
Abrupt closure	1.5% (5)	0.3% (10)	0.01
Distal embolization	0.9% (3)	0.1% (3)	0.02
IPTE pre-stent	4.1% (14)	1.3% (40)	0.0006
IPTE post-stent	8.8% (30)	1.7% (51)	<0.0001
Intraprocedural stent thrombosis	1.8% (6)	0.1% (4)	0.0001
	1-Yr MACE (n = 692)	**No 1-Yr MACE (n = 2,736)**	**p Value**
All IPTE	6.4% (44)	2.8% (77)	<0.0001
Main branch IPTE	5.8% (40)	2.5% (68)	<0.0001
New or worsened thrombus	1.3% (9)	0.4% (12)	0.02
Abrupt closure	1.4% (10)	0.6% (17)	0.049
No reflow (new TIMI flow grade 0 or 1)	0.9% (6)	0.4% (11)	0.13
Slow reflow (new TIMI flow grade 2)	4.0% (28)	1.6% (43)	0.0001
Distal embolization	2.2% (15)	0.9% (24)	0.008
Side branch IPTE	1.0% (7)	0.6% (16)	0.29
New or worsened thrombus	0.4% (3)	0.2% (6)	0.40
Abrupt closure	0.7% (5)	0.4% (10)	0.20
Distal embolization	0.4% (3)	0.1% (3)	0.10
IPTE pre-stent	2.5% (17)	1.4% (37)	0.06
IPTE post-stent	4.9% (34)	1.7% (47)	<0.0001

Values are n (%).
Abbreviations as in Tables 1 and 4.

The occurrence of IPTE during PCI increases procedural complexity, and is linked to lower rates of angiographic and procedural success. Several prior retrospective and observational studies have linked procedural complications to MACE (1–4). However, none of these studies performed frame-by-frame analysis at an independent core laboratory blinded to patient outcomes. In the present analysis, blinded core laboratory determination of an IPTE was performed, and IPTE was strongly associated with adverse outcomes in both univariable and multivariable analyses. Moreover, all of the individual components of IPTE were associated with the occurrence of independently adjudicated composite ischemic events.

Patients with IPTE less commonly had cardiovascular risk factors or prior PCI, more commonly had elevated baseline cardiac biomarkers, and were less likely to be using cardiac medications. Moreover, patients who had an IPTE had more severe stenoses in larger vessels (often with angiographic thrombus evident), with worse TIMI flow grade and myocardial blush scores. Thus, it is interesting to note that IPTE occurred in some of the highest risk NSTEACS lesions occurring in patients not previously on adequate preventive medical therapies.

The occurrence of IPTE was strongly associated with subsequent ischemic events, including MACE, MI, and stent thrombosis. The vast majority of effect of IPTE upon outcomes occurred early, with parallel event curves for most endpoints after 30 days. A Q-wave MI was particularly likely to develop after IPTE, the occurrence of which has been strongly related to subsequent early and late mortality after PCI. In addition, it is a novel and important observation that angiographically documented thrombotic stent occlusion (ARC definite stent thrombosis) is more likely to subsequently occur in stents patent at the end of a procedure complicated by IPTE . While 1 explanation for this association is the intrinsic link between IPTE and residual thrombus and/or diminished coronary flow, it is also possible that the occurrence of IPTE led operators to perform fewer and/or lower pressure balloon/stent inflations and/or otherwise change their practice to avoid worsening IPTE. Finally, patients with IPTE had notably more non-CABG major bleeding than did patients without IPTE, possibly due to intraprocedural bailout therapy with GPI (bailout GPI in bivalirudin alone patients with an IPTE vs. without an IPTE was 28.9% vs. 7.6%, respectively; $p < 0.0001$), prolonged anticoagulation therapy, and/or other therapies.

Table 6 Independent Predictors of Adverse Events at 30 Days and 1 Year

Independent Predictor	Odds Ratio (95% CI)	p Value
Death or MI at 1 month		
IPTE	5.45 (3.51–8.47)	<0.0001
Previous MI	1.35 (1.03–1.77)	0.023
Renal insufficiency	2.20 (1.64–2.95)	<0.0001
3-vessel disease	1.64 (1.25–2.14)	0.0003
Death or MI at 1 yr		
IPTE	3.36 (2.39–4.73)	<0.0001
Insulin-treated diabetes	1.57 (1.17–2.12)	0.0029
Previous MI	1.35 (1.10–1.66)	0.0042
Renal insufficiency	1.93 (1.54–2.42)	<0.0001
3-vessel disease	1.65 (1.34–2.03)	<0.0001
Definite/probable ST at 1 month		
IPTE	4.08 (1.68–9.90)	0.003
Renal insufficiency	2.29 (1.23–4.28)	0.009
3-vessel disease	2.10 (1.14–3.86)	0.02
Definite/probable ST at 1 yr		
IPTE	4.00 (1.79–8.93)	0.0007
LVEF, per 10-U decrease	1.21 (0.97–1.49)	0.1090
Insulin-treated diabetes	2.12 (0.99–4.54)	0.0530
3-vessel disease	2.34 (1.27–4.30)	0.0065
MACE at 1 month		
IPTE	4.74 (3.08–7.29)	<0.0001
Previous MI	1.44 (1.13–1.85)	0.004
Renal insufficiency	1.92 (1.45–2.55)	<0.0001
3-vessel disease	1.63 (1.28–2.09)	<0.0001
MACE at 1 yr		
IPTE event	2.41 (1.68–3.44)	<0.0001
LVEF, per 10-U decrease	1.08 (1.00–1.16)	0.0415
Insulin-treated diabetes	1.59 (1.22–2.09)	0.0007
Previous PCI	1.37 (1.15–1.64)	0.0006
Renal insufficiency	1.66 (1.35–2.04)	<0.0001
3-vessel disease	1.53 (1.28–1.84)	<0.0001

CI = confidence interval; LVEF = left ventricular ejection fraction; MI = myocardial infarction; other abbreviations as in Tables 1, 3, and 4.

Study limitations. The present study is a post-hoc retrospective analysis from a multicenter clinical trial. Thus, even though core laboratory analyses in the ACUITY trial were prospectively performed blinded to clinical events, these findings merit further validation from other studies. The overall number of IPTE was relatively small, although strongly related to subsequent adverse events. A larger study may have revealed a relationship between IPTE and all-cause mortality, as expected from the increased rates of Q-wave MI and stent thrombosis. Conversely, although IPTE was an important predictor of MACE, MI, and stent thrombosis, after multivariable adjustment for high-risk baseline features, the role of unmeasured confounders cannot be excluded. Additionally, the correlation (and relative predictive accuracy) between site-assessed versus core laboratory-assessed IPTE has never been studied, which is necessary to know whether these results fully translate to clinical practitioners.

Conclusions

The results of the present study suggest that the occurrence of IPTE during PCI for NSTEACS is a strong predictor of subsequent MACE, including Q-wave MI, and subsequent stent thrombosis. Prevention of IPTE by optimizing patient selection, adjunct pharmacotherapy, and technique is, therefore, essential to optimize patient outcomes. Further studies are warranted to determine whether therapeutic measures should be undertaken when IPTE occurs to mitigate their sequelae, such as the use of more potent adenosine diphosphate antagonists to prevent subsequent stent thrombosis (8,9). Finally, the rate of IPTE might be considered an appropriate surrogate endpoint in clinical trials investigating new antithrombin and antiplatelet agents during PCI.

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REFERENCES

1. Bauer T, Möllmann H, Weidinger F, et al. Predictors of hospital mortality in the elderly undergoing percutaneous coronary intervention for acute coronary syndromes and stable angina. Int J Cardiol 2011; 151:164–9.
2. Fefer P, Daoulah A, Strauss BH, et al. Visible angiographic complications predict short and long-term outcomes in patients with post-procedural creatine-phosphokinase elevation. Catheter Cardiovasc Interv 2010;76:960–6.
3. Stone GW, Moses JW, Ellis SG, et al. Safety and efficacy of sirolimus- and paclitaxel-eluting coronary stents. N Engl J Med 2007;356:998–1008.
4. Fokkema ML, Vlaar PJ, Svilaas T, et al. Incidence and clinical consequences of distal embolization on the coronary angiogram after percutaneous coronary intervention for ST-elevation myocardial infarction. Eur Heart J 2009;30:908–15.
5. Cutlip DE, Windecker S, Mehran R, et al, for the Academic Research Consortium. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007;115:2344–51.
6. Stone GW, McLaurin BT, Cox DA, et al. Bivalirudin for patients with acute coronary syndromes. N Engl J Med 2006;355:2203–16.
7. Stone GW, Bertrand M, Colombo A, et al. Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial: study design and rationale. Am Heart J 2004;148:764–75.
8. Wiviott SD, Braunwald E, McCabe CH, et al., for the TRITON-TIMI 38 Investigators. Intensive oral antiplatelet therapy for reduction of ischaemic events including stent thrombosis in patients with acute coronary syndromes treated with percutaneous coronary intervention and stenting in the TRITON-TIMI 38 trial: a subanalysis of a randomised trial. Lancet 2008;371:1353–63.
9. Cannon CP, Harrington RA, James S, et al., for the Platelet Inhibition and Patient Outcomes Investigators. Comparison of ticagrelor with clopidogrel in patients with a planned invasive strategy for acute coronary syndromes (PLATO): a randomised double-blind study. Lancet 2010;375:283–93.

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