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Association Between Angiographic Complications and Clinical Outcomes Among Patients With Acute Coronary Syndrome Undergoing Percutaneous Coronary Intervention

An EARLY ACS (Early Glycoprotein IIb/IIIa Inhibition in Non–ST-Segment Elevation Acute Coronary Syndrome) Angiographic Substudy

Yuri B. Pride, MD,* Satishkumar Mohanavelu, MS,† Cafer Zorkun, MD,* Vijayalakshmi Kunadian, MBBS, MD,* Robert P. Giugliano, MD, SM,† L. Kristin Newby, MD, MHS,‡ Eugene Braunwald, MD,† Robert M. Califf, MD,‡ Robert A. Harrington, MD,‡ C. Michael Gibson, MS, MD,* for the EARLY ACS Investigators

Boston, Massachusetts; and Durham, North Carolina

Objectives The goal of this analysis was to determine the association between intraprocedural complications and clinical outcomes among patients with high-risk non–ST-segment elevation acute coronary syndrome (NSTEACS) undergoing percutaneous coronary intervention (PCI).

Background Among patients undergoing PCI for NSTEACS, the relationship between intraprocedural complications and clinical outcomes, independent of epicardial and myocardial perfusion, has not been well characterized.

Methods The EARLY ACS (Early Glycoprotein IIb/IIIa Inhibition in Non–ST-Segment Elevation Acute Coronary Syndrome) trial enrolled 9,406 patients with high-risk NSTEACS undergoing an early invasive strategy. Of these, 1,452 underwent angiographic assessment in an independent core laboratory and did not have a myocardial infarction (MI) between enrollment and angiography. We assessed the relationship between abrupt closure, loss of side branch(es), distal embolization, and no-reflow phenomenon and 30-day clinical outcomes in these patients.

Results Of the patients, 166 (11.4%) experienced an intraprocedural complication. Baseline clinical characteristics were similar between patients who did and did not have complications. The 30-day composite of death or MI was significantly higher among patients with an intraprocedural complication (28.3% vs. 7.8%, odds ratio [OR]: 4.68, 95% confidence interval [CI]: 3.2 to 7.0, $p < 0.001$). Individually, both mortality (3.0% vs. 0.9%, OR: 3.60, 95% CI: 1.2 to 10.5, $p = 0.019$) and MI (27.1% vs. 7.4%, OR: 4.66, 95% CI: 3.1 to 7.0, $p < 0.001$) were significantly increased. After adjusting for differences in post-PCI epicardial and myocardial perfusion, the association with 30-day death or MI remained significant.

Conclusions Among high-risk NSTEACS patients undergoing an invasive strategy, the incidence of intraprocedural complications is high, and the occurrence of these complications is associated with worse clinical outcomes independent of epicardial and myocardial perfusion. (Early Glycoprotein IIb/IIIa Inhibition in Patients With Non–ST-segment Elevation Acute Coronary Syndrome [EARLY ACS]; NCT00089895) (J Am Coll Cardiol Intv 2012;5:927–35) © 2012 by the American College of Cardiology Foundation

From the *Cardiovascular Division, Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts; †Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts; and the ‡Duke Clinical Research Institute, Durham, North Carolina. The EARLY ACS trial was supported by Schering-Plough and Millennium Pharmaceuticals. All authors received research grant support from the sponsor of the trial, Merck-Schering Plough.

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Periprocedural myocardial infarction (MI), which has been independently associated with a higher incidence of subsequent major adverse cardiovascular events, is common among patients with non–ST-segment elevation acute coronary syndrome (NSTEACS) undergoing percutaneous coronary intervention (PCI) (1–5). However, both the definition and clinical significance of periprocedural MI are difficult to evaluate, as many patients with ACS have elevated biomarkers at the time of PCI related to their index event. Intraprocedural complications, such as loss of a coronary artery side branch, abrupt closure, distal embolization, and the no-reflow phenomenon can be objectively defined and occur in patients both with and without biomarker elevation at presentation.

The EARLY ACS (Early Glycoprotein IIb/IIIa Inhibition in Non–ST-Segment Elevation Acute Coronary Syndrome) trial enrolled 9,406 evaluable patients with high-risk NSTEACS undergoing an early invasive strategy (6). The goal of this analysis was to determine the incidence of intraprocedural complications and to determine whether these complications were associated with adverse cardiovascular events independent of epicardial and myocardial perfusion at the completion of the procedure. An additional goal was to determine whether the intraprocedural complications were associated with adverse outcomes independent of the patient's baseline troponin status prior to PCI.

Abbreviations and Acronyms

CI = confidence interval

cTFC = corrected Thrombolysis In Myocardial Infarction frame count

MI = myocardial infarction

NSTEACS = non–ST-segment elevation acute coronary syndrome

OR = odds ratio

PCI = percutaneous coronary intervention

TFG = Thrombolysis In Myocardial Infarction flow grade

TIMI = Thrombolysis In Myocardial Infarction

TMPG = Thrombolysis In Myocardial Infarction myocardial perfusion grade

Methods

Patient population. EARLY ACS enrolled patients with high-risk NSTEACS intended to undergo an early invasive treatment strategy. The patient population has been previously described (6,7). Briefly, patients who were at least 18 years of age were eligible if they had cardiac ischemia at rest lasting for at least 10 min and occurring within 24 h before study entry, with a planned invasive strategy no sooner than the next calendar day after randomization. They had to be enrolled within 8 h (12 h after a protocol amendment during the trial) of arrival in the emergency department. Patients were considered to have a high-risk condition if they met 2 or more of the following criteria: ischemic changes on electrocardiography (ST-segment depression of 0.1 mV or more, or transient [<30 min] ST-segment elevation of 0.1 mV or more in 2 or more contiguous leads), troponin or creatine kinase-myocardial band (CK-MB) above the local laboratory upper limit of normal, and an age ≥60 years. A protocol amendment during enrollment permitted the enrollment of patients who were between the ages of 50 and 59 years if they had elevated levels of troponin or CK-MB and documented coronary, cerebrovascular, or peripheral artery disease.

Study procedures. Patients in EARLY ACS were randomized to either double-bolus eptifibatide plus infusion or matching placebo, in addition to standard antithrombotic therapy, including aspirin, clopidogrel, and anticoagulant. Before PCI, investigators could opt to use a "PCI active kit" if they felt a glycoprotein inhibitor was needed during PCI. In addition, investigators could request a "bailout eptifibatide" kit if during PCI, the subject had a thrombotic complication and the PCI active kit had not been administered.

Angiographic cohort. For the EARLY ACS angiographic substudy, investigators were asked to send copies of their patients' angiograms to the PERFUSE Angiographic Core Laboratory at Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts. Sites were urged to submit angiograms for this substudy. The goal was to obtain 2,000 angiograms for analysis. From this population, patients who did not have an MI between enrollment and angiography were included in the current analysis. An MI between enrollment and angiography was defined as elevation of cardiac biomarkers above the upper limit of normal following enrollment and before angiography when the first set of cardiac biomarkers was normal.

Angiographic analysis. All angiograms were evaluated independently by trained reviewers who were blinded to treatment assignment, clinical and procedural data from the case report form, and clinical outcomes. Angiograms were evaluated for epicardial coronary flow using the Thrombolysis In Myocardial Infarction (TIMI) flow grade (TFG) and the corrected TIMI frame count (cTFC) (8,9). Myocardial perfusion was evaluated using the TIMI myocardial perfu-

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sion grade (TMPG) (10). Angiographic perfusion score was calculated as previously described (11). Quantitative coronary angiography was also used to determine the degree of coronary stenosis. Intraprocedural complications were defined as transient or sustained loss of side branch, abrupt closure, distal embolization, and the no-reflow phenomenon.

Loss of a side branch was defined as the development of TFG 0 or 1 in a side branch that was >1.5 mm in diameter before the procedure and that was initially patent with TFG 2 or 3. Distal embolization was defined as the appearance of an abrupt cutoff in the distal vessel following PCI. No-reflow was defined as markedly delayed flow down the artery with minimal residual stenosis. Abrupt closure was defined as shown in Table 1. The thrombus grade was defined as described by Gibson et al. (12).

Statistical analysis. Baseline characteristics, angiographic findings, and clinical outcomes were summarized using means with standard deviations for continuous variables and frequencies for categorical variables. The Wilcoxon rank sum test was used for comparisons of continuous variables, and the chi-square or Fisher exact test was used for comparisons of categorical variables. Odds ratios (ORs) with 95% confidence intervals (CIs) obtained using logistic regression modeling were used to describe the association of intraprocedural complications with the 30-day composite of death or MI (both spontaneous and periprocedural) and secondarily with death and MI separately. Adjusted comparisons considered post-PCI epicardial and myocardial perfusion as described by TFG and TMPG. Additionally, we assessed the association of intraprocedural complications with clinical outcomes after adjusting for pre-PCI troponin status as reported by the individual sites, on the basis of local laboratory findings. The p values are reported using the log-rank test for the Kaplan-Meier failure curves. p Values (2-tailed) <0.05 were considered statistically significant. No adjustments were made for multiple comparisons. All analyses were performed using Stata/IC, version 10.1 (StataCorp, College Station, Texas).

Table 1. Definitions of Abrupt Closure

Pre-PTCA Flow	Post-PTCA Flow
TFG 0 with vessel patency established (TFG 2 or 3) during the procedure	TFG 0
TFG 1	TFG 0
TFG 2	TFG 0 or 1
TFG 3	TFG 0 or 1

PTCA = percutaneous transluminal coronary angioplasty; TFG = Thrombolysis In Myocardial Infarction flow grade.

Results

Patient population and baseline characteristics. Of 9,406 EARLY ACS patients, 1,452 did not have an MI between enrollment and angiography, and had angiograms available for analysis at an independent core laboratory. Baseline clinical characteristics comparing patients who had angiograms available for analysis and those who did not are shown in Table 2. Patients who had angiograms available for analysis were, on average, younger, more likely to be male, have dyslipidemia and elevated troponin at baseline, and less likely to have a TIMI risk score >2, present to a tertiary care hospital, or have a prior MI, hypertension, creatinine clearance <50 ml/min, or be in Killip class II, III, or IV heart failure at presentation. There were also differences in the use of eptifibatide, antithrombotic therapy, and antiplatelet therapy.

Of the 1,452 patients, 166 (11.4%) had at least 1 intraprocedural complication (49.4% loss of side branch, 42.2% abrupt closure, 30.3% distal embolization, 3.6% no-reflow; these categories are not mutually exclusive). Among patients with loss of a side branch, 22.0% were rescued with PCI. Of the patients with abrupt closure, 71.4% had transient closure and 27.1% had sustained closure.

The baseline characteristics of patients with and without intraprocedural complications are shown in Table 3. The groups were generally similar, except that patients with an intraprocedural complication tended to have diabetes mellitus ($p = 0.07$) more often and less prior PCI ($p = 0.07$). Troponin elevation as reported by the individual sites using local laboratory findings before angiography was similar between groups. The use of bailout eptifibatide was significantly higher among those with an intraprocedural complication.

Angiographic characteristics. Angiographic findings before PCI are shown in Table 4. Patients who had an intraprocedural complication had significantly worse pre-PCI TFG, higher mean cTFC, and higher TMPG. In addition, patients who experienced an intraprocedural complication had more severe stenoses and were also more likely to have a thrombus present.

Following PCI, patients who experienced an intraprocedural complication had significantly worse epicardial coronary flow (TFG and cTFC), myocardial perfusion (TMPG), and angiographic perfusion score (Table 5).

Unadjusted outcomes according to occurrence of intraprocedural complications. Patients who had an intraprocedural complication had significantly worse clinical outcomes. At 30 days, patients who had an intraprocedural complication had a significantly higher incidence of the composite of death or MI (28.3% vs. 7.8%, OR: 4.68, 95% CI: 3.2 to 7.0, $p < 0.001$) (Fig. 1A). Individually, both mortality (3.0% vs. 0.9%, OR: 3.60, 95% CI: 1.2 to 10.5, $p = 0.019$) and MI (27.1% vs. 7.4%, OR: 4.66, 95% CI: 3.1 to 7.0, $p < 0.001$) were also significantly increased among patients who had an

intraprocedural complication (Figs. 1B and 1C). At 1 year, the difference in mortality was no longer significant (3.01% vs. 3.90%, p = 0.58).

As the number of intraprocedural complications increased, the rate of the composite of death or MI increased from 7.6% (97 of 1,275) for patients with no complications to 24.8% (32

Table 2. Baseline Clinical Characteristics: Angiography Versus No Angiography or MI Before Angiography

Characteristic	Substudy Cohort (n = 1,452)	No Angiogram Available or Intervening MI (n = 7,954)	p Value
Age, yrs	66.3±10.5	67.2±10.7	<0.001
Female	385 (26.5%)	2,590 (32.6%)	<0.001
Region of enrollment			<0.001
North America	403 (27.8%)	2,485 (31.2%)	
Western Europe	419 (27.9%)	3,371 (42.4%)	
Eastern Europe	99 (6.8%)	919 (11.6%)	
Middle East, Africa, or Asia-Pacific	531 (36.6%)	1,179 (14.8%)	
Medical history			
Diabetes mellitus	429 (29.6%)	2,431 (30.6%)	0.44
Dyslipidemia	893 (61.5%)	4,547 (57.2%)	0.002
Hypertension	968 (66.7%)	5,730 (72.0%)	<0.001
Previous CABG	203 (14.0%)	1,079 (13.6%)	0.67
Previous MI	360 (24.8%)	2,235 (28.1%)	0.009
Previous PCI	401 (27.6%)	1,919 (24.1%)	0.005
Creatinine clearance <50 ml/min	230 (16.2%)	1,436 (18.7%)	0.021
Killip class II, III, or IV	127 (8.8%)	915 (11.6%)	0.002
Qualifying high-risk features			<0.001
Age ≥60 yrs, elevated biomarkers, and ST-segment changes	270 (18.6%)	1,701 (21.4%)	
Age ≥60 yrs and elevated biomarkers	634 (43.7%)	3,311 (41.6%)	
Elevated biomarkers and ST-segment changes	219 (15.1%)	1,140 (14.3%)	
Age ≥60 yrs and ST-segment changes	127 (8.8%)	914 (11.5%)	
Age 50–59 yrs, elevated biomarkers, and previous vascular disease	97 (6.7%)	445 (5.6%)	
Elevated troponin	1,251 (88.1%)	6,399 (83.1%)	<0.001
Presentation to tertiary care hospital	1,106 (76.2%)	6,530 (82.1%)	<0.001
TIMI risk score			<0.001
0–2	301 (21.1%)	1,220 (15.7%)	
3–4	682 (47.7%)	3,733 (48.1%)	
5–7	447 (31.3%)	2,811 (36.2%)	
Medical therapy during hospitalization			
Randomized to early eptifibatide	734 (50.6%)	3,988 (50.1%)	0.77
PCI active eptifibatide kit used	658 (45.3%)	1,518 (19.1%)	<0.001
Antithrombin therapy			<0.001
UFH	430 (29.6%)	2,807 (35.3%)	
LMWH	846 (58.3%)	4,127 (51.9%)	
UFH and LMWH	121 (8.3%)	528 (6.6%)	
Neither UFH nor LMWH	55 (3.8%)	492 (6.2%)	
Aspirin	1,419 (98.5%)	7,647 (97.1%)	0.002
Clopidogrel			
At any time	1,440 (99.2%)	7,058 (88.8%)	<0.001
Early use intended	1,178 (81.1%)	5,879 (73.9%)	<0.001
Beta-blocker	1,291 (89.9%)	6,944 (87.3%)	0.088
Statin	1,295 (89.2%)	6,841 (86.0%)	0.001
ACE inhibitor	988 (68.0%)	5,454 (68.6%)	0.69
ARB	139 (9.6%)	787 (9.9%)	0.71

Values are mean ± SD or n (%).

ACE = angiotensin-converting enzyme; ARB = angiotensin-receptor blocker; CABG = coronary artery bypass graft; LMWH = low molecular weight heparin; MI = myocardial infarction; PCI = percutaneous coronary intervention; TIMI = Thrombolysis In Myocardial Infarction; UFH = unfractionated heparin.

of 129) for patients with 1 complication to 38.9% (14 of 36) among patients with more than 1 intraprocedural complication ($p < 0.001$ for all comparisons) (Fig. 2).

When patients were stratified by troponin elevation prior to PCI, the incidence of the composite of death or MI again was significantly higher among patients who had an intrap-

Table 3. Baseline Clinical Characteristics: Intraprocedural Complication Versus None

Characteristic	Intraprocedural Complication (n = 166)	No Intraprocedural Complication (n = 1,286)	p Value
Age, yrs	66.6±10.7	66.2±10.5	0.68
Female	45 (27.1%)	340 (26.4%)	0.85
Region of enrollment			0.53
North America	43 (25.9%)	360 (28.0%)	
Western Europe	56 (33.7%)	363 (28.2%)	
Eastern Europe	10 (6.0%)	89 (6.9%)	
Middle East, Africa, or Asia-Pacific	57 (34.3%)	474 (36.9%)	
Medical history			
Diabetes mellitus	59 (35.5%)	370 (28.8%)	0.07
Dyslipidemia	94 (56.6%)	799 (62.2%)	0.17
Hypertension	111 (66.9%)	857 (66.6%)	0.95
Previous CABG	26 (15.7%)	177 (13.8%)	0.51
Previous MI	48 (28.9%)	312 (24.3%)	0.19
Previous PCI	36 (21.7%)	365 (28.4%)	0.07
Creatinine clearance <50 ml/min	29 (17.9%)	201 (15.9%)	0.520
Killip class II, III, or IV	15 (9.1%)	112 (8.8%)	0.90
Qualifying high-risk features			0.63
Age ≥60 yrs, elevated biomarkers, and ST-segment changes	30 (18.1%)	240 (18.7%)	
Age ≥60 yrs and elevated biomarkers	75 (45.2%)	559 (43.5%)	
Elevated biomarkers and ST-segment changes	30 (18.1%)	189 (14.7%)	
Age ≥60 yrs and ST-segment changes	12 (7.2%)	115 (9.0%)	
Age 50–59 yrs, elevated biomarkers, and previous vascular disease	7 (4.2%)	90 (7.0%)	
Elevated troponin	145 (89.0%)	1,106 (88.0%)	0.72
Presentation to tertiary care hospital	126 (75.9%)	980 (76.2%)	0.93
TIMI risk score			0.61
0–2	30 (18.3%)	271 (21.4%)	
3–4	83 (50.6%)	599 (47.3%)	
5–7	51 (31.1%)	396 (31.3%)	
Medical therapy during hospitalization			
Antithrombin therapy			0.37
UFH	54 (32.5%)	376 (29.2%)	
LMWH	87 (52.4%)	759 (59.0%)	
UFH and LMWH	18 (10.8%)	103 (8.0%)	
Neither UFH or LMWH	7 (4.2%)	48 (3.7%)	
Aspirin	162 (99.4%)	1,257 (98.4%)	0.50
Clopidogrel			
At any time	165 (99.4%)	1,275 (99.1%)	1.000
Early use intended	139 (83.7%)	1,039 (80.8%)	0.36
Beta-blocker	148 (89.2%)	1,143 (88.9%)	0.92
Statin	143 (86.1%)	1,152 (89.6%)	0.18
ACE inhibitor	115 (69.3%)	873 (67.9%)	0.72
ARB	18 (10.8%)	121 (9.4%)	0.55
Randomized to early eptifibatide	69 (41.6%)	665 (51.7%)	0.01
PCI active eptifibatide kit used	102 (61.4%)	556 (43.2%)	<0.001
Use of bailout eptifibatide	64 (8.1%)	102 (15.5%)	<0.001

Values are mean ± or n (%).
Abbreviations as in Table 2.

Table 4. Angiographic Findings Prior to PCI

	Intraprocedural Complication (n = 166)	No Intraprocedural Complication (n = 1,286)	p Value
Culprit lesion location			0.38
LAD	43 (25.9%)	418 (32.5%)	
LCX	51 (30.7%)	377 (29.3%)	
RCA	50 (30.1%)	356 (27.7%)	
LM	3 (1.8%)	9 (0.7%)	
Diagonal	3 (1.8%)	28 (2.2%)	
SVG	16 (9.6%)	96 (7.5%)	
Pre-PCI TIMI flow grade			0.001
0/1	44 (27.0%)	221 (17.6%)	
2	43 (26.4%)	255 (20.3%)	
3	76 (46.6%)	778 (62.0%)	
Pre-PCI corrected TIMI frame count	38.9 (21.6%)	34.0 (19.5%)	0.03
Pre-PCI TIMI myocardial perfusion grade			<0.001
0/1	89 (59.3%)	580 (49.8%)	
2	8 (5.3%)	17 (1.5%)	
3	53 (35.3%)	567 (48.7%)	
2/3	61 (40.7%)	584 (50.2%)	0.03
Pre-PCI MLD, mm	0.42±0.34	0.53±0.41	<0.001
Pre-PCI % stenosis	84.7±11.9	80.0±13.8	<0.001
Pre-PCI reference diameter, mm	2.66±0.71	2.63±0.72	0.30
Pre-PCI thrombus grade			0.02
0	63 (38.2%)	643 (50.2%)	
1	34 (20.6%)	266 (20.8%)	
2	6 (3.6%)	44 (3.4%)	
3	14 (8.5%)	95 (7.4%)	
4	6 (3.6%)	36 (2.8%)	
5	42 (25.5%)	193 (15.1%)	
6	0	4 (0.3%)	

Values are mean ± SD or n (%).
LAD = left anterior descending coronary artery; LCX = left circumflex coronary artery; LM = left main coronary artery; MLD = minimal lumen diameter; RCA = right coronary artery; SVG = saphenous vein graft; other abbreviations as in Table 2.

rocedural complication, both among those with (n = 1,251, 26.2% vs. 8.1%, OR: 4.01, 95% CI: 2.6 to 6.2, p < 0.001) and those without (n = 169, 44.4% vs. 5.3%, OR: 14.3, 95% CI: 4.4 to 46.1, p < 0.001) elevated troponin (p = 0.046 for interaction). Patients who experienced an intraprocedural complication with (2.8% vs. 1.0%, OR: 2.82, 95% CI: 0.9 to 9.0, p = 0.079) and without (5.6% vs. 0%, p = 0.004) elevated troponin at enrollment had higher 30-day mortality. The findings were similar for MI alone (25.5% vs. 7.7%, OR: 4.11, 95% CI: 2.7 to 6.4, p < 0.001 among those with elevated troponin; 38.9% vs. 5.3%, OR: 11.38, 95% CI: 3.5 to 37.2, p < 0.001 among those with normal troponin; p = 0.11 for interaction).

The analysis was then restricted to patients with a patent infarct-related artery before PCI (TFG: 2 or 3, n = 1,152). The incidence of the composite of death or MI at 30 days was significantly higher among patients who experienced an intraprocedural complication (32.8% vs. 7.8%, OR: 5.73, 95% CI: 3.7 to 8.9, p < 0.001). The same held true when evaluating death (4.2% vs. 0.6%, OR: 7.51, 95% CI: 2.3 to 25.0, p = 0.001) and MI (31.1% vs. 7.6%, OR: 5.52, 95% CI: 3.5 to 8.7, p < 0.001) alone.

Adjusted outcomes according to occurrence of intraprocedural complications. After adjusting for differences in parameters of epicardial and myocardial perfusion following PCI as well as elevated troponin before PCI, the relationship between intraprocedural complications and the composite of death or MI at 30 days remained significant (adjusted OR [OR_{adj}]: 3.56, 95% CI: 2.2 to 5.7, p < 0.001). The same held true for MI (OR_{adj}: 3.58, 95% CI: 2.2 to 5.8, p < 0.001) alone, but the difference in mortality alone was directionally similar but no longer statistically significant (OR_{adj}: 2.30, 95% CI: 0.5 to 10.2, p = 0.27).

Discussion

Intraprocedural complications occurred in more than 11% of patients with NSTEACS undergoing an early invasive strategy. Such complications were associated with a more than 4-fold increase in the risk of death or spontaneous or periprocedural MI at 30 days, even after adjusting for differences in post-PCI epicardial flow and myocardial perfusion and elevated troponin before PCI. Further, the greater the number of intraprocedural complications, the worse were the clinical outcomes. Among patients with a patent artery before PCI, the relationship between intraprocedural complications and the risk of 30-day death or

Table 5. Post-PCI Angiographic Results

	Intraprocedural Complication (n = 166)	No Intraprocedural Complication (n = 1,286)	p Value
Post-PCI TIMI flow grade			<0.001
0/1	28 (17.3%)	28 (2.2%)	
2	15 (9.3%)	74 (5.9%)	
3	119 (73.5%)	1,155 (91.9%)	
Post-PCI corrected TIMI frame count	25.9 ± 14.1	23.3 ± 14.0	0.055
Post-PCI TIMI myocardial perfusion grade			<0.001
0/1	92 (65.7%)	423 (42.3%)	
2	8 (5.7%)	30 (3.0%)	
3	40 (28.6%)	546 (54.7%)	
2/3	92 (65.7%)	423 (42.3%)	<0.001
Angiographic perfusion score			<0.001
0–3	20 (15.2%)	37 (3.9%)	
4–9	75 (56.8%)	438 (46.4%)	
10–12	37 (28.0%)	469 (49.7%)	

Values are mean ± or n (%).
Abbreviations as in Table 2.

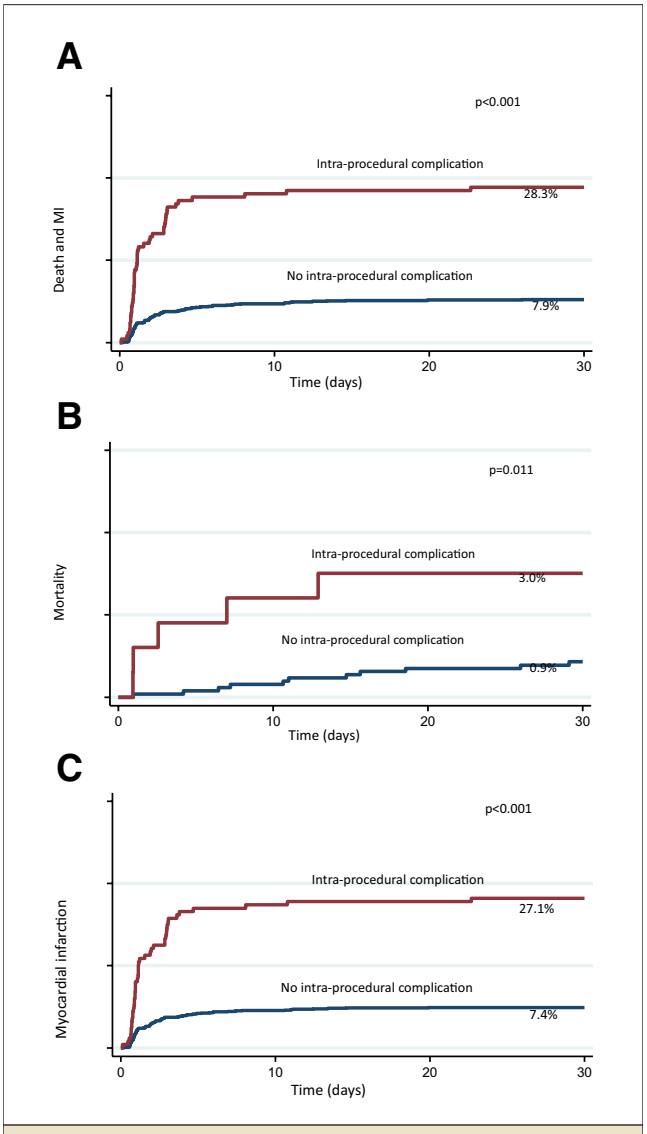

Figure 1. Estimates of the Rate of the Composite of Death or MI

Kaplan-Meier estimates of the rate of the composite of death and myocardial infarction (MI) **(A)**, mortality **(B)**, and myocardial infarction **(C)** comparing patients with and without intraprocedural complications (loss of side branch, abrupt closure, distal embolization, and the no-reflow phenomenon). OR = unadjusted odds ratio.

MI remained significant. Moreover, there was a strong relationship between intraprocedural complications and 30-day outcomes among patients with and without elevated troponin before PCI. These results from a blinded angiographic core laboratory build upon results of previous analyses using site investigator–reported angiographic complications and clinical outcomes, and suggest a potential role for intraprocedural complications as an intermediate endpoint in clinical trials (13).

Elevated cardiac biomarkers following PCI in patients who already have elevated biomarkers before the procedure may represent the consequence of myocardial injury and biomarker release both before and following the procedure. The relative contribution of pre-procedure biomarker release can therefore confound the interpretation of biomarker elevations following PCI, including the assessment of the association of procedure-related biomarkers with subsequent ischemic outcomes. The present study indicates that independent of troponin elevation before PCI, the occurrence of a complication during the procedure is associated with an increased risk of adverse events during follow-up, including mortality.

This angiographic endpoint also provides additional prognostic information independent of epicardial flow and downstream myocardial perfusion. Indeed, closure of side branches may not be counted as an adverse outcome using traditional measures of angiographic success, which focus exclusively on outcomes in the parent artery or distal to the parent artery. Cardiovascular magnetic resonance imaging data indicate that hyperenhancement consistent with myonecrosis may occur not only distal to the parent artery, presumably due to embolization, but also adjacent to the parent artery in the vicinity of branches (14). Side branches are frequently present at the site of culprit lesions in patients with ACS (15), and in this setting, side branch occlusion may occur in more than 20% of patients, most commonly following stent dilation (15,16). In the present study, about one-quarter of occluded side branches were successfully recanalized with PCI.

Both patients with and without troponin elevation before PCI had a significantly higher composite of death and MI. Patients without troponin elevation before PCI who had an intraprocedural complication had a much higher increase in the risk of death and MI than those with elevation of cardiac biomarkers before PCI. This may be the play of chance, as there were far more patients with normal cardiac bio-

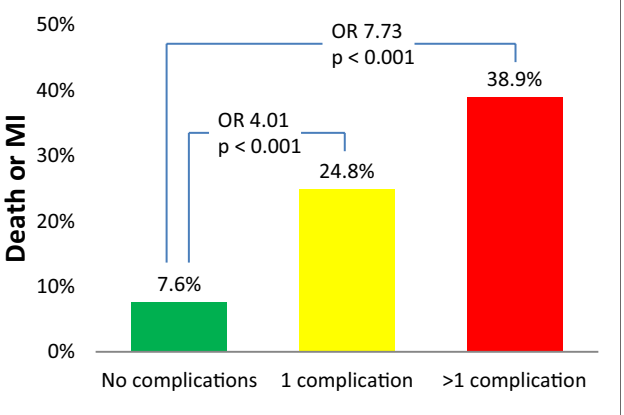

Figure 2. Rate of the Composite of Death or MI by Number of Complications

There was a step-wise increase in the risk of the composite of death or myocardial infarction (MI) as the number of thrombotic complications increased in a given patient. OR = odds ratio.

markers before PCI. However, 1 potential reason for this finding is that patients who are already having an MI have less myocardium at risk in the downstream territory, and patients who have a periprocedural MI when no MI was ongoing lose more myocardium.

Abrupt closure occurs in about 3% to 6% of PCIs and is more common after balloon angioplasty than stent implantation (17,18). In prior studies, abrupt closure was associated with periprocedural MI in approximately 5% of patients and an in-hospital mortality of approximately 2% (17). In the present study, abrupt closure was transient in three-quarters of patients, having resolved by the end of the case.

Distal embolization is common among patients undergoing PCI, especially during ACS. Predictors of distal embolization are largely related to plaque burden and constitution. A larger necrotic core, the presence of thrombus, a thin fibrous cap atheroma, and large lipid arc size detected via intravascular ultrasound and optical coherence tomography have been strongly associated with a higher incidence of distal embolization and the no-reflow phenomenon (18–20). The occurrence of no-reflow in contemporary treatment of ACS patients may be as high as 35%, although its incidence is significantly higher among ST-segment elevation MI patients undergoing primary PCI (21). It is likely related to a combination of distal embolization, ischemia-related injury, and reperfusion-related injury (21), and it has been strongly related to adverse clinical outcomes (22–24).

Prior clinical outcomes studies among patients with stable coronary artery disease and ACS undergoing PCI have focused largely on a periprocedural rise in cardiac biomarkers as a surrogate outcome. However, particularly among patients with NSTEACS, increased cardiac biomarkers measured following PCI may be the result of ongoing myocardial necrosis that occurred as a consequence of their presenting ACS itself rather than as a result of the PCI. Intraprocedural complications are objective, definable outcomes that the current study suggests are clinically relevant.

Study limitations. Several limitations are acknowledged. This is a small subset from a randomized controlled trial, and the population may be inherently different from a real-world population. Patients included in this analysis were from a convenience sample of angiograms, and so were significantly different from the population enrolled in EARLY ACS as a whole. Although this does not alter the significant relationship between complications and outcomes, it is an acknowledged limitation of the study. The patients in the present study were high-risk NSTEACS patients, and it is unknown whether these findings would apply to patients with stable coronary disease undergoing elective procedures or those with ST-segment elevation MI. Because the groups we compared were formed on the basis of whether or not complications occurred, and patients were treated according to local standard of care, there were likely inherent baseline differences between the cohorts, due to unmeasured confounders. These differences may have led to the occurrence of intraprocedural complications or may have led to differences in treatment strategies after the procedure that influenced outcomes. In particular, physician behavior, which may be dictated by any of a number of factors, including regional or local practice patterns or operator, patient, or lesion characteristics, may have been important considerations but were not measured. Therefore, these findings should be validated in other cohorts.

Conclusions

Among patients with NSTEACS undergoing an early invasive strategy, intraprocedural complications (loss of side branch, abrupt closure, distal embolization, and the no-reflow phenomenon) occurred in more than 11% of patients and were associated with a more than 4-fold increase in the composite of death or MI at 30 days, even after adjusting for differences in post-PCI TFG and TMPG and elevated troponin before PCI. Intraprocedural complications are objective, definable outcomes that should be considered as intermediate endpoints in future clinical trials.

Reprint requests and correspondence: Dr. C. Michael Gibson, Beth Israel Deaconess Medical Center, 185 Pilgrim Road, Deaconess 319, Boston, Massachusetts 02215. E-mail: mgibson@perfuse.org.

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