Acta Cardiol Sin 2017;33:362–376
Original Article
doi: 10.6515/ACS20161130A

Percutaneous Coronary Intervention

SYNTAX Score of Infarct-Related Artery Other Than the Number of Coronary Balloon Inflations and Deflations as an Independent Predictor of Contrast-Induced Acute Kidney Injury in Patients with ST-Segment Elevation Myocardial Infarction

Cheng-Wei Liu,[1] Pen-Chih Liao,[2] Kuo-Chin Chen,[2] Jung-Cheng Hsu,[2] Chung-Ming Tu,[2,3] Yen-Wen Wu,[2,4,5,6,7] Ai-Hsien Li,[2] Shin-Rong Ke[2] and Jiunn-Lee Lin[4]

Background: Although remote ischemic post-conditioning (RIPC) has been shown to prevent contrast-induced acute kidney injury (CIAKI) in patients with acute coronary syndrome, its efficacy in patients with ST-segment elevation myocardial infarction (STEMI) remains unclear. We examined the relationship among balloon inflations and deflations (BID) times, SYNTAX score of infarction-related artery (SI), periprocedural complications, and CIAKI in STEMI patients undergoing primary percutaneous coronary intervention (pPCI).

Methods: Patients with STEMI undergoing pPCI with Mehran risk score (MRS) ≥ 5 were enrolled between February 2007 and September 2012. The study end point was the development of CIAKI.

Results: Of 206 patients, the median age was 65 years [interquartile range (IQR): 55-77] with 72.8% male and Mehran risk score (MRS) 8 (IQR: 6-12). Receiver operating characteristic curve showed that BID times > 9 times or SI > 10 was the best cut-off associated with CIAKI. In univariate analysis, significant association with CIAKI existed in BID > 9 times [odds ratio (OR): 3.106, 95% confidence interval (CI): 1.284-7.513, p = 0.012] and SI > 10 (OR: 3.909, 95% CI: 1.570-9.735, p = 0.003). Other variables associated with CIAKI included creatinine, hemoglobin, angiotensin converting enzyme inhibitor or angiotensin receptor blocker use at discharge. In multivariate analysis, SI > 10 remained an independent predictor of CIAKI in different adjustment model, even on top of MRS (adjusted OR: 3.498, 95% CI: 1.086-11.268, p = 0.036).

Conclusions: Vascular complexity of infarct-related artery rather than higher BID times (> 9) was the major determinant of the development of CIAKI after pPCI in STEMI patients.

Key Words: Acute kidney injury • Acute myocardial infarction • Primary percutaneous coronary intervention

Received: March 29, 2016 Accepted: November 30, 2016
[1]Department of Internal Medicine, Tri-Service General Hospital, Songshan Branch, National Defense Medical Center, Taipei; [2]Cardiology Division of Cardiovascular Medical Center, Far Eastern Memorial Hospital, New Taipei City, Taiwan; [3]Chihlee University of Technology; [4]Departments of Internal Medicine; [5]Departments of Nuclear Medicine, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei; [6]Department of Nuclear Medicine, Far Eastern Memorial Hospital, New Taipei City; [7]National Yang-Ming University School of Medicine, Taipei, Taiwan.
Corresponding author: Dr. Shin-Rong Ke, Cardiology Division of Cardiovascular Medical Center, Far Eastern Memorial Hospital, New Taipei City, Taiwan. Tel: +886-929830318; Fax: +886-2-7738-6057; E-mail: ksrung@yahoo.com.tw

INTRODUCTION

The development of contrast-induced acute kidney injury (CIAKI) is associated with both short- and long-term adverse events in patients with acute coronary syndrome (ACS) undergoing percutaneous coronary intervention (PCI).[1-6] A novel technique, known as remote ischemic post-conditioning (RIPC), has been used successfully to avoid CIAKI in patients with ACS. In cases involving acute myocardial myocardial infarction,

results from both animal models and human studies have shown an association between ischemic post-conditioning (IPC) and myocardial infarct size.[7,8] However, specific evidence that correlates RIPC and kidney function is limited in these patients. Some studies have suggested that RIPC by means of coronary balloon inflation had a protective effect on kidney function during angioplasty.[9,10] Nevertheless, it is unclear if RIPC has the same effect on preservation of kidney function in ST-segment elevation myocardial infarction (STEMI) patients undergoing primary PCI. Therefore, the goal of this study was to determine if the number of coronary balloon inflations and deflations (BID), which mimicked RIPC, was associated with CIAKI. In addition, we sought to ascertain potential predictors of CIAKI, such as thrombolysis in myocardial infarction (TIMI) flow before and after primary PCI, complexity of infarct-related artery (IRA), and development of periprocedural complications.[11]

MATERIAL AND METHODS

Study design

Between February 2007 and September 2012, we conducted a retrospective cohort study on consecutive patients admitted to a single high-volume medical center in Northern Taiwan with the diagnosis of STEMI.[12,13] All patients with a diagnosis of STEMI undergoing primary PCI and at intermediate risk of CIAKI [defined as the Mehran risk score (MRS) ≥ 5] were included for analysis. STEMI was diagnosed using the following criteria: 1) new ST elevation at the J point in at least two contiguous leads of ≥ 2 mm (0.2 mV) in men, or ≥ 1.5 mm (0.15 mV) in women in leads V2-V3 and/or of ≥ 1 mm (0.1 mV) in other contiguous chest leads or the limb leads; and 2) new or presumably new LBBB.[14] We excluded those patients who were 1) on maintenance hemodialysis, and/or 2) had a paucity of door-to-balloon time, such as (a) STEMI transferred from another hospital or out-patient department, (b) STEMI which occurred within the hospital, (c) cardiac arrest before initiation of primary PCI, (d) difficult consent process, or (e) missing data. In those patients deemed eligible, the following data were collected by medical records: baseline demographics, full procedural details, and results of coronary angiography. The main therapeutic strategies underlying primary PCI at our hospital were thrombus aspiration if the culprit vessel was totally occluded, and use of glycoprotein IIb/IIIa inhibitor if no bleeding tendency existed. Iopamidol (370 mg of iodine per ml) was used during coronary angiography. All patients received standard care that adhered to current guidelines.[12,14-16] The study was approved by the Institutional Review Board of Far Eastern Memorial Hospital in Taiwan.

Definitions

CIAKI was defined as: 1) an absolute elevation of serum creatinine > 0.5 mg/dl in patients with baseline serum creatinine ≤ 2.0 mg/dl, or 2) a relative increase of ≥ 25% from the baseline value in patients with baseline creatinine > 2.0 mg/dl within 96 hours after primary PCI was performed.

The MRS is acknowledged to be a simple predictor of risk for CIAKI in patients undergoing PCI.[15] MRS is the summation of the following items: hypotension (5 points), intra-aortic balloon pump use (5 points), congestive heart failure (5 points, defined as New York Heart Association functional classification III/IV and/or history of pulmonary edema), age > 75 years (4 points), diabetes (3 points), anemia (3 points, defined as hematocrit < 39% in men and < 36% in women), and serum creatinine > 1.5 mg/dl (4 points).

The lesion complexity of IRA was represented as SYNTAX score of IRA (SI) in this study,[11,17] After antegrade coronary flow was restored at IRA, and SI was calculated by using SYNTAX score calculator version 2.11 (http://www.syntaxscore.com/calc/start.htm). Dissection was defined according to the National Heart, Lung and Blood Institute classification system. Periprocedural complications were defined as a composite of dissection and acute no-reflow.

Study endpoints

We examined the relationships among the number of BIDs performed, SYNTAX score, periprocedural complications, potential confounders and CIAKI in our patients. The primary endpoint was CIAKI. All-cause in-hospital mortality, 30-day and 1-year mortality, and myocardial infarct size were collected using medical records and telephone surveys.

Statistical analysis

Categorical or continuous variables were expressed as number and percentage, or median and interquartile range (IQR), respectively. The chi-square test was used for categorical variables, and the Mann-Whitney test was utilized for continuous variables. The receiver operating characteristic (ROC) curve was used to determine the relationships between the number of BIDs performed and CIAKI, and between SYNTAX score and CIAKI. The associations between all variables and CIAKI were examined by univariate logistic regression analyses. If significant association existed between those variables and CIAKI in univariate analyses, multivariate analyses were used for further investigation. If there were a trend toward significant association ($p < 0.09$) between CIAKI and variables, those variables would be adjusted as confounders in multivariate analysis. All p values were two-tailed, and a p value < 0.05 was considered statistically significant. Analysis was performed using SPSS software, version 18.0.

RESULTS

A total of 206 patients were enrolled and analyzed in this investigation. The study flow sheet was illustrated in Figure 1. These patients had a median age of 65 years (IQR: 55-77), body mass index 24.6 kg/m^2 (IQR: 22.2-26.9), creatinine 1.11 mg/dl (IQR: 0.85-1.47), hemoglobin 13.9 mg/dl (12.2-15.3), and 72.8% of the patients were male. Other baseline characteristics were listed in Table 1. Coronary angiography showed 73.2% of patients with multi-vessel disease. During diagnostic coronary angiography, 70.9% of these patients had TIMI 0 flow, and only 1.5% of them still had TIMI 0 flow after primary PCI was performed. All patients received successful PCI except 4 patients. One of those 4 patients with inferior-STEMI received alternative PCI to the circumflex artery because of failure of PCI to the right coronary artery. Another 3 patients underwent failed PCI, with a final TIMI 0 flow. CIAKI did not develop in these patients with failure PCI. Bare-metal stents (BMS) were implanted in 80.6% of patients and drug-eluting stents (DES) were implanted in 8.7% of patients. One patient received simultaneous BMS and DES implantation. One patient received successful thrombus aspiration without any stent implantation. The rest of the 21 patients received percutaneous occlusive balloon angioplasty for in-stent restenosis, small-caliber vessels, or an ectasia vessel. Dissection of all types developed in 51% of patients during PCI. Of these patients, type D and type F dissection accounted for 11.4% and 11.7% of patients, respectively. No patient experienced type C dissection during PCI. Other procedural characteristics and periprocedural complications were shown in Table 2.

The median number of BIDs performed on these patients was 7 (IQR: 5-11). ROC curve showed that the

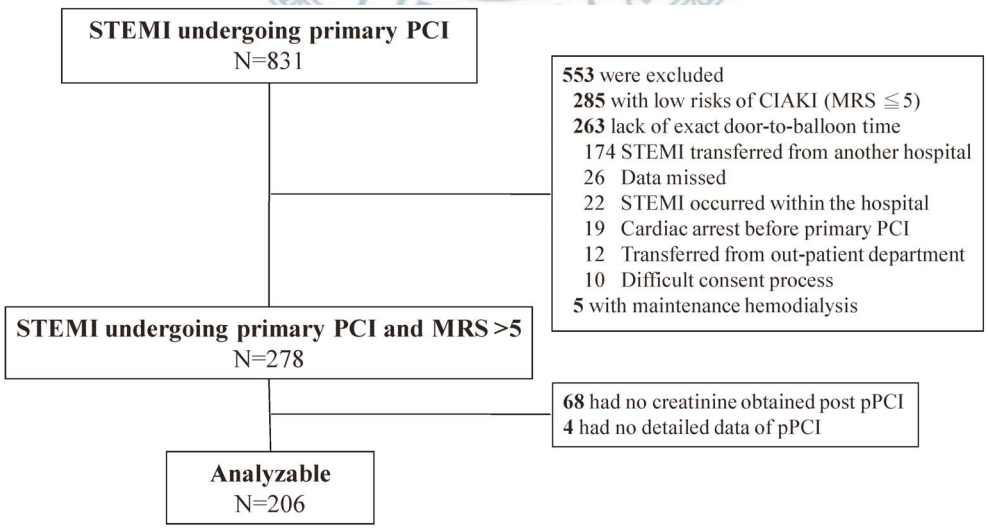

Figure 1. *Study flow sheet. CIAKI, contrast-induced acute kidney injury; MRS, Mehran risk score; PCI, percutaneous coronary intervention; pPCI, primary percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.*

Table 1. Baseline characteristics and outcomes in the STEMI patients undergoing primary PCI and MRS ≥ 5

Variables	All (N = 206)	BID ≤ 9 times (N = 139)	BID > 9 times (N = 67)	p value
Age (years)	55 (65-77)	64 (55-78)	66 (58-76)	0.583
Body mass index (kg/m^2)	24.6 (22.2-26.9)	24.8 (22.5-27.1)	23.9 (22.0-26.4)	0.364
Creatinine (mg/dl)	1.11 (0.85-1.47)	1.1 (0.9-1.5)	1.1 (0.9-1.6)	0.612
Hemoglobin (g/dl)	13.9 (12.2-15.3)	14.2 (12.5-15.4)	13.7 (11.6-15.2)	0.233
CAD risk factors				
Male	150 (72.8)	105 (75.5)	45 (67.2)	0.242
Current/past smoker	99 (48.1)	66 (47.5)	33 (49.3)	0.97
Hypertension	145 (70.4)	95 (68.8)	50 (74.6)	0.418
Diabetes	96 (46.6)	63 (45.7)	33 (49.3)	0.657
Hyperlipidemia	55 (26.7)	41 (29.7)	14 (21.2)	0.239
Known CAD	32 (15.5)	20 (14.5)	12 (17.9)	0.543
Previous MI	10 (4.9)	6 (4.5)	4 (6.1)	0.734
Ischemic stroke	23 (11.2)	15 (10.8)	8 (11.9)	0.839
Killip class				
I	78 (37.9)	55 (39.6)	23 (34.3)	0.54
II	63 (30.6)	41 (29.5)	22 (32.8)	0.632
III	19 (9.3)	7 (5.0)	9 (13.4)	0.049
IV	46 (22.3)	34 (24.5)	12 (17.9)	0.372
MRS	8 (6-12)	8 (6-11)	8 (6-12)	0.22
Hypotension	46 (22.3)	34 (24.5)	12 (17.9)	0.372
IABP use	61 (29.6)	39 (28.1)	22 (32.8)	0.517
Congestive heart failure	16 (7.8)	7 (5.0)	9 (13.4)	0.049
Age > 75 (years)	64 (31.1)	43 (30.9)	21 (31.3)	1
Anemia[a]	65 (31.6)	42 (30.2)	23 (34.3)	0.632
Creatinine > 1.5 (mg/dl)	47 (22.8)	30 (21.6)	17 (25.4)	0.596
Medication use at discharge				
Aspirin	195 (94.7)	130 (93.5)	65 (97.0)	1
Beta-blocker	122 (59.2)	86 (61.9)	36 (53.7)	0.148
ACEI or ARB	131 (63.6)	93 (66.9)	38 (56.7)	0.167
Outcomes				
CIAKI	23 (11.2)	10 (7.2)	13 (19.4)	0.016
In-hospital mortality	5 (2.4)	3 (2.2)	2 (3.0)	1.000
30-day mortality	10 (4.9)	5 (3.6)	5 (7.5)	0.299
1-year mortality	20 (9.7)	13 (9.4)	7 (10.4)	0.805

Values were median (interquartile range) or n (%).

* New York Heart Association functional classification III/IV and/or history of pulmonary edema. # Hematocrit < 39% in men and < 36% in women.

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BID, balloon inflations and deflations; CAD, coronary artery disease; CIAKI, contrast-induced acute kidney injury; IABP, intra-aortic balloon pump; MI, myocardial infarction; MRS, Mehran risk score; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

number of BIDs performed correlated with CIAKI [area under curve (AUC): 0.651, 95% confidence interval (CI): 0.541-0.760, p = 0.019]. The best cut-off point for the association between the number of BID performed and CIAKI was a BID equal to 9 times. The median of SI was 9 (IQR: 6-12); the ROC curve demonstrated that SI also was associated with CIAKI (AUC: 0.666, 95% CI: 0.539-0.794, p = 0.009). The best cut-off point for the association between SI and CIAKI was a score of 10. There were 67 patients (32.5%) receiving BID > 9 times, and 75 patients (36.4%) with SI > 10, respectively.

At discharge, all patients received clopidogrel and statin. Of these patients, 94.7% received aspirin, 63.6% of these patients received angiotensin-converting en-

Table 2. Procedural characteristics and peri-procedural complications in patients with STEMI undergoing primary PCI and MRS ≥ 5

Variables	All (N = 206)	BID ≤ 9 times (N = 139)	BID > 9 times (N = 67)	p value
Procedural characteristics				
Numbers of BID performed	7 (5-11)	6 (4-7)	14 (12-18)	< 0.001
Contrast volume (ml)	180 (150-200)	160 (150-200)	200 (180-260)	< 0.001
Fluoroscopy times (min)*	12.6 (9.8-18.1)	11 (8.8-14.5)	19.2 (13.7-25.4)	< 0.001
Door-to-balloon time (min)	76 (62-112)	74 (60-107)	81 (64-113)	0.193
Trans-femoral approach	184 (89.3)	129 (92.8)	55 (82.1)	0.02
Thrombus aspiration	116 (56.3)	86 (61.9)	30 (44.8)	0.025
Glycoprotein IIb/IIIa inhibitor	122 (59.2)	83 (59.7)	39 (58.2)	0.88
IABP use	53 (25.7)	34 (24.5)	19 (28.4)	0.549
Multiple-vessel disease	150 (73.2)	93 (66.9)	57 (85.1)	0.007
IRA				
LAD	96 (46.6)	67 (48.2)	29 (43.3)	0.507
Non-LAD	110 (53.4)	72 (51.8)	38 (56.7)	0.553
LM	2 (1)	1 (0.7)	1 (1.5)	0.546
Stent implantation[#]	182 (88.3)	118 (84.9)	64 (95.5)	0.035
Bare-metal stent	166 (80.6)	110 (79.1)	56 (83.6)	0.573
Drug-eluting stent	17 (8.3)	8 (5.8)	9 (13.4)	0.101
Numbers of stent implantations				
1	117 (56.8)	95 (68.3)	22 (32.8)	< 0.001
2	49 (23.8)	22 (15.8)	27 (40.3)	< 0.001
3	14 (6.8)	1 (0.7)	13 (19.4)	< 0.001
4	3 (1.5)	0 (0)	3 (4.5)	0.033
Initial TIMI flow*				
0	146 (70.9)	106 (76.3)	39 (58.2)	0.009
1	15 (7.3)	8 (5.8)	7 (10.4)	0.257
2-3	45 (21.9)	24 (17.3)	21 (31.3)	0.03
Final TIMI flow*				
0	3 (1.5)	3 (2.2)	0 (0)	0.552
1	2 (1)	2 (1.4)	0 (0)	1
2-3	201 (97.6)	133 (67.0)	67 (0.2)	0.18
PCI to non-IRA	6 (2.9)	3 (2.2)	3 (4.5)	0.395
Heavy calcification of IRA	33 (16)	23 (16.7)	10 (14.9)	0.841
IRA lesion > 20 mm	173 (84)	115 (83.3)	58 (86.6)	0.683
Bifurcation lesion of IRA	135 (65.5)	89 (64.0)	46 (68.7)	0.536
Side branch > 1.5 mm	87 (42.2)	54 (38.8)	33 (49.3)	0.177
Side branch < 1.5 mm	48 (23.3)	35 (25.2)	13 (19.4)	0.385
Periprocedural complications				
Any dissection	105 (51)	69 (50.0)	36 (53.7)	0.657
Type D dissection	12 (5.8)	7 (5.1)	5 (7.5)	0.533
Type F dissection	18 (8.7)	12 (8.7)	6 (9.0)	1

Values were median (interquartile range) or n (%).

* Thirty-two data missing for fluoroscopy times and one datum missing for TIMI flow. [#] One patient received simultaneous implantation of bare-metal (2.75 mm * 18 mm) and drug-eluting stent (2.25 mm * 16 mm).

BID, balloon inflations an deflations; IABP, intra-aortic balloon pump; IRA, infarct-related artery; LAD, left anterior descending artery; LM, left main coronary artery; MRS, Mehran risk score; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

zyme inhibitor (ACEI) or angiotension II receptor blocker (ARB), and 59.2% of these patients received beta-blockade. The incidence of death in hospital, 30-day mortality, and 1-year mortality were 2.4%, 4.9%, and 9.7%, re-

spectively. Myocardial infarct size, expressed as a peak value of creatine kinase (CK) and CK-MB, were 1,169 IU/L (IQR: 2,700-4,899) and 229 U/L (IQR: 121-411), respectively. CIAKI occurred in 23 of 206 patients (11%), consistent with MRS prediction and previous studies.[5,6,18] No CIAKI developed in patients with failure of PCI. If we divided these patients by the number of BIDs performed, there were 139 patients with BID ≤ 9 times and 67 patients with BID > 9 times, respectively. Baseline and procedural characteristics were similar in these two groups, except that patients with BID > 9 times received more contrast (200 ml, IQR: 180-260 vs. 160 ml, IQR: 150-200, p < 0.001) and had less single-vessel disease (14.9% vs. 33.1%, p = 0.006) than those with BID ≤ 9 times (detailed in supplemental Table 1 and Table 2). CIAKI rates were significantly higher in the BID > 9 times group compared with the BID ≤ 9 times group (19.4% vs. 7.2%, p = 0.016).

In univariate analysis, BID > 9 times was significantly associated with CIAKI [Odds Ratio (OR): 3.106, 95% CI: 1.284-7.513, p = 0.012], although the significance did not exist when the number of BIDs performed was expressed as a continuous variable (OR: 1.045, 95% CI: 0.989-1.105, p = 0.118). Other variables associated with CIAKI included creatinine (OR: 1.960, 95% CI: 1.180-3.257, p = 0.009), hemoglobin (OR: 0.844, 95% CI: 0.720-0.989, p = 0.036), MRS (OR: 1.218, 95% CI: 1.101-1.348, p < 0.001), SI (OR: 1.157, 95% CI: 1.039-1.288, p = 0.008) or SI > 10 (OR: 3.909, 95% CI: 1.570-9.735, p = 0.003), as well as ACEI or ARB use at discharge (OR: 7.958, 95% CI: 2.815-22.493, p < 0.001). The association between CIAKI and multi-vessel disease was borderline significant (OR: 4.395, 95% CI: 0.996-19.401, p = 0.051). There were trends toward significant associations among CIAKI and age (OR: 1.031, 95% CI: 0.997-1.066, p = 0.071), any types of dissection during PCI (OR: 2.388, 95% CI: 0.938-6.081, p = 0.068), periprocedural complications (OR: 2.311, 95% CI: 0.908-5.882, p = 0.079) or beta-blockade use at discharge (OR: 0.405, 95% CI: 0.159-1.305, p = 0.059). No association existed in patients with acute no-reflow (OR: 0.988, 95% CI: 0.212-4.602, p = 0.988). Table 3 demonstrated associations among CIAKI and variables.

In multivariate analysis, Model 1 adjusted for confounders in univariate analysis and demonstrated significant associations between CIAKI and variables included SI > 10 (adjusted OR: 4.179, 95% CI: 1.197-14.593, p = 0.025), age (adjusted OR: 1.068, 95% CI: 1.013-1.127, p = 0.015), and ACEI/ARB use at discharge (adjusted OR: 13.27, 95% CI: 2.582-68.207, p = 0.002). BID > 9 times and SI as continuous variable was no longer associated with CIAKI in multivariable analysis. In Model 2, SI > 10 was still independently correlated with CIAKI on top of MRS (adjusted OR: 4.434, 95% CI: 1.650-11.912, p = 0.003). In Model 3, we adjusted MRS and other confounders not included in MRS. SI > 10 remained significantly associated with CIAKI (adjusted OR: 3.498, 95% CI: 1.086-11.268, p = 0.036). Adjustment in different models was shown in Table 4.

We also performed a subgroup analysis involving the following: patients with normal kidney function (serum creatinine of 1.5 mg/dl or less) vs. patients with kidney dysfunction (serum creatinine more than 1.5 mg/dl); patients with simple vascular lesion (SI of 10 or less) vs. patients with complex vascular lesion (SI > 10); and patients with cardiogenic shock vs. those patients without cardiogenic shock (shown in supplemental Table 1-3). A subgroup analysis showed that BID > 9 times was associated with increased risks of incident CIAKI in the patients of 75 years old or less (crude OR: 7.54, 95% CI: 1.93-29.41, p < 0.001), male (crude OR: 5.71, 95% CI: 1.83-17.87, p < 0.001), low body mass index less than 25 kg/m^2 (crude OR: 23.47, 95% CI: 2.7-204, p < 0.001), cardiogenic shock (crude OR: 14.63, 95% CI: 1.83-11.43, p = 0.01), and use of IABP (crude OR: 6.86, 95% CI: 1.59-29.62, p = 0.01) in the STEMI patients undergoing primary PCI at MRS > 5 (shown in Figure 2). In the subgroups of patients with normal kidney function and patients with complex vascular lesion, the risk of CIAKI were not significantly greater in the BID > 9 times group than the BID ≤ 9 times group (in patients with normal kidney function: crude rate of CIAKI: 4.5% vs. 14%, p = 0.052 and crude OR: 2.395, 95% CI: 0.792-7.242; in patients with complex vascular lesion: crude rate of CIAKI: 27.3% vs. 14.6%, p = 0.246 and crude OR: 2.187, 95% CI: 0.688-6.952).

DISCUSSIONS

The main findings of the present study included that: 1) more balloon inflation (i.e. BID > 9 times during PCI) was associated with risk of CIAKI in univariate an-

Table 3. Association between variables and CIAKI in STEMI patients undergoing primary PCI by univariate regression analysis

Variables	Crude OR	95% CI	p value
Age (years)	1.031	0.997-1.066	0.071*
Body mass index	0.938	0.828-1.104	1.062
Creatinine (mg/dl)	1.960	1.180-3.257	0.009#
Hemoglobin (g/dl)	0.844	0.720-0.989	0.036#
Killip class	1.216	0.848-1.745	0.288
I	0.544	0.205-1.445	0.222
II	1.536	0.627-3.716	0.348
III	0.509	0.064-4.044	0.523
IV	1.615	0.621-4.202	0.326
Mehran risk score	1.218	1.101-1.348	< 0.001#
IABP use	2.504	1.026-6.114	0.044#
Congestive heart failure	0.509	0.064-4.404	0.523
Age > 75 (years)	2.248	0.934-5.411	0.071
Anemia	1.458	0.596-3.566	0.409
Creatinine > 1.5 (mg/dl)	3.743	1.528-9.116	0.004
Procedural characteristics			
Multi-vessel disease	4.395	0.996-19.41	0.051*
Contrast volume use (ml)	1.001	0.992-1.009	0.906
Fluoroscopy times (mins)†	1.027	0.980-1.076	0.268
IRA-LAD	1.566	0.653-3.755	0.314
Initial TIMI flow	0.862	0.570-1.303	0.481
Final TIMI flow	1.172	0.435-3.158	0.753
SYNTAX score of IRA‡	1.157	1.039-1.288	0.008#
SYNTAX score > 10 of IRA‡	3.909	1.570-9.735	0.003#
PCI to non-IRA	4.238	0.732-24.55	0.107
Numbers of BID performed	1.045	0.989-1.105	0.118
BID > 9 times	3.106	1.284-7.513	0.012#
Door-to-balloon time (mins)	1.000	0.994-1.007	0.897
Trans-femoral approach	2.852	0.365-22.26	0.318
Thrombus aspiration	0.681	0.286-1.624	0.386
Glycoprotein IIb/IIIa inhibitor use	0.724	0.303-1.728	0.467
Bare-metal stent implantation	0.851	0.296-2.450	0.765
Drug-eluting stent implantation	0.995	0.233-4.253	0.994
Numbers of stent implantation	1.285	0.757-2.181	0.353
Peri-procedural complications	2.311	0.908-5.882	0.079*
Any dissection	2.388	0.938-6.081	0.068*
Spiral dissection	1.638	0.336-7.987	0.542
Acute no-reflow after stenting	0.988	0.212-4.602	0.988
Heavy calcification	2.026	0.733-5.599	0.173
IRA lesion > 20 mm	4.517	0.587-34.768	0.148
Bifurcation lesion	0.874	0.488-1.567	0.652
Medication use at discharge			
Aspirin	0.509	0.054-4.758	0.553
Beta-blocker	0.405	0.159-1.035	0.059*
ACEI or ARB	7.958	2.815-22.49	< 0.001#

* Trends toward significant associations among variables and CIAKI. # Statistical significance among variables and CIAKI. † 32 data missing for flurotime. ‡ see detailed in material and methods

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BID, balloon inflations and deflations; CI, confidence interval; CIAKI, contrast-induced acute kidney injury; IABP, intra-aortic balloon pump; IRA, infarct-related artery; LAD, left anterior descending coronary artery; OR, odds ratio; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; TIMI flow, thrombolysis in myocardial infarction flow.

Table 4. Association among variables and CIAKI in STEMI patients undergoing primary PCI by multivariate regression analysis

Variables	Adjusted OR	95% CI	p value
Model 1			
Age (years)	1.055	1.004-1.109	0.033*
Creatinine (mg/dl)	1.427	0.778-2.620	0.251
Hemoglobin (g/dl)	0.908	0.689-1.197	0.493
Multi-vessel disease	6.373	0.698-58.17	0.101
SI > 10	4.179	1.197-14.59	0.025*
BID > 9 times	1.846	0.543-6.271	0.326
Any dissection	1.161	0.322-4.185	0.82
IABP use	1.748	0.497-6.145	0.384
Beta-blocker	1.539	0.407-5.812	0.525
ACEI or ARB	13.27	2.582-68.21	0.002*
Model 2			
SI > 10	4.434	1.650-11.91	0.003*
MRS	1.243	1.113-1.387	< 0.001*
Model 3			
SI > 10	3.498	1.086-11.27	0.036*
MRS	1.172	1.026-1.339	0.020*
Multi-vessel disease	5.851	0.672-50.94	0.11
BID > 9 times	1.866	0.600-5.804	0.281
Any dissection	1.123	0.332-3.800	0.852
Beta-blocker	1.781	0.493-6.430	0.379
ACEI or ARB	9.864	2.292-42.46	< 0.001*

* Statistical significance among variables and CIAKI.
ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BID, balloon inflations and deflations; CI, confidence interval; CIAKI, contrast-induced acute kidney injury; IABP, intra-aortic balloon pump; MRS, Mehran risk score; OR, odds ratio; PCI, percutaneous coronary intervention; SI, SYNTAX score of infarct-related artery; STEMI, ST-segment elevation myocardial infarction.

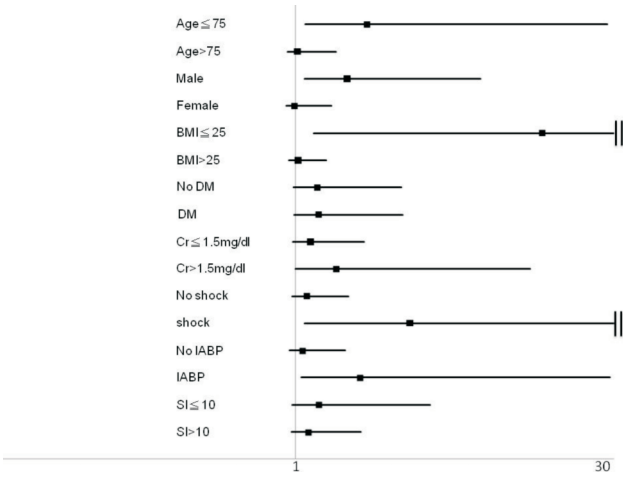

Figure 2. *Relative risks of CIAKI in the BID > 9 times vs. ≤ 9 times groups in different subgroups. The horizontal axis represented an odds ratio for incident CIAKI. BID, balloon inflations and deflations; CIAKI, contrast-induced acute kidney injury.*

alysis, although the association disappeared after adjustment for potential confounders; 2) an independent predictor of development of CIAKI was vascular complexity rather than the number of BIDs performed or TIMI flow or periprocedural complications; and 3) ACEI or ARB was associated with an increased incidence of CIAKI in STEMI patients with intermediate risks of CIAKI.

In the present study, BID > 9 times was significantly associated with increased rates of CIAKI in univariate analysis but the significance disappeared after confounders were adjusted. This indicated that vascular complexity behind the number of BIDs might be the true culprit of CIAKI. In contrast to our study, Whittaker et al. suggested that BID ≥ 4 times in STEMI patients were associated with preserved estimated glomerular filtration rate.[9] The conflicting results might be partly explained by two main reasons. First, we enrolled STEMI patients with intermediate risks of CIAKI, whereas Whittaker et al. selected those study subjects with low risks. Therefore, the incidence of CIAKI was 11.2% in our study while no CIAKI developed in their study. Second, we enrolled consecutive patients, even including patients with cardiogenic shock and multi-vessel disease; on the other hand, Whittaker et al. selected those with single-vessel occlusion. We believed that a difference in baseline CIAKI risks and vascular complexity of study population results in the opposed effect of the number of BIDs performed.

The phenomenon of BIDs for renal protection was reported in patients with non ST-segment elevation myocardial infarction (NSTEMI). Deftereos et al. had designed a well-controlled randomized trial to test the hypothesis of renal protection between BID and CIAKI.[10] To induce the effect of RIPC, they used an additional four cycles of intermittent BID composed of inflation for 30 sec and deflation for another 30 sec immediately after PCI to the presumed culprit lesion of myocardial infarction. CIAKI was significantly lower in the RIPC group than in the control group (12.4% vs. 29.5%, p = 0.002). RIPC was an independent negative predictor of CIAKI with adjustment for age, body mass index, baseline EGFR, and contrast volume use (adjusted OR = 0.23, 95% CI: 0.11 to 0.50; p < 0.001). The vessel number was no

statistically different between two groups. However, the vascular complexity was not taken into the statistical adjustment.

The relationship between SYNTAX score and CIAKI had been investigated in patients with NSTEMI or unstable angina. Madhavan et al. demonstrated that the highest tertile (> 12 within their study) of SYNTAX score was associated with increased rates of CIAKI as well as in-hospital, 30-day and 1-year mortality in multivariate analyses.[19] Although SYNTAX score was used as an independent predictor of acute no-reflow or 1-year all-cause mortality in STEMI patients, the association between SYNTAX score and CIAKI was not yet extensively explored in these populations.[20,21] Our study was the first to extend this parameter (SI) to STEMI, which demonstrated that SI > 10 was independently associated with the development of CIAKI on top of MRS.

Most studies discussing STEMI patients have focused on the association between IPC and infarct myocardial size rather than RIPC and CIAKI. In Hahn et al.'s study, IPC was induced by 4 cycles of repetitive coronary balloon inflations for 1-minute and deflations for the other 1-minute at the culprit lesion, using low-pressure coronary balloon, immediately after restoration of coronary flow. This largest prospective randomized control trial showed that IPC did not improve myocardial reperfusion in STEMI patients under the current standards of practice, with respect to all possible confounders.[22] Theoretically, IPC using alternative coronary balloon inflations and deflations may induce coronary micro-embolism and coronary artery dissection. Hence, using a blood pressure cuff on an upper arm emerged as a safe procedure of remote ischemic pre-conditioning (RIPreC) in patients undergoing elective PCI.[23] In the CRISP study, patients in the intervention group received 3 cycles of 5-minute inflations of a blood pressure cuff to 200 mm Hg around the non-dominant upper arm, followed by 5-minute deflations before PCI. This study demonstrated that patients receiving RIPreC vs. shamed procedures significantly reduced ischemic chest discomfort during PCI and attenuated cardiac troponin-I release after PCI than those who received a shamed procedure. Furthermore, the study showed that RIPreC was associated with better long term outcomes during 6-year follow-up.[24] Unfortunately, the beneficial effect of RIPreC could not be translated to RIPC in patients with stable or unstable angina undergoing elective PCI.[25] In the Carrasco-Chinchilla study, patients in the RIPC group underwent similar procedures to RIPreC of the CRISP study except that it was performed 5 min after the last stent implantation or balloon post-dilation. Contrary to the results of the CRISP stent study, the peak level of cardiac troponin I at 24-hour and mortality at 1-year were not significantly different between the RIPC and the control group. In the subgroup of diabetic patients, RIPC was associated with more periprocedural myocardial infarction.[25] Lavi et al. investigated the effect of RIPC by a blood pressure cuff placed on the left arm or thigh in patients with stable angina or unstable angina and negative cardiac troponin T at baseline.[26] The inflation cuff pressure was more than 200 mm Hg in the arm, 300 mm Hg in the thigh, or more than 50 mm Hg above systolic blood pressure. The RIPC cycle was performed with cuff inflation for 5 minutes, followed by 5-minute deflations, and repeated for a total of 3 cycles. They suggested that RIPC applied to the arm or thigh during non-urgent PCI did not reduce periprocedural myocardial injury.[26] In the Er et al. study, RIPreC consisted of 4 cycles of 5-minute inflations and 5-minute deflations, with a standard blood pressure cuff placed on an upper-arm by inflating additional 50 mm Hg over individual's systolic blood pressure before coronary angiography. RIPreC was strongly associated with prevention from CIAKI. The peak level of urinary neutrophil gelatinase-associated lipocalin and serum cystatin C were also significantly lower in the RIPreC group than in the control group.[27] Despite the conflicting results among the above studies, several key points of successful ischemic conditioning may be postulated. First, the timing of conditioning is a critical point. Renal protection was disclosed in the pre-conditioning studies rather than in the post-conditioning studies in patients with stable and unstable angina.[23,25,27] Although IPC was usually performed immediately after restoration of coronary activity in conditioning the heart, the optimal time between the first blood pressure cuff inflation and the last coronary stenting or balloon dilation remained controversial in the circumstance of RIPC. Further studies are necessary to investigate the association between time interval of RIPC and the last stenting or balloon dilation. Second, our study showed that RIPC "to the heart" had a harmful effect on renal function in contrast to results in other studies, which showed beneficial or

neutral renal protection effects with conditioning of the extremities.[9,10] Given that the "possible" beneficial effect on renal function by RIPC may be "compensated" by intra-coronary BID related "coronary" complications, we suggest that an extremity rather than the heart should be "conditioned" during the RIPC. Third, it is not clear how many cycles and how much time should be devoted to ischemia/reperfusion. The optimal protocol of RIPC, such as the number of cycles and the time interval of ischemia and reperfusion has not been established. According to a recent meta-analysis, 5-min stimulation is essential to elicit the effect of conditioning.[28] The meta-analysis suggested that 3-4 cycles of conditioning was widely used in most studies, although only one study reported one cycle of conditioning as effective as 3-4 cycle of conditioning. It is unknown if more cycles of conditioning are associated with additional renal protection. A large-scale study is needed to test the correlation between cycles of RIPC and prevention of CIAKI.

Several limitations of our study should be emphasized. This was a retrospective study with a rather small and heterogeneous population, while it reflects clinical practice in Taiwan. Some possible confounders were not recorded such as index ischemic time and duration of each BID, pre-use of nephrotoxic agents (ex. non-steroid anti-inflammatory drug). The CIAKI prevention strategy, e.g., N-acetylcysteine, hydration, or sodium bicarbonate administration, was not well-standardized in such emergent condition. A large-scaled prospective study is warranted to further elucidate the renoprotective effect of balloon inflation and deflation times in different target populations.

CONCLUSIONS

Higher balloon inflation and deflation times (> 9) was associated with increased rates of CIAKI on top of Mehran risk score. After adjustment, vascular complexity of IRA was the major determinant of the development of CIAKI after primary percutaneous coronary intervention in STEMI patients.

ACKNOWLEDGEMENTS

We thank Yung-Cheng Chen, Yung-Chu Tsai and the Cath Lab of Far Eastern Memorial Hospital for the assistance. This work was supported in part by grant FEMH-2013-HHC-002, FEMH-2014-HHC-002 from Far Eastern Memorial Hospital, and MOST 103-2325-B-418-001 from the Ministry of Science Technology of Taiwan.

REFERENCES

1. Rihal CS, Textor SC, Grill DE, et al. Incidence and prognostic importance of acute renal failure after percutaneous coronary intervention. *Circulation* 2002;105:2259-64.
2. Lindsay J, Apple S, Pinnow EE, et al. Percutaneous coronary intervention-associated nephropathy foreshadows increased risk of late adverse events in patients with normal baseline serum creatinine. *Catheter Cardiovasc Interv* 2003;59:338-43.
3. Gupta R, Gurm HS, Bhatt DL, et al. Renal failure after percutaneous coronary intervention is associated with high mortality. *Catheter Cardiovasc Interv* 2005;64:442-8.
4. Roghi A, Savonitto S, Cavallini C, et al. Impact of acute renal failure following percutaneous coronary intervention on long-term mortality. *J Cardiovasc Med* 2008;9:375-81.
5. Kim MJ, Choi HS, Oh SH, et al. Impact of acute kidney injury on clinical outcomes after ST elevation acute myocardial infarction. *Yonsei Med J* 2011;52:603-9.
6. Kume K, Yasuoka Y, Adachi H, et al. Impact of contrast-induced acute kidney injury on outcomes in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention. *Cardiovasc Revasc Med* 2013;14:253-7.
7. Skyschally A, van Caster P, Iliodromitis EK, et al. Ischemic post-conditioning: experimental models and protocol algorithms. *Basic Res Cardiol* 2009;104:469-83.
8. Schevchuck A, Laskey WK. Ischemic conditioning as an adjunct to percutaneous coronary intervention. *Circ Cardiovasc Interv* 2013;6:484-92.
9. Whittaker P, Przyklenk K. Remote-conditioning ischemia provides a potential approach to mitigate contrast medium-induced reduction in kidney function: a retrospective observational cohort study. *Cardiology* 2011;119:145-50.
10. Deftereos S, Giannopoulos G, Tzalamouras V, et al. Renoprotective effect of remote ischemic post-conditioning by intermittent balloon inflations in patients undergoing percutaneous coronary intervention. *J Am Coll Cardiol* 2013;61:1949-55.
11. Serruys PW, Morice MC, Kappetein AP, et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med* 2009;360:961-72.
12. O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the American

College of Emergency Physicians and Society for Cardiovascular Angiography and Interventions. *Catheter Cardiovasc Interv* 2013; 82:E1-27.
13. Liu CW, Liao PC, Chen KC, et al. Baseline hemoglobin levels associated with one-year mortality in ST-segment elevation myocardial infarction patients. *Acta Cardiol Sin* 2016;32:656-66.
14. Li YH, Yeh HI, Tsai CT, et al. 2012 guidelines of the Taiwan Society of Cardiology (TSOC) for the management of ST-segment elevation myocardial infarction. *Acta Cardiol Sin* 2012;28:63-89.
15. Huang CC, Chen JW. Contemporary management of coronary artery disease and acute coronary syndrome in patients with chronic kidney disease and end-stage renal disease. *Acta Cardiol Sin* 2013;29:132-41.
16. Li YH, Hsieh IC, Shyu KG, Kuo FY. What could be changed in the 2012 Taiwan ST-segment elevation myocardial infarction guideline? *Acta Cardiol Sin* 2014;30:360-4.
17. Chang CC, Hsu CY, Huang PH, et al. Association of serum bilirubin with SYNTAX score and future cardiovascular events in patients undergoing coronary intervention. *Acta Cardiol Sin* 2016;32:412-9.
18. Mehran R, Aymong ED, Nikolsky E, et al. A simple risk score for prediction of contrast-induced nephropathy after percutaneous coronary intervention: development and initial validation. *J Am Coll Cardiol* 2004;44:1393-9.
19. Madhavan MV, Genereux P, Rubin J, et al. Usefulness of the SYNTAX score to predict acute kidney injury after percutaneous coronary intervention (from the Acute Catheterization and Urgent Intervention Triage Strategy Trial). *Am J Cardiol* 2014;113:1331-7.
20. Sahin DY, Gur M, Elbasan Z, et al. SYNTAX score is a predictor of angiographic no-reflow in patients with ST-elevation myocardial infarction treated with a primary percutaneous coronary intervention. *Coron Artery Dis* 2013;24:148-53.
21. Su MI, Tsai CT, Yeh HI, Chen CY. The impact of SYNTAX score of non-infarct-related artery on long-term outcome among patients with acute ST segment elevation myocardial infarction undergoing primary percutaneous coronary intervention. *PloS One* 2014;9:e109828.
22. Hahn JY, Yu CW, Park HS, et al. Long-term effects of ischemic postconditioning on clinical outcomes: 1-year follow-up of the POST randomized trial. *Am Heart J* 2015;169:639-46.
23. Hoole SP, Heck PM, Sharples L, et al. Cardiac Remote Ischemic Preconditioning in Coronary Stenting (CRISP Stent) Study: a prospective, randomized control trial. *Circulation* 2009;119:820-7.
24. Davies WR, Brown AJ, Watson W, et al. Remote ischemic preconditioning improves outcome at 6 years after elective percutaneous coronary intervention: the CRISP stent trial long-term follow-up. *Circ Cardiovasc Interv* 2013;6:246-51.
25. Carrasco-Chinchilla F, Munoz-Garcia AJ, Dominguez-Franco A, et al. Remote ischaemic postconditioning: does it protect against ischaemic damage in percutaneous coronary revascularisation? Randomised placebo-controlled clinical trial. *Heart* 2013;99:1431-7.
26. Lavi R, D'Alfonso S, Diamantouros P, et al. Response to letter regarding article, "Remote ischemic postconditioning during percutaneous coronary interventions: remote ischemic postconditioning-percutaneous coronary intervention randomized trial". *Circ Cardiovasc Interv* 2014;7:423.
27. Er F, Nia AM, Dopp H, et al. Ischemic preconditioning for prevention of contrast medium-induced nephropathy: randomized pilot RenPro Trial (Renal Protection Trial). *Circulation* 2012;126:296-303.
28. Pei H, Wu Y, Wei Y, et al. Remote ischemic preconditioning reduces perioperative cardiac and renal events in patients undergoing elective coronary intervention: a meta-analysis of 11 randomized trials. *PloS one* 2014;9:e115500.

SUPPLEMENT

Supplemental Table 1. Subgroup analysis of STEMI patients regarding baseline kidney function

Variables	Creatinine ≤ 1.5 mg/dl			Creatinine > 1.5 mg/dl		
	BID ≤ 9 times (N = 110)	BID > 9 times (N = 50)	p	BID ≤ 9 times (N = 29)	BID > 9 times (N = 17)	p
Age (years)	63 (54-79)	66 (59-76)	0.592	67 (56-76)	68 (55-82)	0.838
Body mass index (kg/m^2)	24.7 (22.4-27.3)	23.7 (21.9-26.4)	0.193	24.8 (22.3-26.6)	25.0 (22.2-27.7)	0.725
Creatinine (mg/dl)	1 (0.8-1.3)	0.9 (0.8-1.2)	0.373	1.8 (1.6-2.4)	2.4 (1.8-2.76)	0.023
Hemoglobin (g/dl)	14.5 (12.6-15.5)	14 (11.9-15.5)	0.596	12.9 (12.4-15.3)	12.1 (10.5-14.3)	0.148
CAD risk factors						
Male	80 (72.7)	33 (66)	0.455	4 (13.8)	5 (29.4)	0.258
Current/past smoker	51 (46.4)	28 (56)	0.514	15 (51.7)	5 (29.4)	0.219
Hypertension	74 (67.3)	37 (74)	0.464	21 (72.4)	13 (76.5)	1.000
Diabetes	49 (44.5)	24 (48)	0.735	14 (48.3)	9 (52.9)	1.000
Hyperlipidemia	31 (28.2)	11 (22)	0.560	10 (34.5)	3 (17.6)	0.315
Known CAD	14 (12.7)	9 (18)	0.467	6 (20.7)	3 (17.6)	1.000
Previous MI	6 (5.5)	3 (6)	1.000	0 (0)	1 (5.9)	0.386
Ischemic stroke	10 (9.1)	7 (14)	0.390	5 (17.2)	1 (5.9)	0.390
Killip class						
I	47 (42.7)	21 (42)	1.000	10 (34.5)	3 (17.6)	0.315
II	33 (30.0)	14 (28)	0.853	8 (27.6)	8 (47.1)	0.213
III	7 (6.4)	6 (12)	0.229	0 (0)	3 (17.6)	0.045
IV	23 (20.9)	9 (18)	0.832	11 (37.9)	3 (17.6)	0.195

Supplemental Table 1. Continued

Variables	Creatinine ≤ 1.5 mg/dl			Creatinine > 1.5 mg/dl		
	BID ≤ 9 times (N = 110)	BID > 9 times (N = 50)	p	BID ≤ 9 times (N = 29)	BID > 9 times (N = 17)	p
Mehran risk score						
Hypotension	23 (20.9)	9 (18)	0.832	11 (37.9)	3 (17.6)	0.195
IABP support	33 (30.0)	17 (34)	0.713	6 (20.7)	5 (29.4)	0.722
Congestive heart failure	7 (6.4)	6 (12)	0.229	0 (0)	3 (17.6)	0.045
Age > 75 (years)	35 (31.8)	14 (28)	0.713	8 (27.6)	7 (41.2)	0.516
Anemia	31 (28.2)	15 (30)	0.852	11 (37.9)	8 (47.1)	0.757
Procedural characteristics						
Numbers of BID performed	5 (4-7)	14 (12-18)	< 0.001	6 (5-8)	15 (12-18)	< 0.001
Contrast volume (ml)	160 (150-200)	215 (180-285)	< 0.001	150 (150-200)	200 (163-260)	0.010
Fluoroscopy times (min)	10.6 (9-13.7)	20.2 (14.1-26.0)	< 0.001	12.2 (8.0-16.5)	15.8 (12.0-22.9)	0.026
Door-to-balloon time (min)	74 (61-106)	81 (64-115)	0.178	78 (55-150)	83 (64-131)	0.690
Trans-femoral approach	103 (93.6)	41 (82)	0.043	26 (89.7)	14 (82.4)	0.655
Thrombus aspiration	66 (60.0)	25 (50)	0.302	20 (69.0)	5 (29.4)	0.014
Glycoprotein IIb/IIIa inhibitor	52 (47.3)	26 (52)	0.169	17 (58.6)	11 (64.7)	0.761
IABP support	0 (0)	0 (0)	-	5 (17.2)	4 (23.5)	0.707
Multiple-vessel disease	70 (63.6)	43 (86)	0.005	23 (79.3)	14 (82.4)	1.000
Infarct-related artery						
LAD	59 (53.6)	22 (44)	0.307	8 (27.6)	7 (41.2)	0.516
LM	0 (0)	0 (0)	-	0 (0)	1 (5.9)	0.370
Stent implantation[#]	95 (86.4)	49 (98)		23 (79.3)	16 (94.1)	0.234
Bare-metal stent	89 (80.9)	41 (82)	1.000	21 (72.4)	15 (88.2)	0.282
Drug-eluting stent	6 (5.5)	8 (16)	0.058	2 (6.9)	1 (5.9)	1.000
Number of stent implantations						
1	77 (70.0)	16 (32)	< 0.001	18 (62.1)	6 (35.3)	0.126
2	17 (15.5)	22 (44)	< 0.001	5 (17.2)	5 (29.4)	0.462
3	1 (0.9)	9 (18)	< 0.001	0 (0)	4 (23.5)	0.015
4	0 (0)	2 (4)	< 0.001	0 (0)	1 (5.9)	0.370
Initial TIMI flow						
0	82 (74.5)	31 (62)	0.134	24 (82.8)	8 (47.1)	0.019
1	7 (6.4)	3 (6)	1.000	1 (3.4)	4 (23.5)	0.055
2~3	21 (19.1)	16 (32)	0.104	3 (10.3)	5 (29.4)	0.125
Final TIMI flow						
0	2 (1.8)	0 (0)	1.000	1 (3.4)	0 (0)	1.000
1	1 (0.9)	0 (0)	1.000	1 (3.4)	0 (0)	1.000
2~3	107 (97.3)	50 (100)	0.553	27 (93.1)	17 (100.0)	0.294
PCI to non-IRA	2 (1.8)	3 (6)	0.177	1 (3.4)	0 (0)	1.000
Heavy calcification of IRA	21 (19.1)	5 (10)	0.172	2 (6.9)	5 (29.4)	0.086
IRA lesion > 20 mm	93 (84.5)	43 (86)	1.000	22 (75.9)	15 (88.2)	0.690
Bifurcation lesion of IRA	72 (65.5)	34 (68)	0.453	17 (58.6)	11 (64.7)	0.578
Side branch > 1.5 mm	48 (43.6)	27 (54)		6 (20.7)	6 (35.3)	
Side branch < 1.5 mm	24 (21.8)	7 (14)		11 (37.9)	5 (29.4)	
Periprocedural complications						
Any dissection	52 (47.3)	26 (52)	0.612	17 (58.6)	10 (58.8)	1.000
Type D dissection	3 (2.7)	3 (6)	0.378	4 (13.8)	2 (11.8)	1.000
Type F dissection	8 (7.3)	5 (10)	0.546	4 (13.8)	1 (5.9)	0.635
Outcome						
CIAKI	5 (4.5)	7 (14)	0.052	3 (10.3)	6 (35.3)	0.058

Supplemental Table 2. Subgroup analysis of STEMI patients regarding vascular complexity

Variables	Simple vascular lesion (SI ≤ 10)			Complex vascular lesion (SI > 10)		
	BID ≤ 9 times (N = 98)	BID > 9 times (N = 34)	p	BID ≤ 9 times (N = 41)	BID > 9 times (N = 33)	p
Age (years)	64 (54-78)	67 (59-77)	0.465	66 (55-88)	64 (57-76)	0.948
Body mass index (kg/m^2)	22.1 (24.8-27.1)	23.7 (22.0-26.5)	0.297	24.8 (22.5-27.6)	24.7 (22.23-26.6)	0.826
Creatinine (mg/dl)	1.1 (0.9-1.5)	1.1 (0.9-1.8)	0.791	1.1 (0.9-1.8)	1.0 (0.8-1.3)	0.469
Hemoglobin (g/dl)	14.5 (12.6-15.4)	14 (12.0-14.8)	0.364	14.0 (12.0-14.8)	13.0 (10.7-16.0)	0.364
CAD risk factors						
Male	25 (25.5)	10 (29.4)	0.658	9 (22.0)	12 (36.4)	0.202
Current/past smoker	52 (53.1)	13 (38.2)	0.273	21 (51.2)	13 (39.4)	0.354
Hypertension	68 (69.4)	27 (79.4)	0.374	27 (65.9)	33 (100.0)	0.805
Diabetes	47 (48.0)	15 (44.1)	0.694	16 (39.0)	18 (54.5)	0.242
Hyperlipidemia	29 (29.6)	6 (17.6)	0.257	12 (29.3)	8 (24.2)	0.793
Known CAD	14 (14.3)	5 (14.7)	1.000	6 (14.6)	7 (21.2)	0.545
Previous MI	5 (5.1)	0 (0)	0.325	1 (2.4)	4 (12.1)	0.172
Ischemic stroke	13 (13.3)	5 (14.7)	0.709	2 (4.9)	3 (9.1)	0.651
Killip class						
I	39 (39.8)	13 (38.2)	1.000	16 (39.0)	10 (30.3)	0.472
II	29 (29.6)	14 (41.2)	0.288	12 (29.3)	8 (24.2)	0.793
III	3 (3.1)	2 (5.9)	0.603	5 (12.2)	7 (21.2)	0.352
IV	26 (26.5)	4 (11.8)	0.097	8 (19.5)	8 (24.2)	0.777
Mehran risk score						
Hypotension	26 (26.5)	4 (11.8)	0.097	8 (19.5)	8 (24.2)	0.777
IABP support	20 (20.4)	12 (35.3)	0.104	19 (46.3)	10 (30.3)	0.231
Congestive heart failure	3 (3.1)	2 (5.9)	0.603	4 (9.8)	7 (21.2)	0.201
Age > 75 (years)	29 (29.6)	11 (32.4)	0.829	14 (34.1)	10 (30.3)	0.805
Anemia	26 (26.5)	8 (23.5)	0.823	16 (39.0)	15 (45.5)	0.640
Procedural characteristics						
Numbers of BID performed	6 (4-7)	13 (12-17)	< 0.001	6 (14-8)	16 (12-19)	< 0.001
Contrast volume (ml)	160 (150-200)	200 (160-260)	< 0.001	150 (150-200)	230 (180-268)	< 0.001
Fluoroscopy times (min)*	11.3 (8.9-14.7)	18.3 (14.1-26.1)	< 0.001	10.5 (8.7-13.1)	19.7 (12.9-21.4)	< 0.001
Door-to-balloon time (min)	74 (59-108)	81 (64-126)	0.341	75 (60-110)	81 (63-112)	0.341
Trans-femoral approach	89 (90.8)	28 (82.4)	0.212	40 (97.6)	27 (81.8)	0.040
Thrombus aspiration	64 (65.3)	14 (41.2)	0.016	22 (53.7)	16 (48.5)	0.815
Glycoprotein IIb/IIIa inhibitor	64 (65.3)	24 (70.6)	0.675	19 (46.3)	15 (45.5)	1.000
IABP support	17 (17.3)	10 (29.4)	0.145	17 (41.5)	9 (27.3)	0.230
Multiple-vessel disease	65 (66.3)	32 (94.1)	0.001	28 (68.3)	25 (75.8)	0.606
Infarct-related artery						
LAD	33 (33.7)	3 (8.8)	0.006	34 (82.9)	26 (78.8)	0.768
LM	0 (0)	0 (0)	1.000	1 (2.4)	1 (3.0)	1.000
Stent implantation#	83 (84.7)	33 (97.1)	0.069	35 (85.4)	32 (97.0)	0.296
Bare-metal stent	77 (78.6)	29 (85.3)	0.463	33 (80.5)	27 (81.8)	1.000
Drug-eluting stent	6 (6.1)	4 (11.8)	0.280	2 (4.9)	5 (15.2)	0.267
Number of stent implantations						
1	70 (71.4)	10 (29.4)	< 0.001	25 (61.0)	12 (36.4)	0.061
2	13 (13.3)	14 (41.2)	0.001	9 (22.0)	13 (39.4)	0.128
3	0 (0)	8 (23.5)	< 0.001	1 (2.4)	5 (15.2)	0.083
4	0 (0)	1 (2.9)	0.258	0 (0)	2 (6.1)	0.195

Supplemental Table 2. Continued

Variables	Simple vascular lesion (SI ≤ 10)			Complex vascular lesion (SI > 10)		
	BID ≤ 9 times (N = 98)	BID > 9 times (N = 34)	p	BID ≤ 9 times (N = 41)	BID > 9 times (N = 33)	p
Initial TIMI flow						
0	72 (73.5)	16 (47.1)	0.011	35 (85.4)	23 (69.7)	0.155
1	6 (6.1)	5 (14.7)	0.150	2 (4.9)	2 (6.1)	1.000
2~3	20 (20.4)	13 (38.2)	0.064	4 (9.8)	8 (24.2)	0.119
Final TIMI flow						
0	3 (3.1)	0 (0)	0.569	0 (0)	0 (0)	-
1	1 (1.0)	0 (0)	1.000	1 (2.4)	0 (0)	1.000
2~3	94 (95.9)	34 (100)	0.327	40 (97.6)	33 (100.0)	1.000
PCI to non-IRA	2 (2.0)	2 (5.9)	0.276	1 (2.4)	1 (3.0)	1.000
Heavy calcification of IRA	13 (13.3)	3 (8.8)	0.761	10 (24.4)	7 (21.2)	0.788
IRA lesion > 20 mm	78 (79.6)	30 (88.2)	0.433	37 (90.2)	28 (84.8)	0.501
Bifurcation lesion of IRA	52 (53.1)	17 (50.0)	0.918	37 (90.2)	29 (87.9)	0.914
Side branch > 1.5 mm	23 (23.5)	8 (23.5)		31 (75.6)	25 (75.8)	
Side branch < 1.5 mm	29 (29.6)	9 (26.5)		6 (14.6)	4 (12.1)	
Periprocedural complications						
Any dissection	43 (43.9)	16 (47.1)	0.843	26 (63.4)	20 (60.6)	0.815
Type D dissection	5 (5.1)	2 (5.9)	1.000	2 (4.9)	3 (9.1)	0.651
Type F dissection	8 (8.2)	3 (8.8)	1.000	4 (9.8)	3 (9.1)	1.000
Outcome						
CIAKI	4 (4.1)	4 (11.8)	0.203	6 (14.6)	9 (27.3)	0.246

Supplemental Table 3. Subgroup analysis of STEMI patients with vs. without cardiogenic shock

Variables	With cardiogenic shock			Without cardiogenic shock		
	BID ≤ 9 times (N = 105)	BID > 9 times (N = 55)	p	BID ≤ 9 times (N = 34)	BID > 9 times (N = 12)	p
Age (years)	68 (55-80)	67 (59-77)	0.931	59 (53-67)	60 (51-72)	0.871
Body mass index (kg/m^2)	24.8 (22.2-27.2)	23.8 (22.0-26.6)	0.363	24.2 (22.7-27.4)	24.5 (22.0-26.4)	0.797
Creatinine (mg/dl)	1.1 (0.8-1.4)	1.1 (0.8-1.7)	0.698	1.3 (0.9-1.6)	1.2 (0.9-1.6)	0.774
Hemoglobin (g/dl)	13.8 (12.0-15.3)	13.7 (11.7-15.2)	0.748	14.9 (13.0-15.9)	13.6 (10.3-15.3)	0.118
CAD risk factors						
Male	31 (29.5)	18 (32.7)	0.720	3 (8.8)	4 (33.3)	0.064
Current/past smoker	43 (41.0)	30 (54.5)	0.132	23 (67.6)	3 (25.0)	0.017
Hypertension	75 (71.4)	41 (74.5)	0.852	14 (41.2)	3 (25.0)	0.489
Diabetes	53 (50.5)	26 (47.3)	0.739	24 (70.6)	5 (41.7)	0.093
Hyperlipidemia	33 (31.4)	12 (21.8)	0.266	8 (23.5)	2 (16.7)	1.000
Known CAD	16 (15.2)	9 (16.4)	1.000	4 (11.8)	3 (25.0)	0.355
Previous MI	4 (3.8)	3 (5.5)	0.699	2 (5.9)	1 (8.3)	1.000
Ischemic stroke	11 (10.5)	6 (10.9)	1.000	4 (11.8)	2 (16.7)	0.644
Killip class						
I	55 (52.4)	23 (41.8)	0.245	0 (0)	0 (0)	-
II	41 (39.0)	22 (40.0)	1.000	0 (0)	0 (0)	-
III	10 (9.5)	9 (16.4)	0.120	0 (0)	0 (0)	-
IV	0 (0)	0 (0)	-	34 (100.0)	12 (100.0)	-

Supplemental Table 3. Continued

Variables	With cardiogenic shock			Without cardiogenic shock		
	BID ≤ 9 times (N = 105)	BID > 9 times (N = 55)	p	BID ≤ 9 times (N = 34)	BID > 9 times (N = 12)	p
Mehran risk score						
Hypotension	0 (0)	0 (0)	-	34 (100.0)	12 (100.0)	-
IABP support	27 (25.7)	17 (30.9)	0.576	22 (64.7)	7 (58.3)	0.737
Congestive heart failure	7 (6.7)	9 (16.4)	0.093	0 (0.0)	0 (0.0)	-
Age > 75 (years)	39 (37.1)	19 (34.5)	0.863	4 (11.8)	2 (16.7)	0.644
Anemia	35 (33.3)	19 (34.5)	1.000	7 (20.6)	4 (33.3)	0.441
Procedural characteristics						
Numbers of BID performed	6 (4-7)	13 (12-17)	< 0.001	5 (4-7)	16 (12-19)	< 0.001
Contrast volume (ml)	155 (150-200)	200 (175-265)	< 0.001	180 (150-200)	260 (165-280)	0.022
Fluoroscopy times (min)*	10.8 (8.8-13.7)	17.6 (13.4-25.4)	< 0.001	11.2 (8.4-16.0)	20.6 (13.3-25.8)	0.018
Door-to-balloon time (min)	74 (60-110)	77 (63-110)	0.519	77 (60-96)	112 (85-141)	0.040
Trans-femoral approach	96 (91.4)	44 (80.0)	0.046	33 (97.1)	11 (91.7)	0.458
Thrombus aspiration	66 (62.9)	25 (45.5)	0.044	14 (41.2)	7 (58.3)	0.335
Glycoprotein IIb/IIIa inhibitor	65 (61.9)	31 (56.4)	0.503	18 (52.9)	8 (66.7)	0.509
IABP support	10 (9.5)	5 (9.1)	0.701	10 (29.4)	5 (41.7)	0.488
Multiple-vessel disease	69 (65.7)	48 (87.3)	0.004	24 (70.6)	9 (75.0)	1.000
Infarct-related artery						
LAD	51 (48.6)	24 (43.6)	0.618	16 (47.1)	5 (41.7)	1.000
Non-LAD	0 (0)	0 (0)	-	0 (0)	0 (0)	-
LM	1 (1.0)	0 (0)	1.000	0 (0)	1 (8.3)	0.261
Stent implantation	88 (83.8)	53 (96.4)	0.021	30 (88.2)	11 (91.7)	1.000
Bare-metal stent	83 (79.0)	45 (81.8)	0.836	27 (79.4)	11 (91.7)	0.660
Drug-eluting stent	5 (4.8)	9 (16.4)	0.035	3 (8.8)	0 (0.0)	0.557
Number of stent implantations						
1	69 (65.7)	18 (32.7)	< 0.001	26 (76.5)	4 (33.3)	0.013
2	18 (17.1)	23 (41.8)	< 0.001	4 (11.8)	4 (33.3)	0.178
3	1 (1.0)	10 (18.2)	< 0.001	0 (0)	3 (25.0)	0.014
4	0 (0)	3 (5.5)	0.039	0 (0)	0 (0)	-
Initial TIMI flow						
0	80 (76.2)	30 (54.5)	0.007	26 (76.5)	9 (75.0)	1.000
1	7 (6.7)	5 (9.1)	0.753	1 (2.9)	2 (16.7)	0.162
2~3	18 (17.1)	20 (36.4)	0.010	6 (17.6)	1 (8.3)	0.657
Final TIMI flow						
0	2 (1.9)	0 (0)	0.546	1 (2.9)	0 (0)	1.000
1	2 (1.9)	0 (0)	0.546	0 (0)	0 (0)	1.000
2~3	101 (96.2)	55 (100.0)	0.300	2 (5.9)	0 (0)	1.000
PCI to non-IRA	2 (1.9)	2 (3.6)	0.608	1 (2.9)	1 (8.3)	0.467
Heavy calcification of IRA	29 (27.6)	12 (21.8)	1.000	4 (11.8)	0 (0.0)	0.561
IRA lesion > 20mm	85 (81.0)	48 (87.3)	0.378	30 (88.2)	10 (83.3)	0.598
Bifurcation lesion of IRA	68 (64.8)	37 (67.3)	0.642	21 (61.8)	9 (75.0)	0.330
Side branch > 1.5mm	40 (38.1)	25 (45.5)		14 (41.2)	8 (66.7)	
Side branch < 1.5mm	28 (26.7)	12 (21.8)		7 (20.6)	1 (8.3)	
Periprocedural complications						
Any dissection	54 (51.4)	27 (49.1)	0.868	15 (44.1)	9 (75.0)	0.101
Type D dissection	4 (3.8)	5 (9.1)	0.277	3 (8.8)	0 (0.0)	0.553
Type F dissection	11 (10.5)	5 (9.1)	1.000	32 (94.1)	11 (91.7)	0.467
Outcome						
CIAKI	8 (7.6)	8 (14.5)	0.176	2 (5.9)	5 (41.7)	0.009