The Relation between the Timing of Percutaneous Coronary Intervention and Outcomes in Patients with Acute Coronary Syndrome with Routine Invasive Strategy − Data from Taiwan Acute Coronary Syndrome Full Spectrum Data Registry

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Background: Several large trials have indicated that a routine invasive strategy was favored for high-risk patients with non-ST-elevation acute coronary syndromes. However, the optimal timing for this intervention is unclear.
Methods: We included patients with unstable angina or non-ST elevation myocardial infarction (NSTEMI) undergoing percutaneous coronary intervention (PCI) from the Taiwan acute coronary syndrome registry. Thrombolysis in Myocardial Infarction (TIMI) score was used to stratify our patients into three groups: low (TIMI 0-2), intermediate (TIMI 3-4) and high risk (TIMI 5-7).We analyzed outcomes according to the timing of PCI.
Results: Overall, 984 patients were included in this study. For primary outcomes including cardiac death and recurrent myocardial infarction, early PCI within 24 hours did not show benefits over late PCI (24-72 or > 72 hours) (p > 0.05) in the low and intermediate risk groups. However, in the high risk group, patients who underwent PCI after 72 hours had significantly worse primary outcomes than those who underwent PCI within 24-72 hours. For secondary outcomes including non-cardiac death, unplanned revascularization, and major bleeding, the events rate was significantly higher for early or delayed PCI in low-risk patients when compared with patients who underwent PCI within 24-72 hours.
Conclusions: In our study, for high-risk NSTE-ACS patients, PCI within 24-72 hours from symptom onset is demonstrably the optimum time for PCI. Delayed PCI over 72 hours is associated with the worst outcomes and should be avoided. For patients with low risks, routine early PCI < 24 hours after PCI is not beneficial.

Key Words: Acute coronary syndrome ● Early invasive strategy

INTRODUCTION

Patients with suspected acute coronary syndrome (ACS) should be risk stratified based on the likelihood of ACS and adverse outcomes to determine the optimal treatment.[1-4] For patients with Non ST elevation acute coronary syndrome (NSTE-ACS) with refractory angina, hemodynamic or electrical instability, urgent invasive strategy (diagnostic angiography with intent to perform revascularization if appropriate) is suggested according

to the current practice medical guidelines.[1-4] Among initially stabilized patients, an early invasive strategy of coronary angiography is favored;[5-8] however, the optimal timing of angiography has not been well-defined. Urgent or early invasive strategy may prevent ischemic events that would otherwise occur during medical therapy.[9,10] Conversely, delayed invasive strategy with intensive antithrombotic therapy first may diminish thrombus burden and stabilize unstable plaques, improving procedural safety.[9,10] Several large trials have compared different strategies of early versus delayed intervention in patients with NSTE-ACS but the optimal timing is still a matter of ongoing debate.[11-15]

The Taiwan ACS registry is a nationwide study to assess real-world clinical practices and outcomes of patients with ACS in Taiwan.[16,17]

For each patient, the study started from the time of admission and continued for 1 year post-discharge. To our knowledge, there is limited available information in Taiwan about the outcomes of patients with NSTE-ACS with respect to early or delayed percutaneous coronary intervention. The primary purpose of our study was to first stratify these patients into low, intermediate and high risk groups; then, we would review their clinical outcomes including in-hospital and 1 year outcomes. We thereafter would categorize them into different time intervals for percutaneous coronary intervention (PCI).

MATERIALS AND METHODS

Study design

This study was a prospective, national, multicenter, and observational design. From October 2008 to January 2010, patients ≥ 20 years of age, and admitted after onset of symptoms within 24 hours at any of the 39 participating hospitals in Taiwan were enrolled for the study. Patients who fulfilled the criteria of unstable angina or Non ST elevation myocardial infarction (NSTEMI) and who received coronary angiography and PCI were included. The criteria included typical chest pain or overwhelming shortness of breath, electrocardiogram (ECG) showing pathological Q wave or persistent or dynamic ECG change of ST depression > 0.5 mm, or new deep T wave inversion in more than 2 contiguous leads

and either rise of cardiac markers or absence of rise. Patients who fulfilled the criteria of unstable angina or NSTEMI and received PCI for revascularization were included in the study.

We used the TIMI risk score to stratify the patients because the TIMI score system is conveniently and widely used in our daily practice. The seven TIMI risk score predictor variables were: 1) age 65 years or older; 2) at least three risk factors for CAD; 3) prior coronary stenosis of 50% or more; 4) ST-segment deviation on ECG at presentation; 5) at least two angina events in the prior 24 hours; 6) use of aspirin in prior seven days; and 7) elevated serum cardiac markers. The patients were classified as low risk (group 1), intermediate (group 2) or high risk (group 3) according to their TIMI score.

The low risk patients (group 1) had a TIMI risk score of 2 or below, the intermediate risk patients (group 2) had a TIMI risk score of between 3 and 4, and the high risk patients (group 3) had a score of 5 or above.

Patients with NSTE-ACS were categorized according to the time interval from the onset of cardiac symptoms to PCI. In this study, we used three time intervals from the onset of symptoms: < 24 hour, between 24 and 48 hours, and after 48 hours.

We analyzed each group to establish the relationship between outcomes and the timing of PCI. Our primary endpoint was cardiac death and recurrent non-fatal myocardial infarction (Re-MI) for 1 year. The secondary endpoint was the composite of non-cardiac death, unplanned revascularization, and major bleeding for 1 year. Unplanned revascularization was defined as revascularization precipitated by 20 mins or more recurrent chest pain occurring after first 2 hours of admission. The major bleeding was defined as overt clinical bleeding associated with a drop of hemoglobin greater than 5g/dl, or hematocrit greater than 15%.

Statistical analysis

In this article, continuous variables were shown as means ± standard deviations (SD); categorical variables were shown as absolute numbers and percentage and they were compared by use of one way ANOVA. For categorical variables, Chi-square test or Fisher's exact test was applied. One year follow-up event analysis was

performed using Kaplan-Meier survival curves and the log-rank test. The Cox regression model was used for survival analysis and to study the risk factors. Cox regression model was used for survival analysis and risk factors study. A p value of less than 0.05 was considered to indicate significance for all factors. All analyses were conducted with the use of SPSS software, version 20.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Clinical characteristics

In a Taiwan nationwide registry, 3183 patients were enrolled from October 2008 to January 2010. 1470 patients suffered from NSTE-ACS. Table 1 shows the baseline patient characteristics. Only 984 of them received PCI for revascularization and were included in the study.

Table 1. Baseline characteristics of patients

Number (%)/Mean (SD)	Group 1 (Low risk) n = 264 (26.8%)	Group 2 (Intermediate risk) n = 569 (57.9%)	Group 3 (High risk) n = 151 (15.3%)	p-value
Demographic characteristics				
Age (years)	57.5 ± 11.4	65.5 ± 12.7	71.4 ± 10.8	< 0.001
Sex, male	206 (78%)	407 (71.4%)	104 (68.9%)	0.07
Medical history				
Dialysis status	12 (4.5%)	27 (4.7%)	7 (4.6%)	0.99
Dyslipidemia	83 (31.7%)	275 (48.8%)	111 (73.5%)	< 0.001
Hypertension	123 (46.9%)	436 (77.6%)	130 (86.7%)	< 0.001
Diabetes	62 (23.5%)	239 (42.3%)	100 (66.7%)	< 0.001
Known CAD	28 (10.6%)	207 (36.3%)	98 (64.9%)	< 0.001
History of atrial fibrillation	6 (2.3%)	25 (4.4%)	5 (3.3%)	0.31
Previous heart failure	16 (6.1%)	36 (6.3%)	22 (14.6%)	0.002
COPD	2 (0.8%)	28 (4.9%)	8 (5.3%)	0.009
Obstructive sleep apnea	0 (0%)	4 (0.7%)	1 (0.7%)	0.44
Peripheral arterial disease	5 (1.9%)	18 (3.2%)	4 (2.6%)	0.65
Malignancy	9 (3.4%)	12 (2.1%)	7 (4.6%)	0.20
Cerebrovascular accident	12 (4.5%)	75 (13.2%)	23 (15.2%)	< 0.001
Killip class				
≥ Class III	27 (15.3%)	76 (20.1%)	40 (35.1%)	< 0.001
Laboratory test				
Peak CK (U/L)	801.8 ± 2243.9	587.3 ± 1251.8	513.9 ± 598.6	0.14
Peak CKMB (U/L)	50.3 ± 79	41.3 ± 58.2	40.4 ± 48.6	0.24
Peak Troponin I (ug/L)	8.2 ± 16.5	8.4 ± 18.3	11.4 ± 28.6	0.24
Serum creatinine (mg/dl)	1.5 ± 2	1.8 ± 2	2.1 ± 2.1	0.01
White cell count ($\times 10^3$/uL)	9.3 ± 3.4	9.9 ± 4.3	10.1 ± 6.6	0.19
Total cholesterol (mg/dl)	187.2 ± 41.6	179.5 ± 43.6	168.3 ± 40	< 0.001
HDL (mg/dl)	39.4 ± 11	38.7 ± 11.2	38.9 ± 11.1	0.80
LDL (mg/dl)	116.6 ± 36.7	114 ± 39.1	99.4 ± 33	0.001
TG (mg/dl)	167.2 ± 127.4	150.8 ± 115	134.1 ± 87.9	0.02
Medication				
Aspirin	217 (82.2%)	526 (92.3%)	143 (94.7%)	< 0.001
Clopidogrel	241 (91.3%)	537 (94.2%)	147 (97.4%)	0.04
Glycoprotein IIb/IIIa inhibitor	22 (8.3%)	56 (9.8%)	11 (7.3%)	0.56
ACEI	119 (45.1%)	257 (45.1%)	62 (41.1%)	0.66
ARB	32 (12.1%)	110 (19.3%)	38 (25.2%)	0.003
B-blocker	114 (43.2%)	245 (43%)	77 (51%)	0.19
Statin	117 (44.3%)	271 (47.5%)	76 (50.3%)	0.47

a. (n, %) Chi-square test or Fisher's exact test. b. (mean ± SD) One-way ANOVA or Robust ANOVA.
ACEI, angiotensin converting enzyme inhibitor; ANOVA, analysis of variance; ARB, angiotensin II receptor blocker; CAD, coronary artery disease; CK, creatine kinase; COPD, chronic obstructive pulmonary disease; HDL, high density lipoprotein cholesterol; LDL, low density lipoprotein cholesterol; SD, standard deviation; TG, triglyceride.

264 (26.8%) of them belong to the low risk group (group 1), 569 (57.9%) of them belong to the intermediate group (group 2), and 151 of them belong to the high risk group (group 3). There is a significant difference in age among the three groups. The mean age is highest in group 3 (71.4 years), and the mean age of group 2 and 3 are 65.5 and 57.5 years, respectively. About the sex, 78%, 71.4%, and 68.9% are men among the 3 groups, respectively, without statistical significance.

The history of dyslipidemia, hypertension, diabetes, known coronary artery disease (CAD), congestive heart failure, chronic obstructive pulmonary disease and cerebral vascular disease was significantly different among the 3 groups. The incidence rate was highest in group 3 and lowest in group 1 (In group 1, the rate was 31.7%, 46.9%, 23.5%, 10.6%, 6/1%, 0.8%, and 4.5, respectively. In group 2, the rate was 48.8%, 77.6%, 42.3%, 36.3%, 6.3%, 4.9%, 13.2%, respectively. In group 3, the rate was 73.5%, 86.7%, 66.7%, 64.9%, 14.6%, 5.3%, and 15.2%, respectively.). Regarding the higher Killip class (≥ 3), the rate was highest in group 3 (35.1%) with statistical significance. The rate was 20.1% in group 2 and 15.3% in group 1. For the laboratory data, the serum creatinine was higher in group 3 (2.1 mg/dl) than in group 2 (1.8 mg/dl) and group 1 (1.5 mg/dl), with statistical significance. The serum total cholesterol, low density lipoprotein and triglyceride have significant difference among the 3 groups (group 1 > group 2 > group 3). In group 1, they are 187.2, 116.6, and 167.2 mg/dl, respectively. In group 2, the level was 179.5, 114.0, and 150.8 mg/dl. In group 3, the level was 82.2%, 91.3%, and 12.1%. Regarding medications, the use of aspirin, Clopidogrel and angiotensin II receptor blocker (ARB) is significantly higher in group 3 (group 3 > group 2 > group 1). About the glycoprotein IIb/IIIa inhibitor use, in group 1, the mean was 1.7; in group 2, the mean was 3.5; and in group 3, the mean is 5.2 and the p value is > 0.05.

Table 2 shows the results of coronary angiography. For the extent of coronary disease, the proportion of single vessel disease was highest in group 1 (44.9%), with group 2 second (34.5%) and group 3 the least (21.1%) with statistical significance. The 3 vessel disease is highest in group 3 (36.7%); group 2 is the second (27.4%) and group 3 is the least (24.8%). For the stent

Table 2. Coronary angiographic characteristics

Variables	Group 1 (Low risk) n = 264 (26.8%)	Group 2 (Intermediate risk) n = 569 (57.9%)	Group 3 (High risk) n = 151 (15.3%)	p-value
Extent of coronary disease				
1-vessel disease	123 (44.9%)	210 (34.5%)	35 (21.1%)	< 0.001
2-vessel disease	70 (25.5%)	189 (31%)	53 (31.9%)	0.10
3-vessel disease	68 (24.8%)	167 (27.4%)	61 (36.7%)	0.006
Left main	13 (4.7%)	43 (7.1%)	17 (10.2%)	0.06
Stent type				0.006
BMS	127 (48.1%)	323 (56.7%)	92 (61.3%)	
DES	93 (35.2%)	164 (28.8%)	38 (25.3%)	
Both	6 (2.3%)	15 (2.6%)	10 (6.7%)	
None	32 (12.1%)	62 (10.9%)	10 (6.7%)	
Unknown	6 (2.3%)	6 (1.1%)	0 (0%)	
Target vessel				
Left main	7 (2.9%)	25 (4.4%)	6 (3.6%)	0.48
LAD	103 (42%)	242 (42.5%)	60 (36.1%)	0.60
LCX	64 (26.1%)	140 (24.6%)	45 (27.1%)	0.38
RCA	71 (29%)	162 (28.5%)	55 (33.1%)	0.10
Mean TIMI risk score	1.7 ± 0.5	3.5 ± 0.5	5.2 ± 0.4	< 0.001
Glycoprotein IIb/IIIa inhibitor	22 (8.3%)	56 (9.8%)	11 (7.3%)	0.56

a. (n, %) Chi-square test or Fisher's exact test. b. (mean ± SD) One-way ANOVA or Robust ANOVA.
ANOVA, analysis of variance; BMS, bare metal stent; DES, drug eluting stent; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; TIMI, thrombosis in myocardial infarction.

type, bare metal stent (BMS) is used more widely than drug eluting stents (DESs) for patients with NSTE-ACS in all 3 groups (group1: 48.1%, group 2: 56.7%, group 3: 61.3%; p < 0.05).

Clinical outcomes

There were 55 (5.6%) patients who suffered from primary outcomes. Of that total, 20 (2%) of them had cardiac death and 37 (3.8%) of them suffered a non-fatal myocardial infarction. Also, 98 patients (9.9%) suffered from secondary outcomes, including 17 (1.7%) from non-cardiac related death, 79 (8%) with unplanned revascularization, and 4 (0.4) with TIMI major bleeding. Table 3 shows the primary and secondary outcomes in the whole population.

Figure 1A shows the results of primary outcomes (cardiac death and non-fatal MI) in low risk patients (group 1). There are 6 patients with primary outcomes; one of them underwent PCI within 24 hours of symptom presentation, 2 patients underwent PCI within 24-72 hours, and another 3 patients underwent PCI more that 72 hours after symptoms first appeared. Subsequent to log rank test analysis, there was no significant difference among these 3 time intervals (p = 0.65).

Regarding the group 2 patients (intermediate risk), the Figure 1B shows there are 36 cases of primary outcomes. There were 11 that underwent PCI within 24 hours, a further 11 underwent PCI in 24-72 hours, and 14 of them underwent PCI over 72 hours. After log rank test analysis, the cumulative event rate was statistically insignificant among these 3 time intervals (p = 0.62).

Among the group 3 patients (high risk), there were 12 cases of primary outcomes, wherein 4 of them un-derwent PCI within 24 hours, 1 of them underwent PCI in 24-72 hours, and 7 of them underwent PCI over 72 hours. After log rank test analysis, the cumulative event rate was statistically significant among these 3 time intervals (p < 0.05). The post hoc analysis with Bonferroni correction showed that the cumulative event rate was significantly higher in patients who underwent PCI over 72 hours after symptoms first appeared than those who underwent PCI in 24-72 hours (p = 0.01).

The secondary outcomes are non-cardiac death, Re-PCI and TIMI major bleeding. Figure 2A shows the result of low risk patients (group 1). There are 25 patients with secondary outcomes; 13 of them underwent PCI within 24 hours, 3 of them underwent PCI in 24 to 72 hours, and 9 of them underwent PCI over 72 hours. After log rank test analysis, the cumulative rate among the 3 time interval has significant difference (p < 0.05). The post hoc analysis with Bonferroni correction shows the cumulative event rate is significantly higher in the early PCI (< 24 hours) group than 24-72 hours PCI group (p < 0.001), and event rate is higher in late PCI (> 72 hours) than 24-72 hours PCI group (p = 0.02). However, when comparing early and late PCI, there is no significant difference (p = 0.053).

Figure 2B shows there are 60 cases with secondary outcomes among the intermediate risk patients (group 2). Of those patient cases, 18 of them underwent PCI within 24 hours, 17 of them received PCI in 24-72 hours, and 25 of them received PCI over 72 hours. After log test rank analysis, the cumulative event rate is statistically insignificant among these 3 time intervals (p > 0.05).

Figure 2C show the secondary outcomes of high risk

Table 3. Primary and secondary endpoint in whole population

| Variables	Group 1 (Low risk) n = 264 (26.8%)	Group 2 (Intermediate risk) n = 569 (57.9%)	Group 3 (High risk) n = 151 (15.3%)	Overall n = 984
Primary endpoint	6 (2.3%)	37 (6.5%)	12 (7.9%)	55 (5.6%)
Cardiac death	1 (0.4%)	15 (2.6%)	4 (2.6%)	20 (2%)
Nonfatal-MI	5 (1.9%)	23 (4%)	9 (6%)	37 (3.8%)
Secondary endpoint	25 (9.5%)	60 (10.5%)	13 (8.6%)	98 (9.9%)
Non-cardiac death	3 (1.1%)	11 (1.9%)	3 (2%)	17 (1.7%)
Unplanned revascularization	22 (8.3%)	48 (8.4%)	9 (6%)	79 (8%)
TIMI major bleeding	0 (0%)	3 (0.5%)	1 (0.7%)	4 (0.4%)

Primary endpoint includes cardiac death and nonfatal-myocardial Infarction. Secondary endpoint includes non cardiac death, unplanned revascularization and TIMI major bleeding.
MI, myocardial infarction; PCI, percutaneous coronary intervention; TIMI, thrombosis in myocardial infarction.
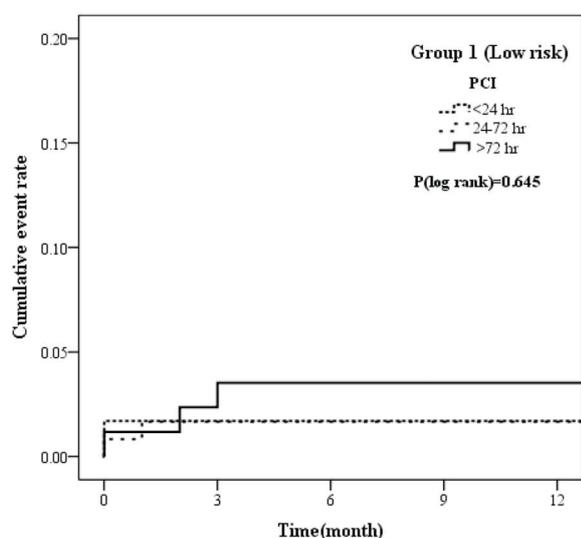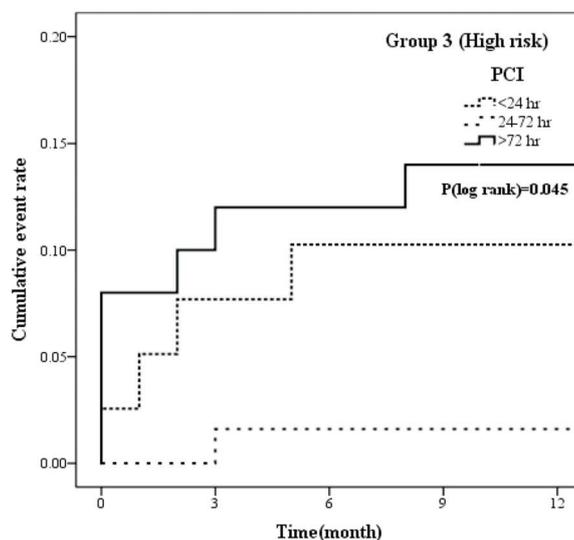
Group 1 (Low TIMI risk)	HR	p value	95% C.I. for HR	
			Lower	Upper
Time intervals [h]				
24-72/< 24	1.47	0.737	0.15	14.16
> 72/< 24	2.16	0.504	0.23	20.81

Analysis and cumulative events rate of Group 1 (Low risk).

A
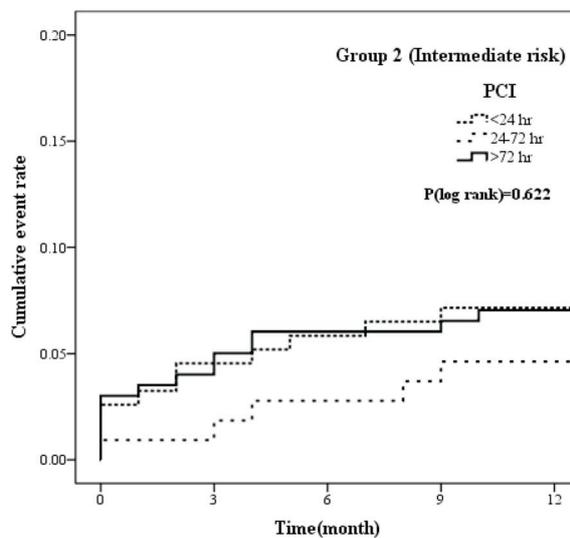
Group 2 (Intermediate risk)	HR	p value	95% C.I. for HR	
			Lower	Upper
Time intervals [h]				
24-72/< 24	0.88	0.751	0.41	1.89
> 72/< 24	0.83	0.646	0.38	1.82

Analysis and cumulative events rate of Group 2 (Intermediate risk).

B

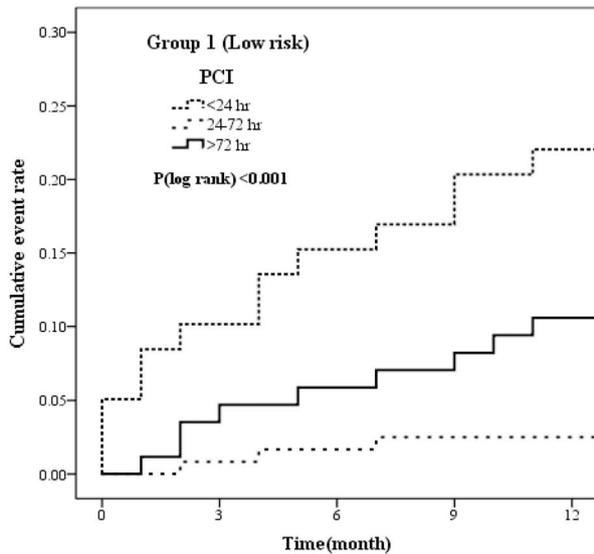| Group 3 (High risk)	p value*
Time intervals [h]	
24-72 vs. < 24	0.050
> 72 vs. < 24	0.592
24-72 vs. > 72	0.011

* Bonferroni method.

C Analysis and cumulative events rate of Group 3 (High risk).

Figure 1. *Cumulative event rate and hazard ratio of primary outcomes for (A) low risk patients, (B) intermediate risk patients, and (C) high risk patients. CI, confidence interval; HR, hazard ratio; PCI, percutaneous coronary intervention.*

patients. There were13 patients with secondary outcomes. Of that number, 3 of them underwent PCI within 24 hours, 5 underwent PCI in 24-72 hours, and 5 of them underwent PCI over 72 hours. After log rank test

analysis, the cumulative event rate is statistics insignificant among these 3 time interval (p > 0.05).

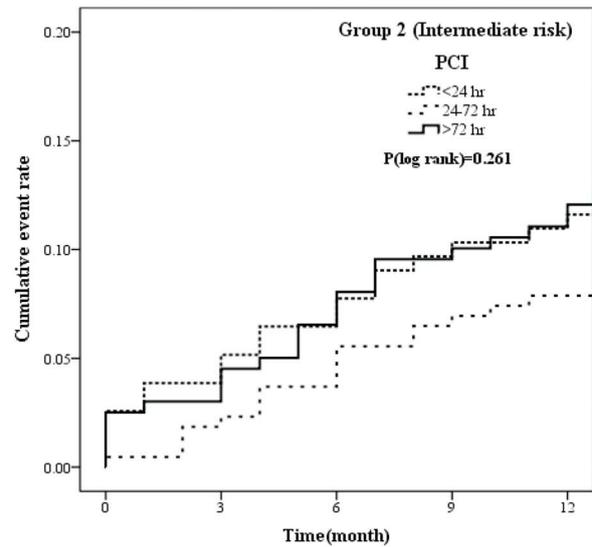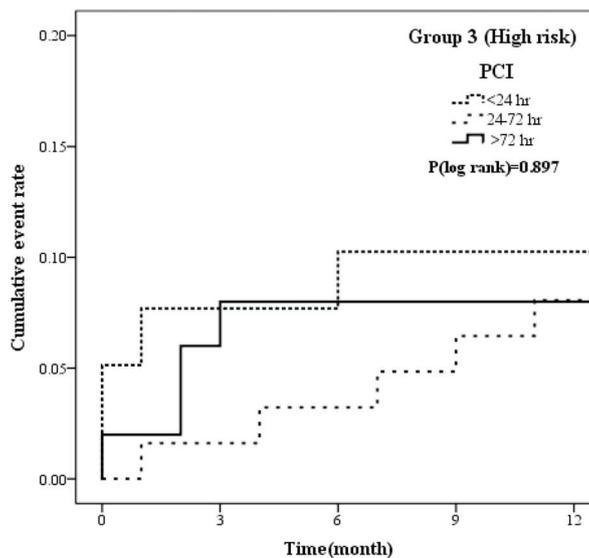Table 4 shows the result of Cox regression model for primary outcomes. The hazard ratio is 3.32 for patients

Group 1 (low risk)	p value*
Time intervals [h]	
24-72 vs. < 24	< 0.001
> 72 vs. < 24	0.053
24-72 vs. > 72	0.015

* Bonferroni method.

A Analysis and cumulative events rate of Group 1 (Low risk).

B Analysis and cumulative events rate of Group 2 (Intermediate risk).

C Analysis and cumulative events rate of Group 3 (High risk).

Figure 2. *Cumulative event rate and hazard ratio of secondary outcomes for (A) low risk patients, (B) intermediate risk patients, and (C) high risk patients. CI, confidence interval; HR, hazard ratio; PCI, percutaneous coronary intervention.*

with unplanned revascularization (p < 0.05, and 2.22 for patients with Killip class ≥ 3 (p < 0.05).

Table 5 shows the result of cox regression model for secondary outcomes. The hazard ratio is 0.4 for patients underwent PCI within 24-72 hours in comparison with < 24 hours (p = 0.005). The hazard ratio for statin use was 0.59 (p = 0.05).

DISCUSSION

Several random control trials such as TACTICS-TIMI 18 (Treat Angina With Aggrastat and Determine the Cost of Therapy With an Invasive or Conservative Strategy), FRISC II (FRagmin and Fast Revascularization during In-Stability in Coronary artery disease), and ISAR-COOL

Table 4. Cox regression (primary outcome)

Variables	HR	p value	95% C.I. for HR	
			Lower	Upper
Time intervals [h]				
24-72/< 24	0.70	0.41	0.30	1.63
> 72/< 24	0.88	0.75	0.39	1.98
Unplanned revascularization (Yes/No)	3.23	0.005	1.42	7.34
Multi-vessel disease (≥ 2 disease/< 2 disease)	0.83	0.61	0.42	1.67
Killip class (≥ Class III/< Class III)	2.22	0.03	1.09	4.52
Creatinine (≥ 1.5 mg/dL/< 1.5 mg/dL)	1.51	0.28	0.71	3.19
Dialysis status (Yes/No)	1.52	0.52	0.42	5.55
Dyslipidemia (Yes/No)	1.09	0.81	0.54	2.20
Hypertension (Yes/No)	1.19	0.66	0.54	2.64
Diabetes (Yes/No)	0.91	0.80	0.45	1.86
Glycoprotein IIb/IIIa inhibitor (Yes/No)	0.72	0.55	0.24	2.11
Aspirin (Yes/No)	3.27	0.25	0.43	24.84
Clopidogrel (Yes/No)	0.68	0.61	0.16	2.95
Renin-angiotensin blocker (Yes/No)	2.12	0.06	0.97	4.63
Statin (Yes/No)	0.58	0.13	0.29	1.18

CI, confidence interval; HR, hazard ratio; PCI, percutaneous coronary intervention.

Table 5. Cox regression (secondary outcome)

Variables	HR	p value	95% C.I. for HR	
			Lower	Upper
Time intervals [h]				
24-72/< 24	0.40	0.005	0.21	0.76
> 72/< 24	0.73	0.28	0.42	1.29
Multi-vessel disease (≥ 2 disease/< 2 disease)	1.08	0.79	0.64	1.82
Killip class (≥ Class III/< Class III)	1.64	0.08	0.94	2.86
Creatinine (≥ 1.5 mg/dL/< 1.5 mg/dL)	0.84	0.59	0.46	1.56
Dialysis status (Yes/No)	0.66	0.57	0.15	2.84
Dyslipidemia (Yes/No)	1.25	0.41	0.74	2.09
Hypertension (Yes/No)	0.65	0.11	0.38	1.10
Diabetes (Yes/No)	0.96	0.88	0.56	1.63
Glycoprotein IIb/IIIa inhibitor (Yes/No)	0.86	0.69	0.40	1.84
Aspirin (Yes/No)	1.09	0.86	0.41	2.91
Clopidogrel (Yes/No)	0.88	0.84	0.26	3.01
Renin-angiotensin blocker (Yes/No)	1.12	0.66	0.67	1.89
Statin (Yes/No)	0.59	0.05	0.35	0.99

CI, confidence interval; HR, hazard ratio.

(Intracoronary Stenting with Antithrombotic Regimen Cooling-Off) studies have shown the benefits of early invasive strategy, especially for high risk patients with elevated cardiac markers.[11-15] TACTICS-TIMI 18 and FRISC II showed a significant reduction in the combined endpoint of death and MI with the routine invasive approach, but no significant mortality benefit. The difference was driven primarily by an excess in MI in the early invasive group. TIMACS (The Timing of Intervention in Patients with Acute Coronary Syndromes) study showed early intervention did not differ greatly from delayed intervention in preventing the death, new myocardial infarction and stroke, but it did reduce the rate of the composite secondary outcome of death, myocardial infarction, or refractory ischemia and was superior to delayed intervention in high-risk patients.[18] According to the latest practice guidelines, the early invasive approach is recommended for high-risk patients with NSTE-ACS.[1-4] However, the optimal timing of intervention remains unclear. However, no confirming data exists indicating whether catheterization should be done early (within 24 hours) or whether it can be delayed while the patient receives medical therapy.

With early invasive management, an early approach may facilitate rapid diagnosis, earlier mechanical revascularization, and shorter hospital stays; but there may also be the potential for early hazard arising from intervention on unstable plaques with fresh thrombus. Conversely, a delayed strategy may provide benefits through plaque passivation by optimal medical treatment followed by intervention on more stable plaques; this potential advantage, however, may be offset by a higher risk for events while waiting for angiography.[9,10]

TIMI risk score is a prevalent and useful tool to estimate patients' prognosis in our daily practice. The TIMI score system facilitates decisionmaking for NSTE-ACS patients.[19-22] From Table 1, it shows that elevated TIMI scores are highly correlated with more cardiac vascular comorbidities and a higher incidence of cardiac events.

From our study, Figure 1C shows PCI in 24-72 hours carries the least primary outcomes. Although there is no significant difference between PCI < 24 hours and 24-72 hours, the trend strongly favors 24-72 hours from symptom onset as the optimum time for administration of PCI in high risk patients. The unplanned revascularization and Killip class $\geq$ 3 are predictors for primary outcomes.

Our results did not favor routine early invasive strategy for low risk patients. PCI < 24 hours carries the worst secondary outcomes, and PCI within 24-72 hours appears most beneficial. In addition, the use of statin is beneficial and can minimize the secondary outcomes.

To review the medications use for our NSTE-ACS patients, we found that the use of Aspirin, Clopidogrel, and ARB was significantly higher for intermediate and high-risk patients than for low risk patients. These drugs may be closely associated with survival and major adverse cardiac outcomes in ACS patients. These may reflect the fact that the process of diagnosing ACS in low risk patients might not be very confirmative, so doctors may hesitate to prescribe dual anti-platelet regimens.

Our study did have several limitations. First, we used a small sample size of patients, and the study was based on registry data, not on randomized control subjects. In our study, we only counted those patients that received PCI. Those who received coronary artery bypass surgery were not included. Besides, we categorize our patients according to the time from symptoms onset to PCI, rather than to diagnostic angiography. These factors may influence our results.

CONCLUSIONS

In our study, for NSTE-ACS patients with high risks, PCI in 24-72 hours from symptom onset is the most ideal time for PCI. Delaying PCI for more than 72 hours carries the worst outcomes and should be avoided. For patients with low risks, routine early PCI < 24 hours is not beneficial and can be harmful.

REFERENCES

1. Ezra AA, Nanette KW, Ralph GB. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/ American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014;64:e139-228.
2. Jacobs AK, Kushner FG, Ettinger SM, et al. ACCF/AHA clinical practice guideline methodology summit report: a report of the American College of Cardiology Foundation/American Heart As-

sociation Task Force on Practice Guidelines. *J Am Coll Cardio* 2013;61:213-65.

3. Jacobs AK, Anderson JL, Halperin JL. The evolution and future of ACC/AHA clinical practice guidelines: a 30-year journey. *J Am Coll Cardiol* 2014;64:1373-84.

4. Arnett DK, Goodman RA, Halperin JL, et al. AHA/ACC/HHS strategies to enhance application of clinical practice guidelines in patients with cardiovascular disease and comorbid conditions: from the American Heart Association, American College of Cardiology, and U.S. Department of Health and Human Services. *J Am Coll Cardiol* 2014;64:1851-6.

5. Cannon CP, Weintraub WS, Demopoulos LA, et al. Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. *N Engl J Med* 2001;344:1879-87.

6. Invasive compared with non-invasive treatment in unstable coronary-artery disease: FRISC II prospective randomized multicenter study. *Lancet* 1999;354:708-15.

7. Fox KA, Poole-Wilson P, Clayton TC, et al. 5-Year outcome of an interventional strategy in non-ST-elevation acute coronary syndrome: the British Heart Foundation RITA 3 randomized trial. *Lancet* 2005;366:914-20.

8. Spacek R, Widimsky P, Straka Z, et al. Value of first day angiography/angioplasty in evolving non-ST segment elevation myocardial infarction: an open multicenter randomized. *Eur Heart J* 2002;23:230-8.

9. Fibrinolytic Therapy Trialists' (FTT) Collaborative Group. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomized trials of more than 1000 patients. *Lancet* 1994;343:311-22.

10. Neumann FJ, Kastrati A, Pogatsa-Murray G, et al. Evaluation of prolonged antithrombotic pretreatment ("cooling-off" strategy) before intervention in patients with unstable coronary syndromes: a randomized controlled trial. *JAMA* 2003;290:1593-9.

11. Becker R, Tracy R, Thompson B, et al. Effects of tissue plasminogen activator and a comparison of early invasive and conservative strategies in unstable angina and non-Q-wave myocardial infarction: Results of the TIMI IIIB trial. *Circulation* 1994; 89:1545-56.

12. Boden WE, O'Rourke RA, Crawford MH, et al. Outcomes in patients with acute on-Q-wave myocardial infarction randomly assigned to an invasive as compared with a conservative management strategy. *N Engl J Med* 1998;338:1785-92.

13. Lagerqvist B, Husted S, Kontny F, et al.The Fast Revascularisation during InStability in Coronary artery disease (FRISC-II) Investigators. Invasive compared with non-invasive treatment in unstable coronary-artery disease: FRISC II prospective: 13-randomized multicentre study. *Lancet* 1999;354:708-15.

14. Cannon CP, Weintraub WS, Demopoulos LA, et al. Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. *N Engl J Med* 2001;344:1879-87.

15. Fox KA, Poole-Wilson PA, Henderson RA, et al. Randomized Intervention Trial of unstable Angina Investigators. Interventional versus conservative treatment for patients with unstable angina or non-ST-elevation myocardial infarction: The British Heart Foundation RITA 3 randomized trial. *Lancet* 2002;360:743-51.

16. Chiang FT, Shyu KG, Wu CJ, et al. Predictors of one-year outcomes in the Taiwan acute coronary syndrome full spectrum registry. *J Formos Med Assoc* 2014;113(11):794-802.

17. Shyu KG, Wu CJ, Mar GY, et al. Clinical characteristics, management and in-hospital outcomes of patients with acute coronary syndrome-observation from the Taiwan ACS full spectrum registry. *Acta Cardio Sin* 2011;27:135-44.

18. Shamir RM, Christopher BG, William EB, et al. Early versus delayed invasive intervention in acute coronary syndromes. *N Engl J Med* 2009;360:2165-75.

19. Elliott MA, Marc C, Peter JLMB. The TIMI risk score for unstable angina/non-ST elevation myocardial infarction: a method for prognostication and therapeutic decision making. *JAMA* 2000; 284:835-42.

20. An SG, Park TI, Lee SH, et al. Prognosis according to the timing of percutaneous coronary intervention in an acute non-ST segment elevation myocardial infarction. *Korean Circ J* 2008;38:23-8.

21. Al-Mallah MH, Hatahet H, Cavalcante JL, Khanal S. Low admission LDL-cholesterol is associated with increased 3-year all-cause mortality in patients with non ST segment elevation myocardial infarction. *Cardiol J* 2009;16:227-33.

22. Dziewierz A, Siudak Z, Rakowski T, et al. Prognostic significance of new onset atrial fibrillation in acute coronary syndrome patients treated conservatively. *Cardiol J* 2010;17:57-64.