ORIGINAL ARTICLE

Prognosis according to the timing of percutaneous coronary intervention in non-ST segment elevation myocardial infarction, based on the Korean Acute Myocardial Infarction Registry (KAMIR)

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Abstract

Background: *Patients with acute coronary syndrome without ST-segment elevation (ACS--NSTE) are at risk for adverse cardiac events. Based on data in the Korean Acute Myocardial Infarction Registry (KAMIR), we analyzed the prognosis according to the timing of percutaneous coronary intervention (PCI) in patients with NSTEMI in Korea.*

Methods and results: *2,455 patients with NSTEMI in KAMIR were classified according to the time interval from the onset of cardiac symptoms to PCI. Patients in Group I underwent PCI within 24 hours of the onset of symptoms; in Group II between 24 and 48 hours; and in Group III after 48 hours. Major adverse cardiac events (MACEs) are defined as cardiac death, non-cardiac death, myocardial infarction, revascularization and coronary-artery bypass graft surgery. The MACEs were compared between groups. Of the 2,455 patients, 743 (30.2%) were assigned to Group I, 583 (23.7%) to Group II, and 1,129 (45.9%) to Group III. The total incidence of MACEs was higher in Group I than Group III, and similar between Groups I and II (Group I: 15.1%, Group II: 14.4%, Group III: 11.6%, p = 0.053). The incidence of MACEs in the intermediate TIMI risk score group had decreased as the intervention time was delayed.*

Conclusions: *The prognosis according to the timing of PCI in patients with NSTEMI was similar based on the data in KAMIR. TIMI risk score was related to a high incidence of MACEs.* (Cardiol J 2011; 18, 4: 421–429)

Key words: myocardial infarction, percutaneous transluminal angioplasty, early intervention

Introduction

Patients with acute coronary syndrome without ST-segment elevation (ACS-NSTE) are at risk for adverse cardiac events [1]. There have been five large randomized trials: VANQWISH, FRISC II, TACTICS-TIMI 18, TIMI IIIB, and RITA-3. A routine early invasive strategy of early angiography

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followed by revascularization was compared to a conservative strategy of angiography and subsequent revascularization only if medical therapy failed, or if substantial residual ischemia was documented [2–6].

An early invasive strategy was shown to be beneficial in the FRISC II, TACTICS-TIMI 18, and RITA-3 studies, especially in high risk subgroups of patients with an elevated cardiac troponin level. As a result, the latest guidelines from the American College of Cardiology-American Heart Association and the European Society of Cardiology recommend an early invasive approach in high-risk patients with ACS-NSTE [7, 8].

According to the TIMACS investigators, an early invasive strategy in patients with ACS-NSTE did not differ much from a delayed invasive strategy in preventing death, myocardial infarction (MI), or stroke at six months [9]. Another trial from the ICTUS investigators showed that a selective invasive strategy in patients with ACS-NSTE and elevated cardiac troponin produced similar rates of death or MI compared to routine early invasive strategy. And there was no benefit associated with early invasive strategy, even after patients were stratified into low-, medium-, and high-risk groups according to the FRISC risk score [10]. Neumann et al. [11] reported that the early invasive group of patients with ACS-NSTE showed reduced MI and death at 30 days compared to the delayed invasive group after prolonged anti-thrombotic pretreatment.

Thus, the question of when to perform percutaneous coronary intervention (PCI) in patients with non-ST segment elevation myocardial infarction (NSTEMI) has not yet been definitively answered. Clinical trials comparing the early invasive versus the delayed invasive strategy in patients with NSTEMI in Korea have been limited. Based on the data in the Korean Acute Myocardial Infarction Registry (KAMIR), we decided to analyze the prognosis according to the timing of PCI in patients with NSTEMI in Korea.

Methods

Study population and study design

This study was based on 2,455 patients with NSTEMI whose details were in the KAMIR between October 2005 and February 2008, gathered from 40 hospitals in Korea. These hospitals were high-volume centers with facilities for PCI and on-site cardiac surgery. Eligible patients met all three of the following criteria: 1) symptoms of ischemia that were increasing or occurred at rest; 2) an elevated cardiac troponin I level (≥ 0.07 ng/mL); 3) ischemic changes as documented by electrocardiography (ECG), or a documented history of coronary artery disease (CAD).

Optimal medical treatment

The patients received 200 to 300 mg of aspirin at the time of admission, and this was followed by at least 100 mg aspirin daily for an indefinite period; 300 to 600 mg of clopidogrel was also immediately given, with 75 mg clopidogrel daily thereafter. The doses of aspirin and clopidogrel varied among the hospitals; 200 mg of cilostazol was selectively given daily. Angiotensin converting enzyme inhibitor, angiotensin receptor blocker, glycoprotein IIb/IIIa inhibitor (abciximab and tirofiban), statin, unfractionated heparin, low molecular weight heparin and beta-blocker were administered according to the attending doctor's decision.

Treatment strategy

Patients with NSTEMI were classified according to the time interval from the onset of cardiac symptoms to PCI. Patients in Group I underwent PCI within 24 hours of the onset of symptoms, Group II between 24 and 48 hours, and Group III after 48 hours. All patients with NSTEMI were eventually treated with PCI.

Clinical outcomes

The clinical outcomes were evaluated based on major adverse cardiac events (MACEs) during the follow-up period. These comprise cardiac death, non-cardiac death, MI, revascularization and coronary-artery bypass graft surgery. The MACEs were compared between groups. MI is defined as documented myocardial necrosis, such as the elevation of myocardial enzymes or the occurrence of ECG evidence of a new Q wave. Revascularization is defined as repeated PCI during the follow-up period including target-vessel revascularization or target-lesion revascularization. Coronary-artery bypass surgery is defined as open heart surgery for any reason.

Risk stratification using TIMI risk score

The seven TIMI risk score predictor variables were: age 65 years or older; at least three risk factors for CAD; prior coronary stenosis of 50% or more; ST-segment deviation on ECG at presentation; at least two anginal events in prior 24 hours; use of aspirin in prior seven days; and elevated serum cardiac markers. The patients were classified

into three groups according to their TIMI score. The Low group had a TIMI risk score of 2 or below, the Intermediate group had a TIMI risk score of between 3 and 4, and the High group had a score of 5 or above. We analyzed each group in its relations between incidence of MACEs and PCI-time interval.

The study was approved by the local bioethical committee and all patients gave their informed consent.

Statistical analysis

Continuous variables with normal distributions were expressed as means ± standard deviation and compared with the use of an ANOVA. Categorical variables were compared with the use of the χ^2 test. The authors performed statistical analysis to find out the relation between the timing of intervention and cardiac events. Multiple variables affecting the incidence of cardiac events were identified using univariate Cox regression analysis. The incidence of cardiac events between groups was calculated using multivariate Cox regression analysis. A p value of less than 0.05 was deemed statistically significant. All statistical analysis was done using Statistical Package for Social Sciences software (SPSS 17.0 for Windows).

Results

Baseline characteristics

Of the total of 2,455 patients, 743 (30.2%) patients were assigned to Group I, 583 (23.7%) to Group II, and 1,129 (45.9%) to Group III. Baseline characteristics are listed in Tables 1 and 2. Age, sex, risk factor, and angiographic characteristics were all similar among the three groups. There were no differences of medication among the three groups except glycoprotein IIb/IIIa inhibitor, which was used more in Groups I and II than in Group III (Group I: 14.8%, Group II: 13.4%, Group III: 10.5%, p = 0.018). Regarding the Killip class, Group III was higher than Group I (Killip class I, II — Group I: 67.0% *vs* Group II: 58.6%, Killip class III, IV — 3.1% *vs* 7.5% respectively). The level of pro-brain natriuretic peptide (BNP) was higher in Group III than Group I (Group I: 1,790 pg/mL, Group III: 2,945 pg//mL, p < 0.01). Cardiac marker, peak level of troponin I and creatine kinase (CK)-MB had a higher serum level in Group I than Group III (peak CK--MB: 134 μg/L *vs* 53.5 μg/L, troponin I: 34.7 ng/mL *vs* 18.2 ng/mL respectively, p < 0.01). The overall incidence of procedure-related complication was higher in Group I compared to Group III (9.2% in Group I, 7.1% in Group III, p < 0.01). Considering

Killip class, pro-BNP, and peak cardiac enzyme, group I was probably higher than Group III. But mean TIMI risk scores were statistically no different among the three groups (Group I: 2.15 ± 1.15, Group II: 2.20 ± 1.17, Group III: 2.27 ± 1.18, p = 0.094). Mean time intervals from symptom onset to PCI were 11.9 ± 6.5 h in Group I, 33.6 ± 6.8 h in Group II, and 136.8 ± 212 h in Group III (p < 0.01).

Clinical outcomes

The incidence of MACEs during the follow-up period is shown in Table 3. Total median follow-up period was 338 days, i.e. nearly one year. In Group I, the median follow-up period was 328 days, similar to the 345 days in Group III. A total of 329 patients experienced major adverse cardiac events. The total incidence of MACEs was higher in Group I than in Group III and similar between Groups I and II (Group I: 113/743, 15.1%; Group II: 83/583, 14.4%; Group III: 132/1129, 11.6%, p = 0.053). By using uni- and multivariate analysis, we found that Group I had a higher incidence of MACEs than Group III, and this difference was statistically significant (p = 0.008, multivariable adjusted hazard ratio [HR] 0.551, 95% confidence interval [CI] 0.351–0.865). Group II had a lower incidence of MACEs than Group I, but without statistical significance: p = 0.18, multivariable adjusted HR 0.74, 95% CI 0.436–1.256 (Table 4). Further factors potential influencing the incidence of MACEs were the presence of procedure-related complications (HR 2.335, 95% CI 1.45–3.77), cases of multi-vessel disease (HR 2.157, 95% CI 1.36–3.43), and the use of glycoprotein IIb/IIIa inhibitors (abciximab, tirofiban) (HR 1.761, 95% CI 1.27–2.43) (Table 4). We analyzed cardiac death and MI according to PCI timing, and found the risk of cardiac death and MI was similar among the three groups (Fig. 1)

Risk stratification by TIMI risk score

The TIMI risk scores between the three groups are set out in Table 5 as well as mean TIMI risk score between the groups. Patients who had delayed invasive intervention had a higher TIMI risk score than patients who had early invasive intervention, but the difference was statistically insignificant (Group I: 2.15 ± 1.15, Group II: 2.20 ± ± 1.17, Group III: 2.27 ± 1.18, p = 0.094). There were no differences in the proportion of TIMI risk among the three groups. The higher the TIMI risk score, the higher the incidence of MACE (analysis between the groups of Low and High TIMI risk score, HR 1.824, 95% CI 1.03–3.21). The TIMI risk scores from each group show that the incidence of MACE

Table 1. Baseline characteristics of patients.

	Group I n = 743 (30.2%)	Group II n = 583 (23.7%)	Group III n = 1,129 (45.9%)	P
Demographic characteristics:				
Age (years ± STD)	64.8 ± 13	65.5 ± 12	66.7 ± 12	0.004
Male (%)	563 (71.2)	425 (67.4)	794 (66.6)	0.09
Medical history (n, %):				
Diabetes	215 (27.2)	198 (31.4)	404 (33.9)	0.03
Hypertension	389 (49.2)	335 (53.2)	654 (54.9)	0.15
History of IHD	150 (19)	118 (18.7)	236 (19.8)	0.82
Dyslipidemia	97 (12.3)	96 (15.2)	158 (13.3)	0.10
Family Hx of IHD	57 (7.3)	63 (10)	74 (6.2)	0.05
Medical conditions (n, %):				
Chest pain	617 (83)	452 (77.5)	886 (78.5)	0.003
Dyspnea	149 (20.1)	139 (23.8)	304 (26.9)	0.004
Resuscitation prior to arrival	7 (0.9)	3 (0.5)	7 (0.6)	0.6
Previous angina before MI	412 (55.5)	356 (61.1)	596 (52.8)	0.005
Killip stage (n, %):				
Stage III	16 (2.2)	19 (3.3)	71 (6.3)	0.012
Stage IV	7 (0.9)	2 (0.3)	14 (1.2)	0.045
Laboratory test (mean ± STD):				
Glucose [mg/dL]	163 ± 75	153 ± 70	162 ± 85	0.026
Pro-BNP [pg/mL]	1,878 ± 4,918	2,392 ± 6,533	2,919 ± 6,038	0.009
Creatinine [mg/dL]	0.67 ± 0.87	0.62 ± 1.2	0.81 ± 1.7	0.015
CRP [mg/dL]	18.2 ± 84	13.7 ± 63	18.7 ± 96	0.57
Creatine kinase-MB [μg/L]	134.8 ± 391	80.1 ± 394	53.5 ± 80	0.00
Troponin I [ng/mL]	34.7 ± 64	20.8 ± 39	18.2 ± 46	0.00
Medication (n, %):				
Aspirin	702 (94.5)	548 (94.0)	1,061 (93.9)	0.265
Clopidogrel	681 (91.7)	536 (92.0)	1,043 (92.4)	0.281
Cilostazol	226 (30.4)	144 (24.7)	260 (23.0)	0.00
Statin	547 (73.6)	426 (73.1)	824 (72.9)	0.112
Beta-blocker	520 (69.9)	408 (70.0)	785 (69.5)	0.702
ACEI	444 (59.8)	342 (58.7)	643 (57.0)	0.412
ARB	145 (19.5)	103 (17.7)	190 (16.8)	0.045
Glycoprotein IIb/IIIa inhibitor	110 (14.8)	79 (13.4)	118 (10.5)	0.018

IHD — ischemic heart disease; MI — myocardial infarction; BNP — brain natriuretic peptide; CRP — C-reactive protein; ACEI — angiotension converting enzyme inhibitor; ARB — angiotension receptor blocker

Table 2. Coronary angiographic characteristics.

	Group I n = 743 (30.2%)	Group II n = 583 (23.7%)	Group III n = 1,129 (45.9%)	P
Extent of coronary disease (n, %):				
1-vessel disease	328 (41.5)	235 (37.2)	443 (37.2)	0.12
2-vessel disease	226 (28.6)	224 (35.5)	382 (32.1)	0.02
3-vessel disease	213 (26.9)	150 (23.8)	316 (26.5)	0.34
Left main	24 (3)	22 (3.5)	50 (4.2)	0.39
Target vessel (n, %):				
LAD	319 (40.3)	246 (39)	503 (42.2)	0.39
LCx	235 (29.7)	203 (32.2)	318 (26.7)	0.41
RCA	217 (27.4)	168 (26.6)	331 (27.8)	0.87
Left main	20 (2.5)	14 (2.2)	40 (3.4)	0.31
Time interval from symptom to PCI [h]	11.9 ± 6.5	33.6 ± 6.8	136.8 ± 212	0.00
Glycoprotein IIb/IIIa inhibitor (n, %):	110 (14.8)	79 (13.4)	118 (10.5)	0.018

LAD — left anterior descending; LCx — circumflex; RCA — right coronary artery; PCI — percutaneous coronary intervention

Table 3. Incidence of major adverse cardiac events during follow-up period.

	Group I n = 743 (30.2%)	Group II n = 583 (23.7%)	Group III n = 1,129 (45.9%)	P
Overall incidence of MACE	113 (15.1%)	83 (14.2%)	132 (11.6%)	0.053
Cardiac death	28 (3.8%)	16 (2.7%)	26 (2.3%)	0.173
Non-cardiac death	16 (2.2%)	8 (1.4%)	15 (1.3%)	0.336
Non-fatal myocardial infarction	6 (0.8%)	7 (1.2%)	13 (1.2%)	0.722
Re-PCI	59 (7.9%)	49 (8.4%)	75 (6.6%)	0.351
Coronary artery bypass grafting	4 (0.5%)	3 (0.5%)	3 (0.3%)	0.595

MACE — major adverse cardiac events; re-PCI — repeat revascularization of stenotic lesion; Non-cardiac death — death not by cardiac origin; Cardiac death — death by cardiac origin

Table 4. Factors influencing major adverse cardiac events by multi-variate analysis.

Variables	Hazard ratio	Confidence interval
Time interval [h]		
24–47.9	0.740	0.436–1.256
≥ 48	0.551	0.351–0.865
PCI-related complications (+)	2.335	1.45–3.77
Multi-vessel coronary arteries	2.157	1.36–3.43
Glycoprotein IIb/IIIa inhibitor (+)	1.761	1.27–2.43
Glucose ≥ 200 mg/dL	1.287	0.79–2.09
Creatinine ≥ 1.5 mg/dL	0.774	0.36–1.65
Diabetes	1.045	0.65–1.68
Killip stage III, IV	1.163	0.66–2.06

PCI — percutaneous coronary intervention

Time intervals [h]	HR/CI	P
24–47.9	0.98/0.398–2.414	0.965
Over 48	0.80/0.394–1.624	0.537

HR — hazard ratio; CI — confidence interval

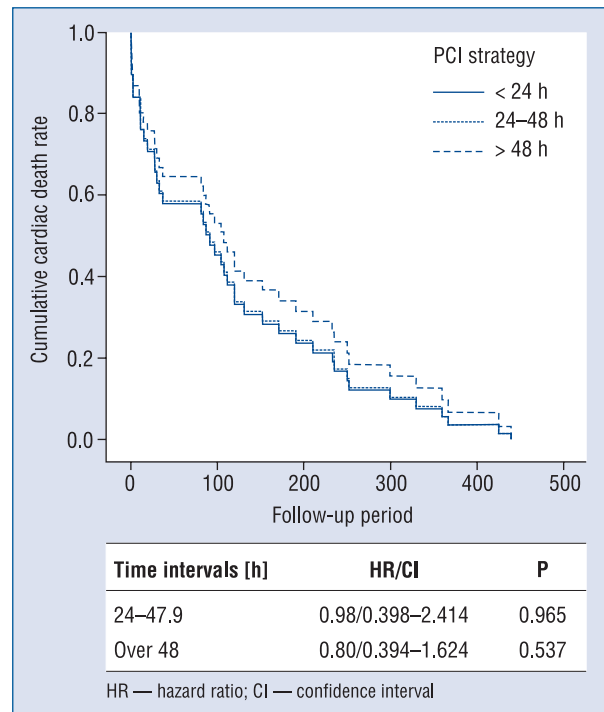**Figure 1.** Analysis and cumulative cardiac death and myocardial infarction rate; PCI — percutaneous coronary intervention.

is related to the time interval from symptom onset to PCI. Results acquired from the group of Low TIMI risk score show there was increased incidence of MACE from Group I to Group III, but without statistical significance.

In the group of intermediate TIMI risk score, there was decreased incidence of MACE from Group I to Group III (HR 0.446, 95% CI 0.29––0.69).
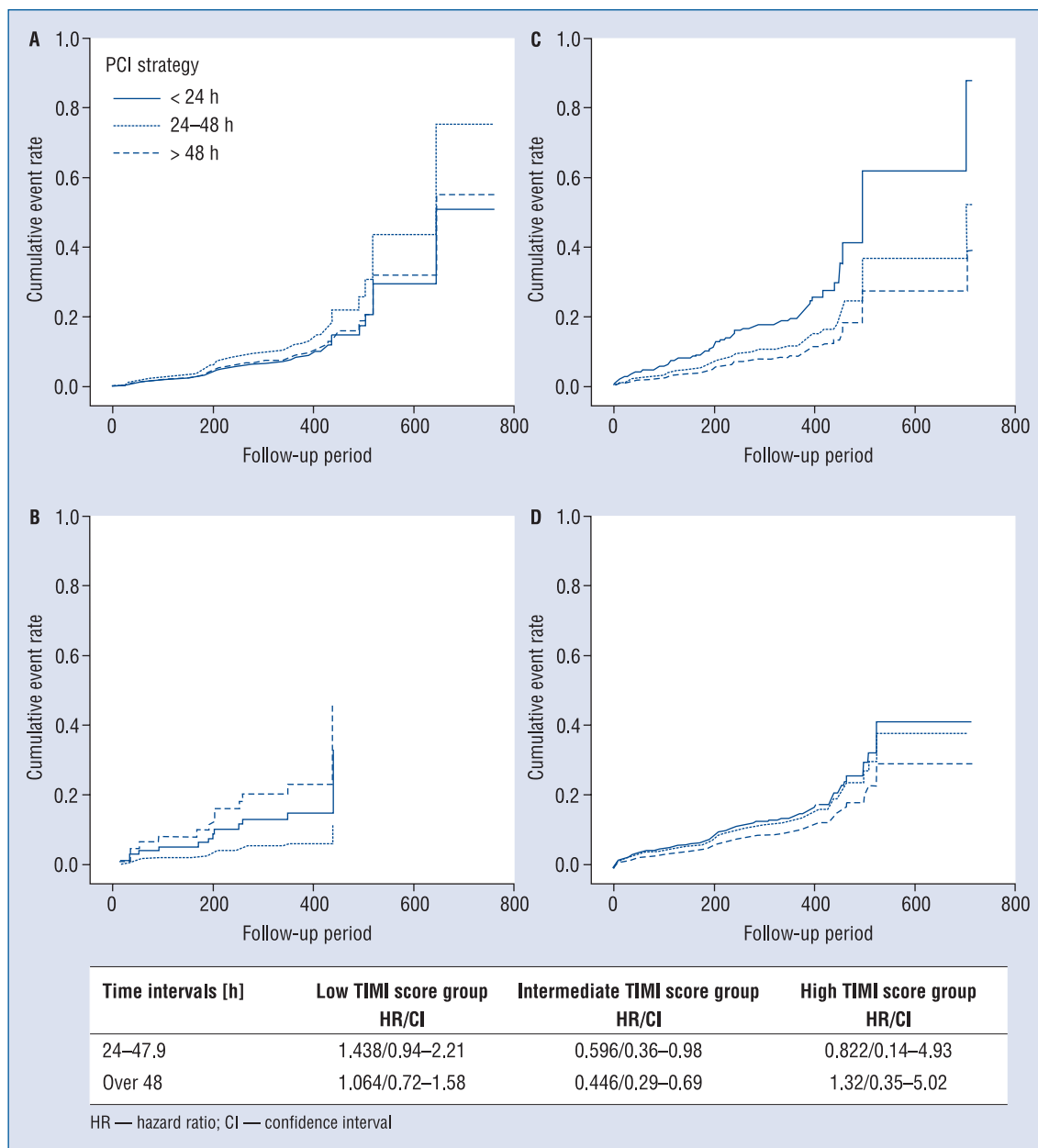
In the group of high TIMI risk score, as the procedure was delayed, there was a higher incidence of MACE, but with no statistical significance (HR 1.32, 95% CI 0.35–5.02) (Fig. 2).

Table 5. TIMI risk score.

	Group I n = 743 (30.2%)	Group II n = 583 (23.7%)	Group III n = 1,129 (45.9%)	P
Low risk (1–2)	495 (66.6%)	370 (63.5%)	692 (61.3%)	0.064
Intermediate risk (3–4)	225 (30.3%)	199 (34.1%)	393 (34.8%)	0.112
High risk (5–7)	23 (3.1%)	14 (2.4%)	44 (3.9%)	0.242
Mean TIMI risk score	2.15 ± 1.15	2.20 ± 1.17	2.27 ± 1.18	0.094

Time intervals [h]	Low TIMI score group HR/CI	Intermediate TIMI score group HR/CI	High TIMI score group HR/CI
24–47.9	1.438/0.94–2.21	0.596/0.36–0.98	0.822/0.14–4.93
Over 48	1.064/0.72–1.58	0.446/0.29–0.69	1.32/0.35–5.02

HR — hazard ratio; CI — confidence interval

Figure 2. Analysis and cumulative events rate of TIMI risk groups; **A**. Low TIMI risk group; **B**. High TIMI risk group; **C**. Intermediate TIMI risk group; **D**. All patients TIMI risk group; PCI — percutaneous coronary intervention.

Discussion

Many recent studies have shown that a selective invasive strategy after conservative treatment obtains better results in the low ACS-NSTE risk group, but an early invasive strategy is recommended in the high risk ACS-NSTE group [8, 12]. An early invasive strategy was shown to be beneficial compared to a conservative strategy in the FRISC II, TACTICS-TIMI 18, and RITA-3 studies, especially in high risk subgroups of patients with an ele-

vated cardiac troponin level. As a result, the latest guidelines of the American College of Cardiology-American Heart Association and the European Society of Cardiology recommend an early invasive approach in high-risk patients with ACS-NSTE [7, 8]. An early invasive strategy is indicated in ACS-NSTE patients who have refractory angina or hemodynamic or electrical instability and who have an elevated risk for clinical events.

The optimal PCI time in patients with NSTEMI remains controversial. In the TIMACS study,

3,031 patients with ACS underwent either routine early intervention (coronary angiography ≤ 24 h after randomization) or delayed intervention (coronary angiography ≥ 36 h after randomization). At six months, death, MI, or stroke had occurred in 9.6% of patients in the early-intervention group, compared to 11.3% in the delayed intervention group. Early intervention did not differ greatly from delayed intervention in preventing death, MI, or stroke [9]. Another trial by the ICTUS investigators showed that routine early invasive strategy in patients with ACS-NSTE and an elevated cardiac troponin produced similar rates of death or MI over the course of four years compared to selective invasive strategy, where catheterization was done if the patient had refractory angina or recurrent ischemia. And there was no benefit associated with an early invasive strategy, even after patients were stratified into low-, medium-, and high-risk groups according to the FRISC risk score [10]. Neumann et al. [11] reported that the early invasive group of patients with ACS-NSTE showed reduced MI and death over the course of 30 days compared to the delayed invasive group after prolonged anti-thrombotic pretreatment. Mean time intervals from symptom onset to PCI were 2.4 hours in the early invasive group, and 86 hours in the delayed invasive group. The weak point of this study is the 30 day short-term follow-up.

Our study did not show that an early invasive strategy was a superior clinical outcome to a delayed invasive strategy in patients who had an NSTEMI who had an elevated cardiac troponin I level. The incidence of follow-up cardiac events in Group I was significantly higher than in other groups. The incidence of cardiac events between Group II and Group III did not show statistical significance, but there were numerically fewer in Group III. Peak CK-MB and troponin-I were high in our study compared to other studies (peak CK-MB: 134 μg/L in Group I, 53.5 μg/L in Group III, troponin I: 34.7 ng/mL in Group I *vs* 18.2 ng/mL in Group III). Killip class was also higher in Group I compared to Group III. These results meant that we performed early intervention, because the risk of cardiovascular events had been higher in Group I than Group III.

Other variables affected the incidence of cardiac events, including PCI-related complications, multi-vessel CAD, and the use of glycoprotein IIb/IIIa inhibitors. There might be evidence of risk associated with early invasive intervention, and obviously the complication rate was higher than the delayed invasive intervention. But, we consider that the risk of cardiovascular events is high in Group I.

There were relatively high TIMI scores in patients with a delayed invasive strategy. But the TIMI risk scores between the patients did not differ greatly, and were not statistically significant. Although meta-analyses of previous randomized trials that compared an invasive strategy to a conservative strategy in patients with ACS-NSTE have shown a benefit for an invasive strategy [13, 14], the timing of intervention in the invasive management group of these previous studies ranged from as early as 2.4 hours after randomization in one large trial, to as late as 96 hours in another large trial [2–6, 11, 15]. Given this wide variation in the timing of intervention, there remains substantial uncertainty regarding the optimal timing for intervention in patients with NSTEMI [13]. After analyzing our figures about the optimal timing of intervention, delayed intervention may not be inferior to early intervention because fewer cardiac events occurred. It remains difficult to ascertain the optimal timing of intervention in patients with NSTEMI. The main benefit of an early invasive strategy is the prevention of cardiac events over a longer period of time. Unfortunately, this treatment is associated with an increase in periprocedural events [16]. The time–event relationship in patients with NSTEMI in the early invasive management could be that of a U-shaped curve: sufficient time is needed to allow pharmacological stabilization of plaque [11]. The early hazard seen in the early invasive strategy in older studies appeared still valid and could not be adequately prevented by the use of extensive pharmacological anti-thrombotic and antiplatelet regimens. Conceivably, medical pretreatment for at least 24 hours might considerably decrease the risk of intervention [17]. The early invasive group had fewer pharmacological benefits than the delayed invasive group. In our study, procedure-related complications were higher in Group I than in the other groups. And Group I showed a higher incidence of cardiac events because of procedure-related complications.

In patients with NSTEMI, TIMI risk score is a simple prognostic way of categorizing a patient's risk of death and ischemic events, and provides a basis for therapeutic decision-making [18–21]. According to our study, the higher the TIMI score, the higher the incidence of cardiac events. We failed to prove this proposal, but as can be seen from the results, there is a tendency linking delayed procedure to more frequent cardiac events. The number of patients in the group of high TIMI risk scorewas only 82. Further clinical analysis on a larger population might be required in order to acquire satisfactory results.

Limitations of the study

A limitation of our study was that even with a large sample size of more than 2,000 patients, the trial was simply based on registry data, not on randomized control subjects. As can be seen in the baseline characteristics, the patients in Group I had greater cardiovascular risk compared to Group III. The patients in Group I were confronted with a higher risk for intervention. These circumstances may have led to higher mortality and morbidity in Group I. There was limited data to estimate cardiac function, which represents a further prognosis of patients in MI.

Conclusions

The incidence of MACE in patients with NSTEMI presented an insignificant difference according to the timing of PCI based on the data in KAMIR. The clinical outcome of PCI in patients with NSTEMI seems irrelevant to the timing of PCI. TIMI risk score was related to a high incidence of MACE.

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