

In-Hospital Outcome According to the Initial Management and the “Thrombolysis in Myocardial Infarction Risk Score” of Acute Non-ST Segment Elevation Myocardial Infarction

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ABSTRACT

Background and Objectives: The current guidelines recommend an early invasive strategy for patients suffering with non-ST segment elevation myocardial infarction (NSTEMI). However, there is still debate about the timing of revascularization in patients with NSTEMI. To analyze the clinical efficacy of the timing of revascularization, we compared the in-hospital clinical outcome of NSTEMI patients from the Korea Acute Myocardial Infarction Registry (KAMIR) between the early and selective invasive therapeutic groups. **Subjects and Methods:** Between Nov. 2005 and Apr. 2007, 2762 acute NSTEMI patients (mean age=64.6±12.8 years, 1847 males) were enrolled in the KAMIR. The therapeutic strategy of NSTEMI was categorized into early invasive treatment (within 48 hours, Group I mean age: 63.1±13.1 years, 1085 males) and selective invasive treatment (Group II mean age: 66.5±12.1 years, 762 males). The initial clinical status and the in-hospital mortality and morbidity rate were compared between these two groups. The in-hospital outcomes were also compared between the two groups according to each level of the Thrombolysis In Myocardial Infarction (TIMI) risk score. **Results:** There were significant differences in the mortality and morbidity rate between the groups (6.5% vs. 10.3%, respectively, $p<0.001$). According to TIMI risk score, there were no significant differences of mortality and morbidity for the low to moderate risk patients (5.3% vs. 7.8%, respectively, $p=0.123$ for the risk score 0-2, 6.4% vs. 8.7%, $p=0.139$ for the risk score 3-4). **Conclusion:** Early invasive treatment improves the hospital outcome for the high-risk NSTEMI patients. The use of abciximab, a low ejection fraction, a high Killip class, a high TIMI risk score and old age are the predictive factors of in-hospital mortality and morbidity. (**Korean Circ J 2007;37:550-558**)

KEY WORDS: Myocardial infarction ; Angioplasty ; Thrombolytic therapy ; Prognosis.

Introduction

More than half of all acute myocardial infarctions in the United States each year are classified as non-ST elevation myocardial infarction (NSTEMI),¹⁾ and the proportion of NSTEMI is rising in Korea as well. Patients with NSTEMI are at risk for adverse cardiac events,²⁾ and so the initial treatment of NSTEMI is very important.

However, there is still debate about the timing of revascularization in NSTEMI patients.

Some large randomized trials that compared an “early invasive” strategy (early angiography followed by revascularization, depending on the angiographic findings) with a “conservative” strategy (perform angiography and then subsequent revascularization only if medical therapy has failed or if substantial residual ischemia has been documented).

The recent guidelines of the American College of the Cardiology-American Heart Association and the European Society of Cardiology recommended an early invasive approach for high-risk patients who suffer with acute coronary syndromes without ST-segment elevation.^{3,4)} Despite these recommendations, it is not clear that an early invasive strategy reduces the mortality, and

Received: July 6, 2007

Revision Received: August 1, 2007

Accepted: August 3, 2007

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the recent ICTUS trial did not show superiority of an early invasive strategy for NSTEMI patients at the 1-year and 4-year clinical follow-up.^{5,6)} Moreover, such recent advances in medical therapy as the early use of clopidogrel and intensive lipid-lowering therapy have been shown to improve the prognosis for patients suffering with acute coronary syndromes.^{7,8)}

Therefore, we conducted the present study to analyze the clinical efficacy of the timing of revascularization and to test the hypothesis that an early invasive strategy is superior to a selectively invasive strategy for treating the NSTEMI patients who are registered in the KAMIR. We compared the in-hospital clinical outcome of NSTEMI patients between the early and selective invasive therapeutic groups, and these 2 groups of cases were taken from the KAMIR.

Subjects and Methods

Study population and study design

Between November 2005 and April 2007, 2762 NSTEMI patients (mean age: 64.6 ± 12.8 years, 1847 males) were enrolled from 40 hospitals; these hospitals were high-volume centers with facilities for percutaneous coronary intervention and on-site cardiac surgery, and these hospitals were included in the KAMIR.

The eligible patients had to have all three of the following: 1) symptoms of ischemia that were increasing or they occurred at rest, 2) an elevated cardiac troponin I level (≥ 2.0 ng/mL) and an elevated CK-MB level (19 U/L, exceeding twice the upper limit of normal) and 3) ischemic changes as assessed by electrocardiography (these were defined as ST-segment depression or T-wave inversion of ≥ 0.2 mV in two contiguous leads).

We analyzed the age, gender, the body mass index, the risk factors for coronary artery disease (hypertension, diabetes, smoking, hyperlipidemia and a family and/or past history of ischemic heart disease) of both groups. In addition, the symptoms of chest pain and dyspnea, the blood pressure and the Killip class were evaluated at admission. Blood chemistry tests (cardiac enzymes, lipid profiles and Pro-B-type N-terminal natriuretic peptide), electrocardiography and echocardiography were performed for all the patients, and we calculate the Thrombolysis In Myocardial Infarction (TIMI) risk score⁹⁾ for each patient.

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 immediately and this was followed by 75 mg clopidogrel daily (the dose of aspirin and clopidogrel was variable among the hospitals), and/or 200 mg of cilostazol daily. Angiotensin converting enzyme inhibitor, angiotensin receptor blocker, glycoprotein IIb/IIIa inhibitor (Abciximab and Tirofiban), statin, unfractionated heparin, low molecular weighted heparin and

beta blocker were administered according to the attending doctor's decision.

Treatment strategy

The patients who were assigned to the early invasive strategy group (Group I: 63.1 ± 13.1 years, 1085 males) were scheduled to undergo angiography via the radial or femoral approach within 48 hours after hospitalization and then percutaneous coronary intervention when appropriate; the decision to perform percutaneous coronary intervention was based on the coronary anatomy. The patients who were assigned to the selectively invasive strategy group (Group II: 66.5 ± 12.1 years, 762 males) were treated medically. These patients were scheduled to undergo angiography and subsequent revascularization only if they had refractory angina despite optimal medical treatment, and they also had hemodynamic or rhythmic instability.

Primary end points

The primary end point was a composite of in-hospital death and the complications. Death was defined as death from any cause. Cardiogenic shock, ventricular tachycardia and fibrillation (the need for an anti-arrhythmic agent and/or defibrillation), atrioventricular block (the need for a pacemaker), recurrent ischemia and myocardial infarction, cerebrovascular accident, major bleeding, acute renal failure, multi organ failure and sepsis were included as complications. The in hospital mortality and morbidity rates were compared between both groups and then for each of the groups that were divided by the TIMI risk score.

Statistical analysis

Continuous variables with normal distributions were expressed as means \pm SD and they were compared with the use of an unpaired Student's t-test. Categorical variables were compared with the use of the chi-square test, where appropriate. The relative risks were calculated by dividing the Kaplan-Meier estimated rate of an event in the early-invasive strategy group by that of the selectively invasive strategy group. The 95 percent confidence interval for the relative risk was calculated with the use of the standard errors from the Kaplan-Meier curve. The predictive factors for in hospital mortality were calculated by multiple logistic regression analysis. A p less than 0.05 was deemed as significant. Statistical analysis was done with the Statistical Package for Social Sciences software (SPSS 12.0 for Windows).

Results

Clinical characteristics of the study population

A total of 2762 patients with NSTEMI were enrolled in the KAMI registry between November 2005 and April

2007; there were 1561 early invasive treatment strategy patients and 1201 selective invasive strategy patients. The baseline clinical characteristics of the study population were well matched between the two strategy groups (Table 1). The mean age was 63.2 years and 66.5 years, 70.0% and 63.4% were males and the body mass index was 25.0 and 24.4 in group I and group II, respectively. No significant differences were noted between both groups.

The risk factors for coronary artery disease were eva-

luated. There were more smokers and patients with a family history of ischemic heart disease in group I, and there was more diabetes and a more frequent history of ischemic heart disease in group II. There no significant differences in hypertension and hyperlipidemia between both groups (Table 1).

The symptoms and hemodynamic status at admission

The symptom to door time was 1783.3 ± 690.9 minutes

Table 1. Baseline clinical characteristics and hemodynamics

	Group I (n=1561)	Group II (n=1201)	p
Age (years)	63.2 ± 13.1	66.5 ± 12.1	0.333
Male (%)	1085 (70.0)	762 (63.4)	0.083
Body mass index (kg/m ²)	25.0 ± 12.7	24.4 ± 14.5	0.441
Risk factor (%)			
Hypertension	818 (52.4)	662 (55.1)	0.073
Diabetes mellitus	437 (28.0)	436 (36.3)	<0.001
Smoking	885 (56.7)	590 (49.1)	<0.001
Hyperlipidemia	190 (12.2)	132 (10.1)	0.379
Family history	119 (7.6)	54 (4.5)	0.001
Previous IHD history	296 (19.0)	287 (23.9)	0.001
Symptom to door time (min)	1783.3 ± 690.9	1412.2 ± 422.2	0.116
Chest pain (%)	1274 (81.6)	914 (76.1)	0.005
Dyspnea (%)	374 (24.0)	407 (33.9)	<0.001
SBP (mmHg)	133.5 ± 26.4	134.3 ± 28.8	0.453
Killip class	1.2 ± 0.6	1.5 ± 0.8	<0.001
TIMI risk score	3.2 ± 1.5	3.3 ± 1.5	0.283
Electrocardiogram findings at admission (%)			
Within normal limit	537 (34.4)	325 (27.1)	<0.001
ST segment depression	594 (38.1)	525 (43.7)	0.003
T wave inversion	485 (31.1)	408 (34.0)	0.120
Left bundle branch block	16 (0.1)	8 (0.1)	0.310
Atrioventricular block	22 (1.4)	25 (2.1)	0.179
Atrial fibrillation	60 (3.8)	47 (3.9)	0.196
Ventricular fibrillation	6 (0.0)	3 (0.0)	0.535
Echocardiogram findings			
Left ventricular EF (%)	56.7 ± 28.8	52.7 ± 26.6	0.108
Total wall motion score	17.4 ± 10.0	19.7 ± 10.4	0.279
Laboratory findings			
Creatine kinase (U/L)	807.4 ± 1163.1	662.6 ± 1317.8	0.004
CK-MB (U/L)	90.8 ± 272.6	52.5 ± 76.3	<0.001
Troponin I (ng/mL)	25.4 ± 56.8	17.8 ± 40.9	0.001
Troponin T (ng/mL)	6.1 ± 58.3	6.7 ± 71.2	0.625
Total cholesterol (mg/dL)	185.0 ± 43.2	183.1 ± 46.4	0.291
Triglyceride (mg/dL)	137.5 ± 103.1	130.2 ± 88.0	0.062
HDL-C (mg/dL)	45.3 ± 22.4	44.6 ± 20.8	0.685
LDL-C (mg/dL)	119.6 ± 40.9	117.0 ± 41.5	0.131
High sensitive CRP (mg/dL)	22.9 ± 81.7	20.3 ± 87.1	0.488
Pro-BNP (pg/mL)	2168.8 ± 5670.7	4003.0 ± 7730.3	<0.001

CRP: C-reactive protein, IHD: ischemic heart disease, SBP: systolic blood pressure, TIMI: thrombolysis in myocardial infarction, EF: ejection fraction, HDL: high density lipoprotein, LDL: low density lipoprotein, BNP: B-type natriuretic peptide, CK-MB: creatine kinase-MB

in group I and 1421.2 ± 422.2 minutes in group II; there was no significant difference between the groups ($p=0.116$). There were more patients who complained chest pain in group I (81.6%), and more patients who complained of dyspnea in group II (33.9%) ($p=0.005$, $p<0.001$ respectively). The Killp class was higher in group II ($p<0.001$). There was no significant difference between the two groups for the TIMI risk score: 3.2 in Group I and 3.3 in group II, respectively (Table 1).

Electrocardiography, echocardiography and the laboratory findings at admission

ST-segment depression was presented on the electrocardiogram (ECG) by 43.7% of the patients of group II, and this was more frequently observed in group II than in group I. There were no significant differences between both groups for T-wave inversion, conduction disturbance and arrhythmia.

The ejection fraction on echocardiography was 56.7% for group I and 52.7% for group II. The total wall motion score was 17.4 for group I and 19.7 for group II. There were no significant differences for these factors between both groups.

The levels of the cardiac enzymes [creatinine kinase (CK), CK-MB and troponin I] were higher in group I than those levels in group II ($p=0.004$, $p<0.001$, $p=0.001$ respectively). However, the levels of the lipid profiles, the high sensitive C-reactive protein and pro-B type natriuretic peptide were not significantly different between both groups.

Medical therapy during hospitalization

Pharmacological therapy during hospitalization was frequently given: 97.8% of the group I and 97.2% of group II received aspirin, 97.0% of group I and 93.4% of group II received clopidogrel, and 72.9% of group I and 71.8% of group II received statin (Table 2). The medical therapy during hospitalization was similar between group I and group II except for the use of cilostazol (32.2% vs. 27.1%, respectively, $p=0.003$), unfractionated heparin (58.1% vs. 53.1%, respectively, $p=0.007$), Abciximab (4.5% vs. 1.4%, respectively, $p<0.001$), beta blocker (69.8% vs 74.4%, respectively, $p=0.012$), angiotensin receptor blockers (16.3% vs. 24.8%, respectively, $p=0.001$), nicorandil (22.3% vs. 28.1%, respectively, $p=0.001$) and vasopressor (8.4% vs. 11.9%, respectively, $p=0.003$ respectively) (Table 2).

Cardiac procedures during hospitalization

Coronary angiography was done for 100% of the patients in the early invasive strategy group during hospitalization, compared with 93.5% for the selective invasive strategy group. The number of involved vessels was 2.1 for the early invasive strategy group, compared with 1.9 for the early conservative strategy group. There were

Table 2. Medical therapy on admission

Medical therapy (%)	Group I (n=1561)	Group II (n=1201)	P
Aspirin	1526 (97.8)	1167 (97.2)	0.138
Clopidogrel	1514 (97.0)	1122 (93.4)	0.420
Cilostazol	503 (32.2)	325 (27.1)	0.003
Unfractionated heparin	907 (58.1)	638 (53.1)	0.007
Low molecular weight heparin	586 (37.5)	483 (40.2)	0.173
Abciximab	71 (4.5)	17 (1.4)	<0.001
Tirofiban	117 (7.5)	92 (7.7)	0.890
Beta blocker	1090 (69.8)	894 (74.4)	0.012
Angiotensin converting enzyme inhibitor	1025 (65.7)	833 (69.4)	0.054
Angiotensin receptor blocker	254 (16.3)	298 (24.8)	0.001
Nitrate	1086 (69.6)	894 (74.4)	0.051
Statin	1138 (72.9)	862 (71.8)	0.426
Nicorandil	348 (22.3)	338 (28.1)	0.001
Vasopressor	132 (8.4)	143 (11.9)	0.003

Table 3. Coronary angiographic findings and revascularization

	Group I (n=1561)	Group II (n=1201)	P
Coronary angiogram (%)	1561 (100)	1123 (93.5)	0.076
Involved vessel number	1.9 ± 0.7	2.1 ± 0.8	<0.001
Lesion type* (%)			0.020
A	99 (6.3)	69 (6.1)	
B1	310 (19.9)	176 (15.7)	
B2	431 (27.6)	282 (25.1)	
C	721 (46.2)	596 (53.1)	
PCI (%)	1561 (100.0)	802 (66.6)	<0.001
Success rate (%)	1472 (94.3)	755 (94.1)	0.254
Stent type			0.863
Bare metal stent	104 (7.4)	64 (8.8)	
Drug eluting stent	1304 (92.6)	666 (91.2)	
Stent length (mm)	25.2 ± 6.8	25.8 ± 7.3	0.054
Stent diameter (mm)	3.1 ± 0.4	3.1 ± 0.4	0.929
CABG (%)	11 (0.7)	151 (12.6)	<0.001
Revascularization (%)	1483 (95.0)	906 (75.4)	<0.001

*Lesion type according to the American College of Cardiology/American Heart Association classification. PCI: percutaneous coronary intervention, CABG: coronary artery bypass graft

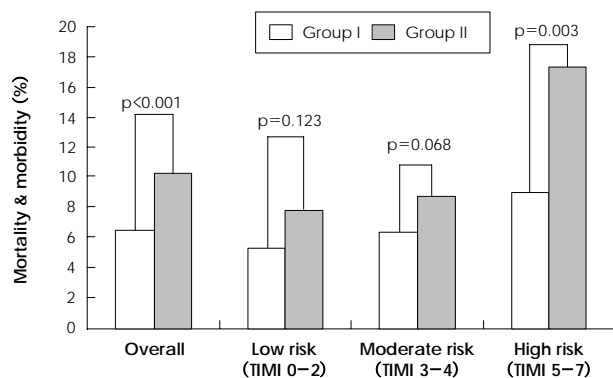
more diffuse and complicated lesion on the coronary angiogram for the selective invasive strategy group ($p=0.020$).

Percutaneous coronary intervention was done during hospitalization in 100% and 66% of the patients in the early invasive group and the selective invasive group, respectively. The success rate was 94% for both groups. For the early invasive strategy group, 90% of the patients treated with PCI during the hospitalization received one or more stents, and 92% of the PCI patients received at least one drug-eluting stent compared with 91% and 91%, respectively, for the PCI patients of the selective

Table 4. Cumulative rates of the composite primary end points

Outcomes	Group I (n=1561)	Group II (n=1201)	P
Death (%)	30 (1.9)	34 (2.8)	0.117
Complications (%)	95 (6.0)	116 (9.7)	<0.001
In-hospital event (%)	102 (6.5)	124 (10.3)	<0.001
CCU admission duration (days)	3.0 ± 3.1	4.9 ± 5.2	<0.001

CCU: coronary care unit

**Fig. 1.** Primary outcome according to the TIMI risk score. TIMI: thrombolysis in myocardial infarction.

invasive strategy group. Coronary bypass graft surgery was done during hospitalization in 0.7% and 12.6% of the patients in the early invasive group and the selective invasive group, respectively. The revascularization rate was 95% for the early invasive strategy group and 75%, respectively, for selective invasive strategy group (Table 3).

Primary end points

A total of 2762 patients (1561 patients in the early invasive strategy group and 1201 patients in the selective invasive strategy group) reached the primary end point. The estimated in hospital death and complication rate was 6.5% in the early invasive strategy group and 10.3%, respectively, in the selective invasive group (relative risk: 1.78, 95% confidence interval: 1.36 to 2.33; $p < 0.001$) (Table 4) (Fig. 2). The in hospital mortality and morbidity was 1.9% and 6.0%, respectively, for the early invasive strategy group and 2.8% and 9.7%, respectively, for the selective invasive strategy group ($p = 0.117$, $p < 0.001$, respectively). The duration of admission to the coronary care unit was significantly longer for the selective invasive strategy group, 4.9 days ($p < 0.001$).

The patients in both groups were classified into 3 groups according to the TIMI risk score. 925 patients (527 patients of group I and 398 patients of group II) had a TIMI risk score of 0-2 points (the low risk group), 1254 patients (723 patients of group I and 531 patients of group II) had a TIMI risk score of 3-4 points (the moderate risk group) and 583 patients (311 patients of group I and 272 patients of group II) had a TIMI risk score

of 5-7 points (the high risk group). For the low risk group, there was no significant difference of the in hospital death and complication rate (5.3%) for the early invasive strategy group (5.3%) and the selective invasive group (7.3%) ($p = 0.123$). For the moderate risk group, there was also no significant difference of the in hospital outcome, 6.4% for the early invasive strategy group and 8.7% for the selective invasive group ($p = 0.123$). But for the high risk group, there was a significantly lower in-hospital mortality and morbidity rate for the early invasive strategy group than for the selective invasive strategy group (9.0% vs. 17.3%, respectively, $p = 0.003$) (Fig. 1). Further, the in hospital mortality and morbidity were increased in proportion to the TIMI risk scores.

There was a significant difference in the frequency of the primary end point among the subgroups that were defined according to age, gender, the presence or absence of diabetes mellitus and the level of cardiac troponin I. Several baseline clinical features were examined on a subgroup analysis for their potential effects. The relative risks were different among the major subgroups that were defined according to age, gender, the presence or absence of diabetes mellitus, the presence or absence of ST-segment deviation, or the level of cardiac troponin. For the old age patients (above 65 years) group, the early invasive strategy reduced the in hospital mortality and morbidity (relative risk: 1.64, 95% confidence interval: 1.18 to 2.26; $p = 0.003$). The male group (relative risk: 1.91, 95% confidence interval: 1.33 to 2.74, $p < 0.001$), the presence of diabetes group (relative risk: 2.15, 95% confidence interval: 1.39 to 3.33, $p < 0.001$) and the group with a troponin level above 2 ng/mL (relative risk: 1.85, 95% confidence interval: 1.28 to 2.66; $p = 0.001$) within the early invasive strategy group also had lower in-hospital mortality and morbidity than that for the comparable groups of the selective invasive group (Fig. 2).

Multivariate analysis of the in hospital mortality and morbidity

After univariate analysis of the in hospital mortality and morbidity, age, the Killip class, the ejection fraction on echocardiography, diabetes, beta blocker treatment, angiotensin converting enzyme inhibitor treatment, early invasive treatment, abciximab treatment, ST-segment depression and the level of troponin I were significant difference between the without end points group and the end points group ($p < 0.001$, $p < 0.001$, $p < 0.001$, $p < 0.001$, $p < 0.001$, $p < 0.005$, $p < 0.001$, $p = 0.001$, $p = 0.001$ and $p = 0.005$, respectively) (Table 5). Multivariate analysis was conducted with using the above factors and also the other factors that have been reported to improve the prognosis of patients with acute myocardial infarction, such as administration of angiotensin receptor blocker, statin, tirofiban and low molecular weight heparin.

Abciximab treatment, a lower ejection fraction, a high Killip class, a high TIMI risk score, old age, angiotensin converting enzyme inhibitor treatment, ST segment depression, early invasive treatment and diabetes were

predictive factors of in hospital mortality and morbidity (p<0.001, p<0.001, p<0.001, p=0.001, p=0.001, p=0.023, p=0.023, p=0.032 and p=0.042, respectively) (Table 6).

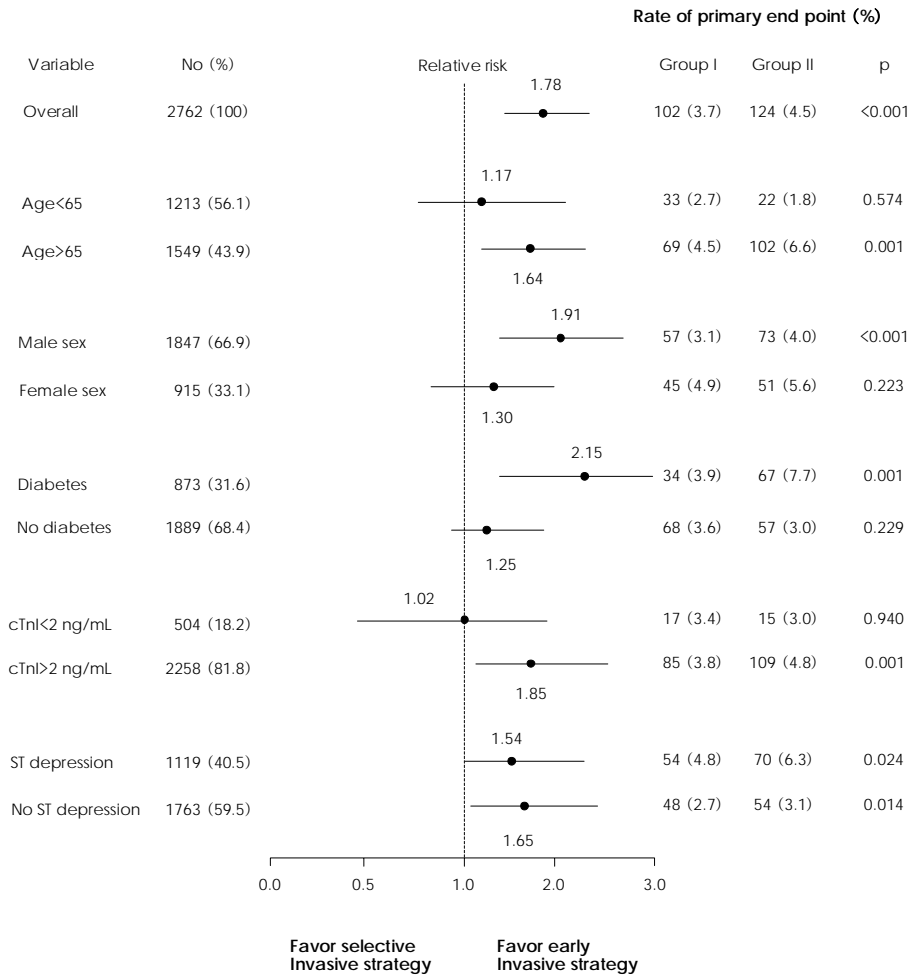


Fig. 2. Estimated rates and relative risk of the composite primary end points of the in hospital mortality and morbidity according to the subgroups.

Table 5. Univariate analysis of the in-hospital mortality and morbidity

	Survived group without events (n=2536)	Moribund or morbid group (n=226)	p
Age (years)	64.2 ± 12.7	68.6 ± 12.7	<0.001
Killip class	1.3 ± 0.7	1.9 ± 1.0	<0.001
Ejection fraction (%)	55.6 ± 12.6	46.9 ± 15.4	<0.001
Diabetes (%)	775 (30.6)	98 (43.4)	<0.001
Beta blocker (%)	1846 (72.9)	138 (61.1)	<0.001
Angiotensin converting enzyme inhibitor (%)	1731 (68.3)	127 (56.2)	<0.001
Early invasive treatment (%)	1070 (42.2)	131 (58.4)	<0.001
Abciximab (%)	82 (3.2)	6 (2.6)	0.001
ST segment depression (%)	1000 (39.4)	119 (52.6)	0.001
Troponin I (ng/mL)	21.0 ± 48.8	33.0 ± 65.3	0.005
Angiotensin receptor blocker (%)	504 (19.8)	48 (21.2)	0.288
Statin (%)	1838 (72.5)	162 (71.7)	0.322
Low molecular weight heparin (%)	975 (38.4)	94 (41.6)	0.579
Tirofiban (%)	191 (7.5)	18 (8.0)	0.919

Table 6. Multivariate analysis of the in-hospital mortality and morbidity

	Odd ratio	95% confidence interval		p
		Lower	Upper	
Use of abciximab	0.15	0.07	0.32	<0.001
High killip class	1.70	1.30	2.23	<0.001
Low ejection fraction	1.04	1.02	1.05	<0.001
High TIMI risk score	1.22	1.09	1.36	0.001
Old age	1.04	1.02	1.06	0.001
Use of angiotensin converting enzyme inhibitor	0.56	0.34	0.92	0.023
ST segment depression	1.71	1.07	2.71	0.023
Early invasive treatment	0.69	0.49	0.97	0.032
Diabetes	3.12	1.04	9.43	0.042
Use of tirofiban	0.64	0.29	1.44	0.284
Use of beta blocker	1.30	0.79	2.13	0.298
Use of statin	0.91	0.64	1.35	0.681
Use of unfractionated heparin	0.94	0.66	1.32	0.718
Use of angiotensin receptor blocker	1.07	0.71	1.62	0.754
High troponin I	1.00	0.99	1.00	0.815
Use of low molecular weight heparin	1.02	0.72	1.45	0.906

TIMI: thrombolysis in myocardial infarction

Discussion

Acute coronary syndrome has been categorized into unstable angina, NSTEMI and STEMI.¹⁰⁾ The most effective treatment for acute coronary syndrome is revascularization via performing percutaneous coronary intervention (PCI).¹¹⁾ Many clinical studies have tried to decide the optimal time for performing coronary intervention for NSTEMI patients. Our results demonstrated that an early invasive strategy is effective for reducing the in-hospital mortality for high-risk patients. The relative risks were different according to age, gender, diabetes, the ST-T changes and the troponin levels. These findings were comparable to the previously reported clinical trials.¹²⁻¹⁶⁾

In five large, randomized trials¹⁷⁻²¹⁾[Veterans Affairs Non-Q-Wave Infarction Strategies in Hospital (VANQWISH), Fragmin and Fast Revascularization during Instability in Coronary Artery Disease (FRISC) II, Treat Angina with Aggrastat and Determine the Cost of Therapy with an Invasive or Conservative Strategy-Thrombolysis in Myocardial Infarction 18 (TACTICS-TIMI 18), TIMI IIIB and the Third Randomized Intervention Treatment of Angina (RITA-3)], a routine, early invasive strategy (early angiography followed by revascularization, depending on the angiographic findings) was compared with a "conservative" strategy (angiography and subsequent revascularization only if medical therapy failed or substantial residual ischemia was documented). An early invasive strategy was shown to be beneficial by the FRISC II, TACTICS-TIMI 18 and RITA-3 studies, and especially for the subgroups of patients who were at a high risk, such as those patients presenting with an elevated cardiac troponin level. Yet the most recent randomized

ICTUS trial showed that an early invasive strategy was not superior to a selective invasive strategy, even for the high risk patients, on the short term and long term clinical follow up.^{5,6)}

In our study, an early invasive strategy was better than a selective invasive strategy for patients with NSTEMI, and especially for the high risk patients. The results of our present study are not in accordance with those of the previous trials owing to differences in the study design, and particularly the period of comparison (the in hospital outcome vs. the 6 months-4 year clinical follow up), the risk profile of the included patients and the definition of the end points. There are several possible explanations for the observed differences in outcome between the present study and the previous trials.

First, our study is a comparison of the in hospital outcome, but the other studies were comparisons of the clinical follow up of a long duration for the major adverse cardiac events. The ICTUS study had 4 years of follow up data, the TIMI-IIIB had 1 year of follow up data, the VANQWISH had 23 months of follow up data, the FRISC II had 6 months of follow up data, the TACTICS-TIMI 18 had 6 months of follow up data and the RITA-3 had 1 year of follow up data. Yet our study focused on in hospitalization only, and the prognosis of patients with NSTEMI is decided during the first hospitalization and during the acute stage. Although period of our study is short, our study also has very important implications.

Second, the revascularization rates were high in the two groups in our study (95% for the early invasive strategy group and 75% for the selectively invasive strategy group during the hospitalization) as compared with those

in the ICTUS (76% vs. 40%, respectively), TIMI-IIIb (64% vs. 58%, respectively), VANQWISH (44% vs. 33%, respectively), FRISC II (77% vs. 37%, respectively), TACTICS-TIMI 18 (61% vs. 44%, respectively), and RITA-3 (57% vs. 28%, respectively). The patients had a higher cardiac troponin I level (25.4 in group I and 17.8 in group II) in our study as compared to that of the other studies. So, the patients who were enrolled in our study were at a high risk (as evidenced by their elevated troponin levels), and this may explain the earlier and more frequent revascularization that was done in both groups, and also the significantly higher cardiac enzyme level in group I as compared to group II; the revascularization rate was higher in group I than that in group II, and this is explained by the same reasoning. The 2003 European Society of Cardiology guidelines have been published, and physicians familiar with the guidelines would probably be inclined to perform angiography in most patients with an elevated cardiac troponin T level. The KAMIR investigators preferred to perform PCI and CABG rather than medical therapy.

Third, the incidence of in hospital mortality and morbidity for both groups was lower than expected. We incorporated the recent advances in background medical therapy, such as the use of abciximab at the time of percutaneous coronary intervention procedures,²²⁾ the early use of clopidogrel⁷⁾ and intensive lipid lowering therapy,⁸⁾ which have all been shown to improve outcomes of the patients who have acute NSTEMI. This may partially explain the lower than expected event rate for the group assigned to a selectively invasive strategy, and this occurred despite of the selectively invasive strategy group's low revascularization rate.

Fourth, infarction that is related to PCI is a disadvantage of early invasive treatment. The prognostic implications of peri-procedural myocardial damage are controversial,²³⁾²⁴⁾ but some reports have suggested that the prognosis of patients with such injury should be regarded as similar to that of patients with spontaneous necrosis. Long term follow-up will be necessary to determine whether the increased incidence of procedure-related myocardial infarction in the early invasive strategy group in our study eventually results in a worse prognosis.

Finally, all the procedures were performed at high volume medical centers that had facilities for cardiac surgery on site and this resulted in a low overall mortality, including a low mortality rate related to coronary artery bypass grafting. In our view, advances in the background medical therapy in combination with better detection of myocardial infarctions with frequent, carefully timed measurements of the CK-MB levels can best explain the differences between our results and those of the previous trials.

This study has some limitations. First, our study is multi-center prospective registry study, and it was not a randomized, controlled study. So, there was probably

a selection bias when enrolling patients into both study groups. The level of cardiac enzymes were higher in the group I patients than that in the group II patients. The patients who complained of chest pain were more frequent in group I as compared to group II. High levels of cardiac enzymes and ongoing chest pain are representative markers of progressive myocardial ischemia.²⁵⁾²⁶⁾ There was also a tendency for the doctors to perform early invasive treatment for the patients with high levels of cardiac enzyme. Thus, the high risk patients could be included in group I. Second, there were big differences for the medical therapy administered during hospitalization between both groups, and especially for the uses of abciximab, beta blocker, angiotensin converting enzyme inhibitor, angiotensin receptor blocker, statin and low molecular weighted heparin. These drugs are known to reduce the mortality of myocardial infarction patients.²²⁾²⁷⁻³⁰⁾ Abciximab was administered to the group I patients, presumably because of the medical insurance of our country. Third, the patients who have more diffuse and complicated lesions underwent coronary artery bypass grafting and there were significantly more of these patients in group II. These findings might have affected that early invasive treatment was associated with better clinical results.

Conclusion

An early invasive strategy improves the hospital outcome for the KAMIR patients with a high risk (exceeding 5 points of the TIMI risk score) of acute NSTEMI. These results were obtained with using contemporary medical therapies, including low-molecular-weight heparin, glycoprotein IIb/IIIa inhibition at the time of percutaneous procedures, clopidogrel and intensive lipid-lowering therapy.

Acknowledgments

This study was performed with the support of The Korean Society of Circulation in the memorandum of the 50th Anniversary of The Korean Society of Circulation.

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