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Clinical Benefit of Low Molecular Weight Heparin for ST-segment Elevation Myocardial Infarction Patients Undergoing Primary Percutaneous Coronary Intervention with Glycoprotein IIb/IIIa Inhibitor

Jung Sun Cho[1], Sung-Ho Her[1], Ju Yeal Baek[1], Mahn-Won Park[1], Hyoung Doo Kim[1], Myung Ho Jeong[2], Young keun Ahn[2], Shung Chull Chae[3], Seung Ho Hur[4], Taek Jong Hong[5], Young Jo Kim[6], In Whan Seong[7], Jei Keon Chae[8], Jay Young Rhew[9], In Ho Chae[10], Myeong Chan Cho[11], Jang Ho Bae[12], Seung Woon Rha[13], Chong Jim Kim[14], Donghoon Choi[15], Yang Soo Jang[15], Junghan Yoon[16], Wook Sung Chung[1], Jeong Gwan Cho[2], Ki Bae Seung[1], Seung Jung Park[17] and other Korea Acute Myocardial Infarction Registry Investigators

Cardiovascular Center, Seoul St. Mary's Hospital[1], Seoul; Cardiovascular Center, Chonnam National University Hospital[2], Gwangju; Cardiovascular Center, Kyungpook National University[3], Daegu; Cardiovascular Center, Keimyung University Dongsan Medical Center[4], Daegu; Cardiovascular Center, Pusan National University Hospital[5], Busan; Cardiovascular Center, Yeungnam University Hostpial[6], Daegu; Cardiovascular Center, Chungnam National University Hostpial[7], Daejon; Cardiovascular Center, Chonbuk National University Hospital[8], Jeonju; Cardiovascular Center, Jeonju Presbyterian Medical Center[9], Jeonju; Cardiovascular Center, Seoul National University Bundang Hospital[10], Seongnam; Cardiovascular Center, Chungbuk National University[11], Cheongju; Cardiovascular Center, Konyang University[12], Daejon; Cardiovascular Center, Korea University Guro Hospital[13], Seoul; Cardiovascular Center, Kyunghee University Hospital[14], Seoul; Cardiovascular Center, Yonsei University Hospital[15], Seoul; Cardiovascular Center, Wonju University Hospital[16], Wonju; Cardiovascular Center, Ulsan University Asan Medical Center[17], Seoul, Korea

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Address for Correspondence:
Myung Ho Jeong, M.D.
Principal Investigator of Korea Acute Myocardial Infarction Registry, Director of The Heart Research Center Chonnam National University Hospital Designated by Korea Ministry of Health and Welfare, 671 Jaebong-ro, Dong-gu, Gwangju 501-757, Korea
Tel: +82.62-220-6243, Fax: +82.62-228-7174
E-mail: myungho@chollian.net

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The efficacy of low molecular weight heparin (LMWH) with low dose unfractionated heparin (UFH) during percutaneous coronary intervention (PCI) with or without glycoprotein (Gp) IIb/IIIa inhibitor compared to UFH with or without Gp IIb/IIIa inhibitor has not been elucidated. Between October 2005 and July 2007, 2,535 patients with ST elevation acute myocardial infarction (STEMI) undergoing PCI in the Korean Acute Myocardial Infarction Registry (KAMIR) were assigned to either of two groups: a group with Gp IIb/IIIa inhibitor (n=476) or a group without Gp IIb/IIIa inhibitor (n=2,059). These groups were further subdivided according to the use of LMWH with low dose UFH (n=219) or UFH alone (n=257). The primary end points were cardiac death or myocardial infarction during the 30 days after the registration. The primary end point occurred in 4.1% (9/219) of patients managed with LMWH during PCI and Gp IIb/IIIa inhibitor and 10.8% (28/257) of patients managed with UFH and Gp IIb/IIIa inhibitor (odds ratio [OR], 0.290; 95% confidence interval [CI], 0.132-0.634; *P*=0.006). Thrombolysis In Myocardial Infarction (TIMI) with major bleeding was observed in LMHW and UFH with Gp IIb/IIIa inhibitor (1/219 [0.5%] vs 1/257 [0.4%], *P*=1.00). For patients with STEMI managed with a primary PCI and Gp IIb/IIIa inhibitor, LMWH is more beneficial than UFH.

Key Words: Myocardial Infarction; Heparin; Blood Platelets; Prognosis

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INTRODUCTION

Several randomized large-scale studies have demonstrated that low molecular weight heparin (LMWH) is not inferior to unfractionated heparin (UFH) in the treatment of non-ST elevation acute myocardial infarction patients (1-3). In ST-elevation acute myocardial infarction (STEMI) patients receiving fibrinolytic therapy, LMWH is known to be better than UFH (4-7).

Furthermore, the FINESSE trial (Facilitated Intervention with Enhanced Reperfusion Speed to Stop Events) demonstrated that enoxaparin is beneficial as a primary and facilitated percutaneous coronary intervention (PCI) (8). However, the efficacy of LMWH compared to UFH with or without glycoprotein IIb/IIIa inhibitor (Gp IIb/IIIa inhibitor) has not yet been elucidated in patients with STEMI, though co-medication of UFH with Gp IIb/IIIa inhibitor has been demonstrated to attenuate platelet inhibition in a few studies (9-12).

The aim of this analysis of a non-randomized, prospective registry was to determine whether LMWH during PCI with Gp IIb/IIIa inhibitor for patients undergoing primary PCI was more beneficial than UFH with Gp IIb/IIIa inhibitor.

MATERIALS AND METHODS

Study population

KAMIR is a Korean, prospective, open, observational, multicenter, on-line registry of patients with acute myocardial infarction (AMI) started in November 2005 with support from the Korean Society of Cardiology. The 50 participating hospitals are capable of primary PCI. Details of the KAMIR have been published (13-18). From November 2005 to January 2008, 10,959 patients with a final diagnosis of AMI were enrolled in the KAMIR. Of these patients, 3,739 patients with STEMI underwent primary or facilitated PCI; a total of 1,204 patients were excluded from the analysis because of missing data of the detailed use LMWH or UFH or timing of PCI data (Fig. 1).

Patients with STEMI managed with primary PCI and Gp IIb/IIIa inhibitor were divided into two groups; the two groups included patients managed with Gp IIb/IIIa inhibitor and LMWH during PCI (n=219) or patients managed with Gp IIb/IIIa inhibitor and UFH alone (n=257). Patients managed with primary PCI without Gp IIb/IIIa inhibitor were also divided into two groups; patients using LMWH during PCI (n=902) or patients using UFH alone (n=1,157).

ST-segment elevation MI was defined by new ST elevation in ≥2 contiguous leads, measuring >0.2 mV in leads V_1 to V_3, or 0.1 mV in all other leads. Primary PCI was defined as emergency PCI performed within 12 hr after admission. Most of the patients in the LMWH group received subcutaneous enoxaparin (Clexane®; Bristol-Myers Squibb, New York, USA and Sanofi-Aventis, Paris, France) 1 mg/kg B.i.d. for 3-5 days from the emergency room plus a reduced dose of UFH (50 U/kg). Patients of the UFH group received a bolus of UFH 5,000 U in the emergency room, and 50-70 U/kg were given during the primary PCI followed by 24,000 U/day infusions for 2 days. Platelet glycoprotein IIb/IIIa receptor blockers during the index PCI were used at the decision of the interventional cardiologists. All patients received a loading dose of 200-300 mg aspirin and 300-600 mg clopidogrel. Cilostazol as the third antiplatelet agent was left to the individual operator's decision. Epicardial coronary blood flow in the infarct-related artery before and after stent implantation was graded according to the classification used in the Thrombolysis In Myocardial Infarction (TIMI) trials. Successful PCI was defined as a residual stenosis <50% in diameter with final grade 3 TIMI flow.

Clinical endpoints

The primary endpoints of the study were cardiac death or recurrent MI during 30 days. The primary safety outcome was TIMI major bleeding. Secondary outcome measures included the incidence of cardiac death or recurrent MI at 14 days.

Statistical analysis

Data are expressed as mean±SD or medians with interquartile

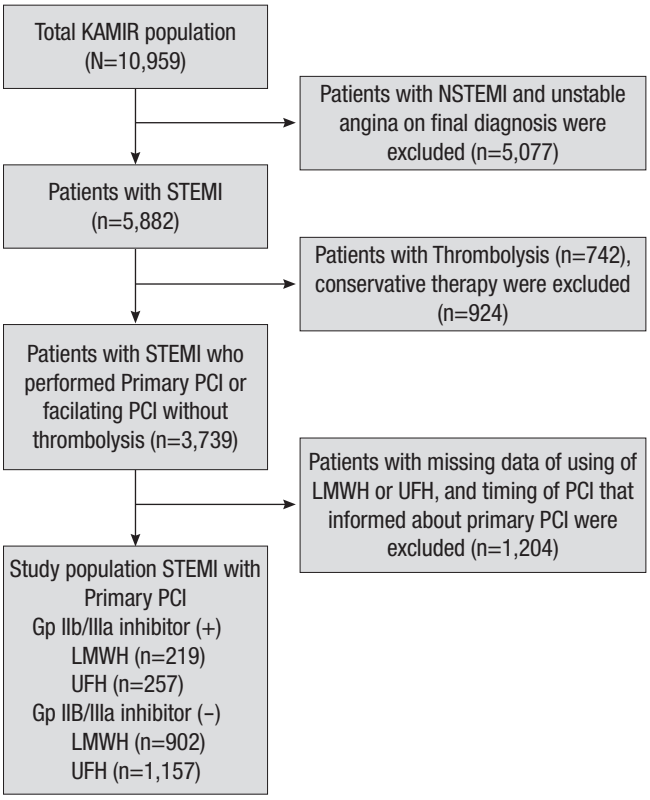

Fig. 1. Flow chart of patients who entered the study.
KAMIR, Korean Acute Myocardial Infarction Registry; STEMI, ST-elevation myocardial infarction; LMWH, low molecular weight heparin; PCI, percutaneous coronary intervention; UFH, unfractionated heparin.

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ranges for continuous variables and percentage for categorized as UFH alone with Gp IIb/IIIa inhibitor or LMWH with low dose UFH during PCI and Gp IIb/IIIa inhibitor. Comparisons between baseline variables were made via the Pearson chi-square test. Comparisons of major adverse cardiac events (MACE) rates in groups were adjusted according to baseline variables using Cox proportional hazards models. Multiple logistic regression analysis was used to estimate the relative risk for mortality in 30 days. In all statistical tests, a 2-sided *P* value <0.05 was considered statistically significant. Statistical analysis was performed using SPSS 15.0 for Windows (SPSS, Inc., Chicago, IL, USA). Survival analysis was estimated using the Kaplan-Meier method with log-rank tests to compare survival between groups.

Ethics statement

Korea Acute Myocardial Infarction Registry was approved by Institutional Review Board of Chonnam National University Hospital (IRB No. I-2008--1-009) and informed consents were obtained from all registered patients.

RESULTS

Patient population

A total of 2,535 patients had STEMI managed with primary PCI (Fig. 1). Clinical characteristics and laboratory findings of four groups, the LMWH and UFH group with Gp IIb/IIIa inhibitors (LMWH, n=219; UFH, n=257) and without Gp IIb/IIIa inhibitors (LMWH, n=902; UFH, n=1,157) are listed in Tables 1 and 2. Rates of dyslipidemia and a family history of coronary artery disease were higher in the UFH group without Gp IIb/IIIa inhibitor than in the LMWH group without Gp IIb/IIIa inhibitor (92/1,157 [7.9%] vs 41/902 [4.5%], *P*<0.001; 82/1,157 [7.0%] vs 51/902 [5.6%], *P*< 0.001 [Table 1]). The median time from symptom onset to door time was longer in the LMWH group without Gp IIb/IIIa inhibitor than in the UFH group without Gp IIb/IIIa inhibitor (123 min [46.2-360.0] vs 100.0 min [33.0-270.0], *P*<0.001 [Table 1]), but the median time from arrival to ballooning was not different between the two groups (173.5 min [95.0-420.0] vs 170.0 min [90.0-384.0] *P*=0.702). There were no differences in laboratory findings between the two groups, except that high-sensitivity C-reactive protein was higher in the UFH with Gp IIb/IIIa inhibitor group than in the LMWH with Gp IIb/IIIa inhibitor group (2.36±3.79 mg/dL vs 4.27±6.10 mg/dL, *P*=0.003 [Table 2]).

Antithrombotic regimen and antiplatelet medication

Platelet glycoprotein IIb/IIIa receptor blockers during index PCI were used at the decision of the interventional cardiologists. The rate of use of cilostazol in addition to dual antiplatelet medications was higher in the UFH group compared to the LMWH group (263/692 [38.0%] vs 418/930 [44.8%], *P*=0.006) (Fig. 2).

Table 1. Clinical characteristics in patients

Parameters	Glycoprotein IIb/IIIa inhibitor (+)			Glycoprotein IIb/IIIa inhibitor (-)		
	LMWH (n=219)	UFH (n=257)	*P* value	LMWH (n=902)	UFH (n=1,157)	*P* value
Age (yr)	64.7±2.9	65.7±12.1	0.405	65.8±13.1	65.1±12.8	0.355
Men (%)	165 (75.3%)	203 (78.4%)	0.447	631 (70.7 %)	879 (76.7%)	0.017
Clinical variables, median (IQR)						
Body mass index	24.4 (22.8-26.4)	23.8 (22.0-25.8)	0.680	23.7 (21.7-26.2)	23.8 (21.8-25.5)	0.536
Waist to hip ratio	0.93 (0.89-0.97)	0.93 (0.90-0.97)	0.705	0.94 (0.90-0.96)	0.94 (0.90-0.97)	0.426
Heart rate (beats/min)	72.0 (60.0-82.2)	74.0 (58.7-88.0)	0.928	74.0 (62.0-86.0)	75.0 (63.0-86.0)	0.148
Blood pressure (mmHg)						
Systolic	130.0 (110.0-149.2)	120.0 (100.0-140.0)	0.264	120.0 (100.0-140.0)	120.0 (106.0-140.0)	0.508
Diastolic	80.0 (70.0-90.0)	80.0 (60.0-90.0)	0.250	80.0 (65.0-90.0)	80.0 (67.0-90.0)	0.616
Killip class			0.072			0.006
≥III	14 (6.3%)	34 (13.2%)		130 (14.4 %)	108 (9.3%)	
≤II	205 (93.6%)	223 (86.7%)		766 (84.9 %)	1,048 (90.5%)	
Risk factor (%)						
Hypertension	97 (44.2%)	107 (41.6%)	0.937	423 (46.8%)	474 (40.9%)	0.177
Diabetes mellitus	43 (19.6%)	47 (18.2%)	0.679	225 (24.9%)	259 (22.3%)	0.354
Current smoking	105 (47.9%)	128 (49.8%)	0.613	432 (47.8%)	590 (50.9%)	0.371
Dyslipidemia*	12 (5.4%)	16 (6.2%)	0.149	41 (4.5%)	92 (7.9%)	0.000
Family history of coronary artery disease†	10 (4.5%)	18 (7.0%)	0.509	51 (5.6%)	82 (7.0%)	0.000
Symptom onset to door time, median (IQR) (min)	60.0 (30.0-300.0)	83.0 (30.0-251.0)	0.368	123.0 (46.2-360.0)	100.0 (33.0-270.0)	0.000
Door to balloon time, median (IQR) (min)	170.0 (100.0-316.7)	160.0 (87.7-294.7)	0.550	173.5 (95.0-420.0)	170.0 (90.0-384.0)	0.702

Data are expressed as medians with interquartile ranges.
*Defined as previously diagnosed by a physician and/or receiving lipid lowering drugs; †Defined as coronary heart disease in first-degree male relative <55 yr old or coronary heart disease in first-degree female relative <65 yr old.
LMWH, low molecular weight heparin; UFH, unfractionated heparin; IQR, interquartile range.

Procedures

All the patients underwent primary PCI. Stents were implanted in 89.4% of patients in the LMWH with Gp IIb/IIIa inhibitor group, 91.0% of patients in the UFH with Gp IIb/IIIa inhibitor group, 93.9% of patients in the LMWH without Gp IIb/IIIa inhibitor group, and 95.7% of patients in the UFH without Gp IIb/IIIa inhibitor group. The number of diseased coronary arteries was not different between the LMWH and UFH groups with and without Gp IIb/IIIa inhibitor. There were no significant differences between patients of both groups in the initial TIMI flow grade and the final TIMI flow grade (LMWH plus low dose UFH during PCI with Gp IIb/IIIa inhibitor and UFH with Gp IIb/IIIa inhibitor initial TIMI grade 0, 169/219 [77.1%] vs 181/257 [70.4%], *P*=0.210; final TIMI grade 3, 190/219 [86.7%] vs 232/257 [90.2%], *P*=0.380 [Table 3]). Lesion types according to the American College of Cardiology/American Heart Association criteria were more complex in the UFH with Gp IIb/IIIa inhibitor group than in the LMWH with Gp IIb/IIIa inhibitor group (Table 3).

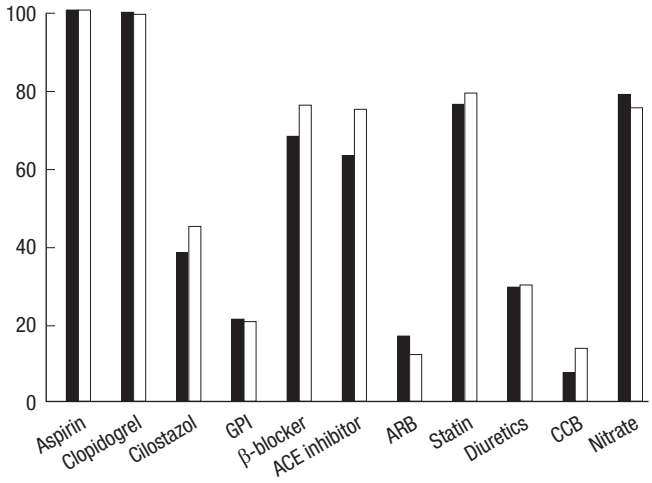

Fig. 2. Concomitant medications during hospitalization.
GPI, glycoprotein IIb/IIIa inhibitor; ACE, angiotensin converting enzyme; ARB, aldosterone receptor inhibitor; CCB, calcium channel blocker.

Multivariate analysis

Use of LMWH was an independent predictor of mortality and

Table 2. Laboratory findings

Variables	Glycoprotein IIb/IIIa inhibitor (+)			Glycoprotein IIb/IIIa inhibitor (-)		
	LMWH (n=219)	UFH (n=257)	*P* value	LMWH (n=902)	UFH (n=1,157)	*P* value
Peak creatine kinase-MB (ng/mL)	234.1±384.1	272.5±464.2	0.42	211.7±199.1	218.3±386.1	0.718
Glucose (mg/dL)	183.2±84.9	188.4±84.4	0.582	174.1±76.3	178.0±78.4	0.308
Serum creatinine (mg/dL)	1.14±1.11	1.04±0.37	0.244	1.06±0.50	1.21±2.4	0.098
Total cholesterol (mg/dL)	181.0±39.5	175.2±43.0	0.21	183.9±46.0	182.1±46.3	0.500
Triglyceride (mg/dL)	124.3±72.1	121.7±74.7	0.76	130.4±146.5	117.7±95.6	0.089
High-density lipoprotein cholesterol (mg/dL)	44.1±12.2	44.5±11.0	0.792	45.9±25.2	44.8±16.8	0.335
Low-density lipoprotein cholesterol (mg/dL)	118.3±34.5	112.1±35.5	0.134	119.5±39.5	117.6±43.8	0.467
High-sensitivity C-reactive protein (mg/dL)	2.36±3.79	4.27±6.10	0.003	3.00±5.1	3.2±5.2	0.549
N-terminal pro-B-type natriuretic peptide (pg/mL)	1,620.8±4,100.3	1,134.0±1,899.6	0.253	2,202.8±5,789.1	1,937.4±5,370.1	0.549

Data expressed as mean±SE.
LMWH, low molecular weight heparin; UFH, unfractionated heparin.

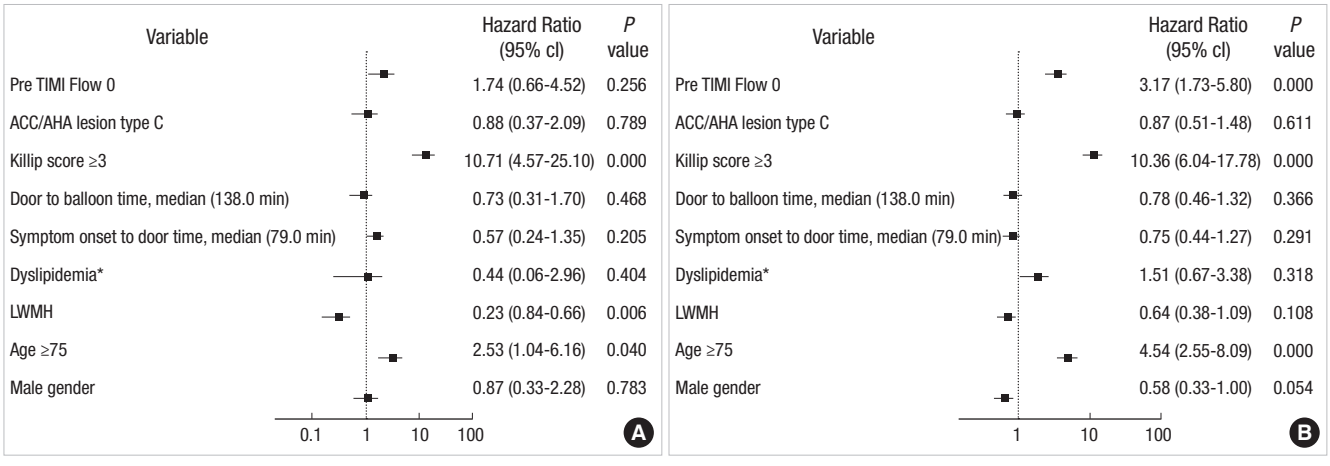

Fig. 3. Hazard ratio plots of independent predictors with the multivariable analyses for death or myocardial infarction in 30 days in UFH and LMWH groups with glycoprotein IIb/IIIa inhibitor (**A**) and without glycoprotein IIb/IIIa inhibitor (**B**) in STEMI patients who underwent primary PCI.
*Defined as coronary heart disease in first-degree male relative <55 yr old or coronary heart disease in first-degree female relative <65 yr old.
LMWH, low molecular weight heparin; UFH, unfractionated heparin; STEMI, ST-elevation myocardial infarction; PCI, percutaneous coronary intervention.

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Table 3. In-hospital events and procedures through 30 days

Events	Glycoprotein IIb/IIIa inhibitor (+)			Glycoprotein IIb/IIIa inhibitor (-)		
	LMWH (n=219)	UFH (n=257)	*P* value	LMWH (n=902)	UFH (n=1,157)	*P* value
Cardiogenic shock	17 (7.7%)	37 (14.3%)	0.121	63 (6.9%)	83 (7.1%)	0.913
New atrial flutter/fibrillation	2 (0.9%)	5 (1.9%)	0.394	14 (1.5%)	23 (1.9%)	0.681
Ventricular tachycardia/ ventricular fibrillation	21 (9.5%)	37 (14.3%)	0.185	75 (8.3%)	87 (7.5%)	0.602
Acute renal failure	0	1 (0.3%)	1.00	4 (0.4%)	5 (0.4%)	1.00
Atrioventricular block	19 (8.6%)	28 (10.8%)	0.587	41 (4.5%)	34 (2.9%)	0.135
Cerebral vascular accident	0	4 (1.5%)	0.507	4 (0.4%)	9 (0.7%)	0.741
Coronary angiographic findings			0.375			0.218
Left main coronary artery	5 (2.2%)	12 (4.6%)		19 (2.1%)	11 (0.9%)	
1-vessel disease	124 (56.6%)	125 (48.6%)		440 (48.7%)	555 (47.9%)	
2-vessel disease	58 (26.4%)	74 (28.7%)		263 (29.1%)	334 (28.8%)	
3-vessel disease	31 (14.1%)	46 (17.8%)		175 (19.4%)	255 (22.0%)	
Infarct related artery			0.629			0.462
Left main coronary artery	3 (1.3%)	9 (3.5%)		8 (0.8%)	10 (0.9%)	
Left anterior descending coronary artery	100 (45.6%)	115 (44.7%)		430 (47.6%)	613 (52.9%)	
Left circumflex coronary artery	17 (7.7%)	18 (7.0%)		106 (11.7%)	131 (11.3%)	
Right coronary artery	97 (44.2%)	113 (43.9%)		349 (38.6%)	401 (34.6%)	
ACC/AHA lesion type			0.001			0.152
A	5 (2.2%)	7 (2.7%)		49 (5.4%)	42 (3.6%)	
B1	67 (30.5%)	48 (18.6%)		144 (15.9%)	170 (14.6%)	
B2	62 (28.3%)	45 (17.5%)		265 (29.3%)	307 (26.5%)	
C	84 (38.3%)	156 (60.7%)		442 (49.0%)	635 (54.8%)	
Initial TIMI flow grade 0	169 (77.1%)	181 (70.4%)	0.210	568 (62.9%)	710 (61.3%)	0.599
Stent implantation	196 (89.4%)	234 (91.0%)	0.711	847 (93.9%)	1,108 (95.7%)	0.192
Final TIMI flow grade 3	190 (86.7%)	232 (90.2%)	0.380	832 (92.2%)	1,078 (93.1%)	0.583

Data expressed as number of patients (percentage).
ACC/AHA, American College of Cardiology/American Heart Association; TIMI, Thrombolysis In Myocardial Infarction.

Table 4. Primary outcomes at 14 and 30 days

Variables	Glycoprotein IIb/IIIa inhibitor (+)			Glycoprotein IIb/IIIa inhibitor (-)		
	LMWH (n=219)	UFH (n=257)	*P* value	LMWH (n=902)	UFH (n=1,157)	*P* value
14 days						
Cardiac death or MI	8 (3.6%)	26 (10.1%)	0.007	33 (3.7%)	56 (4.8%)	0.230
30 days						
Cardiac death or MI	9 (4.1%)	28 (10.8%)	0.006	37 (4.2%)	60 (5.3%)	0.250
Major bleeding	1 (0.5%)	1 (0.4%)	1.00	0 (0%)	3 (0.3%)	0.261

Data expressed as number of patients (percentage).

MI at 30 days in groups managed with primary PCI with Gp IIb/IIIa inhibitor. High Killip score (≥3), and old age (≥75 yr) were also independent predictors of the primary end point in groups managed with primary PCI with and without Gp IIb/IIIa inhibitor (Fig. 3).

Clinical outcomes

The primary end point occurred in 4.1% (9/219) of patients managed with LMWH with low dose UFH during PCI with Gp IIb/IIIa inhibitor and 10.8% (28/191) of patients managed with UFH alone with Gp IIb/IIIa inhibitor (Odds ratio [OR], 0.290; 95% confidence interval [CI], 0.132-0.634; *P*=0.001 [Table 4, Fig. 4]). There was no significant occurrence of the primary end point in the LMWH and UFH groups without Gp IIb/IIIa inhibitor (OR, 0.870; 95% CI, 0.527-1.437; *P*=0.250 [Table 4]).

TIMI major bleeding was observed with LMWH with low dose UFH and UFH alone with Gp IIb/IIIa inhibitor and without Gp IIb/IIIa inhibitor (1/219 [0.5%] vs 1/257 [0.4%], *P*=1.00; 0/902 [0%] vs 3/1157 [0.3%], *P*=0.261 [Table 4]).

DISCUSSION

In the present study, the effectiveness of LMWH with Gp IIb/IIIa inhibitor for STEMI patients undergoing primary PCI is beneficial compared to UFH with Gp IIb/IIIa inhibitor. The rate of cardiac death or myocardial infarction in 30 days was lower in the LMWH with low dose UFH during PCI with Gp IIb/IIIa inhibitor group than in the UFH with Gp IIb/IIIa inhibitor group. Heparin has been reported to modify platelet function in vitro and in vivo in both patients and healthy individuals. In vitro, low doses of heparin are more apt to reduce platelet aggregation, while high doses are more likely to increase it (19, 20). In unstable an-

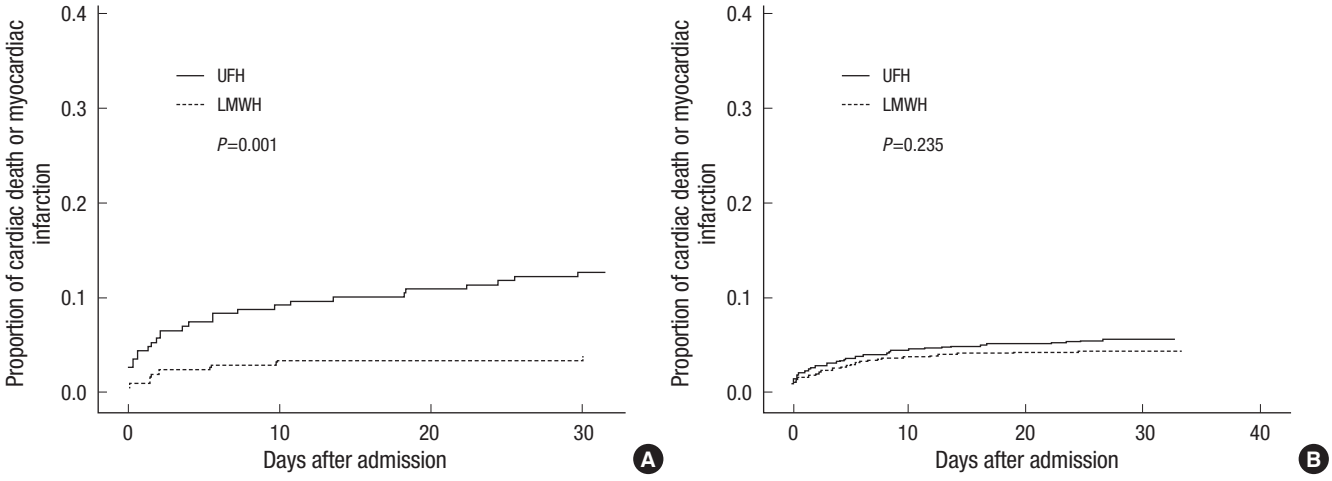

Fig. 4. Kaplan-Meier analysis of primary endpoint of UFH and LMWH groups with glycoprotein IIb/IIIa inhibitor (**A**) and without glycoprotein IIb/IIIa inhibitor (**B**) in STEMI patients who underwent primary PCI.
LMWH, low molecular weight heparin; UFH, unfractionated heparin; STEMI, ST-elevation myocardial infarction; PCI, percutaneous coronary intervention.

gina, UFH increased the percentage of activated platelets, and platelets became hyperresponsive to stimulation with adenosine diphosphate (ADP) and thrombin receptor agonist peptide (TRAP) (11). Several clinical studies, including the GOLD study, IMPACT II, and the GUSTO IV-ACS trials, demonstrated the adverse effects of concomitant UFH and Gp IIb/IIIa inhibitor administration (21-23). LMWH may be less likely than UFH to induce platelet activation (10, 11, 24).

LMWH is more convenient than UFH as it has a more stable and predictable dose response. Anti-Xa levels correlate with the anticoagulant effects of LMWH but cannot be routinely monitored in the catheterization laboratory (3). LMWH reduces ischemic events more effectively than UFH in patients treated conservatively for non-ST-segment elevation acute coronary syndrome. Furthermore, in high-risk patients undergoing early percutaneous coronary intervention for acute coronary syndrome, LMWH avoids the need for monitoring and achieves similar effectiveness to UFH but has been associated with more bleeding (3).

According to a 2007 meta-analysis of trials, including the ASSENT-3 trial, ASSEMT-3 PLUS trial, and ExTRACT-TIMI 25 trial, which compared UFH to LMWH in over 27,000 STEMI patients receiving fibrinolytic therapy, LMWH was shown to be better than UFH in ST-elevation acute myocardial infarction (STEMI) patients receiving fibrinolytic therapy (23-25). Furthermore, a substudy of the FINESSE trial (Facilitated INtervention with Enhanced Reperfusion Speed to Stop Events showed that enoxaparin was beneficial in primary and facilitated percutaneous coronary intervention (8). In the KAMIR data, enoxaparin plus a reduced dose of UFH (50 U/kg) during PCI in acute STEMI patients undergoing primary PCI with drug-eluting stents (DES) showed lower incidences of in-hospital cardiac deaths and total deaths compared to those from UFH alone (18). However, medications including Gp IIb/IIIa inhibitors in both groups were different in this study. As a result, we considered the benefits of concomitant LMWH administration with Gp IIb/IIIa inhibitor (21-23, 26, 27). In the present study, the group that received Gp IIb/IIIa inhibitor showed more benefits of LMWH with low dose UFH during PCI than UFH alone, the group without Gp IIb/IIIa inhibitor did not.

This study has several limitations. KAMIR is the largest registry of patients with acute myocardial infarction in Korea. We could not analyze the relationship between anticoagulant dose and risk of bleeding, and laboratory finding of activated partial thromboplastin time. The use of Gp IIb/IIIa inhibitor was limited due to medical insurance in Korea. Therefore Gp IIb/IIIa could be used in very high-risk patients with STEMI. This analysis needs a large scale, randomized prospective study to form conclusive results. Platelet glycoprotein IIb/IIIa receptor blockers during PCI were used at the discretion of the interventional cardiologists.

In conclusion, for STEMI patients managed with a primary PCI and Gp IIb/IIIa inhibitor, LMWH plus a reduced dose of UFH (50 U/kg) during PCI is more beneficial than UFH.

Korean Acute Myocardial Infarction Registry (KAMIR) Investigators

Myung Ho Jeong, Young Jo Kim, Chong Jin Kim, Myeong Chan Cho, Young Keun Ahn, Jong Hyun Kim, Shung Chull Chae, Seung Ho Hur, In Whan Seong, Taek Jong Hong, Dong Hoon Choi, Jei Keon Chae, Jae Young Rhew, Doo Il Kim, In Ho Chae, Junghan Yoon, Bon Kwon Koo, Byung Ok Kim, Myoung Yong Lee, Kee Sik Kim, Jin Yong Hwang, Seok Kyu Oh, Nae Hee Lee, Kyoung Tae Jeong, Seung Jea Tahk, Jang Ho Bae, Seung Woon Rha, Keum Soo Park, Kyoo Rok Han, Tae Hoon Ahn, Moo Hyun Kim, Joo Young Yang, Chong Yun Rhim, Hyeon Cheol Gwon, Seong Wook Park, YoungYoup Koh, Seung Jae Joo, Soo Joong Kim, Dong Kyu Jin, Jin Man Cho, Wook Sung Chung, Yang Soo

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Jang, Jeong Gwan Cho, Ki Bae Seung, Seung Jung Park.

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