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Original article

Clinical impact of thrombus aspiration during primary percutaneous coronary intervention: Results from Korea Acute Myocardial Infarction Registry

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KEYWORDS
ST-elevation myocardial infarction;
Thrombus aspiration;
Percutaneous coronary intervention

Summary
Background: The role of thrombus aspiration (TA) as an adjunct to primary percutaneous coronary intervention (PPCI) remains a matter of controversy.
Methods and results: A total of 2105 patients enrolled in the nationwide prospective Korea Acute Myocardial Infarction Registry, a cohort of 745 (35.4%) patients who underwent TA during PPCI was compared with 1360 (64.6%) patients who underwent conventional PCI without TA. Clinical outcomes at 12-months of overall enrolled patients and subgroups according to key variables were assessed using Cox regression models adjusted by propensity score. Although there was no significant difference among overall patients, in subgroup analyses, administration of glycoprotein (GP) IIb/IIIa inhibitor during PPCI [adjusted hazard ratio (HR) 0.329, 95% confidence interval (CI) 0.126—0.860, $p = 0.023$] and left anterior descending (LAD) as a culprit lesion (adjusted HR 0.516, 95% CI 0.275—0.971, $p = 0.040$) were the settings, in which TA was associated with a lower major adverse cardiac events (MACE) rate compared with non-TA.
Conclusions: Although TA does not improve clinical outcomes in overall patients who underwent PPCI, TA for LAD occlusion improves 12-month MACE. Furthermore, use of GP IIb/IIIa inhibitor with TA has a synergistic effect on clinical outcomes.

Introduction

Primary percutaneous coronary intervention (PCI) in patients with acute ST-segment elevation myocardial infarction (STEMI) is the gold standard strategy [1]. Stent implantation has been shown to increase reperfusion rate, and improve mid- and long-term outcomes [2]. Regarding thrombus aspiration (TA) during primary PCI, TAPAS (thrombus aspiration during percutaneous coronary intervention in acute myocardial infarction study) [3,4], EXPIRA (thrombectomy with export catheter in infarct-related artery during primary percutaneous coronary intervention) [5] and two different meta-analyses [6,7] demonstrated that TA improved clinical outcomes as well as reperfusion status. American College of Cardiology/American Heart Association (ACC/AHA) guidelines for the management of patients with STEMI recommend TA as Class II a, Level of Evidence B [8].

However, some meta-analyses [9—11] and randomized controlled trials (RCTs) [12—15] have shown that TA did not improve clinical outcomes but improved only reperfusion surrogate endpoints. Consequently, the effectiveness of TA remains a matter of controversy. Even if TA is effective in STEMI patients, it is unclear which clinical settings are more effective in those who underwent TA.

We therefore investigated not only clinical impacts of TA, but also which settings were effective for reducing clinical events as subgroup analyses.

Methods

Korea Acute Myocardial Infarction Registry

The Korea Acute Myocardial Infarction Registry (KAMIR) is a Korean prospective multicenter online registry designed to describe characteristics and clinical outcomes of Korean patients with acute MI and reflect current practice of management in Korea. The registry included 52 community and university hospitals for primary PCI. Data were collected at each site by a well-trained study coordinator based on a standardized protocol. The study protocol was approved by the ethics committee at each participating institution and all patients were informed about their participation in this registry and written informed consent was taken.

Study population

A total of 2105 patients who underwent primary PCI were enrolled in the present study from December 2007 to October 2009, and 745 (35.4%) patients received manual TA during primary PCI and 1360 (64.6%) did not. As subgroup analyses, age <65 years ($n = 1150$), age ≧ 65 years ($n = 952$), male ($n = 1583$), female ($n = 521$), door to balloon time < 90 min ($n = 820$), door to balloon time ≧ 90 min ($n = 1159$), symptom to balloon time < 4 h ($n = 1294$), symptom to balloon time ≧ 4 h ($n = 709$), history of diabetes mellitus ($n = 501$), non-diabetes mellitus ($n = 1561$), history of hyperlipidemia ($n = 248$), non-hyperlipidemia ($n = 1721$), use of glycoprotein (GP) II b/III a inhibitor during PCI ($n = 639$), non-use of GP II b/III a inhibitor during PCI ($n = 1450$), culprit lesion in left anterior descending (LAD) ($n = 1073$), left circumflex (LCX) ($n = 230$), right coronary artery (RCA) ($n = 755$), Type A/B1 lesion ($n = 452$), Type B2/C lesion ($n = 1415$), preprocedural Thrombolysis In Myocardial Infarction (TIMI) flow grade 0 ($n = 1142$), preprocedural TIMI flow grade 1—3 ($n = 834$), left ventricular ejection fraction (LVEF) <35% ($n = 133$), LVEF ≧ 35% ($n = 1798$) were evaluated.

Definitions and clinical endpoints

In this registry, manual thrombus aspiration devices such as Thrombuster® (Kaneka, Japan) were used and decision of whether to use depended on operators. Acute MI was defined by clinical signs or symptoms, increased cardiac biomarkers (creatine kinase-MB, troponin-I, or troponin-T), and 12-lead electrocardiographic findings. Among acute MI patients, ST-segment elevation myocardial infarction (STEMI) was defined by the presence of new ST-segment elevation of at least 1 mm (0.1 mv) in continuous leads or new left bundle-branch block on the index of electrocardiogram. Recurrent MI was defined as recurrence of clinical symptoms or occurrence of electrocardiographic changes accompanied by a recurrent increase of creatine kinase-MB

to 3 times the upper limit of normal. Stent thrombosis was defined as definite and probable stent thrombosis according to the Academic Research Consortium definition [16]. Left main (LM) complex lesion was defined as significant stenosis of LM trunk artery with the presence of other epicardial coronary artery stenosis. The morphology of lesions in coronary angiography was classified by criteria of ACC/AHA [17]. The degree of coronary flow was classified by TIMI grade flow [18]. Renal function was assessed by estimated glomerular filtration rate (eGFR) using the new Japanese equation of eGFR [19] was used to calculate eGFR because Korean and Japanese have a lot in common in terms of race or physical constitution and so on. GP IIb/IIIa inhibitors during PCI was administered intravenously or through intracoronary at a dose of 0.25 mg/kg. LVEF was checked by 2-dimensional echocardiography. Door-to-balloon time was defined as the time between arrival at the hospital and the first balloon inflation or device deployment, and symptom-to-balloon time was defined as the time between onset of MI and the first balloon inflation or device deployment. Success of primary PCI was defined as residual diameter stenosis less than 30% and a final TIMI 3 grade flow. Use of supportive treatment was defined as necessity of cardio-pulmonary resuscitation, intra-aortic balloon pumping, intubation, defibrillation/cardioversion, and temporary pacemaker.

Clinical follow up was performed at 12 months. Major adverse cardiac events (MACE) included cardiac death, non-fatal MI, repeat revascularization. Repeat revascularization included target lesion revascularization (TLR) and target vessel revascularization (TVR). TLR was defined as a repeat intervention in the stent or within 5 mm proximal or distal to the stent, and TVR was defined as a repeat revascularization of a lesion in the same epicardial vessel treated in the index procedure [20].

Statistical analysis

All analyses were performed using SPSS software version 17.0 (SPSS Inc. Chicago, IL, USA). Continuous variables are presented as mean ± standard deviation or medians and interquartile ranges, and compared by Student's *t* tests, Welch *t* tests, or Mann—Whitney nonparametric tests. Categorical variables are expressed as percentages and compared by means of chi-square test or Fisher's exact test. All statistical tests were 2-tailed, with statistically significance defined as a *p*-value <0.05. The crude survival curves were made using the Kaplan—Meier method, and log-rank tests were applied to evaluate differences between the treatment groups. A propensity score was created to adjust confounding factors using a logistic regression model. Pretreatment variables which occurred before TA included: age, gender, body mass index, symptom to balloon time, door to balloon time, resuscitation prior to admission, cardiopulmonary arrest on arrival, symptom aspects, presence of chest symptom, presence of dyspnea, presence of previous angina symptoms before MI onset, systolic blood pressure, heart rate, Killip class on presentation, previous ischemic heart disease, history of hypertension, diabetes mellitus, hyperlipidemia, smoker, family history of heart disease, eGFR, location of culprit coronary lesion, LM complex disease, multivessel disease, thrombolysis before PCI, preprocedural TIMI flow grade, use of GP IIb/IIIa inhibitors during PCI, and use of intravascular ultrasound (IVUS) examination. The predicted accuracy of the logistic model was assessed by the area under the receiver operating characteristic curve (c statistic), which was 0.718. Adjusted survival curves were calculated with the use of the Cox regression models adjusted by propensity score and important risk covariates which showed $p < 0.2$ in univariate analysis for end-points and other variables that have been reported to be associated with prognosis of patients with acute MI. Included covariates are age, gender, types of stent, LVEF, eGFR, use of GP IIb/IIIa inhibitors in hospital, medications at discharge [e.g. β-blocker, angiotensin-converting enzyme inhibitor (ACE-I) or angiotensin II receptor blocker (ARB), nitrate, nicorandil, spironolactone, and statin]. The results are presented as adjusted hazard ratios (HRs) with 95% confidence intervals (CIs). Although subgroup analyses were also analyzed using the Cox regression models adjusted by propensity score, only MACE could be analyzed due to a diminished number of patients.

Results

Baseline clinical and procedural characteristics

Baseline clinical characteristics and medication are given in Table 1. Patients in the non-TA group were older, had a higher prevalence of previous angina symptoms before MI onset, and received thrombolysis therapy prior to PCI. Patients in the TA group had a higher prevalence of family history, cardiopulmonary arrest on arrival, low blood pressure on admission, high Killip class, low LVEF, and low eGFR. The use of nitrate and nicorandil was higher in the non-TA group. Patients in the TA group were more often men and the use of spironolactone was higher in this group.

The prevalence of LAD as culprit lesion and type B2/C were higher in non-TA group whereas RCA was higher in TA group. Periprocedural TIMI flow grade of the TA group was lower than that of the non-TA group. Time to procedure was shorter in the TA group than in the non-TA group. The frequency of IVUS usage was higher in the non-TA group and drug-eluting stent implantation was higher in the TA group (Table 2).

Twelve-month clinical outcomes

Clinical outcomes at 12 months are shown in Table 3. While there were no significant differences in the incidence of MACE, cardiac death, repeat revascularization, and stent thrombosis, the rate of non-fatal MI was significantly lower in the TA group than in the non-TA group (0.7% vs 2.2%, $p = 0.010$).

According to the multivariate analysis, LVEF < 35% was identified as an independent predictor of 12-month MACE (adjusted HR: 2.152, 95% CI 1.124—4.121). Prescription of β-blockers was associated with a decreased non-fatal MI (adjusted HR: 0.182, 95% CI 0.055—0.607). Adjusted survival curves are shown in Fig. 1. There were no significant

Table 1 Baseline clinical characteristics and medication.

	TA (−) ($n = 1360$)	TA (+) ($n = 745$)	p-Value
Clinical			
Age (years)	62.6 ± 12.9	61.0 ± 12.9	0.005
Male gender, *n* (%)	998 (73.4%)	585 (78.7%)	0.007
Body mass index (kg/m^2)	24.0 ± 3.2	24.2 ± 3.1	0.138
Risk factors			
Hypertension, *n* (%)	609 (45.6%)	344 (47.1%)	0.549
Diabetes mellitus, *n* (%)	329 (24.7%)	172 (23.5%)	0.555
Hyperlipidemia, *n* (%)	155 (12.3%)	93 (13.2%)	0.571
Coronary artery disease, *n* (%)	148 (11.0%)	72 (9.8%)	0.413
Smoker, *n* (%)	828 (61.9%)	476 (65.5%)	0.115
Family history of heart disease, *n* (%)	102 (8.2%)	96 (14.0%)	<0.001
Previous angina symptoms before onset, *n* (%)	549 (40.8%)	220 (29.9%)	<0.001
Resuscitation prior to arrival, *n* (%)	25 (1.8%)	12 (1.6%)	0.863
Cardiopulmonary arrest on arrival, *n* (%)	0 (0%)	4 (0.5%)	0.016
Systolic blood pressure <100, *n* (%)	143 (10.8%)	99 (13.9%)	0.044
Heart rate > 100, *n* (%)	108 (8.2%)	67 (9.4%)	0.362
Killip class > 1, *n* (%)	318 (24.3%)	268 (38.6%)	<0.001
Thrombolysis prior to PCI, *n* (%)	111 (8.2%)	39 (5.2%)	0.013
Left ventricular ejection fraction	52.4 ± 13.6	50.9 ± 19.8	0.043
Left ventricular ejection fraction < 35%, *n* (%)	91 (7.2%)	42 (6.3%)	0.509
eGFR (mL/min/1.73 m^2)	61.6 ± 30.5	58.8 ± 20.4	0.028
eGFR < 60, *n* (%)	708 (52.3%)	402 (54.5%)	0.336
Medication in hospital			
Platelet GPIIb/III a inhibitor, *n* (%)	322 (24.4%)	199 (27.1%)	0.186
Low molecular weight heparin, *n* (%)	241 (19.7%)	122 (21.0%)	0.530
Medication at discharge			
Aspirin, *n* (%)	1296 (98.9%)	717 (98.5%)	0.538
Clopidogrel, *n* (%)	1301 (98.9%)	714(98.5%)	0.537
Cilostazol, *n* (%)	346 (27.3%)	177 (24.7%)	0.203
Ca channel blocker, *n* (%)	82 (6.5%)	42 (5.9%)	0.630
Beta blocker, *n* (%)	1102 (84.7%)	616 (85.6%)	0.649
ACE-I or ARB, *n* (%)	1148 (87.5%)	638 (87.8%)	0.889
Nitrate, *n* (%)	657 (51.4%)	297 (41.4%)	<0.001
Nicorandil, *n* (%)	280 (22.2%)	110 (15.4%)	<0.001
Diuretics, *n* (%)	221 (17.5%)	140 (19.6%)	0.249
Spironolactone, *n* (%)	106 (8.4%)	84 (11.8%)	0.017
Statin, *n* (%)	984 (75.6%)	559 (77.3%)	0.384
Fibrate, *n* (%)	5 (0.4%)	6 (0.8%)	0.221

Values are expressed as number (%) or mean (±SD). TA, thrombus aspiration; PCI, percutaneous coronary intervention; eGFR, estimated glomerular filtration rate; GP, glycoprotein; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

differences in the incidence of MACE, cardiac death, non-fatal MI, and repeat revascularization.

Subgroup analysis

Fig. 2 represents subgroups' HR, 95% CI and p-value of TA for MACE in comparison with the non-TA group. Administration of GP IIb/IIIa inhibitors during primary PCI (adjusted HR 0.329, 95% CI 0.126—0.860, $p = 0.023$) and LAD as culprit lesion (adjusted HR 0.516, 95% CI 0.275—0.971, $p = 0.040$) were the settings in which TA was associated with a lower MACE rate compared to non-TA.

Discussion

This study was designed to examine whether TA during primary PCI adds benefit in reducing clinical events for patients with acute STEMI. Furthermore, we investigated in which settings TA was effective to reduce clinical events. Although unadjusted analysis showed TA to be associated with a decreased non-fatal MI, Cox regression models adjusted by propensity score revealed no significant differences between the two groups. In subgroup analyses, GP IIb/IIIa inhibitor administration combined with TA gave a synergistic effect and TA for LAD as culprit lesion was effective in terms of reducing MACE.

Table 2 Coronary angiographic and procedural characteristics.

	TA (−) (n = 1360)	TA (+) (n = 745)	p-Value
Angiographic			
Left main complex, n (%)	37 (2.7%)	12 (1.6%)	0.130
Multivessel, n (%)	676 (50.1%)	355 (48.2%)	0.436
Infarct-related artery			
Left main trunk, n (%)	17 (1.3%)	9 (1.2%)	1.000
Left anterior descending, n (%)	733 (54.4%)	340 (46.1%)	<0.001
Left circumflex, n (%)	155 (11.5%)	75 (10.2%)	0.381
Right coronary artery, n (%)	442 (32.8%)	313 (42.5%)	< 0.001
Type B2/C lesion, n (%)	945 (79.0%)	470 (70.0%)	<0.001
Preprocedural TIMI flow grade 0, n (%)	692 (54.7%)	450 (63.3%)	<0.001
Postprocedural TIMI flow grade 3, n (%)	1197 (94.3%)	629 (90.5%)	0.002
Procedural			
Symptom to balloon time, median (IQR), hours	5.7 (3.2—12.6)	4.7 (2.7—12.08)	0.100
Symptom to balloon time < 4 h, n (%)	509 (39.4%)	311 (45.3%)	0.013
Door to balloon time, median (IQR), minutes	71.0 (45.0—172.8)	55.0 (35.0—95.0)	<0.001
Door to balloon time < 90 min, n (%)	814 (62.1%)	480 (69.4%)	0.001
Use of IVUS, n (%)	263 (57.7%)	193 (27.0%)	<0.001
Administration of GP IIb/IIIa inhibitor, n (%)	402 (29.7%)	237 (32.2%)	0.253
Drug-eluting stent implantation, n (%)	1073 (85.0%)	605 (88.7%)	0.027
Stent length ≧ 25 mm, n (%)	474 (37.3%)	260 (38.1%)	0.732
Stent diameter ≦ 2.5 mm, n (%)	89 (7.0%)	42 (6.1%)	0.508
Success of primary PCI, n (%)	1293 (96.9%)	697 (97.2%)	0.688
Intraprocedural complications, n (%)	225 (16.6%)	110 (14.9%)	0.319
Supportive treatment, n (%)	192 (14.2%)	109 (14.9%)	0.696

Values are expressed as number (%) or median (IQR, interquartile range); TA, thrombus aspiration; Type B2/C, according to lesion morphology of American College of Cardiology/American Heart Association; TIMI, Thrombolysis In Myocardial Infarction; IVUS, intravascular ultrasound; GP, glycoprotein; PCI, percutaneous coronary intervention. Supportive treatment: cardiopulmonary resuscitation, intra-aortic balloon pumping, intubation, defibrillation/cardioversion, and temporary pacemaker.

Primary PCI and stenting are considered the gold standard strategy in patients with STEMI [1,2]. Apparent decreased flow in the infarct-related artery and suboptimal myocardial reperfusion make prognosis worse and were caused by multiple factors such as myocardial dysfunction accompanied by vessel endothelial swelling and myocardial edema due to myocardial ischemia, and embolization of plaque, thrombotic, or inflammatory materials [21]. TA may be effective to avoid embolization of plaque or thrombotic debris [22]. Although recent RCTs [3—5] and two different meta-analyses [6,7] demonstrated that TA improved reperfusion surrogate and clinical end points and 2009 ACC/AHA guidelines for STEMI [8] raised advisability of TA to Class II a, level of Evidence B, in this study, we failed to demonstrate that TA improved clinical outcomes in STEMI patients who underwent primary PCI. In our study, since the incidence of 12-month MACE was relatively low (non-TA group: 10.0% and TA group: 7.5%) compared with the TAPAS study (non-TA group: 20.3% and TA group: 16.6%), our study might be substantially underpowered to demonstrate differences in clinical outcomes. In addition, retrospective analyses using propensity score and Cox regression models to correct confounding factors may affect the results.

On another front, in the present subgroup analyses, the use of GP IIb/IIIa inhibitor and culprit lesion in LAD were the settings in which MACE were improved. Since distal

Table 3 Clinical outcomes at 12 months.

	TA (−) (n = 1360)	TA (+) (n = 745)	p-Value
Total major adverse cardiac events, n (%)	134 (10.0%)	56 (7.5%)	0.068
Cardiac death, n (%)	31 (2.3%)	13 (1.7%)	0.430
Non-fatal myocardial infarction, n (%)	29 (2.2%)	5 (0.7%)	0.010
Repeat revascularization, n (%)	60 (4.5%)	25 (3.4%)	0.248
Stent thrombosis (definite/probable), n (%)	25 (2.1%)	19 (3.4%)	0.141

Values are expressed as number (%). TA, thrombus aspiration. Major adverse cardiac events: cardiac death, non-fatal myocardial infarction, repeat revascularization. Repeat revascularization: target lesion revascularization and target vessel revascularization.

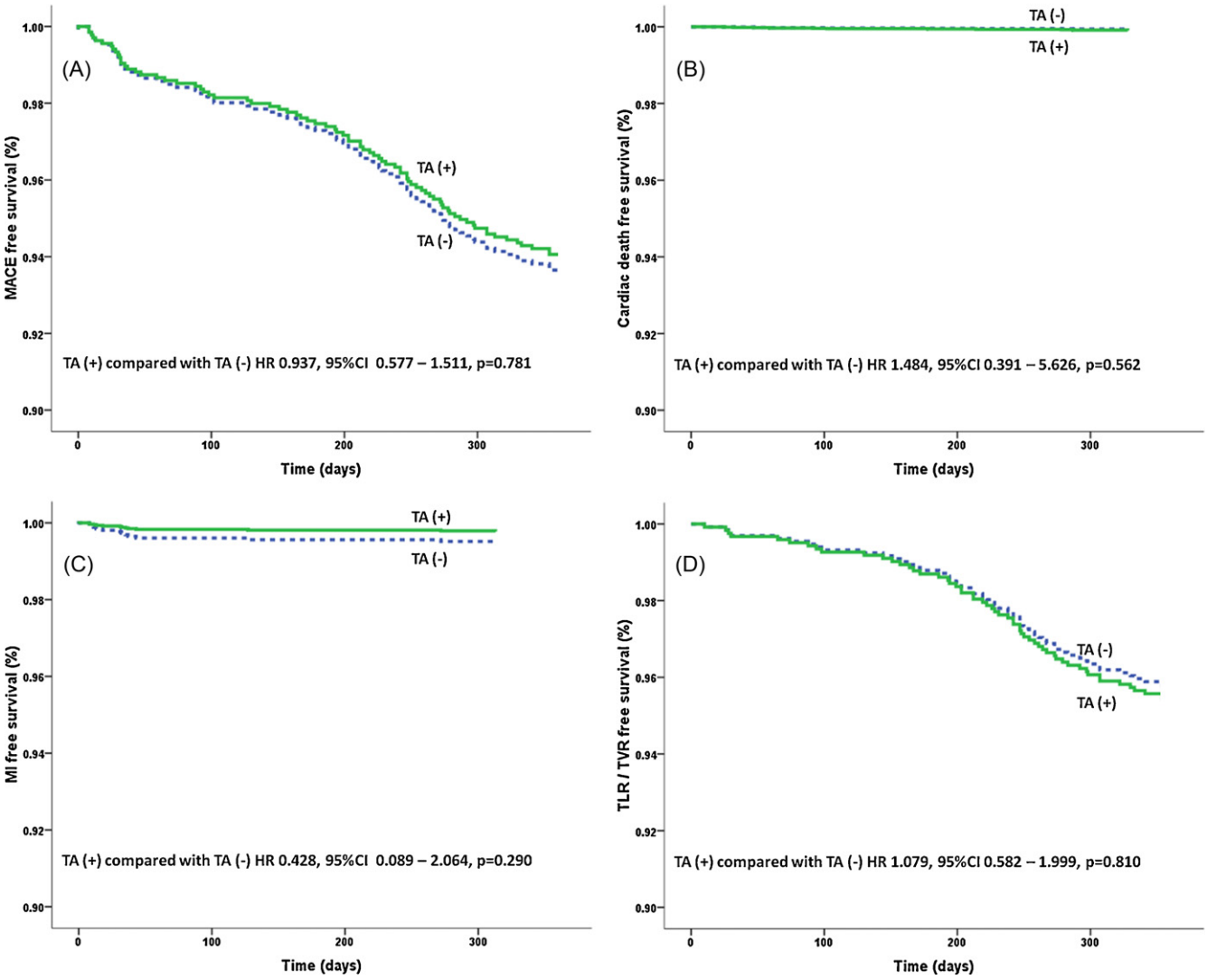

Figure 1 Adjusted 12-month survival curves. Adjusted survival curves stratified according to treatment groups. (A) The composite of major adverse cardiac events (cardiac death, non-fatal myocardial infarction, target lesion revascularization and target vessel revascularization). (B) Cardiac death. (C) Non-fatal myocardial infarction. (D) Target lesion revascularization and target vessel revascularization. MACE, major adverse cardiac events; TA, thrombus aspiration; HR, hazard ratio; CI, confidence interval; MI, myocardial infarction; TLR, target lesion revascularization; TVR, target vessel revascularization.

embolization is the most important cause of impaired epicardial flow and suboptimal myocardial reperfusion, which often occur after ballooning or stenting, physicians might predict and avoid it. In fact, the presence of lipid pool, floating thrombus, and attenuation plaque are linked to no reflow phenomenon, which is defined as an acute reduction in coronary flow (TIMI grade 0—1) without dissection, thrombus, spasm, or high-grade residual stenosis at the target lesion [23]. As shown in Table 2, IVUS was performed more than twice in patients without TA than those with. In the TA group, thrombi might be cleared out and show good angiographical results compared with the non-TA group. On the other hand, in the non-TA group, there might remain some thrombi or plaque burden after ballooning or stenting. This might make physicians decide to use IVUS in the non-TA group. Although mechanical removal of thrombi might reduce the existing source of embolization, platelet aggregates cannot be abolished completely. With respect to the use of GP IIb/IIIa inhibitors, it has been reported that it protects from ill effects of platelet aggregation and improves microvascular dysfunction [24,25]. Therefore, combined use of mechanical removal of thrombi and GP IIb/IIIa inhibitors during primary PCI may have a synergistic effect. Regarding effectiveness of TA for LAD as culprit lesion, though RCA is usually more thrombogenic and therefore at higher risk for distal embolization, one paper has reported that TA had a positive impact on proximal LAD in addition to RCA lesions [26]. If we can avoid no-reflow phenomenon in LAD which supplies the largest territory of epicardial coronary arteries, there is a possibility to improve clinical outcomes.

Limitations

First, this study was based on observational registry data and control status of risk factors during follow-up was not

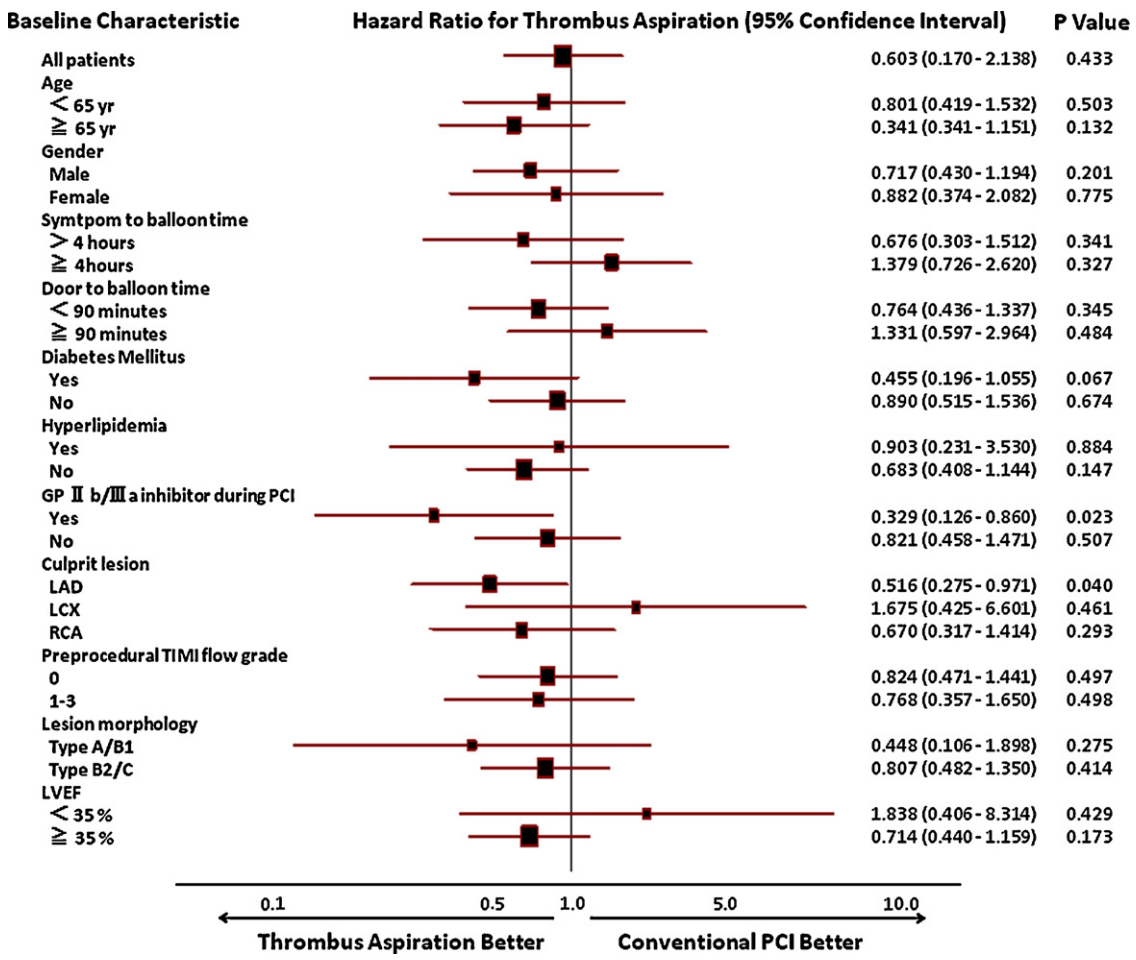

Figure 2 Hazard ratios (HR) and 95% confidence interval (CI) for the composite major adverse cardiac events (cardiac death, myocardial infarction, target lesion revascularization and target vessel revascularization) according to baseline clinical and procedural subgroups. GP, glycoprotein; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; TIMI, Thrombolysis In Myocardial Infarction; IVUS, intravascular ultrasound; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention.

available and only medications at discharge were available as reference index of risk management. We used Cox regression models adjusted by propensity score to correct confounding factors, however, the result may be influenced by the nonrandomized assignment and some confounding factors. Randomized evaluation will be needed for more accurate evaluation. However, we deem this study worthwhile owing to its large number of patients and appropriate method of statistical analysis. Second, in spite of the presence of TIMI flow grade in this registry, there was no information about other markers of myocardial perfusion such as corrected TIMI frame count, myocardial blush grade, and ST-segment resolution that were linked to prognosis more precisely [27—29]. In addition, although collateral flow would affect the prognosis after primary PCI, the data regarding collateral flow to culprit vessels were not available in this registry. Third, thrombus score and presence or absence of thrombus were not recorded, so we could not identify what made physicians decide to use TA device. Forth, adverse events about TA and cumulative data of stent thrombosis were not available. Fifth, we could not evaluate the percent of patients in whom Reopro was administered i.c. vs i.v. and investigate the difference between the two groups.

Conclusions

Although TA did not improve clinical outcomes in overall STEMI patients who underwent primary PCI, the use of TA for LAD occlusion will improve 12-month MACE. Furthermore, combined use of GP IIb/IIIa inhibitors with TA has a synergistic effect.

Acknowledgments

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Appendix A. Korea Acute Myocardial Infarction Registry

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