Abstract

Background: Adjunctive thrombus aspiration (TA) during primary percutaneous coronary intervention (PCI) was reported to promote better coronary and myocardial reperfusion. However, long-term mortality benefit of TA remains controversial. The objective of this study is to investigate the clinical impact of TA on long-term clinical outcomes in patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary PCI.

Methods and Results: The CREDO-Kyoto AMI registry is a large-scale cohort study of acute myocardial infarction (AMI) patients undergoing coronary revascularization in 2005-2007 at 26 hospitals in Japan. Among 5429 patients enrolled in the registry, the current study population consisted of 3536 patients who arrived at the hospital within 12 hours after the symptom onset and underwent primary PCI. Clinical outcomes were compared between the 2 patient groups with or without TA. During primary PCI procedures, 2239 out of 3536 (63%) patients underwent TA (TA group). The cumulative 5-year incidence of all-cause death was significantly lower in the TA group than in the non-TA group (18.5% versus 23.9%, log-rank $P<0.001$). After adjusting for confounders, however, the risk for all-cause death in the TA group was not significantly lower than that in the non-TA group (hazard ratio:0.90, 95% confidence interval:0.76-1.06, $P=0.21$). The adjusted risks for cardiac death, MI, stroke and target-lesion revascularization were also not significantly different between the 2 groups.

Conclusion: Adjunctive TA during primary PCI was not associated with better 5-year mortality in STEMI patients.

Key words: thrombus aspiration, acute coronary syndrome, coronary artery disease, no reflow, percutaneous coronary intervention

Text

Introduction

Acute myocardial infarction (AMI) can be called the disease of thrombus: the plaque rupture and the subsequent thrombus formation results in the occlusion of a coronary artery. Therefore primary percutaneous coronary intervention (PCI) is an established effective therapy for coronary reperfusion in AMI and adjunctive thrombus aspiration (TA), which was presumed to improve microvascular perfusion, was introduced to reduce distal embolism in daily clinical practice. Several randomized control trials (RCTs) comparing PCI with or without adjunctive TA have reported conflicting results and the mortality benefit of TA in STEMI patients treated with primary PCI still remains controversial[1-8]. The Thrombus Aspiration during Percutaneous Coronary Intervention in Acute Myocardial Infarction Study (TAPAS) was one of the largest trial suggesting 1-year mortality benefit of thrombus aspiration[9]. On the other hand, the Thrombus Aspiration in ST-Elevation Myocardial Infarction in Scandinavia (TASTE) trial has reported comparable 1-year mortality between primary PCI with TA versus PCI only[10]. Recently the Trial of Routine Aspiration Thrombectomy with PCI versus PCI Alone in Patients with STEMI (TOTAL) trial has shown no reduction of the risk of cardiovascular death, recurrent myocardial infarction, cardiogenic shock, or New York Heart Association (NYHA) class IV heart failure within 180 days[11].

In an attempt to evaluate whether adjunctive TA has clinical benefits in the real-world clinical practice, we examined the impact of adjunctive TA on long-term cardiovascular outcomes in a large-

scale observational database of AMI patients undergoing primary PCI in Japan.

Methods

Study population

The Coronary Revascularization Demonstrating Outcome study in Kyoto (CREDO-Kyoto) AMI registry is a physician-initiated, non-company sponsored, multi-center registry enrolling consecutive AMI patients undergoing coronary revascularization within seven days of symptom onset among 26 centers in Japan between January 2005 and December 2007 (Supplemental Appendix A). The relevant review boards or ethics committees in all participating centers approved the research protocol. Because of retrospective enrollment, written informed consents from the patients were waived; however, we excluded those patients who refused to participate in the study when contacted at follow-up. This strategy is concordant with the guidelines for epidemiological studies issued by the Ministry of Health, Labor and Welfare of Japan.

Among 5429 AMI patients enrolled in this registry, the current study population consisted of 3536 STEMI patients who had primary PCI within 12 hours after the onset after excluding 9 patients with refusal for study participation, 195 patients with coronary artery bypass grafting (CABG), 789 non-ST segment elevation acute myocardial infarction (non-STEMI) patients, 738 patients with PCI beyond 12 hours after the symptom onset, and 162 patients whose timing of PCI was unidentified (Figure 1).

Definitions and endpoints

The primary outcome measure for the current analysis was all-cause death. Secondary outcome measures included cardiac death, non-cardiac death, myocardial infarction (MI), stent thrombosis, stroke, and target-lesion revascularization (TLR). Death was regarded as cardiac in origin unless obvious non-cardiac causes could be identified. MI was defined according to the Arterial Revascularization Therapy Study[12]. Stent thrombosis (ST) was defined according to the Academic Research Consortium (ARC) definition[13]. TLR was defined as either repeated percutaneous or surgical revascularization for a lesion anywhere within the stent or the 5-mm borders proximal or distal to the stent. The detailed definitions of baseline clinical characteristics were described previously[14].

Data collection for baseline characteristics and follow-up events

Demographic, angiographic, and procedural data were collected from hospital charts or hospital databases according to the pre-specified definitions by experienced clinical research coordinators from the study management center (Research Institute for Production Development, Kyoto, Japan) (Supplemental Appendix B). In this retrospective cohort study, data collection for follow-up events was performed in 2010 and 2012. Collection of follow-up information was mainly conducted through review of in-patient and out-patient hospital charts by the clinical research coordinators, and additional follow-up information was collected through contact with patients, relatives and/or referring physicians by sending mail with questions regarding vital status, subsequent hospitalizations, and status of antiplatelet therapy. Death, MI, ST, and stroke were adjudicated by the

clinical event committee (Supplemental Appendix C). Median follow-up duration was 1843 (inter-quartile range [IQR]: 1496-2157) days. Complete 1-, 3-, and 5-year follow-up information was obtained in 98%, 95%, and 64% of patients.

Statistical analysis

Categorical variables were presented as numbers and percentages and compared using the chi-square test or Fisher's exact test. Continuous variables were presented as the mean and standard deviation or the median and IQR. Continuous variables were compared using the Student's t-test or the Wilcoxon rank sum test based on their distributions. Cumulative incidences were estimated by the Kaplan-Meier method and differences were evaluated with the log-rank test. The effect of the TA group as compared with the non-TA group was expressed as hazard ratio (HR) and their 95% confidence intervals (CI). Multivariable Cox proportional hazard models were employed to assess the HR of the TA group as compared with the non-TA group adjusting for 41 clinically relevant factors listed in Table 1. In addition, we computed the adjusted event curves of the 2 groups using the methods described by Ghali et al[15]. Consistent with our previous reports, continuous variables were dichotomized by clinically meaningful reference values or median values[14]. We also evaluated the effect of TA on the primary outcome measure in several clinically relevant subgroups stratified by age (>=75years or <75years), gender (male or female), diabetes mellitus (with or without diabetes mellitus), total ischemic time (0-2 hours, 2-6 hours, 6-12 hours), culprit lesion (LAD culprit or non-LAD culprit), initial Thrombolysis In Myocardial Infarction (TIMI) flow grade (TIMI flow grade 0 or TIMI flow

grade >=1), and hemodynamic status (Killip 1-3 or Killip 4). Multivariable Cox proportional hazard models were similarly developed for the subgroup analysis. In addition to the adjunctive TA use, 24 variables with P value<0.05 in the previously described full model were included in the multivariable models for the subgroup analysis reflecting our preference for parsimonious models to avoid overfitting. All statistical analyses were conducted using JMP version 10.0.2 (SAS Institute Inc, Cary, NC, USA) or SAS version 9.3 (SAS Institute Inc, Cary, NC, USA). All the statistical analyses were two-tailed and P values <0.05 were considered statistically significant.

Results

Among 3536 STEMI patients with primary PCI in the current study, 2239 patients (63%) received adjunctive TA during primary PCI (TA group). Baseline characteristics differed significantly in several aspects between the TA and the non-TA group (Table 1).

The cumulative five-year incidence of all-cause death was significantly lower in the TA group than in the non-TA group (18.5% versus 23.9%, log-rank P<0.001) (Table 2 and Figure 2). However, after adjusting for confounders, the adjusted risk of the TA group relative to the non-TA group for all-cause death was not significantly different (HR:0.90, 95%CI:0.76-1.06, P=0.21) (Table 2). Similarly, the adjusted risks for cardiac death, non-cardiac death, and TLR were not significantly different between the 2 groups (HR:0.99, 95%CI:0.79-1.24, P=0.91, HR:0.78, 95%CI:0.62-1.03, P=0.08 and HR:0.90, 95%CI:0.76-1.07, P=0.23, respectively), although the cumulative five-year incidences of

cardiac death, non-cardiac death, and TLR were significantly lower in the TA group (11.1% versus 14.5%, log-rank P=0.01, 8.3% versus 11.0%, log-rank P<0.001, and 21.6% versus 25.8%, log-rank P=0.007, respectively) (Table 2). The cumulative five-year incidences of and the adjusted risks for MI, stroke, and ST were not significantly different between the TA and non-TA group (Table 2).

The comparable adjusted risk for all-cause death between the TA and non-TA groups was consistently observed across subgroups stratified by gender, diabetes mellitus, and location of culprit lesion (Figure 3). In the subgroups of patients with <75 years of age, total ischemic time 0-2 hours, initial TIMI flow grade 1-3, and Killip class 4, the adjusted risk for all-cause death in the TA group was significantly lower than that in the non-TA group. However, there was not significant interaction between those 4 subgroup factors and the effect of TA on the risk for all-cause death (Figure 3).

Discussion

The main finding of the current analysis is that mortality benefit of adjunctive TA during primary PCI was not observed in STEMI patients with primary PCI in the real world clinical practice. Several RCTs reported the benefits of adjunctive use of TA during primary PCI[4, 7, 9]. The TAPAS trial demonstrated significantly lower one-year mortality by TA use. Reflecting these results, the current STEMI guidelines recommend the use of adjunctive TA during primary PCI as class IIa indication with a level of evidence B [16]. Most of these trials, however, did not have adequate power to detect mortality benefit of TA and evaluated surrogate endpoints such as myocardial blush grade or resolution

of ST-segment elevation instead of mortality [4-8]. Indeed, the recent 3 RCTs reported the absence of clinical benefit of TA in STEMI patients with primary PCI[2, 3, 11]. First, the INFUSE-AMI trial, comparing primary PCI plus adjunctive TA with primary PCI alone in 452 STEMI patients, reported no benefit of TA use in terms of infarct size at 30-day assessed by cardiac magnetic resonance imaging [3]. Second, the TASTE trial is a multi-center, randomized-controlled clinical trial assessing the mortality benefit of TA with adequate power (enrolling 7244 patients) and characterized by using the national comprehensive registry. The TASTE trial failed to show that routine TA could reduce one-year mortality of STEMI patients treated with primary PCI[10]. Finally, in the TOTAL trial, which has been the most recently presented, routine TA plus primary PCI, as compared with conventional PCI alone, did not reduce the risk of cardiovascular death, recurrent MI, cardiogenic shock, or class IV heart failure within 180 days. The finding of the TOTAL trial concerning the mortality benefit of thrombectomy is consistent with that of the TASTE trial[11]. Moreover, another important finding in the TOTAL trial is that routine TA was associated with a significantly higher rate of stroke. In this respect, previous studies including trials of rheolytic thrombectomy reported the similar finding[17, 18]. Certainly the mechanism of stroke might be embolization of thrombus or air during the procedure, but the explanation sounded unreasonable because the period of a continued increase in the rate of stroke was between 30 and 180 days, but not within 24 hours after the procedure. As the possibility of a chance finding as the explanation cannot be eliminated because of the relatively small number of events, further studies should be warranted to clarify the safety of TA for stroke risk. In spite of the TOTAL

trial, there is no denying the procedure of TA has the potential to make intervention easier in selected cases without any complex manipulation[1, 4-6, 19]. However, judging from the results of major trials including the safety concern about potential stroke risk, prudent attitudes should be taken toward the procedure in daily clinical practice[3, 10, 11, 17-19].

Several previous observational studies in real world clinical practice reported the mortality benefit of TA[20-23]. Consistent with the findings of the three RCTs, however, long-term mortality benefit of TA during primary PCI could not be observed in the current study reflecting real world clinical practice. The possibility cannot be ruled out that TA might be beneficial in high-risk patients excluded from the trials, but in our analysis, the benefit of TA could not be observed in any subsets of patients including high-risk patients such as elderly people or cardiogenic-shock cases. As in the INFUSE-AMI trial, the efficacy of TA was evaluated according to the total ischemic time as subgroup analysis in our study. In the patients with total ischemic time 0-2 hours, the adjusted risk for all-cause death in the TA group was significantly lower than that in the non-TA group, but there was not significant interaction between the total ischemic time and the effect of TA. Therefore, mortality benefit of adjunctive TA cannot be expected in most STEMI patients undergoing primary PCI in the current clinical practice where the management of STEMI patients has achieved great improvement with respect to both reperfusion therapy and adjunctive medical therapy.

Clinical implications

The three latest RCTs demonstrated no clinical benefit of routine TA, the results of which are

consistent with those of the current analysis. From these clinical trials, the recommendation of routine TA in the current guideline should be reconsidered. However, the clinical efficacy of TA cannot be totally denied and further investigation evaluating the clinical benefit of selective TA should be performed. In some selective cases, TA could facilitate the primary PCI procedure by more clearly delineating the true lesion length for appropriate stenting. In addition, one of the most important findings in the TOTAL trial is an increased rate of stroke. The safety concern about stroke associated with TA should also be investigated in future studies.

Limitations

Our study has several limitations. First, this is not a randomized control trial but an observational study. The indication of TA was at the discretion of the operator or of the hospital, so that outcomes might be affected by the effect of the operator's skill or of the hospital's practice level. In addition, baseline patient characteristics differed significantly between the TA and non-TA groups. Despite the appropriate statistical adjustment for potential confounders, unmeasured confounding factors might have influenced the results of the current study. Second, the current study did not evaluate detailed angiographic findings such as thrombus burden or myocardial blush grade. Third, as Glycoprotein (GP) IIa/IIIb inhibitors are not currently available in Japan, much caution is required in generalizing these results to patients outside Japan.

Conclusions

Adjunctive TA during primary PCI was not associated with better five-year mortality in

STEMI patients with primary PCI.

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Disclosures

None of the authors have conflict of interest to disclose regarding this manuscript.

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Figure titles and legends

Figure 1: Study flow chart

CREDO-Kyoto AMI registry=Coronary Revascularization Demonstrating Outcome Study in Kyoto Acute Myocardial Infarction registry; AMI=acute myocardial infarction; CABG=coronary artery bypass grafting; NSTEMI=non-ST-segment elevation myocardial infarction; PCI=percutaneous coronary intervention; STEMI=ST-segment elevation myocardial infarction; TA=thrombus aspiration

Figure 2: Crude and Adjusted Kaplan-Meier curves for cumulative incidence of all-cause death

TA=thrombus aspiration

Figure 3: Subgroup analyses and forest plots of hazard ratio for all-cause death

LAD=left anterior descending; PCI=percutaneous coronary intervention; TA=thrombus aspiration; TIMI=Thrombolysis In Myocardial Infarction

Tables

Table 1: Baseline patient characteristics-TA group versus non-TA group

Variables	TA group N=2239	non-TA group N=1297	p value
Clinical characteristics			
Age	66.6±12	68.9±12.1	<0.001
*†>75years	640(28.6%)	451(34.8%)	<0.001
*Male gender	1700(75.9%)	933(71.9%)	0.009
Body mass index	23.8±3.5	23.3±3.4	<0.001
*†<25.0kg/m2	1557(69.5%)	977(75.3%)	<0.001
*†Hypertension	1749(78.1%)	1011(77.9%)	0.91
Diabetes mellitus	659(29.4%)	459(35.4%)	<0.001
*†on insulin therapy	83(3.7%)	72(5.6%)	0.01
*Current smoking	953(42.6%)	492(37.9%)	0.007
*†Previous heart failure	686(30.6%)	422(32.5%)	0.24
*†Multivessel disease	1054(47.1%)	738(56.9%)	<0.001
*†Mitral regurgitation3-4/4	55(2.5%)	43(3.3%)	0.14
*Previous myocardial infarction	196(8.8%)	129(9.9%)	0.24
*†Previous stroke	175(7.8%)	136(10.5%)	0.008
*Peripheral vascular disease	65(2.9%)	42(3.2%)	0.58
Previous PCI or CABG	215(9.6%)	121(9.3%)	0.79
*†eGFR<30, without hemodialysis	79(3.5%)	62(4.8%)	0.07
*†Hemodialysis	19(0.9%)	29(2.2%)	<0.001
*†Atrial fibrillation	224(10.0%)	114(8.8%)	0.23
*Anemia(hemoglobin<11.0g/dl)	185(8.3%)	136(10.5%)	0.03
*†Thrombocytopenia(Platelet < 100*109/L)	42(1.9%)	28(2.2%)	0.56
*COPD	69(3.1%)	41(3.2%)	0.90
*†Liver cirrhosis	52(2.3%)	32(2.5%)	0.79
*†Malignancy	173(7.7%)	118(9.1%)	0.16
Presentation			
Killip class<=2	1873(83.7%)	1053(81.2%)	0.06
*†Killip class4	324(14.5%)	206(15.9%)	0.26
*Initial TIMI flow grade=0	1620(72.4%)	664(51.2%)	<0.001
Total ischemic time(median hours)	2.0(1.0-3.9)	2.3(1.1-4.4)	0.004
IABP use	369(16.5%)	218(16.8%)	0.80
PCPS use	62(2.8%)	39(3.0%)	0.68