3．施設間搬送されたST上昇型急性心筋梗塞患者における搬送距離と長期予後の関連に関する研究

厚生労働科学研究費補助金（循環器疾患・糖尿病等生活習慣病対策総合研究事業）
分担研究報告書

- 施設間搬送されたST上昇型急性心筋梗塞患者における搬送距離と長期予後の関連に関する研究 -

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研究要旨

CREDO-Kyoto AMI Registryに登録された発症24時間以内のST上昇型急性心筋梗塞（STEMI）症例のうち、PCI非施行施設からPCI施行施設に施設間搬送を受けた症例における施設間搬送に関する地理的関係や搬送距離が予後に与える影響を検討した。本研究における施設間搬送距離の中央値は8.0kmであった。搬送距離が長い症例(8km以上)では、短い症例(8km未満)に比較して、総虚血時間が有意に長かった（5.2時間 対 4.9時間、P=0.04）。一方で、5年時における累積の死亡/心不全入院の発症率においては有意差を認めなかった(26.4% 対 28.2%、P=0.61）。本検討からSTEMI患者が施設間搬送を必要とした場合、本邦では概ね適切に近隣のPCI施行可能な施設へ搬送されている実態が明らかとなった。今後、施設間搬送を要する患者の予後を更に改善するためには、近隣のPCI施行可能な施設への効率的な搬送を可能にする救急体制作りに加えて、搬送元の医療機関における患者の滞在時間（搬送元の施設に来院し搬送先の施設へ出発するまでの時間）を短縮することで、総虚血時間を更に短縮していくことが重要であると考えられる。

A．研究目的

ST上昇型急性心筋梗塞（STEMI）患者がPCI非施行施設を受診し、その後Primary PCIのためにPCI施行可能な施設へ施設間搬送されることがある。しかしながら、諸外国よりPCI可能な医療機関の多い本邦におけるSTEMI患者の施設間搬送の実態は明らかではない。本研究の目的は、STEMI患者の施設間搬送の実態を明らかにするとともに、搬送元のPCI非施行施設と搬送先のPCI施行施設の間の搬送距離が長期予後に与える影響を検討することである。

B．研究方法

CREDO-Kyoto AMI Registryに登録された発症24時間以内のSTEMI症例のなかで施設間搬送が行われた症例の施設間搬送における距離を直線距離ではなく道路網を加味した距離を距離測定ソフト(ACT 距離計算ワークシート for Excel)を使用して計測した。その後中央値で2群に分け、施設間搬送距離の短い症例と長い症例での臨床的背景及び長期予後の比較を行った。主要評価項目は死亡/心不全入院の複合エンドポイントとした。

C．研究結果

本研究において発症24時間内のSTEMI症例で施設間搬送を受けた症例は1725例であった。このうち、ヘリコプターを使用した搬送が行われた76例及び搬送元施設の情報が入手できなかった24例を除いた1625例を対象として解析を行った。その結果、施設間搬送における搬送距離の中央値は8.0(四分位範囲；3.8-18.4)kmであった。

1．　患者背景

1-①　患者背景

	TD <8 km	TD >=8 km	P value
Number of patients	N = 789	N = 836	
Age (years)	68.8 ± 12.8	68.4 ± 12.1	0.53
Age >=75 years*	290 (37)	277 (33)	0.13
Male sex*	545 (69)	599 (72)	0.26
BMI <25.0*	591 (75)	612 (73)	0.43
Hypertension*	636 (81)	644 (77)	0.08
Diabetes mellitus	250 (32)	277 (33)	0.53
on insulin therapy*	36 (4.6)	35 (4.2)	0.71
Current smoking*	317 (40)	317 (38)	0.35
Heart failure*	246 (31)	259 (31)	0.93
Multivessel disease*	407 (52)	413 (49)	0.38
Ejection fraction <= 40%	102 (16)	113 (19)	0.23
Prior myocardial infarction*	46 (5.8)	48 (5.7)	0.94
Prior stroke (symptomatic)*	75 (9.5)	69 (8.3)	0.37
Peripheral vascular disease*	19 (2.4)	26 (3.1)	0.39
eGFR (ml/min/1.73 m^2)	70.9 ± 27.8	70.7 ± 30.7	0.91
Hemodialysis*	15 (1.9)	15 (1.8)	0.87
Atrial fibrillation*	77 (9.8)	74 (8.9)	0.53
Anemia (Hb <11.0 g/dl)*	105 (13)	89 (11)	0.10
Liver cirrhosis*	19 (2.4)	14 (1.7)	0.29
Malignancy*	57 (7.2)	52 (6.2)	0.42

搬送距離が長い症例(8km 以上)と短い症例(8km 未満)で患者背景を比較すると、高血圧症は搬送距離が短い群でやや多い傾向を認めた(77% 対 81%、P=0.08)が、その他の冠危険因子の保有率や病変背景に両群間で有意な差は認めなかった。

1-②　血行動態

	TD <8 km	TD >=8 km	P value
Number of patients	N = 789	N = 836	
Killip class 1	579 (73)	641 (77)	0.38
Killip class 2	74 (9.4)	76 (9.1)	
Killip class 3	25 (3.2)	20 (2.4)	
Killip class 4*	111 (14)	99 (12)	
IABP use	120 (15)	121 (14)	0.68
PCPS use	17 (2.2)	19 (2.3)	0.36

血行動態に関しては、2 群間で有意な差は認めず、心原性ショックの合併率は約 10%程度であった。

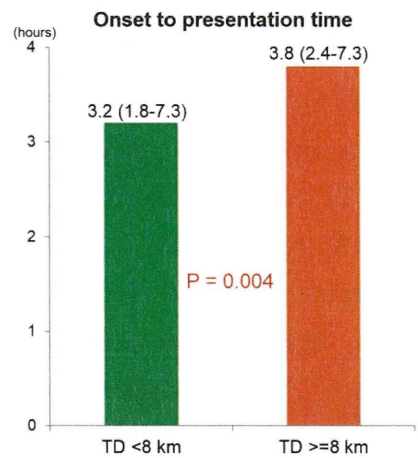
1-③ 病変背景

	TD <8 km	TD >=8 km	P value
Number of patients	N = 789	N = 836	
Infarct related artery location			
LAD	381 (48)	389 (47)	0.37
LCX	74 (9.4)	75 (9.0)	
RCA	323 (41)	352 (42)	
LMCA	10 (1.3)	18 (2.2)	
CABG	1 (0.1)	2 (0.2)	
Number of target lesions	1.40 ± 0.72	1.45 ± 0.78	0.25
Target of proximal LAD*	442 (56)	477 (57)	0.67
Target of bifurcation*	204 (26)	241 (29)	0.18
Minimum stent size <3.0 mm*	254 (35)	273 (35)	0.95

病変背景については、左前下行枝を責任病変とする割合は約 50%で、分岐部病変に対する治療は 30%弱であり、いずれも両群間に有意差は認めなかった。

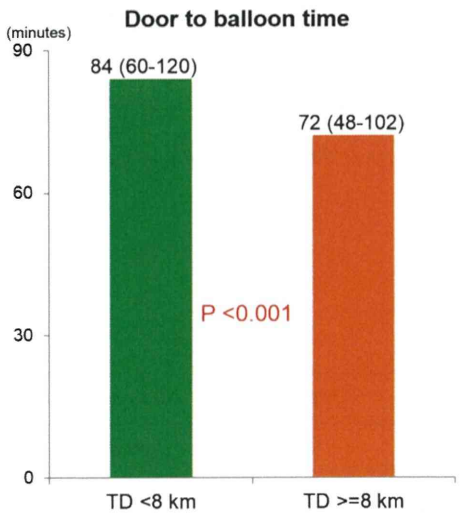
2．結果

2-①　発症-来院時間



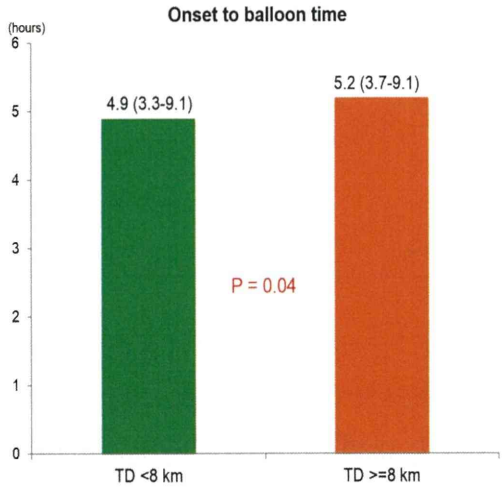
※TD = transfer distance (搬送距離)

2-② 来院-バルーン時間



※TD = transfer distance（搬送距離）

2-③ 総虚血時間

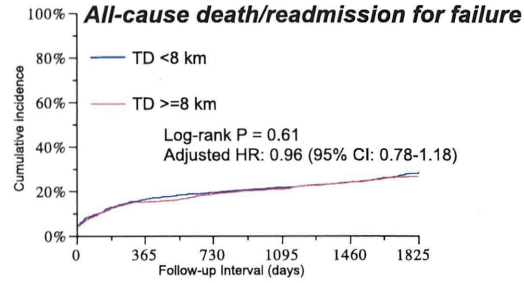


※TD = transfer distance（搬送距離）

発症-来院時間（平均（四分位範囲））に関しては、搬送距離 8km 以上の群 3.8（2.4-7.3）時間に対して搬送距離 8km 未満の群 3.2（1.8-7.3）時間と搬送距離 8km 以上の群で有意に遅延していた（P=0.004）。一方、来院-バルーン時間に関しては、搬送距離 8km 以上の群 72（48-102）分、搬送距離 8km 未満の群 84（60-120）分と搬送距離 8km 以上の群で有意に短かった（P<0.001）。総虚血時間に関しては、搬送距離 8km 以上の群 5.2（3.7-9.1）時間に対して、搬送距離 8km 未満の群では 4.9（3.3-9.1）時間と搬送距離 8km 以上の群で有意に長かった（P=0.04）。

2-④ 長期予後

2-④-1 総死亡/心不全入院（カプラン-マイヤー曲線）



Interval	0 days	30 days	1 year	3 years	5 years
TD <8 km					
N of events		49	127	168	212
N of patients at risk	789	740	652	597	374
Cumulative incidence		6.2%	16.2%	21.5%	28.2%
TD >=8 km					
N of events		46	124	170	212
N of patients at risk	836	784	696	627	391
Cumulative incidence		5.5%	15.0%	20.7%	26.4%

2-④-2 多変量解析結果

	補正後		
	TD >=8 km		
	ハザード比	95% 信頼区間	P 値
総死亡/心不全入院	0.96	(0.78-1.18)	0.69
総死亡	0.99	(0.78-1.24)	0.92
心臓死	1.11	(0.81-1.52)	0.51
心不全入院	1.02	(0.68-1.52)	0.93

5 年間での累積の死亡/心不全入院発症率は、搬送距離 8km 未満の群で 28.2%に対して、搬送距離 8km 以上の群で 26.4%と有意な差を認めなかった（log-rank P=0.61）。この結果は、多変量解析による背景因子の補正後も同様であった（ハザード比 0.96、95%信頼区間 0.78-1.18、P=0.69）。また、総死亡、心臓死、心不全入院に関しても、同様に両群間に有意な差を認めなかった。

D．考察

本研究の結果から本邦において STEMI 症例が PCI 非施行施設から PCI 施行施設に施設間搬送される場合、中央値 8km という比較的近隣の PCI 施行可能な施設に適切に施設間搬送が行われてい

る実態が明らかとなった。搬送距離が短い症例と長い症例で臨床転帰を比較すると、死亡/心不全において両群間で有意差は認めなかった。一方で、総虚血時間については、搬送距離が長い症例では、短い症例に比較して有意に長い結果であった。本研究では施設間搬送距離の中央値が 8 km と比較的短かったために、2 群に分けた場合に総虚血時間の差が 18 分と短かったために、搬送距離の違いのみでは臨床転帰にまで有意な影響を与えなかったものと考えられる。

今後、施設間搬送を要する患者の予後を更に改善するためには、搬送そのものにかかる時間を短縮すべく近隣の PCI 施行可能な施設への効率的な搬送を可能にする救急体制作りに加えて、搬送元の医療機関における患者の滞在時間（搬送元の施設に来院し搬送先施設へ出発するまでの時間）を短縮することで総虚血時間を更に短縮することが重要であると考えられる。実際に海外の研究から、STEMI 症例が施設間搬送を必要とした場合、最も時間を費やすのは搬送前の施設での滞在時間であることが報告されている。本研究では搬送元の医療機関での滞在時間についての検討は行っておらず、今後の検討課題と考えられる。また、今回の検討が医療過疎地を含めた本邦の全体像を反映しているかは明らかでなく、地域毎に施設間搬送の実態を把握する必要があると考えられる。

E．結論

本研究において STEMI 症例に対する施設間搬送の搬送距離は比較的短く、適切に近隣の PCI 施行可能な施設に施設間搬送が行われていた。このため搬送距離の違いによって臨床転帰に有意な差は認めなかった。

F．研究発表

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G．知的財産権の出願・登録状況

該当なし

III. 研究成果の刊行に関する一覧表

III. 研究成果の刊行に関する一覧表

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ
なし							

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Watanabe H, Shiomi H, Nakatsuma K, Morimoto T, Taniguchi T, Furukawa Y, Nakagawa Y, Horie M, Kimura T, on behalf of the CREDO-Kyoto AMI investigators.	The Clinical Efficacy of Thrombus Aspiration on Five-year Clinical Outcomes in Patients with ST-segment Elevation Acute Myocardial Infarction Undergoing Percutaneous Coronary Intervention.	J Am Heart Assoc.			2015 in press.
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Taniguchi T, Shiomi H, Toyota T, Morimoto T, Akao M, Nakatsuma K, Ono K, Makiyama T, Shizuta S, Furukawa Y, Nakagawa Y, Ando K, Kadota K, Horie M, Kimura T.	Effect of preinfarction angina pectoris on long-term survival in patients with ST-segment elevation myocardial infarction who underwent primary percutaneous coronary intervention.	Am J Cardiol.	15;114(8)	1179-86	2014

Ⅳ．研究成果の刊行物・別刷

Title page

Title: The Clinical Efficacy of Thrombus Aspiration on Five-year Clinical Outcomes in Patients with ST-segment Elevation Acute Myocardial Infarction Undergoing Percutaneous Coronary Intervention

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Short title: Thrombus aspiration during primary PCI

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Journal Subject Codes: Acute myocardial infarction

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