

Lack of Long-Term Clinical Benefit of Thrombus Aspiration During Primary Percutaneous Coronary Intervention With Paclitaxel-Eluting Stents or Bare-Metal Stents: Post-Hoc Analysis of the PASSION-Trial

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Background: Although current clinical guidelines recommend the use of thrombus aspiration (TA) during primary percutaneous coronary intervention (PPCI), previous studies evaluating TA demonstrated contradictory results. The aim of this study was to evaluate long-term clinical outcome after TA in adjunct to PPCI for acute ST-segment myocardial infarction (STEMI), as compared with conventional treatment, with the use of paclitaxel-eluting stents or bare-metal stents. **Methods:** We analyzed data of the PASSION trial, in which 619 patients with STEMI were randomly assigned to a paclitaxel-eluting stent or a bare-metal stent. TA was performed in 311 patients (50.2%). Clinical endpoints at 2 years were compared between patients who received TA during PPCI with patients who underwent conventional PPCI. The primary outcome of interest was a composite of cardiac death, recurrent myocardial infarction (MI), or target-lesion revascularization (TLR). A propensity score model was made to account for baseline differences that could have affected the probability of performing TA. **Results:** Complete follow-up was available for 598 patients (96.6%). The cumulative incidence of the combined outcome measure of cardiac death, recurrent MI, or TLR was 40 (13.0%) in the TA group and 41 (13.5%) in the conventional PPCI group (HR 0.96; 95% CI 0.62–1.47; $P = 0.84$). Also after adjusting for propensity score, no significant difference in event rate was observed between both treatment groups. **Conclusions:** In this post-hoc analysis of the PASSION trial, TA in adjunct to PPCI did not affect rates of major adverse cardiac events at 2 years follow-up, as compared with conventional PPCI. © 2011 Wiley Periodicals, Inc.

Key words: acute myocardial infarction; thrombus aspiration; primary percutaneous coronary intervention; drug-eluting stent

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INTRODUCTION

Primary percutaneous coronary intervention (PPCI) is the preferred treatment for acute ST-segment elevation myocardial infarction (STEMI) [1]. In STEMI, the partial or complete occlusion of the infarct related artery is usually preceded by disruption or erosion of an atherosclerotic plaque, resulting in intraluminal thrombus. In a large proportion of patients, this leads to distal embolization and microvascular obstruction; this occurs spontaneously or can be induced by mechanical manipulations [2,3]. The resulting diminished microvascular flow is associated with an increased infarct size and worse prognosis [4,5]. Over the years, several devices have been developed to facilitate removal of thrombus, with the purpose of preventing distal embolization during PPCI. The early studies conducted with both manual and mechanical devices lead to conflicting results [6–12], after which one large prospective randomized trial showed a significant benefit in 1-year survival with manual thrombus aspiration (TA) in adjunct to PPCI [13]. In view of the preceding conflicting data, though, the clinical value of TA is still in debate.

Although drug-eluting stents (DES) have demonstrated to reduce the need for target-lesion revascularization (TLR) in several randomized controlled trials [14], their use in STEMI remains controversial because of a possible higher risk of stent thrombosis (ST) occurring very late after implantation [15,16]. Since it was previously shown that thrombus burden may be associated with a higher risk of ST in DES [17], thrombus removal may in particular be of value with the use of DES in STEMI.

Our aim was to elucidate the impact of the use of TA in PPCI on late clinical outcome. We performed a post-hoc analysis of the clinical follow-up at 2 years of patients included in the Paclitaxel-eluting versus Conventional Stent in Myocardial Infarction with ST-segment Elevation (PASSION) trial.

METHODS

Patient Population

The PASSION trial was a prospective, randomized trial, which evaluated the use of a paclitaxel-eluting stent in PPCI. Six hundred and nineteen patients were included and randomized to treatment with either a paclitaxel-eluting stent (PES), Taxus Express2, Boston Scientific, or a conventional bare-metal stent (BMS), Express2 or Liberté, Boston Scientific. TA was only performed in one of the two study centers, which allowed for evaluation of both treatment strategies in two comparable patient groups.

Details of both design and results of the PASSION trial were published previously [18]. In short, patients presenting with a STEMI defined as >20 minutes of chest pain and at least 1 mm of ST-segment elevation in at least two contiguous leads, or a new left bundle branch block, who were eligible for PPCI within 6 hours of onset of symptoms, were included. Main exclusion criteria were thrombolytic therapy; a contraindication for clopidogrel, aspirin, or both; and evident cardiogenic shock before randomization. The study complied with the principles in the Declaration of Helsinki, was approved by the local ethics committees of both participating centers. All study participants provided informed consent, which was documented in the patients' clinical records.

Procedures

Aspirin (at a dose of 100–500 mg) and clopidogrel (300 mg) were given when patients first arrived at the hospital. A bolus of 10,000 IU of unfractionated heparin (5,000 IU in case of the use of the glycoprotein (GP) IIb/IIIa inhibitor abciximab) was administered before the procedure. This was followed by aspirin 80–100 mg daily for life and clopidogrel 75 mg daily for at least 6 months. Abciximab was administered at the discretion of the operator. Coronary angiography and intervention was performed through either the radial or the femoral artery.

The use of TA was at the operators' discretion. In general, TIMI flow grade 0 or 1 and/or the manifestation of a visible thrombus on coronary angiography were considered an indication for TA. Operators were at liberty to refrain from TA when they judged the target artery to be too small or too calcified. The TA devices used were the X-sizer system (eV3, White Bear Lake, MN) and the Export Aspiration Catheter (Medtronic, Minneapolis, MN). Technical success of TA was defined as the ability to cross the lesion and to increase TIMI flow grade by ≥ 1 and/or if substantial reduction of thrombus was achieved. Subsequently, patients were randomized to receive either a PES or a BMS. Acute procedural success was defined as TIMI flow grade 3 and <30% stenosis at the end of the procedure.

Clinical Follow-Up

Follow-up visits were carried out at 2 years after enrollment. The primary outcome of interest of the current post-hoc analysis was the composite of cardiac death, recurrent myocardial infarction (MI), and TLR including coronary artery bypass grafting (CABG) of the target-vessel. All deaths were considered to be from cardiac causes unless a noncardiac cause could be identified. In addition, the occurrence of ST according

TABLE I. Baseline Clinical and Angiographic Characteristics and Probability of Receiving Thrombus Aspiration

	Thrombus aspiration (<i>n</i> = 311)	Conventional PPCI (<i>n</i> = 308)	<i>P</i>	Odds ratio (95% CI)
Baseline clinical variables				
Age (years)	60 ± 13	62 ± 12	0.03	
Male	240 (77.2)	230 (74.7)	0.47	1.15 (0.79–1.66)
Hypertension	102 (32.8)	91 (29.5)	0.38	1.16 (0.83–1.64)
Hypercholesterolemia	91 (29.3)	67 (21.8)	0.03	1.49 (1.03–2.14)
Diabetes	41 (13.2)	27 (8.8)	0.08	1.58 (0.95–2.64)
Smoking	164 (52.7)	155 (50.3)	0.55	1.10 (0.80–1.51)
Previous MI	26 (8.4)	6 (1.9)	<0.001	4.59 (1.86–11.32)
Previous CABG	4 (1.3)	0 (0.0)	0.05	
Previous PCI	14 (4.5)	13 (4.2)	0.86	1.07 (0.49–2.31)
Family history of CAD	111 (35.7)	124 (40.3)	0.24	0.84 (0.60–1.14)
Anterior infarction	149 (47.9)	167 (53.2)	0.12	0.78 (0.57–1.07)
Total ischemic time (hours)	3.0 ± 1.7	2.9 ± 2.0	0.54	
Sum of ST-elevation (mm)	12.7 ± 8.4	9.8 ± 8.4	<0.001	
Angiographic variables				
Infarct-related artery			0.03	
LAD	144 (46.3)	166 (53.9)		0.74 (0.54–1.01)
RCA	143 (46.0)	104 (33.8)		1.67 (1.21–2.31)
RCX	18 (5.8)	32 (10.4)		0.53 (0.29–0.97)
Other	6 (1.9)	6 (1.9)	0.99	1.01 (0.57–1.78)
Multivessel disease	138 (44.4)	140 (45.4)	0.79	0.96 (0.70–1.31)
Proximal lesion	267 (85.9)	253 (82.1)	0.21	1.32 (0.86–2.03)
TIMI flow grade 0/1	258 (83.0)	181 (58.8)	<0.001	3.42 (2.35–4.96)
TIMI flow grade 0 (%)	75.6	49.7		
TIMI flow grade 1 (%)	7.4	9.2		
TIMI flow grade 2 (%)	11.3	17.6		
TIMI flow grade 3 (%)	5.8	23.5		
Visible thrombus	270 (86.8)	147 (47.7)	<0.001	7.21 (4.85–10.73)
Reference diameter (mm)	3.12 ± 0.46	3.22 ± 0.43	0.006	
Mean minimal luminal diameter (mm)	0.12 ± 0.36	0.20 ± 0.35	0.006	
Degree of stenosis (%)	93.7 ± 13.1	95.2 ± 14.6	0.21	

Values are expressed as number (%) or mean ± SD.

MI = myocardial infarction; CABG = coronary artery bypass grafting; PPCI = primary percutaneous coronary intervention; CAD = coronary artery disease; LAD = left anterior descending artery; RCA = right coronary artery; RCX = ramus circumflexus.

to the criteria set by the Academic Research Consortium (ARC) was examined [19].

Statistical Analysis

Baseline clinical, angiographic, and procedural data were compared using the Student's *t*-test or the Mann-Whitney *U* test (when appropriate) for continuous variables. Comparison of categorical data was performed with the Chi-square test or the Fisher exact test. To account for baseline clinical, angiographic, and procedural differences that might have affected the probability of making use of TA, we fit a logistic regression model to estimate the likelihood of TA. Variables were left out in case of missing values in more than 10% of patients, or if they were present in <1% of patients. Since a number of procedural variables were judged to be directly related to TA, and therefore are part of the treatment regimen, a second propensity score model was made to adjust only for

baseline clinical and angiographic variables. In this model, the variables direct stenting, stent size, stent length, and use of GP IIb/IIIa receptor inhibitor were excluded. Finally, 29 variables were included in a step-wise logistic regression analysis. Ten variables showed significant association with TA. These variables were used to calculate a TA propensity score for each patient in the final model.

The cumulative incidence rates of adverse cardiac events at 2 years were estimated with the Kaplan-Meier method. The differences of incidence rates between the two groups were tested with the log-rank test. Hazard ratios (HR) were calculated with Cox proportional-hazards models, first with TA as the only predictor, then with TA and the calculated propensity score as the two predictors. In all analyses, a two-sided *P*-value of <0.05 was considered statistically significant. Analyses were done with the Statistical Package for Social Sciences software (SPSS 16.0 for Windows).

TABLE II. Procedural Characteristics and Outcomes

	Thrombus aspiration <i>n</i> = 311	Conventional PPCI <i>n</i> = 308	<i>P</i>	Odds ratio (95% CI)
Paclitaxel-eluting stent <i>n</i> (%)	156 (50.2)	154 (50.0)	0.97	1.01 (0.73–1.38)
Direct stenting <i>n</i> (%)	237 (76.2)	84 (27.3)	<0.001	8.54 (5.95–12.27)
Stent size (mm)	3.18 ± 0.34	3.28 ± 0.34	<0.001	
Stent length (mm)	17.67 ± 5.03	20.16 ± 5.74	<0.001	
Number of stents used	1.26 ± 0.58	1.31 ± 0.60	0.25	
Residual stenosis (%)	3.40 ± 7.19	4.23 ± 11.52	0.30	
Procedural success (%)	94.2	95.1	0.61	
GP IIb/IIIa inhibitor <i>n</i> (%)	301 (98.6)	168 (27.1)	<0.001	25.1 (12.9–49.0)
Post procedural TIMI 3 flow <i>n</i> (%)	293 (94.2)	293 (95.1)	0.61	0.83 (0.41–1.69)
TIMI flow grade 0 (%)	1.0	0.6		
TIMI flow grade 1 (%)	1.0	0.3		
TIMI flow grade 2 (%)	3.9	3.9		
TIMI flow grade 3 (%)	94.2	95.1		
X-sizer system used	121 (38.9)			
Export Aspiration Catheter used	190 (61.1)			

Values are expressed as number (%) or mean ± SD. Procedural success was defined as TIMI flow grade 3 and ≤ 30% stenosis at the end of procedure.

RESULTS

Patients

TA was performed in 311 patients (50.2%), either by mechanical aspiration with the X-sizer system (121 patients, 38.9%) or by manual aspiration with the Export catheter (190 patients, 61.1%). The baseline clinical and angiographic characteristics are summarized in Table I. At a mean age of 60 ± 13 versus 62 ± 12 the patients in which thrombus removal was performed were slightly younger than the patients in which conventional PPCI was performed ($P = 0.03$). In addition, these patients more often had suffered a previous MI than patients in the conventional treatment group (8.4% vs. 1.9%, $P < 0.001$).

Angiography and Procedural Outcome

Both TIMI flow grade 0 or 1 (83.0 vs. 58.8%) and angiographic visible thrombus (86.8 vs. 47.7%) were more often observed in the patients treated with TA as opposed to conventional PPCI ($P < 0.001$ for both) (Table I). The procedural characteristics are stated in Table II. At 50.2% versus 50.0%, the percentage of patients receiving a PES was equal ($P = 0.97$). No periprocedural complications related to the use of the TA device were observed. Direct stenting was ensued in 76.2% in the TA groups and 27.3% in the conventional PPCI group ($P < 0.001$). Acute procedural success was comparable in both groups and achieved in 94.2 and 95.1% in the TA group and conventional PPCI group, respectively ($P = 0.61$).

Clinical Outcome

At 2 years follow-up, complete clinical data were available of 96.6% of all patients. The cumulative

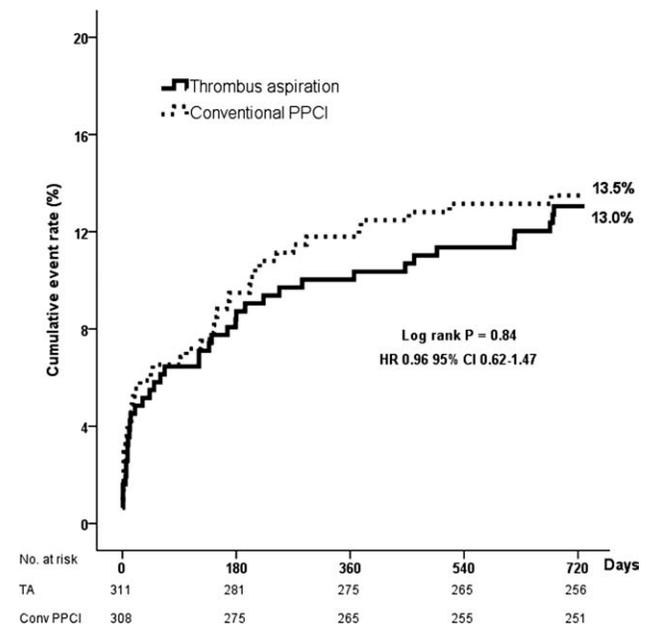


Fig. 1. Kaplan-Meier time-to-event curves of the cumulative incidence of cardiac death, recurrent myocardial infarction, or target-lesion revascularization.

incidence of the composite of cardiac death, recurrent MI, or TLR was observed in 40 patients (13.0%) in the TA group, and in 41 patients (13.5%) in the conventional PPCI group (HR 0.96, 95% C.I. 0.62–1.47; $P = 0.84$; Fig. 1). The incidence of TLR was comparable in both groups, with 23 (7.7%) and 24 (8.3%) patients in the TA group and the conventional PPCI group, respectively, (HR 0.93 95% CI 0.53–1.65; Table III).

In the propensity score model, 10 variables remained statistically significant related to treatment allocation

TABLE III. Adverse Clinical Events at Two Years Follow-Up

	Thrombus aspiration <i>n</i> = 311	Conventional PPCI <i>n</i> = 308	HR (95% CI)	Log rank <i>P</i>
Cardiac death, recurrent MI, or TLR	40 (13.0)	41 (13.5)	0.96 (0.62–1.47)	0.84
Any death	25 (8.1)	23 (7.5)	1.07 (0.61–1.88)	0.83
Recurrent MI	9 (3.1)	7 (2.4)	1.26 (0.47–3.38)	0.65
Cardiac death	19 (6.2)	20 (6.6)	0.93 (0.50–1.75)	0.83
TLR	23 (7.7)	24 (8.3)	0.93 (0.53–1.65)	0.81
Definite stent thrombosis	6 (1.9)	4 (1.3)	1.47 (0.41–5.20)	0.55
Definite or probable stent thrombosis	7 (2.3)	9 (2.9)	0.76 (0.28–2.04)	0.59

Values are expressed as number (%).

MI = myocardial infarction; TLR = target-vessel revascularization.

(Table IV). With a propensity score of 1 being equivalent to a high probability of receiving TA, mean propensity scores were 0.64 ± 0.20 in the TA group and 0.37 ± 0.24 in the conventional PPCI group. The ROC-curve of the propensity score had an area under the curve of 0.80. With procedural variables related to treatment regimen added to the model, propensity scores were 0.78 ± 0.23 and 0.22 ± 0.26 , respectively. When these propensity scores were added as a covariate, there still was no significant difference observed in the occurrence of the composite of cardiac death, recurrent MI, or TLR between the two groups (HR 1.09 95% CI 0.65–1.81, $P = 0.92$ for baseline and angiographic variables, HR 0.82 95% CI 0.43–1.57, $P = 0.55$ for all baseline, angiographic, and procedural variables; Table V). This indicates that the absence of an additional effect of TA on clinical outcome cannot be attributed to differences in variables added to the model.

The incidence of ST was similar between the two treatment groups. Definite or probable ST occurred in 7 patients (2.3%) in the TA group and in 9 patients (2.9%) in the conventional PPCI group, HR 0.76, 95% CI 0.28–2.04, $P = 0.59$ (propensity score adjusted HR 0.85, 95% CI 0.27–2.69). In patients treated with PES, definite or probable ST was observed in 5 patients (3.2%) who had received TA and in 3 patients (1.9%) who underwent conventional PPCI (HR 1.64 95% CI 0.39–6.87, $P = 0.49$).

DISCUSSION

In this post-hoc analysis of the PASSION-trial, the use of TA in adjunct to PPCI with either a manual or a mechanical device did not affect the incidence of major adverse cardiac events at 2 years, as compared with conventional PPCI. Also after adjustment for differences in baseline clinical and procedural characteristics using a propensity score, no differences were observed in the occurrence of the

TABLE IV. Variables That Remained Significant for Undergoing Thrombus Aspiration in the Propensity Score Calculated by Step-Wise Logistic Regression

	Odds ratio	95% CI	<i>P</i>
Previous MI	7.62	2.67–21.76	<0.001
Diabetes mellitus	2.12	1.11–4.06	0.02
Age	1.03	1.02–1.05	<0.001
Anterior MI	0.66	0.45–0.98	0.04
Positive family history	0.59	0.39–0.88	0.01
Visible thrombus	6.42	4.18–9.85	<0.001
Proximal tortuosity	3.90	1.52–10.06	0.01
TIMI flow 0/1	2.97	1.92–4.58	<0.001
Calcified lesion	2.30	1.08–4.94	0.03
Proximal lesion	1.82	1.06–3.12	0.03

Variables offered to the model were: age, sex, hypertension, hypercholesterolemia, current smoking, diabetes mellitus, positive family history, previous PTCA, previous stent, previous myocardial infarction, anterior wall infarction, cardiogenic shock related to index event, >11 mm ST-segment elevation, multivessel coronary artery disease, proximal lesion, reference diameter >3 mm, mean reference diameter, mean minimal luminal diameter, mean percentage of stenosis, TIMI flow 0/1, calcified lesion, proximal tortuosity, DES or BMS, visible thrombus, stent size and stent length, direct stenting, and the use of GP IIb/IIIa inhibitors.

combined outcome measure or in any single major adverse cardiac event.

Most of the previous reported studies on TA devices were designed to investigate surrogate markers of myocardial reperfusion, which, in some studies, were improved with TA, as compared with conventional PPCI [6–12]. In a meta-analysis of these trials, TA was suggested to facilitate reperfusion more effectively than conventional PPCI [20]. The duration of clinical follow-up in these studies was generally short, and, partly due to limited sample sizes, these studies could not prove TA to be beneficiary with regard to clinical outcome, as opposed to conventional PPCI. Conversely, in the TAPAS trial manual TA showed to improve clinical outcome at 1 year. To date, this remains the only RCT demonstrating clinical benefit of TA [13]. An important difference in treatment strategy in the TAPAS trial was direct

TABLE V. Adverse Clinical Events at Two Years Follow-Up

	Hazard ratios (95% Confidence Interval)				
	Thrombus aspiration <i>n</i> = 311	Conventional PPCI <i>n</i> = 308	Unadjusted	Adjusted for full propensity score	Adjusted for preprocedural propensity score
Cardiac death or recurrent MI or TLR	40 (13.0)	41 (13.5)	0.96 (0.62–1.47)	0.82 (0.43–1.57)	1.09 (0.65–1.81)
Any death	25 (8.0)	23 (7.5)	1.07 (0.61–1.88)	1.27 (0.54–3.00)	1.12 (0.58–2.16)
Recurrent MI	9 (3.1)	7 (2.4)	1.26 (0.47–3.38)	1.21 (0.27–5.35)	1.32 (0.42–4.16)
Cardiac death	19 (6.2)	20 (6.6)	0.93 (0.50–1.75)	0.89 (0.35–2.29)	0.98 (0.47–2.04)
TLR	23 (7.4)	24 (7.8)	0.93 (0.53–1.65)	0.71 (0.30–1.66)	1.00 (0.52–1.96)
Stent thrombosis					
Definite	6 (1.9)	4 (1.3)	1.47 (0.41–5.20)	1.28 (0.19–8.45)	1.43 (0.33–6.21)
Definite or probable	7 (2.3)	9 (2.9)	0.76 (0.28–2.04)	0.85 (0.27–2.69)	0.79 (0.18–3.47)

Hazard ratios after adjustment for propensity scores. Full propensity score signifies all baseline, clinical, and procedural variables including those directly related to thrombus aspiration. Variables offered to the model were: age, sex, hypertension, hypercholesterolemia, current smoking, diabetes mellitus, positive family history, previous PCI, previous stent, previous myocardial infarction, anterior wall infarction, cardiogenic shock related to index event, >11 mm ST-segment elevation, multivessel coronary artery disease, proximal lesion, reference diameter >3 mm, mean reference diameter, mean minimal luminal diameter, mean percentage of stenosis, TIMI flow 0/1, calcified lesion, proximal tortuosity, DES or BMS, visible thrombus, stent size and stent length, direct stenting, and the use of GP IIB-IIIa inhibitors. Preprocedural propensity score signifies all variables except stent size and stent length, direct stenting, and the use of GP IIB-IIIa inhibitors.

MI = myocardial infarction; TLR = target-lesion revascularization; ARC = academic research consortium.

stenting of the lesion in the TA group versus predilation in the conventional PCI group. Thereby, the strategy of direct stenting itself, apart from TA, could have led to a favorable angiographic result [21,22]. In addition, in the TAPAS trial a high percentage of patients had reperfusion before intervention, and no effect of TA on distal embolization was observed [23]. Therefore, with regard to TA, removal of intraluminal thrombus to facilitate accurate stenting may be of more importance than the intended prevention of distal embolization.

In this study, both a manual and a mechanical device were used for thrombus removal. After the publication of the TAPAS trial, a meta-analysis of RCTs described manual TA to be superior to mechanical TA in reducing mortality [24]. We recently performed a prospective, randomized comparison of manual TA versus mechanical TA [25]. Despite the modest benefit of manual TA on procedural parameters and surrogate endpoints, no difference in long-term clinical outcome was observed as compared with mechanical TA. Moreover, a recent study showed improved surrogate outcomes with the use of a mechanical aspiration device, as compared with conventional PPCI [26]. Their results were contradictory to an earlier study with the same device, showing increased mortality after thrombus removal [8]. These differences were explained because of a disparity in thrombus burden and to technical aspects of handling the device. The lack of benefit of TA on clinical outcome in this analysis may further question the use of TA, irrespective of the device used, particularly since a large real-world registry suggested

a detrimental effect of TA on mortality [27]. Perhaps the currently recruiting TA in ST-Elevation MI in Scandinavia (TASTE) trial may ultimately prove the advantage of TA expressed in clinical benefits rather than surrogate outcomes [28].

We observed no difference in the occurrence of ST up to two years between patients treated with TA and patients treated with conventional PPCI, both in patients treated with PES and BMS. In the retrospective study of Sianos et al. [17], the use of rheolytic thrombectomy was a negative predictor of ST in DES, although thrombectomy was performed in only a small proportion of patients. Whether thrombus removal could specifically reduce the risk of very late ST with DES in STEMI in case of large thrombus burden needs to be verified in large-scale studies.

Study Limitations

There are several limitations of this study, mainly due to its retrospective design. First, the decision to perform TA was not specified in our study protocol, since it was not formally recommended in clinical practice guidelines. As a result, some differences in baseline clinical and angiographic characteristics between the two groups exist, predominantly with regard to preprocedural epicardial flow, which has been reported to be associated with mortality [28]. We used the propensity score method to correct for these differences, and with the calculated propensity scores as a covariate, clinical outcome of the two treatment groups remained comparable. However, additional

unidentified confounders could have affected outcome. Another limitation is the absence of data on markers of reperfusion like ST-segment resolution or assessment of left ventricular function after PPCI.

In conclusion, in this post-hoc analysis of the PASSION trial, the use of manual or mechanical TA in adjunct to PPCI did not affect the 2-year incidence of major adverse cardiac events, as compared with conventional PPCI.

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