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Impact of thrombus aspiration in patients with ST-elevation versus non-ST-elevation acute coronary syndrome: a report from a multicentre Japanese PCI registry

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KEYWORDS

- acute coronary syndrome
- complications
- non-ST-elevation myocardial infarction
- ST-elevation myocardial infarction
- thrombus aspiration
- unstable angina

Abstract

Aims: Our aim was to determine whether manual thrombus aspiration (TA) is associated with improved patient outcomes in patients with acute coronary syndrome (ACS) in Japan, where a high number of TA procedures has been performed.

Methods and results: We analysed patient data from the multicentre all-comer PCI registry in Japan. The registry included 4,542 consecutive PCI-treated ACS patients between January 2009 and April 2013. The primary endpoint was the occurrence of major in-hospital complications. TA was performed in 1,715 patients (37.8%): 65.4% of ST-elevation myocardial infarction (STEMI), 31.1% of non-STEMI, and 11.3% of unstable angina (UA) patients. After multivariable analysis with propensity score adjustment, TA was not associated with improved primary outcomes (OR 1.279; 95% CI: 0.934-1.750). When each category of ACS was analysed individually, such a trend was observed in STEMI patients (OR 1.284; 95% CI: 0.836-1.972). In non-STEMI/UA patients, TA was associated with a higher risk of primary outcomes (OR 1.905; 95% CI: 1.199-3.025).

Conclusions: Despite its frequent usage in the contemporary Japanese PCI registry, TA does not appear to provide a clear clinical benefit in ACS-related PCI and may be harmful in patients presenting with non-STEMI/UA.

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Abbreviations

ACC	American College of Cardiology
ACS	acute coronary syndrome
CS	cardiogenic shock
HF	heart failure
IABP	intra-aortic balloon pump
JCD-KICS	Japanese Cardiovascular Database-Keio Interhospital Cardiovascular Studies
MI	myocardial infarction
NSTEMI/UA	non-STEMI/unstable angina
PCI	percutaneous coronary intervention
STEMI	ST-segment elevation myocardial infarction
TA	thrombus aspiration

Introduction

A reduction in coronary flow due to thrombus formation is observed in patients with acute coronary syndrome (ACS) as well as in those with ST-segment elevation myocardial infarction (STEMI) and non-STEMI/unstable angina (NSTEMI/UA). Various pharmacological and device-based strategies have been proposed for the direct intervention on this thrombus formation, among which is manual thrombus aspiration (TA)[1]. TA is considered to be a simple, safe, and effective procedure for preventing microvascular obstruction and improving short-term patient prognosis[2-4]. The clinically effective application of TA during primary percutaneous coronary intervention (PCI) in patients presenting with STEMI – while theoretically plausible – remains a controversial topic, despite a number of randomised clinical trials and meta-analyses published in the literature[2-7].

Thrombus formation is the prevailing cause of NSTEMI/UA and accounts for 50-60% of cases of patients presenting with ACS[8,9]. The risks associated with NSTEMI/UA are known to be similar to those of STEMI[10]. In the clinical setting, NSTEMI/UA patients frequently undergo TA to reduce the risk of distal embolisation, particularly when an angiographically proven intracoronary thrombus is present[11]. However, clinical studies investigating the application and effectiveness of TA in the context of NSTEMI/UA remain sparse[12,13].

The risks and benefits of TA must be carefully evaluated, as the procedure involves additional manual coronary manipulation and overall procedure time. We therefore sought to investigate the prognostic benefits of TA in patients presenting with STEMI and NSTEMI/UA. PCI patients registered with the Japanese multicentre PCI registry (Japanese Cardiovascular Database-Keio Interhospital Cardiovascular Studies [JCD-KICS]) were consecutively enrolled in the study between January 2009 and April 2013. Patients were treated at 13 different institutions in Japan where TA is performed relatively frequently. Thus, the present analysis provides insight into the conventional use of TA in the modern era of PCI treatment.

Methods

DATA SOURCE

The JCD-KICS is an ongoing, prospective multicentre registry designed to collect the clinical histories and outcome data of PCI patients[14]. Thirteen academic teaching hospitals within the Tokyo metropolitan area enrolled with the JCD-KICS, and all PCI procedures performed during the study period – including failure cases – were registered online using a web-based interface. Approximately 200 variables were collected for each patient, and clinical variables and in-hospital outcomes were defined in accordance with the National Cardiovascular Data Registry version 4.1. This registry, sponsored by the American College of Cardiology (ACC)[15,16], is the largest national clinical registry programme for diagnostic cardiac catheterisation and PCI, with more than 1,500 centres currently participating across the USA. Clinical research coordinators specifically trained in registering PCI procedures confirmed the correct notarisation of each patient and associated data. In addition, data reported online were monitored and investigators visited each hospital on a quarterly basis for the purpose of auditing the database for completeness and consistency.

STUDY POPULATION

We analysed data from consecutive ACS patients treated with PCI procedures at 13 hospitals in Japan from January 2009 to April 2013. The incidence of cardiogenic shock (CS) and out-of-hospital cardiac arrest was excluded from this study. To reduce patient selection bias, no other specific exclusion criteria were considered. Clinical, angiographic, and procedural complications entered into the JCD-KICS registry database were used. Thrombus aspiration was defined as any manual aspiration regardless of device (in our country several manual aspiration catheters were approved, but they all had a similar mechanism) **(Figure 1)**.

OUTCOME DEFINITION

Complications were defined as severe dissection or coronary perforation, myocardial infarction (MI) after PCI, CS or heart failure (HF), cerebral bleeding or stroke, and bleeding complications.

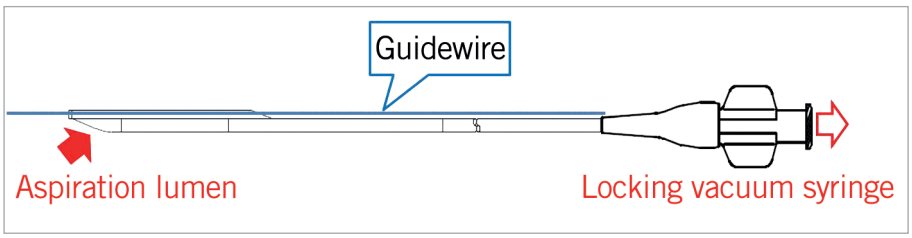

Figure 1. *Scheme of manual aspiration device that is frequently utilised in Japan.*

These definitions are in accordance with the NCDR CathPCI registry, and any additional data elements and definitions can be found at their website (https://www.ncdr.com/webncdr/cathpci/). Post-procedural myocardial infarction was defined as the new occurrence of a biomarker-positive myocardial infarction after PCI; only the patients with normal baseline cardiac biomarkers were included. The bleeding criteria used in this study are also consistent with Bleeding Academic Research Consortium grades 3A-C[17]. The primary endpoint of this study was defined as CS, HF, and in-hospital death.

STATISTICAL ANALYSIS

Continuous variables were expressed as means with standard deviation (SD) and comparisons were performed using the Student's t-test. Categorical variables were expressed as a percentage and the differences were examined using the chi-square test. Multivariate logistic regression analysis was performed to evaluate the relationship between the use of TA and in-hospital mortality, as well as other major in-hospital complications in STEMI and NSTEMI/UA patients. The variables used included baseline patient histories, ACS subtypes, and TA factors, which included the following: TA, age, sex, body mass index, history of old MI, HF, diabetes, cerebral vascular disease, peripheral arterial disease, chronic lung disease, chronic kidney disease, hypertension, smoking, history of PCI/CABG, and type of ACS. Due to the non-randomised nature of the study, a propensity score indicating the likelihood of receiving TA treatment was calculated using multivariate logistic regression analysis which included all significantly different variables between the TA and non-TA patient groups (age, body mass index, hypertension, history of CABG, diabetes, chronic kidney disease, emergency of PCI, left main disease, STEMI/NSTEMI, character of chest pain, and pre-procedural nuclear study). In our final analysis, this propensity score was included in the multivariate adjusted model. All statistical calculations and analyses were performed using the SPSS software package version 15 (SPSS, Chicago, IL, USA). A p-value of <0.05 was considered statistically significant.

Results

PATIENT CHARACTERISTICS

Of the 4,542 ACS patients who underwent PCI during the study period, TA was performed in a total of 1,715 patients (37.8%). TA was performed in 1,281/1,960 (65.4%) patients presenting with STEMI, 223/717 (31.1%) patients presenting with NSTEMI and 200/1,774 (11.3%) patients with unstable angina (UA). Nine patients were counted in both UA and NSTEMI during the course of their hospitalisation. The use of TA was shown to decrease with increased patient age **(Table 1)**. TA was performed more frequently on male patients as opposed to female patients. In comparison with the TA patient group, patients who did not undergo TA presented more frequently with clinical syndromes such as hypertension, diabetes, previous MI, HF, aortic/peripheral arterial disease, chronic lung disease, chronic kidney disease including haemodialysis, and a history of prior PCI and CABG.

Table 1. Comparison of baseline characteristics in patients who underwent TA during PCI, and PCI without TA.

	non-TA, n=2,827	TA, n=1,715	*p*-value
Clinical variables			
Female, n (%)	667 (23.6)	334 (19.5)	0.001
Age, yrs	68.8±11.1	65.1±12.4	<0.001
Height, cm	161.3±9.0	163.4±9.1	<0.001
Weight, kg	62.3±12.6	64.9±13.5	<0.001
Body mass index, kg/m^2	23.9±3.6	24.2±3.7	0.002
Smoking, n (%)	993 (35.1)	778 (45.4)	<0.001
Family history of CAD	63 (2.2)	44 (2.6)	0.481
Acute coronary syndrome, n (%)			
STEMI, n (%)	679 (24)	1,281 (74.7)	<0.001
NSTEMI, n (%)	494 (17.5)	223 (13)	<0.001
Unstable angina, n (%)	1,574 (55.7)	200 (11.7)	<0.001
EF, %	57.3±13.6	53.3±12.4	<0.001
Emergent PCI, n (%)	855 (30.2)	1,186 (69.2)	<0.001
NYHA ≥III, n (%)	266 (9.4)	138 (8)	0.119
Previous medical history			
Hypertension, n (%)	2,085 (73.8)	1,089 (63.5)	<0.001
Hyperlipidaemia, n (%)	1,757 (62.2)	1,033 (60.2)	0.209
Diabetes, n (%)	1,101 (38.9)	552 (32.2)	<0.001
Old myocardial infarction, n (%)	532 (18.8)	173 (10.1)	<0.001
History of heart failure, n (%)	207 (7.3)	60 (3.5)	<0.001
Aortic disease and peripheral arterial disease, n (%)	194 (6.9)	58 (3.4)	<0.001
Chronic lung disease, n (%)	93 (3.3)	45 (2.6)	0.213
Haemodialysis, n (%)	146 (5.2)	21 (1.2)	<0.001
CKD stage 3 or 4, n (%)	232 (8.2)	54 (3.1)	<0.001
History of PCI, n (%)	742 (26.2)	191 (11.1)	<0.001
History of CABG, n (%)	162 (5.7)	19 (1.1)	<0.001
Angiographic variables			
Left main, n (%)	286 (10.1)	92 (5.4)	<0.001
2VD, n (%)	1,302 (46.1)	636 (37.1)	<0.001
3VD, n (%)	730 (25.8)	349 (20.3)	<0.001
Procedural variable			
Access site, n (%)			
Radial, n (%)	785 (27.8)	334 (19.5)	<0.001
Femoral, n (%)	1,983 (70.1)	1,353 (78.9)	<0.001
Use of pre-procedural IABP, n (%)	44 (1.6)	33 (1.9)	0.346
Fluoroscopy time, min	28.2±19.3	25.9±16.3	<0.001
Door to balloon time, min	111±76.3	99.8±53.2	0.001

2VD: two-vessel disease; 3VD: three-vessel disease; CABG: coronary artery bypass grafting; CAD: coronary artery disease; CKD: chronic kidney disease; EF: ejection fraction; IABP: intra-aortic balloon pumping; NSTEMI, non-ST-segment elevation myocardial infarction; PCI: percutaneous coronary intervention; STEMI: ST-segment elevation myocardial infarction; TA: thrombus aspiration

When compared angiographically with the TA groups, non-TA groups were more likely to have undergone PCI for complex lesions (10.1% vs. 5.4% for the left main trunk, 46.1% vs. 37.1% for 2-vessel disease, and 25.8% vs. 20.3% for 3-vessel disease,

respectively). There was no significant difference regarding the use of an intra-aortic balloon pump (IABP) between the two groups. Mean fluoroscopy time was recorded as 28.2±19.3 min for the non-TA group and 25.9±16.3 min for the TA group (p<0.001). Door-to-device time was also longer in the TA group compared to the non-TA group (111±76.3 min versus 99.8±53.2 min, p=0.001).

IN-HOSPITAL OUTCOMES

As seen in **Table 2**, higher complication rates were reported in the TA group (13.6% vs. 10.4%, p=0.001) with no difference observed in in-hospital mortality rates (2.5% vs. 1.8%, p=0.108). Composite outcome (death, HF, and CS) rates were shown to be higher in the TA group (7.6% vs. 4.4%, p<0.001). Post-procedural CS and HF occurred more frequently in the TA group (3.5% vs. 1.8%; p<0.001, 4.0% vs. 2.2%; p<0.001, respectively). No difference in overall bleeding complications was observed between the two groups within a 72-hour period. Multivariate analysis revealed TA was an independent predictor of primary outcomes in NSTEMI/UA patients (OR 1.905, 95% CI: 1.199-3.025) **(Table 3)**.

Multivariable analysis with propensity score adjustment showed that TA was not an independent predictor of primary outcomes (OR 1.279, 95% CI: 0.934-1.750), death (OR 1.341, 95% CI: 0.797-2.255), complications (OR 1.243, 95% CI: 0.991-1.560) or bleeding (OR 1.180, 95% CI: 0.763-1.824), as presented in **Figure 2**.

When each category of ACS was analysed individually, TA performance in patients presenting with STEMI was associated with primary outcomes (death, CS, and HF), complications and bleeding, but not significantly (OR [95% CI]: 1.28 [0.83-1.97], 1.29 [0.61-2.74], 1.16 [0.83-1.62], and 1.14 [0.59-2.19], respectively) **(Figure 3)**. Furthermore, TA in patients presenting with NSTEMI/UA was significantly associated with unfavourable outcomes including complications and primary outcomes (death, CS, and HF) (OR 1.62, 95% CI: 1.19-2.20, and OR 1.90, 95% CI: 1.10-3.02, respectively).

Table 2. In-hospital outcome of patients who underwent thrombus aspiration during PCI, and PCI without TA.

	non-TA, n=2,827	TA, n=1,715	*p*-value
Composite endpoint (death, heart failure, cardiogenic shock)	123 (4.4)	130 (7.6)	*p*<0.001
In-hospital mortality	51 (1.8)	43 (2.5)	0.108
Complications	294 (10.4)	234 (13.6)	0.001
Coronary dissection	32 (1.1)	22 (1.3)	0.673
Coronary perforation	23 (0.8)	12 (0.7)	0.729
Post-procedural myocardial infarction	65 (2.3)	29 (1.7)	0.197
Post-procedural cardiogenic shock	52 (1.8)	60 (3.5)	0.001
Heart failure	61 (2.2)	68 (4)	0.001
Cerebral infarction	15 (0.5)	6 (0.3)	0.500
Cardiac tamponade	7 (0.2)	10 (0.6)	0.083
Newly initiated haemodialysis	35 (1.2)	17 (1)	0.476
Bleeding complications within 72 hours	91 (3.2)	62 (3.6)	0.498
Access-site bleeding	31 (1.1)	15 (0.9)	0.542
Access-site haematoma	25 (0.9)	18 (1)	0.636
Retroperitoneal haemorrhage	2 (0.1)	2 (0.1)	0.636
Bleeding with transfusions or decrease of haemoglobin	78 (2.8)	52 (3)	0.583
Transfusions	76 (2.7)	46 (2.7)	1.000

All values are n (%). CK: creatinine kinase; TA: thrombus aspiration

Table 3. Risk predictors of primary endpoint (death, heart failure, cardiogenic shock).

	STEMI		NSTEMI/UA	
	Odds ratio (95% CI)	*p*-value	Odds ratio (95% CI)	*p*-value
TA	1.284 (0.836-1.972)	0.253	1.905 (1.199-3.025)	0.006
Age	1.049 (1.027-1.071)	<0.01	1.059 (1.034-1.084)	<0.01
Female	0.714 (0.429-1.188)	0.195	1.316 (0.823-2.102)	0.251
Old myocardial infarction	0.498 (0.181-1.372)	0.178	1.349 (0.738-2.463)	0.331
History of heart failure	2.944 (1.318-6.575)	0.008	2.083 (1.194-3.631)	0.01
Diabetes	0.938 (0.612-1.436)	0.768	1.163 (0.763-1.773)	0.482
Aortic disease and peripheral arterial disease	1.437 (0.623-3.317)	0.396	1.016 (0.517-1.996)	0.963
Chronic lung disease	2.797 (1.299-6.021)	0.009	1.105 (0.37-3.304)	0.858
Hypertension	0.774 (0.504-1.189)	0.242	0.548 (0.351-0.856)	0.008
Smoking	1.271 (0.82-1.971)	0.284	1.069 (0.667-1.712)	0.783
Family history of CAD	1.304 (0.44-3.866)	0.632	0.499 (0.066-3.779)	0.501
History of PCI	0.721 (0.282-1.846)	0.495	0.631 (0.35-1.137)	0.125
History of CABG	2.162 (0.588-7.945)	0.246	2.233 (1.116-4.469)	0.023
CKD stage 3 or 4	2.313 (0.977-5.474)	<0.01	3.416 (1.982-5.889)	<0.01
Body mass index, kg/m^2	1.023 (0.966-1.084)	0.431	0.993 (0.933-1.056)	0.814

CABG: coronary artery bypass grafting; CAD: coronary artery disease; CKD: chronic kidney disease; NSTEMI: non-ST-segment elevation myocardial infarction; PCI: percutaneous coronary intervention; STEMI: ST-segment elevation myocardial infarction; TA: thrombus aspiration; UA: unstable angina

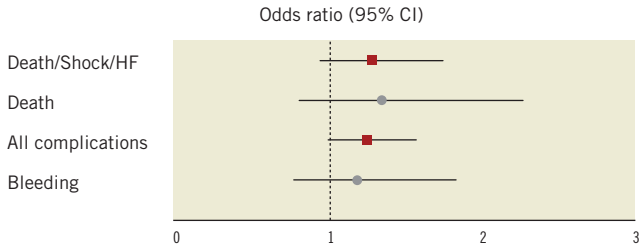

Figure 2. *Forest plot results of odds ratio of thrombus aspiration (TA) efficacy after propensity adjustment. Complications included severe dissection or coronary perforation, myocardial infarction after PCI, cardiac shock or HF, cerebral bleeding or stroke and bleeding complications. CI: confidence interval; HF: heart failure*

Discussion

The usefulness of TA in treating ACS has been a topic of debate for the last decade. Considering the pathophysiology of ACS, it is reasonable to consider carefully the effectiveness of TA in treating ACS patients. However, while previous studies have yielded conflicting results[4,18], in this study no association was shown between TA and improved outcomes in STEMI patients. Furthermore, the use of TA in NSTEMI/UA patients was shown to be associated with in-hospital complications.

TA IN STEMI PATIENTS

In comparison to previously published studies, TA was performed on a significantly higher number of patients in our registry. This accounted for 65.4% of all STEMI-related cases of PCI. During the same time period, TA was performed on just 18.9% of patients in the US national registry (CathPCI registry®)[18]. As previously mentioned, past studies – including meta-analyses – have shown inconsistent results regarding the clinical efficacy of TA[5,7,19]. It is of clinical significance that, despite extensive clinician experience and familiarity with the procedure, TA was once again not associated with improved clinical outcome in this study.

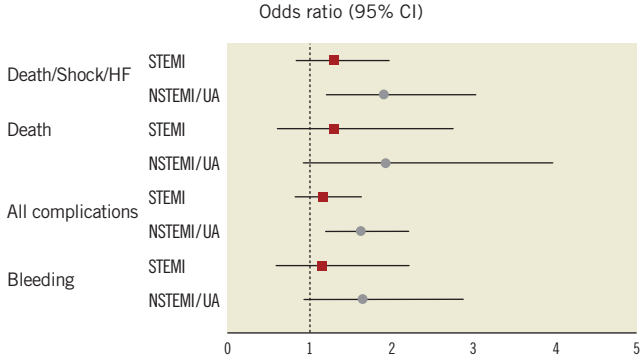

Figure 3. *Forest plot results of odds ratio of thrombus aspiration (TA) efficacy on each condition. Complications included severe dissection or coronary perforation, myocardial infarction after PCI, cardiac shock or heart failure, cerebral bleeding or stroke and bleeding complications. CI: confidence interval; HF: heart failure; NSTEMI: non-ST-elevation myocardial infarction; STEMI: ST-elevation myocardial infarction; UA: unstable angina*

Clinician familiarity with the procedure is further reflected by the shorter fluoroscopy time in the TA group compared to the non-TA group in the present study. It should be noted that shorter fluoroscopy time may also be indicative of less complex lesions in the TA group compared to the non-TA group. However, a similar periprocedural complication rate (coronary dissection and coronary perforation) was observed in both groups. Thus, it would seem that, even under these favourable circumstances, TA was not associated with a better prognosis[20].

TA IN NSTEMI/UA PATIENTS

At present, there are minimal data available for the assessment of the impact of TA in NSTEMI/UA patients. Although Vlaar et al demonstrated the safety and efficacy of TA in NSTEMI patients, their study was based on a small group of patients (n=70) with reduction shown only in "thrombus score" and TIMI flow[12]. To the best of our knowledge, there are no real-world data regarding the usage of TA in NSTEMI/UA patients, and relatively few patients usually undergo TA in these situations, as was the case in STEMI. In Japan, TA in NSTEMI/UA patients was frequently performed within our registry (31.1% in NSTEMI, 11.3% in UA), and this allowed us to compare the TA group to the non-TA group with adjustments made for confounding variables[18]. The reason behind this large number of patients being treated by TA was that its indication largely depended on the physician's subjective considerations rather than evidence-based suggestion, which is virtually non-existent[21]. Our study showed that TA in NSTEMI/UA patients was associated with unfavourable outcome, and this challenges the common belief of Japanese interventionalists.

In accordance with observations in STEMI patients, non-TA-treated NSTEMI/UA patients presented with a slightly higher BMI, less complex lesions and a shorter associated fluoroscopy time when compared to TA-treated patients. Despite these merits, the benefit of TA in the treatment of NSTEMI/UA remains debatable and may be potentially harmful to these patients when taking propensity score adjustment into account.

The reasons behind the unexpected and unfavourable outcomes of TA treatment presented here should be carefully considered. Pathologically, the thrombus burden in NSTEMI/UA is lower than that in STEMI, which could reduce the efficacy of TA in the prevention of distal embolism in NSTEMI/UA patients[22]. Patients with a higher visible thrombus volume might be more likely to benefit from the TA procedure; however, thrombus volume quantification remains a major clinical challenge[23]. Furthermore, according to the previous reports, 24% of patients had an occluded infarct artery, which was associated with a higher complication rate[24]. We might perform TA in an occluded infarct artery without any doubt, and we might not perform TA in a non-occluded artery, which might result in unfavourable patient selection for the TA group. In addition, challenges in the diagnosis of NSTEMI/UA and the subsequent determination of affected arteries may diminish the usefulness of TA treatment.

As the prevalence of NSTEMI increases, the lack of clear benefits and treatment options in this patient group should not be

overlooked[25]. TA does not appear to be a universally applicable strategy in the treatment of NSTEMI/UA patients as shown here and, despite favourable patient selection, an increased risk in procedure-related complications (including HF and CS) was observed.

Limitations

There are several limitations in the present study. First, this was the retrospective analysis of a registry database, and unknown variables such as ischaemic duration, post-angiographic and electrocardiographic data in NSTEMI/UA patients could thus not be excluded in the assessment of the efficacy of TA and patient outcomes. We included PCI patients over four years. Also, we might not have noticed the procedural improvement during this period simply by this registry database. Our study was too small to analyse the effect of time trend. Second, mechanical thrombectomy devices and newly available anticoagulant drugs such as a GP IIb/IIIa inhibitor are not used in Japan. The efficacy of mechanical thrombectomy is widely discussed in the literature and is known to impact on rates of complications and patient outcomes. However, we should not misunderstand that the concept of thrombus removal was not denied. If a more efficient thrombus aspiration device were to be developed, it might be related to a favourable outcome[26]. Thus, the results of this study must be considered within the context of the relevant clinical setting. The differences in outcomes across the different types of ACS in this study highlight the difficulty in selecting patients who would benefit from TA. Third, our data only revealed short-term outcome. Our registry did not contain long-term outcome. We need further investigation about the long-term efficacy of TA. Finally, we included PCI patients over four years. There might have been some procedural improvement during the study period, including implementation of transradial intervention[27]; however, the sample size of our study limited the sub-analysis on the effect of time trend.

Conclusion

Despite its frequent usage in ACS-related PCI, TA was not shown to be associated with improved outcomes in patients presenting with STEMI. TA was further associated with an increased risk of in-hospital complications in NSTEMI/UA patients.

Impact on daily practice

The appropriate use of thrombus aspiration remains a clinical challenge. In our analysis of a multicentre PCI registry, despite its frequent use, TA in STEMI patients was not associated with improved outcome. Furthermore, TA in non-STEMI/UA patients, who present with smaller culprit vessels with multiple comorbidities, may be harmful.

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Conflict of interest statement

The authors have no conflicts of interest to declare.

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