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ORIGINAL ARTICLE

Post-interventional adverse event risk by vascular access site among patients with acute coronary syndrome in Japan: observational analysis with a national registry J-PCI database

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Abstract

This study evaluated whether radial access intervention had a lower risk of post-treatment adverse events in acute coronary syndrome (ACS) even in Japan where the use of a strong antithrombotic regimen was not approved. We retrospectively analyzed a large nation-wide registry in Japan to compare the incidence of post-treatment adverse events according to the types of vessel access (trans-radial; TRI vs. trans-femoral; TFI) among ACS cases ($n=76,835$; 43,288 TRI group and 33,547 TFI group). Primary outcome was a composite of in-hospital death, myocardial infarction associated with percutaneous coronary intervention, bleeding complication requiring transfusion, and stent thrombosis during in-hospital stay. Propensity score matching (PS) and instrumental variable (IV) analyses were used to account for treatment selection. The incidence of post-treatment adverse events was lower in the TRI group by 0.95% compared to the TFI group with PS ($p<0.001$) and by 0.34% with IV ($p=0.127$). A significantly lower risk for access site bleeding was observed by 0.34% with PS ($p<0.001$) and by 0.53% with IV ($p<0.001$). Radial access was related to a significantly lower risk for access site bleeding compared with femoral access, even without strong antithrombotic drugs for ACS in Japan, and may also relate to lower risk for a wider set of post-treatment adverse events.

Keywords Acute coronary syndrome · Trans-radial approach · Access site bleeding · Propensity score · Instrumental variable

Introduction

The use of combined antithrombotic drugs has lowered the risk of recurrent myocardial infarction (MI) in patients with acute coronary syndrome (ACS), but with a significant increase in adverse events such as access site bleeding and related fatal complications [1–3] that require a careful vessel access management of patients with ACS [4, 5].

Percutaneous coronary intervention (PCI) with radial artery access is technically more demanding but makes access site hemostasis more predictable [6, 7]. The MATRIX study showed that radial as compared with femoral access exhibited significantly a lower risk of major bleeding and all-cause mortality in patients with ACS [8]. However, some argue that the benefits of radial access may be over-stated under the use of glycoprotein IIb/IIIa inhibitors or the new P2Y12 inhibitors that increase the risk of access site bleeding [9, 10].

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In Japan, since glycoprotein IIb/IIIa inhibitors or the full recommended dose of new P2Y12 inhibitors have not been approved by the government drug regulatory agency, coronary intervention has been performed exclusively without these drugs in all cases. In this study, we used this opportunity to evaluate whether the benefits of radial access intervention for a lower risk of post-treatment adverse events remain even in Japan without the use of a strong antithrombotic regimen.

Methods

Data source and study design

To compare the major adverse events between after transradial (TRI) and trans-femoral coronary intervention (TFI) for ACS, the present study was designed as a retrospective observational cohort study, using an existing large nationwide registry in Japan (J-PCI) between April 2014 and March 2015. The J-PCI Registry is a national, prospective, multicenter registry of PCI cases in operation since November 2011 controlled by the Japanese Association of Cardiovascular Intervention and Therapeutics. J-PCI is part of a larger National Clinical Database (NCD) that incorporates all surgical in-hospital cases through online registration with standardized format [11]. The registered data elements in the J-PCI database include patients' demographics, PCI procedures, and the in-hospital adverse clinical events.

A flow diagram of the study sample selection is shown in Fig. 1. Data from a total of 217,223 patients who underwent PCI between April 2014 and March 2015 in 883 facilities were extracted from J-PCI database. The present study further limited the sample to the cases with the diagnosis of ACS, including MI and unstable angina (UA). Exclusion criteria were as follows: Patients in whom the access site was unclear, in whom other than radial or femoral access sites were attempted, or patients under age 20 or over 100 years. Consequently, the present study included 76,835 ACS patients (43,288 TRI and 33,547 TFI) for following analysis. Since this study was conducted as a secondary data analysis of anonymous data with official data use approval from the J-PCI data control committee, ethical consent from individual patients was waived.

Clinical variables and definitions

Primary outcome was severe post-treatment adverse events defined as a composite of in-hospital death, MI associated with PCI, bleeding complication requiring transfusion, and stent thrombosis during in-hospital stay. In-hospital death, and access site bleeding complication were also separately assessed as secondary outcomes.

MI associated with PCI was defined as Q wave MI or non-Q wave MI. MI was defined as existing ischemic symptom with increasing cardiac biomarker values of at least one biomarker value above the 99th percentile of upper limit of normal. UA was defined as any of the following conditions. (1) new onset angina within 1 month, (2) increasing angina within 1 month, (3) resting or severe angina restricting activities of daily living, and (4) continuous angina within 1 month after MI without increment of cardiac biomarker values. Bleeding complication was defined as intraoperative or post-operative bleeding requiring transfusion including access and non-access site bleeding. Stent thrombosis was defined a "definite" stent thrombosis based on Academic Research Consortium definitions [12]. Hypertension was defined as at least one of the following criteria: systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or receiving antihypertensive medication. Dyslipidemia was

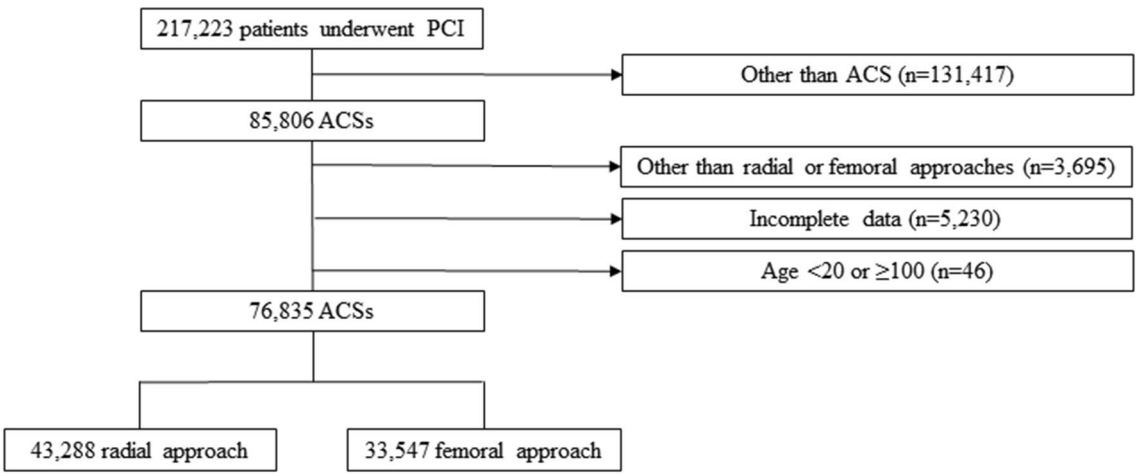

Fig. 1 Flow diagram of patient selection criteria

defined as that meets at least one of the following criteria: Total cholesterol ≥ 220 mg/dL, LDL cholesterol ≥ 140 mg/dL, HDL cholesterol < 40 mg/dl, triglyceride ≥ 140 mg/dL, or receiving cholesterol-lowering medication. Current smoking was defined as a history of smoking within 1 year. Diabetes mellitus was defined as at least one of the following criteria: fasting blood glucose levels ≥ 126 mg/dl, casual blood glucose level ≥ 200 mg/dL, HbA1c ≥ 6.5, a 2-h 75 g oral glucose tolerance test ≥ 200 mg/dL, or receiving medication for diabetes mellitus. Renal dysfunction was defined as at least one of the following criteria: proteinuria, serum creatinine ≥ 1.3 mg/dL, or estimated glomerular filtration rate ≤ 60 ml/min/1.73 m^2. Chronic obstructive pulmonary disease (COPD), excluding bronchial asthma, was defined as forced expiratory volume one second percent ≤ 70% or receiving medication for COPD. Peripheral arterial disease was defined as a vascular disease meeting at least one of the following criteria: history of arterial vascular operation, intermittent claudication, or ankle–brachial index ≤ 0.9.

Statistical analysis

Since this is an observational study, we controlled for selection bias in the choice of TRI/TFI. For this purpose, we adopted in our analysis propensity score matching estimation and instrumental variable estimation, the details of which are provided shortly.

Propensity scores were obtained by logistic regression model where the treatment status (TRI) was regressed on pre-treatment variables as potential confounders listed in Table 1; namely, age, sex, history of prior PCI, history of prior MI, history of prior CABG, history of heart failure, diagnosis, diabetes mellitus, hypertension, dyslipidemia, current smoking, renal dysfunction, hemodialysis, COPD, peripheral arterial disease, cardiopulmonary arrest at onset, cardiogenic shock at onset, and heart failure at onset. We used STATA command "teffects psmatch" to match a treatment case (TRI) with one control (TFI) with the nearest score [13]. Overlapping assumption of propensity score between treatment and control groups was visually checked with kernel density presentation. The covariate balance in the matching pairs was checked using standardized differences and variance ratios. Following, standardized differences larger than 0.1 and variance ratios far lower than 1 indicate meaningful imbalance [14].

Since there are fewer controls with an overlapping range of propensity scores than that of treatment group, we allowed control sampling with replacement. The comparative descriptive statistics of variables between treatment and control groups after propensity score matching was estimated using the number of repeated inclusions as frequency weight. The average treatment effect was presented as risk difference estimation between the groups. Average treatment effect is an expected value of counterfactual difference between treated and control conditions [15].

As a robustness check, we also conducted instrumental variable estimation. We adopted the ratio of TRI among the total PCI procedures by institutions as an instrument to the chance of TRI treatment, following the method used in previous studies [16, 17]. The ratio was translated into dichotomy or quartile variables in the analysis. STATA command "ivregress" with 2-stage least square estimator was used to assess the instrumental variable estimation. We used a linear model rather than a non-linear model such as bivariate probit model, since a non-linear model does not have a suitable test protocol for endogeneity test. We conducted the endogeneity test with Durbin and Wu-Hausman protocol, and reported the model F statistics of the first-stage regression as a test for weak instrument.

All statistical calculations were performed using STATA statistical software Version 14.0 (Stata Corporation, College Station, TX, USA). This study was registered as UMIN000024576.

Results

Baseline study population and unadjusted outcomes

The baseline characteristics, angiographic findings and in-hospital outcomes are shown in Table 1. These variables were significantly different between TRI and TFI groups, except for the prior history of MI and comorbid COPD.

The primary endpoint was met in 2.6% among patients in the original cohort analysis (i.e., unadjusted analysis) and was significantly lower in TRI than that in TFI (1.4% vs. 4.2%, $p < 0.001$). In-hospital death and access site bleeding were also significantly lower in TRI (0.6% vs. 2.9%, $p < 0.001$; 0.04% vs. 0.5%, $p < 0.001$, respectively). Although MI associated with PCI did not have significant difference (0.4% vs. 0.4%, $p = 0.057$), stent thrombosis was significantly lower in TRI (0.3% vs. 0.5%, $p < 0.001$).

Results of propensity score matching

The C-statistic of prediction model for propensity score was 0.69. Figure 2 presents the kernel density of propensity score distributions between TRI and TFI groups, suggesting no remarkable violation of overlapping assumption between the groups. Table 2 shows the cohort matched for propensity score, the standardized differences and variance ratios of included confounding variables before and after matching. After matching, all the covariates exhibited standardized differences less than 0.1 and variance ratios close to 1,

Table 1 Baseline characteristics of full cohort

	Overall, $n=76,835$	TRI, $n=43,288$	TFI, $n=33,547$	p value
Age, years	69.2 ± 12.2	69.0 ± 12.2	69.5 ± 12.2	< 0.001
Male	57,816 (75.2%)	33,186 (76.7%)	24,630 (73.4%)	< 0.001
Prior PCI	21,771 (28.3%)	12,958 (29.9%)	8,813 (26.3%)	< 0.001
Prior CABG	2,137 (2.8%)	758 (1.8%)	1,379 (4.1%)	< 0.001
Prior MI	13,217 (17.2%)	7,415 (17.1%)	5,802 (17.3%)	0.546
Prior heart failure	7,288 (9.5%)	3,430 (7.9%)	3,858 (11.5%)	< 0.001
Diagnosis				
Acute MI	46,661 (60.7%)	23,139 (53.5%)	23,552 (70.2%)	< 0.001
STEMI	36,502 (47.5%)	17,419 (40.2%)	19,083 (56.9%)	
NSTEMI	8,577 (11.2%)	4,915 (11.4%)	3,662 (10.9%)	
Others	1,582 (2.1%)	805 (1.9%)	777 (2.3%)	
UA	30,174 (39.3%)	20,149 (46.5%)	10,025 (29.9%)	
Comorbid disease				
Diabetes mellitus	28,645 (37.3%)	15,697 (36.3%)	12,948 (38.6%)	< 0.001
Hypertension	54,369 (70.8%)	31,029 (71.7%)	23,340 (69.6%)	< 0.001
Dyslipidemia	45,526 (59.3%)	26,697 (61.7%)	18,829 (56.1%)	< 0.001
Smoking	27,105 (35.3%)	15,540 (35.9%)	11,565 (34.5%)	< 0.001
Renal dysfunction	10,490 (13.7%)	4,114 (9.5%)	6,376 (19.0%)	< 0.001
Hemodialysis	3,145 (4.1%)	344 (0.8%)	2,801 (8.3%)	< 0.001
COPD	1,208 (1.6%)	659 (1.5%)	549 (1.6%)	0.207
Peripheral arterial disease	2,799 (3.6%)	1,306 (3.0%)	1,493 (4.5%)	< 0.001
CPA	2,613 (3.4%)	511 (1.2%)	2,102 (6.3%)	< 0.001
Cardiogenic shock	5,108 (6.6%)	1,188 (2.7%)	3,920 (11.7%)	< 0.001
Heart failure	6,620 (8.6%)	2,211 (5.1%)	4,409 (13.1%)	< 0.001
No. of disease vessel				
1VD	42,798 (55.7%)	25,074 (57.9%)	17,724 (52.8%)	< 0.001
2VD	22,467 (29.2%)	12,368 (28.6%)	10,099 (30.1%)	
3VD	11,570 (15.1%)	5,846 (13.5%)	5,724 (17.1%)	
LM lesion	3,378 (4.4%)	1,233 (2.8%)	2,145 (6.4%)	< 0.001
Primary endpoint	2,006 (2.6%)	594 (1.4%)	1,412 (4.2%)	< 0.001
Adverse events	3,464 (4.5%)	1,156 (2.7%)	2,308 (6.9%)	< 0.001
In-hospital death	1,227 (1.6%)	246 (0.6%)	981 (2.9%)	< 0.001
Access site bleeding	181 (0.2%)	21 (0.04%)	160 (0.5%)	< 0.001
MI associated with PCI	313 (0.4%)	193 (0.4%)	120 (0.4%)	0.057
Stent thrombosis	302 (0.4%)	130 (0.3%)	172 (0.5%)	< 0.001
Tamponade	151 (0.2%)	60 (0.1%)	91 (0.3%)	< 0.001
Heart failure/shock	1,426 (1.9%)	436 (1.0%)	990 (3.0%)	< 0.001
Emergency operation	129 (0.2%)	48 (0.1%)	81 (0.2%)	< 0.001
Non-access site bleeding	143 (0.2%)	44 (0.1%)	99 (0.3%)	< 0.001
Others	456 (0.6%)	203 (0.5%)	256 (0.8%)	< 0.001

TRI trans-radial intervention, *TFI* trans-femoral intervention, *PCI* percutaneous coronary intervention, *CABG* coronary artery bypass grafting, *MI* myocardial infarction, *STEMI* ST-elevation myocardial infarction, *NSTEMI* non ST-elevation myocardial infarction, *UA* unstable angina, *COPD* chronic obstructive pulmonary disease, *CPA* cardiopulmonary arrest, *VD* vessel disease, *LM* left main trunk

indicating balanced covariance distribution among matched pairs [14].

Table 3 presents the summary of individual outcomes after matching and average treatment effects of TRI. The primary outcome of severe post-treatment adverse effect was observed 1.4% of TRI group and 2.8% of TFI group ($p<0.001$). Estimated average treatment effect on the primary outcome was − 0.0095 (95% CI − 0.0127 to − 0.0064, $p<0.001$), or 0.95% decrease in the TRI treatment compared with the TFI. The instrumental variable estimation showed that TRI compared to TFI was related to a lower incidence by 0.37% ($p=0.127$). Wu-Hausman test ($F=9.000$,

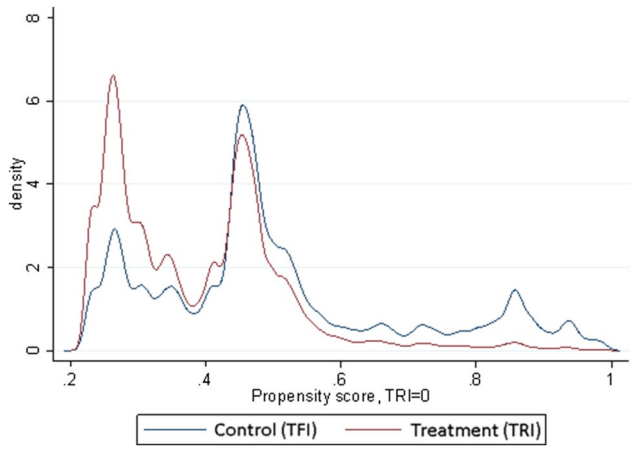

Fig. 2 Kernel density distribution of propensity score by treatment status

$p = 0.003$), and F statistics of the first regression (F statistics = 8,063.9, $p < 0.001$) indicated that instrument variable estimation was valid.

As a secondary outcome, average treatment effect on the in-hospital death rate was − 0.0059 (95% CI − 0.0085 to − 0.0034, $p < 0.001$), and the corresponding instrumental variable estimation was 0.0016 (95% CI − 0.0053 to 0.0020, $p = 0.384$), with significant Wu–Hausman test ($F = 8.714$, $p = 0.003$) and first-stage regression F statistics (8,063.9, $p < 0.001$).

The access site bleeding was significantly lower in TRI group than in TFI group after matching (0.04% vs. 0.3%, $p < 0.001$), and the estimated average treatment effect was − 0.0034 (95% CI − 0.0044 to − 0.0024, $p < 0.001$), or lower incidence by 0.34%. Instrumental variable estimation also indicated that TRI was associated with the lower risk by 0.53% ($p < 0.001$) with significant Wu-Hausman tests ($F = 8.522$, $p = 0.004$) and first-stage regression F statistics ($F = 17{,}141$, $p < 0.001$).

Table 2 Diagnostic results of covariate balance

	Matched cohort		Standardized difference		Variance ratio	
	TRI, $n = 43{,}288$[a]	TFI, $n = 43{,}288$[a]	Raw	Matched	Raw	Matched
Age, years	69.0 ± 12.2	69.1 ± 11.8	− 0.048	0.005	0.997	1.022
Male	33,186 (76.7%)	33,024 (76.3%)	− 0.075	− 0.008	1.083	0.992
Prior PCI	12,958 (29.9%)	12,349 (28.5%)	0.082	− 0.008	1.083	0.997
Prior CABG	758 (1.8%)	673 (1.6%)	− 0.140	0.002	0.436	0.988
Prior MI	7,415 (17.1%)	6,887 (15.9%)	− 0.004	0.003	0.992	1.005
Prior heart failure	3,430 (7.9%)	2,839 (6.6%)	− 0.121	0.007	0.717	1.022
Diagnosis						
STEMI	17,419 (40.2%)	17,655 (40.8%)	− 0.338	0.023	0.980	1.001
NSTEMI	4,915 (11.4%)	4,936 (11.4%)	0.014	− 0.002	1.035	0.994
Others	805 (1.9%)	656 (1.5%)	− 0.320	− 0.00	0.807	1.000
UA	20,149 (46.5%)	20,041 (46.3%)	0.348	− 0.022	1.187	0.990
Comorbid disease						
Diabetes mellitus	15,697 (36.3%)	15,343 (35.4%)	− 0.048	− 0.003	0.975	0.998
Hypertension	31,029 (71.7%)	31,302 (72.3%)	0.046	− 0.009	0.959	1.008
Dyslipidemia	26,697 (61.7%)	26,677 (61.6%)	0.113	0.002	0.960	0.999
Smoking	15,540 (35.9%)	15,223 (35.2%)	0.030	0.013	1.012	1.008
Renal dysfunction	4,114 (9.5%)	3,880 (9.0%)	− 0.274	− 0.009	0.559	0.980
Hemodialysis	344 (0.8%)	398 (0.9%)	− 0.368	− 0.029	0.103	0.869
COPD	659 (1.5%)	412 (1.0%)	− 0.009	0.015	0.931	1.131
Peripheral arterial disease	1,306 (3.0%)	1,052 (2.4%)	− 0.076	0.001	0.688	1.006
CPA	511 (1.2%)	499 (1.2%)	− 0.271	0.006	0.199	1.032
Cardiogenic shock	1,188 (2.7%)	1,146 (2.7%)	− 0.351	0.017	0.259	1.060
Heart failure	2,211 (5.1%)	2,127 (4.9%)	− 0.282	0.012	0.424	1.036

TRI trans-radial intervention, *TFI* trans-femoral intervention, *PCI* percutaneous coronary intervention, *CABG* coronary artery bypass grafting, *MI* myocardial infarction, *STEMI* ST-elevation myocardial infarction, *NSTEMI* non ST-elevation myocardial infarction, *UA* unstable angina, *COPD* chronic obstructive pulmonary disease, *CPA* cardiopulmonary arrest, *VD* vessel disease, *LM* left main trunk

[a]Number of control was matched with that of treated by matching sampling with replacement

Table 3 Adverse event rate and average treatment effects of TRI in matched cohort

	TRI	TFI	*p* value	Average treatment effect
Primary outcome	594 (1.4%)	1,196 (2.8%)	< 0.001	− 0.0095 (95% CI − 0.0127 to − 0.0064, $p<0.001$)
In-hospital death	246 (0.6%)	531 (1.3%)	< 0.001	− 0.0059 (95% CI − 0.0085 to − 0.0034, $p<0.001$)
Access site bleeding	21 (0.04%)	115 (0.3%)	< 0.001	− 0.0034 (95% CI − 0.0044 to − 0.0024, $p<0.001$)

TRI trans-radial intervention, *TFI* trans-femoral intervention, *STEMI* ST-elevation myocardial infarction, *NSTEMI* non ST-elevation myocardial infarction, *MI* myocardial infarction

Ad hoc analysis stratified by ST-elevation myocardial infarction (STEMI)/Non ST-elevation myocardial infarction (NSTEMI) status indicated that TRI exhibited decreasing incidence of primary endpoint similarly both in STEMI and NSTEMI; by 1.16% in STEMI (95% CI − 0.0166 to − 0.0067, $p<0.001$) and 1.41% in NSTEMI (95% CI − 0.0225 to − 0.0058, $p<0.001$), respectively (Table 4). The results using instrumental variable estimation also revealed similar impact between groups.

As for in-hospital death, stratified analysis with propensity score matching suggested that TRI had a significant, and similar impact on decreasing mortality; 0.81% (95% CI − 0.0125 to − 0.0038, $p<0.001$) in STEMI and 1.34% (95% CI − 0.0193 to − 0.0076, $p<0.001$) in NSTEMI. However, access site bleeding was significantly decreased by 0.25% (95% CI − 0.0038 to − 0.0012, $p<0.001$) in STEMI, while the effect did not reach significance in case of NSTEMI (0.02%, 95% CI − 0.0031 to − 0.0034, $p=0.926$).

Discussion

With a nation-wide patient registry data of PCI in Japan, we demonstrated that radial access was related to a lower incidence of access site bleeding requiring blood transfusion using propensity score matching analysis and instrumental variable analysis. Furthermore, ad hoc stratified analysis revealed that the observed benefit of TRI in access site bleeding was particularly notable in STEMI. In terms of severe adverse events including in-hospital death, radial access was consistently related to lower risks, though statistical significance was not observed consistently across analytic methods. Since PCI was performed exclusively without GP IIb/IIIa inhibitor or full recommended dose of new P2Y12 inhibitors in Japan without official approval by the government drug regulatory agency, the findings in this study indicated that the observed benefit of TRI over TFI remains to be observed even without strong antithrombotic agents. In contrast, access site bleeding in NSTEMI showed no significant difference contrary to that in STEMI. Reason for this was considered to be too small event rate for their sample size. Primary cohort showed the higher proportion of non-access site bleeding in TFI than in TRI. Because average treatment effect after propensity matched analysis and instrumental variable estimation did not reach the statistical significance, this difference was considered as selection bias.

The ADMIRAL study showed that early administration of GP IIb/IIIa inhibitor in patients with acute MI improved coronary patency and clinical outcomes [18]. However, in the approval trial in Japan (JEPPORT study), administration of GP IIb/IIIa inhibitor with ACS undergoing PCI did not show efficacy in reducing major coronary events, with

Table 4 Average treatment effects of TRI in STEMI and NSTEMI

	STEMI			
	TRI, $n=17,419$	TFI, $n=17,419$	*p* value	Average treatment effect
Primary outcome	330 (1.9%)	617 (3.5%)	< 0.001	− 0.0116 (95% CI − 0.0166 to − 0.0067, $p<0.001$)
In-hospital death	179 (1.0%)	351 (2.0%)	< 0.001	− 0.0081 (95% CI − 0.0125 to − 0.0038, $p<0.001$)
Access site bleeding	11 (0.1%)	26 (0.2%)	0.014	− 0.0025 (95% CI − 0.0038 to − 0.0012, $p<0.001$)
	NSTEMI			
	TRI, $n=4,915$	TFI, $n=4,915$	*p* value	Average treatment effect
Primary outcome	66 (1.3%)	105 (2.1%)	0.003	− 0.0141 (95% CI − 0.0225 to − 0.0058, $p<0.001$)
In-hospital death	28 (0.6%)	55 (1.1%)	0.003	− 0.0134 (95% CI − 0.0193 to − 0.0076, $p<0.001$)
Access site bleeding	5 (0.1%)	8 (0.2%)	0.405	0.0002 (95% CI − 0.0031 to − 0.0034, $p=0.926$)

TRI trans-radial intervention, *TFI* trans-femoral intervention, *STEMI* ST-elevation myocardial infarction, *NSTEMI* non ST-elevation myocardial infarction, *MI* myocardial infarction

a significant increase in both bleeding and thrombocytopenia [19, 20]. Prasugrel was shown as effective in TRITON-TIMI 38 study [21]. However, in the approval trial in Japan (PRASFIT study), the dose of prasugrel was 3.75 mg/20 mg (maintenance/loading) which was one-third in the regular dose of 10 mg/60 mg. Since the efficacy and bleeding complication rates were similar to clopidogrel, prasugrel was approved in Japan with the reduced one-third dose [22, 23]. Ticagrelor was approved in 2016 as an alternative drug of P2Y12 inhibitor class in Japan. Thus, ticagrelor was not used in this study because the study was conducted prior to approval.

In prior randomized controlled studies comparing TRI and TFI, GP IIb/IIIa inhibitors or new P2Y12 inhibitors were used according to the guidelines. In the RIVAL study, GP IIb/IIIa inhibitor was used for a total of 25% of patients [24]. In the MATRIX study, 13% of patients used GPIIb/IIIa inhibitor, 8% used prasugrel and 9% used ticagrelor [8]. Major bleeding in TRI vs. TFI was 1.9% vs. 4.5% in the RIVAL trial defined by the ACUITY trial, 1.6% vs. 2.3% in the MATRIX trial defined by the Bleeding Academic Research Consortium (BARC) 3 or 5, and 0.1% vs. 0.8% in this study, respectively. Blood transfusion in TRI vs. TFI was 2.8% vs. 2.8% in the RIVAL trial, 1.0% vs. 1.5% in the MATRIX trial, and 0.1% vs. 0.8% in this study, respectively. Bleeding complication in this study was lower than prior studies which can be explained by not using strong antithrombotic drugs.

The benefits of TRI have been considered to be a reduction in mortality due to lower bleeding complications [8, 24–26]. Our results may support the view even under the conditions without strong antithrombotic agents in Japan. Although the treatment and control groups were different in several features, e.g., the prevalence of cardiogenic shock and other serious complications, the diagnostic statistics of covariate balance did not indicate violated covariate balance among matched pairs, and our propensity score matched analysis indicated reduced risk of site bleeding and in-hospital death in favor of TRI. On the other hand, significant difference was not observed in instrumental variable analysis in terms of in-hospital mortality or primary endpoint. Several reasons can be offered. First, the in-hospital death number was small. Second, in-hospital death caused by bleeding was low because the number of bleeding events was small. Third, instrumental variable analysis has tendency to provide conservative estimation compared to propensity score matching [27].

There are several limitations in this study. First, all the clinical endpoints were in-hospital events and longer-term events were not taken into consideration. This study lacks long-term follow-up data. Second, definition of bleeding complications in this study was critical bleeding requiring blood transfusion. We could choose less severe bleeding to define bleeding complication based on BARC definition or ISTH definition, which would increase the number of bleeding complications in this study. Third, urgent coronary revascularization data were not collected in this database. GP IIb/IIIa inhibitors or new P2Y12 inhibitors have been shown to be effective in reducing the ischemic complications. Fourth, this study lacks the data on inserted sheath size.

In conclusion, radial access was related to a significantly lower risk for access site bleeding compared with femoral access, even without strong antithrombotic drugs for ACS in Japan, and may also relate to lower risk for a wider set of post-treatment adverse events.

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