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Original article

What is the optimal duration of triple anti-platelet therapy in patients with acute myocardial infarction undergoing drug-eluting stent implantation?

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Summary
Background: The optimal duration of triple anti-platelet therapy (DTAP) remains unclear in patients with acute myocardial infarction (AMI).
Methods: We retrospectively analyzed 716 AMI patients who received TAP (aspirin, clopidogrel, and cilostazol) after drug-eluting stent (DES) implantation from November 2005 to May 2008. Mean age was 61.9 ± 11.70 years (male gender 74.1%) and mean duration of TAP was 98.1 ± 115.34 days. We compared the major adverse cardiovascular events [MACE, defined as the composite of cardiac death, non-fatal AMI, stent thrombosis, and target vessel revascularization (TVR)] between the group of DTAP ≥3 months ($n = 497$) and those of <3 months ($n = 219$).
Results: There were no significant differences in the incidences of cardiac death, non-fatal AMI, stent thrombosis, and TVR at 1-year follow-up between the two groups. However, the group of DTAP ≥3 months had lower incidence of MACE than those <3 months (5.9% vs. 10.7%, $p = 0.044$). The rate of bleeding complications was similar between the two groups. By Cox regression analysis with propensity score adjustment, Killip class IV and DTAP ≥3 months were

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independent predictors of 1-year MACE [hazard ratio (HR) = 10.417; 95% confidence interval (CI) = 1.587—68.377, $p = 0.015$ and HR = 0.508; 95% CI = 0.269—0.956, $p = 0.036$].
Conclusions: Our data show that the DTAP ≥3 months is associated with better clinical outcomes compared with that of <3 months in patients with AMI undergoing DES implantation without increasing bleeding complications.

Introduction

Drug-eluting stents (DESs) are well known to be safe and efficacious in the ''real world'' practice compared to bare metal stents (BMSs) [1], even if patients suffered acute myocardial infarction (AMI) [2—6]. However, DES was associated with an increased risk for stent thrombosis, especially in patients with AMI [7,8]. Recent studies showed that triple anti-platelet therapy (TAP) such as administration of cilostazol with aspirin and clopidogrel seemed to be safe and superior to dual anti-platelet therapy (aspirin plus clopidogrel) in patients with ST-segment elevation MI (STEMI) or acute coronary syndrome undergoing stent implantation [9—11].

The American College of Cardiology/American Heart Association (ACC/AHA) guidelines recommended that patients with the acute coronary syndrome/non-ST-segment elevation MI (NSTEMI) undergoing DES implantation should receive dual anti-platelet therapy with aspirin and clopidogrel for at least 12 months [12]. However, the optimal duration of TAP varies and remains unclear. Some patients were prescribed TAP for at least 1 month [9], but others for more than at least 6 months [13].

The aim of our study was to compare the clinical outcome based on the duration of TAP and evaluate the optimal duration of TAP in patients with AMI undergoing DES implantation.

Methods

Study population

From November 2005 to May 2008, we retrospectively enrolled patients with AMI including both STEMI and NSTEMI who received TAP (aspirin + clopidogrel + cilostazol) after primary DES implantation at Chonnam National University Hospital. We excluded patients who had suffered major adverse cardiovascular events (MACE) within 3 months after index procedure. Patients were divided into two groups based on the duration of triple anti-platelet therapy (DTAP) of 3 months, because mean DTAP of total patients was about 98 days.

Percutaneous coronary intervention and medications

The emergent or early invasive treatments were determined based on the AMI patient status according to the clinical decision of operators. Following the insertion of a catheter, the guide wire was placed across the occlusive or stenotic lesions and DESs were implanted after prior balloon angioplasty. The type of DES was determined based on the decision of operators. Successful PCI was defined as a target vessel at the treatment site with antegrade Thrombolysis In Myocardial Infarction (TIMI)-3 flow and angiographic residual stenosis less than 50% following the implantation of stents. Anti-platelet agents were administered to all patients prior to the intervention, with aspirin 300 mg and clopidogrel 300—600 mg. After the intervention, the patients received 100 mg of aspirin per day indefinitely and 75 mg of clopidogrel per day for at least one year. Cilostazol was given to patients after the intervention. Following a 200-mg loading dose, the patients received 200 mg of cilostazol per day (100 mg b.i.d.) and stopped receiving it based on the patient status in accordance with the subjective decision of physicians. Other medical treatments including angiotensin-converting enzyme inhibitors (ACEi), angiotensin-II receptor blockers (ARB), beta-blockers, calcium channel blockers, and lipid lowering agents were also used based on the standard treatment regimen for patients with AMI in a non-restrictive manner.

Follow-up and clinical outcomes

Patients were recommended to visit the outpatient clinic one month after discharge and once every 2—3 months thereafter. In lost to follow-up cases, the clinical course was monitored through a telephone call by specialized personnel. The primary endpoint was the incidence of MACE, defined as cardiac death, non-fatal MI, stent thrombosis, and target vessel revascularization (TVR). The secondary endpoints were the incidence of safety endpoints, defined as cardiac death, non-fatal MI, and stent thrombosis within the 1-year follow-up after index procedure and bleeding complications at 1-year follow-up. Stent thrombosis was defined as only definite stent thrombosis according to the criteria of the Academic Research Consortium (ARC). Bleeding rates were also defined based on the TIMI bleeding classification [14].

Statistical analysis

Categorical variables were expressed as a frequency and continuous variables as mean ± SD (SD: standard deviation). An analysis of categorical variables was performed using chi-square test or Fisher's exact test and that of continuous ones using Student's *t*-test. A propensity score analysis was accomplished by performing a multivariable logistic regression analysis using DTAP ≥3 months as the dependent outcome variable and entering all baseline clinical, angiographic, procedural characteristics, and concomitant medications that would affect the probability of DTAP ≥3 months. Multivariate Cox regression analysis was performed with adjustments for the propensity score [15] and identified with the independent factors affecting the incidence

Table 1 Baseline clinical characteristics according to duration of triple anti-platelet therapy.

	DTAP <3 months ($n=497$)	DTAP ≥3 months ($n=219$)	p-Value
Mean DTAP, days	34.10 ± 20.78	243.26 ± 110.20	<0.001
Age, years	62.64 ± 11.32	60.06 ± 12.34	0.006
Male gender	357 (71.8)	175 (79.9)	0.023
Hypertension	225 (45.3)	99 (45.2)	0.987
Diabetes	136 (27.4)	76 (34.7)	0.047
Dyslipidemia	20 (4.0)	9 (4.1)	0.957
Current smoker	217 (43.7)	113 (51.6)	0.050
Family history of CAD	24 (4.8)	10 (4.6)	0.879
History of IHD	53 (10.7)	33 (15.1)	0.095
Killip class on admission			0.188
I	409 (82.3)	187 (85.4)	
II	42 (8.5)	15 (6.8)	
III	34 (6.8)	8 (3.7)	
IV	12 (2.4)	9 (4.1)	
Left ventricular ejection fraction, %	55.84 ± 11.80	56.90 ± 11.01	0.262
Creatinine clearance, ml/min	71.29 ± 28.76	75.06 ± 29.03	0.019
Stage of CKD			0.221
Stage 1	108 (21.9)	64 (29.5)	
Stage 2	210 (42.5)	83 (38.2)	
Stage 3	152 (30.8)	57 (26.3)	
Stage 4	18 (3.6)	10 (4.6)	
Stage 5	6 (1.2)	3 (1.4)	
Diagnosis			0.221
ST elevation MI	331 (66.6)	156 (71.2)	
Non-ST elevation MI	166 (33.4)	63 (28.8)	
Concomitant medications			
Beta-blockers	384 (77.3)	178 (81.3)	0.228
ACE inhibitors	362 (72.8)	155 (70.8)	0.571
ARBs	77 (15.5)	36 (16.4)	0.749
Calcium channel blockers	30 (6.0)	9 (4.1)	0.295
Statin	394 (79.3)	181 (82.6)	0.296

Data are n (%), or mean ± SD. DTAP, duration of triple anti-platelet therapy; CAD, coronary artery disease; IHD, ischemic heart disease; CKD, chronic kidney disease; MI, myocardial infarction; ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers.

of MACE following TAP after the implantation of DES in patients with AMI. All the statistical analyses were performed using SPSS (Statistical Package for Social Science, SPSS Inc., Chicago, IL, USA) for Windows, Version 15.0. A value of $p < 0.05$ was considered statistically significant.

Results

Patients' baseline characteristics

We enrolled 714 AMI patients who received TAP after primary DES implantation. Mean age of the enrolled patients was 61.9 ± 11.70 years (male gender 74.1%) and mean duration (MD) of TAP was 98.1 ± 115.34 days. The enrolled patients were divided in two groups as follows: the group of patients with DTAP of less than 3 months (the DTAP <3 months; $n=497$, MD = 34.1 ± 20.78 days) and the group of patients with DTAP of 3 months or more (the DTAP ≥3 months; $n=219$, MD = 234.3 ± 110.20 days). The mean age and creatinine clearance were significantly higher in the DTAP <3 months than in the DTAP ≥3 months, while male gender and history of diabetes were more frequent in the DTAP ≥3 months than in the DTAP <3 months. However, there were no differences in the other baseline clinical characteristics (Table 1). There were also no significant differences in angiographic and procedural characteristics between the two groups except paclitaxel-eluting stents were predominantly used in the DTAP ≥3 months and zotarolimus-eluting stents were more common in the DTAP <3 months (Table 2).

Follow-up clinical outcomes

All patients were clinically followed up at 12 months. Of these patients, 386 patients (53.9%) were able to perform follow-up angiography within 12 months. There were no significant differences in the incidences of cardiac death, non-fatal AMI, stent thrombosis, target lesion revascularization, and TVR between the two groups during a 12-month clinical follow-up. However, the incidence of safety endpoint and MACE were significantly lower in the DTAP ≥3

Table 2 Baseline angiographic and procedural characteristics according to duration of triple anti-platelet therapy.

	DTAP <3 months ($n=497$)	DTAP ≥3 months ($n=219$)	p-Value
Infarct-related artery (%)			0.821
LAD	262 (52.7)	116 (53.0)	
LCX	71 (14.3)	27 (12.3)	
RCA	152 (30.6)	72 (32.9)	
Left main	12 (2.4)	5 (1.8)	
Diseased vessels (%)			0.973
Single vessel	242 (48.7)	107 (48.9)	
Two vessels	141 (28.4)	59 (26.9)	
Three vessels	83 (16.7)	39 (17.8)	
Left main disease	31 (6.2)	14 (6.4)	
ACC/AHA classification (%)			0.944
Type A or B1	153 (30.8)	68 (31.1)	
Type B2 or C	344 (69.2)	151 (68.9)	
Preprocedural TIMI flow grade (%)			0.301
0	202 (40.6)	98 (44.7)	
I	22 (4.4)	14 (6.4)	
II	131 (26.4)	57 (26.0)	
III	142 (28.6)	50 (22.8)	
Postprocedural TIMI flow grade (%)			0.266
0	2 (0.4)	0 (0.0)	
I	0 (0.0)	1 (0.5)	
II	9 (1.8)	2 (0.9)	
III	486 (97.8)	216 (98.6)	
Type of stent used (%)			0.037
Paclitaxel-eluting	354 (71.2)	173 (79.0)	
Sirolimus-eluting	82 (16.5)	32 (14.6)	
Zotarolimus-eluting	61 (12.3)	14 (6.4)	
Stent diameter at target lesion, mm	3.2 ± 0.36	3.2 ± 0.33	0.485
Stent length at target lesion, mm	25.3 ± 5.82	25.1 ± 5.65	0.757
Total number of stents	1.7 ± 0.98	1.8 ± 0.98	0.598
Use of glycoprotein IIb/IIIa inhibitor (%)	175 (35.2)	78 (35.6)	0.917

Data are n (%), or mean ± SD. DTAP, duration of triple anti-platelet therapy; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; ACC/AHA, American College of Cardiology/American Heart Association; TIMI, Thrombolysis In Myocardial Infarction.

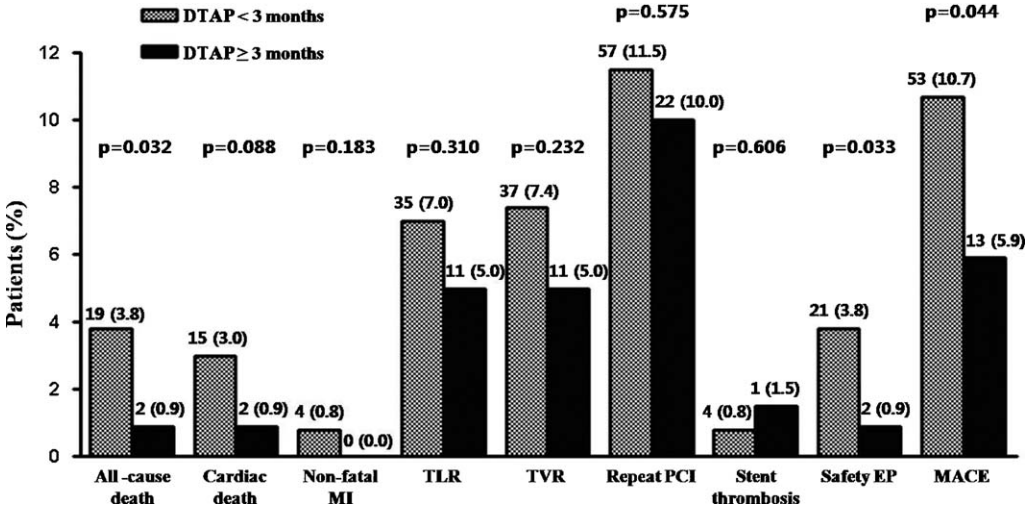

Figure 1 12-Month clinical outcomes according to DTAP of 3 months. The incidence of total death, the safety endpoint, and MACE were significantly lower in the DTAP ≥3 months compared with the DTAP <3 months. DTAP, duration of triple anti-platelet therapy; MI, myocardial infarction; TLR, target lesion revascularization; TVR, target vessel revascularization; PCI, percutaneous coronary intervention; EP, endpoint; MACE, major adverse cardiovascular events.

Table 3 Bleeding complications according to duration of triple anti-platelet therapy.

	DTAP <3 months (n = 497)	DTAP ≥3 months (n = 219)	p-Value
Degree of bleeding according to TIMI criteria			
Major	1 (0.2)	0 (0.0)	1.000
Minor	3 (0.6)	0 (0.0)	0.557
Minimal	5 (1.0)	3 (1.4)	0.706
Need for transfusion	40 (8.0)	13 (6.0)	0.327

Data are n (%). DTAP, duration of triple anti-platelet therapy; TIMI, Thrombolysis In Myocardial Infarction.

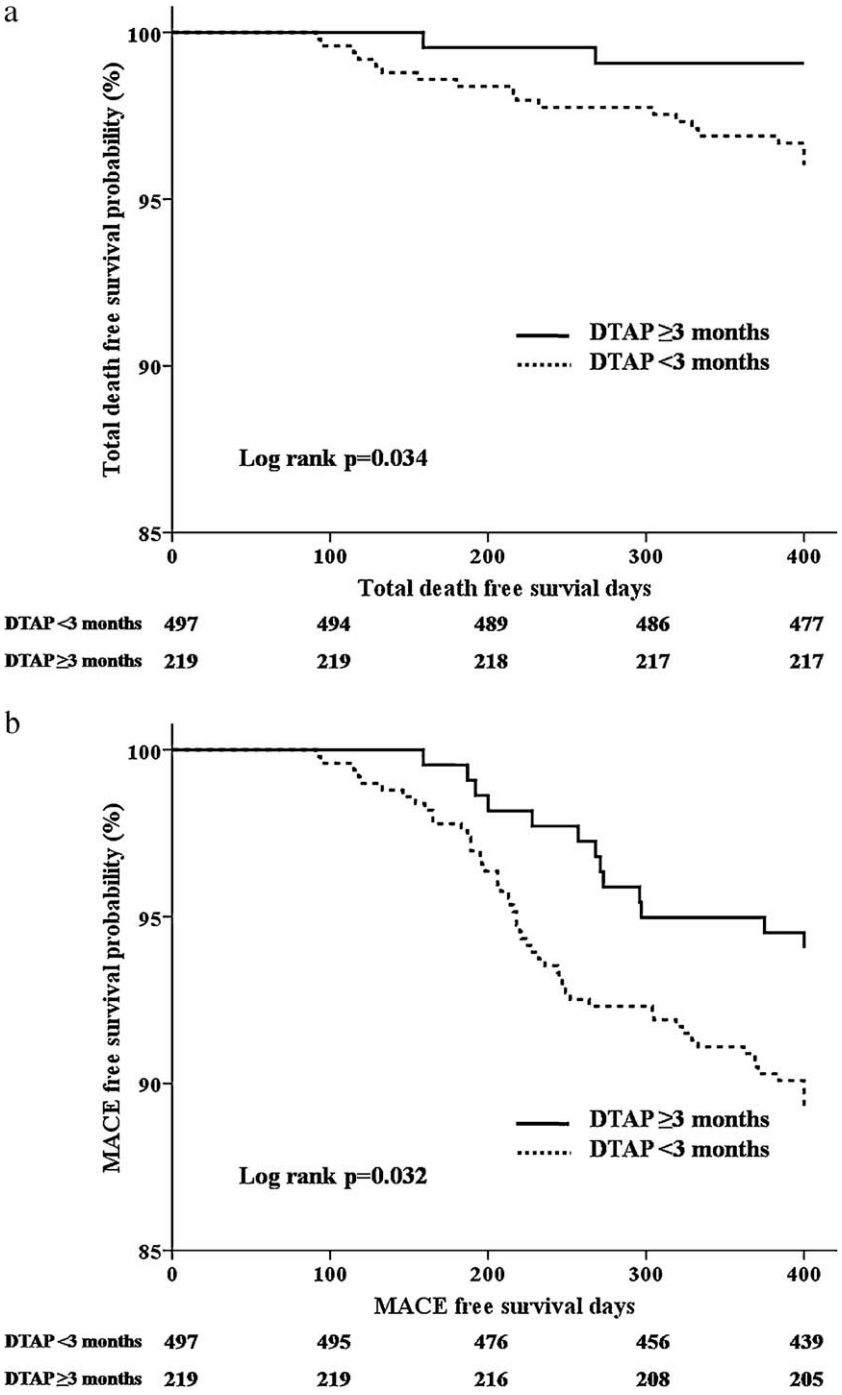

Figure 2 Kaplan—Meier survival curves for total death (A) and MACE (B) according to DTAP of 3 months. These curves demonstrated significant differences in freedom from total death and MACE between the two groups. DTAP, duration of triple anti-platelet therapy; MACE, major adverse cardiovascular events.

Table 4 Independent predictors of 1-year MACE in patients with acute myocardial infarction who received triple anti-platelet therapy after drug-eluting stent implantation.

Variables	HR	95% CI	*p*-Value
Killip class IV (vs. class I)	10.417	1.587—68.377	0.015
DTAP ≥3 months	0.508	0.269—0.956	0.036
Current smoker	1.967	0.991—3.904	0.053
Use of glycoprotein IIb/IIIa inhibitor	0.602	0.337—1.075	0.086
ACC/AHA type B2/C lesion	1.757	0.920—3.353	0.088
History of ischemic heart disease	3.780	0.709—20.171	0.120
Diagnosed ST elevation MI	2.137	0.794—5.750	0.133
History of diabetes mellitus	2.320	0.645—8.340	0.197
Stage 5 of CKD (vs. stage 1)	2.806	0.579—13.589	0.200

MACE, major adverse cardiovascular events; HR, hazard ratio; CI, confidence interval; DTAP, duration of triple anti-platelet therapy; ACC/AHA, American College of Cardiology/American Heart Association; MI, myocardial infarction; CKD, chronic kidney disease.

months compared with the DTAP <3 months (0.9% vs. 3.8%, $p = 0.033$; 0.9% vs. 10.7%, $p = 0.044$) (Fig. 1).

There were no significant differences in the incidences of TIMI bleeding criteria or need for transfusion among the 4 groups during the follow-up period (Table 3).

Kaplan—Meier survival analysis demonstrated significant differences in freedom from death and MACE between the two groups (Fig. 2).

The Cox proportional regression analysis was performed to identify the independent predictors for the occurrence of 1-year MACE in AMI patients receiving TAP after DES implantation. Independent predictors for 1-year MACE in AMI patients receiving TAP after DES implantation included Killip class IV on admission [hazard ratio (HR) = 10.417; 95% confidence interval (CI) = 1.587—68.377] and DTAP ≥3 months (HR = 0.508; 95% CI = 0.269—0.956) (Table 4).

Discussion

Our study was conducted to identify the optimal DTAP in AMI patient undergoing DES implantation. The group of patients with DTAP of 3 months or more had significantly lower incidences of all-cause death, the safety endpoint, and MACE compared with the group of patients with DTAP of less than 3 months.

Therefore, DTAP ≥3 months is associated with better clinical outcomes in patients with AMI undergoing DES implantation without increasing bleeding complications.

While DES reduced the need for repeat revascularization without an increase in death or MI, there tended to be an increased risk of late stent thrombosis [16—18]. However, DES implantation for AMI patients remained debatable, even though some studies have reported that it was safe and efficacious compared to BMS implantation [2,3,19]. DES tended to delay endothelialization, increasing the risk of stent thrombosis. In particular, vessel healing at the culprit site in AMI patients with DES implantation is substantially delayed compared with the culprit site in patients with stable angina [20]. Therefore, AMI patients with DES implantation have an increased risk of thrombotic complications such as MI or stent thrombosis. To prevent thrombotic complications, dual anti-platelet therapy was recommended for at least 12 months in patients with AMI after DES implantation [12]. Indeed, the addition of cilostazol to dual anti-platelet therapy was well known to have a beneficial effect on the prevention of thrombotic complications.

Cilostazol selectively inhibits phosphodiesterase type III which is released from platelets, and it thereby raises the intracellular concentration of cAMP and calcium, therefore, suppresses platelet aggregation and relaxes the vascular smooth muscle cells, thus having anti-platelet, anti-atherosclerotic, anti-proliferative, and vasodilative effects [21—23]. The anti-platelet effect of cilostazol helps prevent thrombotic complications in patients following stent implantation [24]. In addition, a recent study demonstrated TAP including cilostazol could ameliorate platelet responsiveness to clopidogrel in patients undergoing stent implantation [25].

How long should cilostazol be given to prevent thrombotic complications after DES implantation? The appropriate duration of TAP involves balancing the effect of cardiovascular protection and the risk of bleeding. Our study showed DTAP of more than at least 3 months was associated with lower composite incidence of cardiac death, non-fatal MI, or definite stent thrombosis without a significant increased bleeding risk.

Iakovou et al. [26] reported that a total of 71% of subacute stent thrombosis occurred within 1 week of the procedure and more than 50% of late stent thrombosis cases occurred within 3 months of the procedure. However, our study excluded patients who suffered MACE within 3 months, in order to prevent the unintentional increase of MACE in the DTAP <3 months. Therefore, our study was unable to assess the effect of TAP for MACE within 3 months of the procedure. However, considering that stent thrombosis frequently occurred within 3 months of the procedure, our opinion seemed to be proper that cilostazol should be given for more than at least 3 months.

Cilostazol has been known to reduce restenosis after successful balloon angioplasty or stent implantation [27,28]. The reduction of restenosis was associated with the direct or indirect inhibitory effect of cilostazol on the migration and proliferation of vascular smooth muscle cells [29,30]. However, it remains unclear how long should cilostazol be given if the reduction of restenosis appears. Our study showed that there were no differences in target lesion revascularization (TLR) or TVR rates between groups according to DTAP.

Acute lesions of patients with AMI may have more thrombotic burden and less fibrous atheroma and may be less prone to restenosis compared with stable plaques of those with stable angina [31]. Therefore, the impact of TAP may not be prominent in restenosis or TLR rates between DTAP in patients with AMI. However, a large-scale prospective randomized trial is needed to assess the reduction of restenosis according to DTAP.

Study limitations

The main limitation of our study is that it was conducted as a single-center, retrospective non-randomized comparative one. This might have introduced a significant bias in patient selection, even though it was partially compensated for by multivariate Cox regression model using propensity score to control the baseline biases. It was another limitation that there were few medical records about adverse reactions to cilostazol and why the patients stopped taking cilostazol. Also, each patient was very different in DTAP. Accordingly, we were unable to define the exact optimal DTAP. It is the other limitation that a regular follow-up coronary angiography within 12 months was performed for approximately 53.9% of the patients. Most of TLRs were performed based on the judgment of operators on a regular follow-up coronary angiography rather than the ischemic symptoms. Owing to this, the possibility for selection bias could not be completely ruled out.

Conclusion

Our data show that DTAP $\geq$3 months is associated with better clinical outcomes than that of <3 months in patients with AMI undergoing DES implantation without increasing bleeding complications. However, large-scale, long-term, prospective, randomized trials are needed to assess the exact optimal DTAP in AMI patients.

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