Sarpogrelate Based Triple Antiplatelet Therapy Improved Left Ventricular Systolic Function in Acute Myocardial Infarction: Retrospective Study

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Purpose: The purpose of this study was to assess the potential benefit of a 5-hydroxytryptamine receptor antagonist, sarpogrelate-based triple antiplatelet therapy (TAPT) in comparison with dual antiplatelet therapy (DAPT) in patients undergoing primary percutaneous coronary intervention (PCI) for ST-elevation myocardial infarction (STEMI).

Materials and Methods: 119 patients of STEMI were retrospectively assessed. All patients received aspirin and clopidogrel per standard of care. Among them, 53 patients received an additional loading dose of sarpogrelate and a maintenance dose for 6 months post-PCI (TAPT group), while others did not (DAPT group).

Results: The rates of complete ST-segment resolution at 30 minutes post-PCI and post-procedural thrombolysis in myocardial infarction flow were not significantly different between the two groups (52.8% vs. 48.5%, p=0.200; 92.5% vs. 89.4%, p=0.080). In addition, no significant differences were observed between the two groups with regard to 30-day and 12-month clinical outcomes (cardiac death, myocardial infarction, stent thrombosis, target vessel revascularization, and severe bleeding). Meanwhile, improvement in left ventricular (LV) systolic function was observed in the TAPT group [ΔLV ejection fraction (LVEF)=17.1±9.4%, p<0.001; Δglobal longitudinal strain (GLS)=-9.4±4.2% , p<0.001] at 6 months, whereas it was not in the DAPT group (ΔLVEF= 8.8±6.5%, p=0.090; ΔGLS=-4.6±3.4%, p=0.106). In multivariate analyses, TAPT was an independent predictor for LV functional recovery (odds ratio, 2.61; 95% confidence interval, 1.16−5.87; p=0.003).

Conclusion: Sarpogrelate-based TAPT improved LV systolic function at 6 months in STEMI patients undergoing primary PCI.

Key Words: Antiplatelet therapy, left ventricular function, acute myocardial infarction

INTRODUCTION

Aggressive platelet inhibition in patients with ST-segment ele-

vation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PCI) is crucial for myocardial salvage and improvement of survival.[1] Dual antiplatelet therapy (DAPT) with aspirin and clopidogrel have been widely used as a standard regimen in this setting.[2] However, due to its higher rate of hypo-responsiveness in STEMI, clopidogrel has been largely replaced by more potent P2Y12 receptor inhibitors, such as prasugrel and ticagrelor, in line with current US and European PCI guidelines.[3,4] In the meantime, there have been several efforts to overcome clopidogrel hypo-responsiveness in acute coronary syndrome (ACS) patients by adding a third antiplatelet agent (cilostazol, sarpogrelate, etc.) on top of background aspirin and clopidogrel therapy as shown

in large-scale registry data.[5,6]

Sarpogrelate HCl (Anplag™, Mitsubishi Tokyo Pharmaceuticals, Tokyo, Japan) is a selective 5-hydroxytryptamine (5-HT) receptor subtype 2A antagonist that acts as a platelet aggregation inhibitor to improve peripheral circulation in the treatment of ischemic symptoms observed in patients with chronic arterial obstruction.[7] Studies have reported on the effectiveness of sarpogrelate in patients with ischemic heart disease or peripheral vascular disease.[8,9] Also, 5-HT receptor blockade has been reported to have several beneficial effects, including direct inhibition of platelet aggregation, smooth muscle proliferation, and preconditioning-like effect.[10] However, data on sarpogrelate as a part of triple anti-platelet regimen (aspirin, clopidogrel, and sarpogrelate) in patients undergoing PCI are scarce. Accordingly, considering these potential ischemic benefits in patients with acute myocardial infarction, we aimed to evaluate the efficacy and safety of triple antiplatelet therapy (TAPT) with sarpogrelate in patients with STEMI undergoing PCI.

Herein, we retrospectively reviewed data for 119 patients with STEMI who underwent primary PCI with drug-eluting stents (DES) in our institution and compared baseline, echocardiographic. and clinical outcomes between a DAPT (aspirin+clopidogrel) group and a TAPT (aspirin+clopidogrel+sarpogrelate) group to determine whether TAPT offers procedural, clinical, and functional benefits over DAPT.

MATERIALS AND METHODS

Study design
This study was conducted as a single center, retrospective, observational study. We analyzed 119 patients with acute STEMI who underwent DES-based primary PCI at Kangnam Sacred Heart Hospital from January 2008 to December 2009. Inclusion criteria were as follows: 1) patients who presented with acute STEMI underwent primary PCI; 2) patients who underwent serial tests of electrocardiography, cardiac biomarkers (CK-MB), and echocardiography; 3) patients who had a adequate angiographic image at index PCI for the determination of thrombolysis in myocardial infarction (TIMI) flow; and 4) patients who had stable vital signs before undergoing primary PCI. Exclusion criteria were 1) patients with cardiogenic shock (Killip class IV) at presentation, 2) patients who had known hypersensitivity to aspirin, clopidogrel, or sarpogrelate, 3) patients who had known serious hypersensitivity to contrast media, 4) patients who had clinical conditions requiring systemic immune suppression over 2 weeks or anti-cancer therapy, 5) patients who had history of bleeding diathesis or known coagulopathy (including heparin induced thrombocytopenia), 6) patients who refused blood transfusions, 7) patients who had gastrointestinal or genitourinary bleeding within the prior 3 months or major surgery within 2 months, 8) patients who had less than 100000 cells/mm³ of platelet or 10 g/dL of hemoglobin, 9) patients who

had non-cardiac co-morbid conditions with a life expectancy <1 year, 10) patients who had more than 3.0 mg/dL of serum creatinine or patients who were on dialysis, and 11) patients who had severe hepatic dysfunction (AST or ALT over 3 times the normal upper limit).

Study procedures
Primary PCI was performed according to standard techniques. Before the index procedure, all patients received 300 mg of aspirin and 600 of mg clopidogrel as loading doses. Among them, 53 patients received additional 600 mg of sarpogrelate (TAPT), while the others did not (DAPT). Use of additional sarpogrelate was left to the operator's decision. Unfractionated heparin was administered intravenously before PCI, and the active clotting time was maintained at >250 seconds throughout the procedure. Thrombus aspiration, pre-dilation before stenting, or use of glycoprotein IIb/IIIa inhibitors were left to the operators' decision. CK-MB was measured before PCI and every 8 hours after index procedure for 48 hours. Thereafter, CK-MB was measured once daily until normalized. All patients received optimal pharmacological therapy, including statins, beta-blockers, or renin-angiotensin system blockade, following the current guidelines. DAPT (aspirin 100 mg/d plus clopidogrel 75 mg/d) was maintained for at least 12 months. Patients in the TAPT group received additional sarpogrelate 300 mg/d after primary PCI for up to 6 months.

Study end points
The primary endpoint was the rate of complete ST-segment resolution on electrocardiogram (ECG) obtained 30 minutes after the procedure. The sum of ST-segment elevation was measured 20 milliseconds after the end of the QRS complex from leads I, aVL, and V_1 through V_6 for anterior myocardial infarction and leads II, III, aVF, and V_5 and V_6 for nonanterior myocardial infarction.[11] ST-segment resolution was categorized as complete (>70%), partial (30−70%), or absent (<30%).[11]

Secondary end points included TIMI flow after PCI, death, myocardial infarction, severe heart failure, stent thrombosis, target vessel revascularization, and major adverse cardiac events (MACEs) (a composite of death, myocardial infarction, severe heart failure, stent thrombosis or target vessel revascularization) at 30 days and 12 months, as well as changes in left ventricular (LV) end-diastolic dimension (LVEDD), LV end-systolic dimension (LVESD), LV ejection fraction (LVEF), and global longitudinal strain (GLS) at 6 months post index PCI. GLS is a novel method that is automatically calculated from two-dimensional echocardiographic images for the assessment of global LV function. The GLS method shows high sensitivity and specificity in the detection of LV systolic function.[12]

The safety endpoint was severe bleeding event at 12 months. Severe bleeding was defined as subarachnoid, intra-cerebral, or intracranial hemorrhage. Bleeding definition was based on the Global Utilization of Streptokinase and t-PA for Occluded

Coronary Arteries (GUSTO) criteria.[13]

All deaths were considered cardiac unless a definite non-cardiac cause could be established. Myocardial infarction was defined according to the Academic Research Consortium classification.[14] When cardiac enzymes (CK-MB or troponin-I) were elevated, reinfarction was defined as stable or decreasing values on 2 samples and a 20% increase 3 to 6 hours after the second sample. After cardiac enzymes normalized, myocardial infarction was defined as a cardiac enzyme increase greater than the normal upper limit. Severe heart failure was defined as heart failure with documented arterial partial pressure of oxygen <60 mm Hg or with pulmonary edema documented radiographically or requiring intubation, 100% oxygen, or insertion of a mechanical support device.[15] Stent thrombosis was defined as definite or probable according to the Academic Research Consortium classification.[14] LVEDD and LVESD were measured by M-mode echocardiography. LVEF was calculated by a modified Simpson's method. GLS was automatically calculated for the entire U-shaped length of LV myocardium (basal, mid, and apical segments of two opposite walls in each view). ECG, angiographic, and echocardiographic data were analyzed at the core laboratory (Kangnam Sacred Heart Hospital, Seoul, Korea). Patients were monitored for adverse events at every visit, and all adverse events were recorded for assessment.

Statistical analysis
Categorical variables were compared using the χ^2 test. Continuous variables were compared using Student's t-test, the paired t-test, or Fisher's exact test as appropriate. To adjust for potential confounders, a propensity score analysis was performed using a logistic regression model, testing the propensity to receive triple rather than DAPT.

Multiple logistic regression analysis was performed with LVEF improvement >15% as a dependent outcome variable, while use of sarpogrelate was included as a continuous variable. A values of $p<0.05$ in two-tailed test were considered significant. All analyses were performed with PAWS software, version 18.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Baseline characteristics
Most patients maintained antiplatelet therapy for up to 12 months. However, 2 patients in the TAPT group stopped the drug due to gastrointestinal bleeding, and 4 patients died due to cardiac cause. A total of 47 patients maintained TAPT for up to 6 months. In the DAPT group, 1 patient stopped the drug due to intracranial bleeding, 2 patients stopped due to gastrointestinal bleeding, and 7 patients died. A total of 56 patients maintained DAPT up to 12 months.

Symptom to door time was 118.2±56.1 min in TAPT group vs. 109.3±63.4 min in DAPT group. On arrival to the hospital, 85%

were in Killip class I to II in both groups. Baseline clinical, echocardiographic, and laboratory characteristics were well balanced between the two groups (Table 1).

Procedure-related characteristics were comparable between the two groups (Table 2). More than half of all culprit lesions involved the left anterior descending artery (66.0% in TAPT group vs. 62.1% in DAPT group). TIMI 0 flow before PCI was 90.6% in the TAPT group vs. 89.4% in DAPT group. Door-to-reperfusion time was 93.4±140.7 min in TAPT group vs. 107.0±71.9 min in the DAPT group. Percentage of direct stenting, thrombus aspiration, and use of Gp IIb/IIIa inhibitor were well balanced between the two groups (13.2% vs. 13.6%; 39.6% vs. 54.5%; 33.9% vs. 33.3%).

Study end points
Baseline and follow up ECG data were available in all patients. The primary end point of complete ST-segment resolution occurred in 28 of the 53 patients (52.8%) in the TAPT group and 32 of the 66 patients (48.5%) in the DAPT group without statistical significance ($p=0.200$) (Table 3). There was no significant difference in the postprocedural TIMI flow between the two groups. Patients in the TAPT group tended to have a higher rate of postprocedural TIMI grade 3 flow than those in the DAPT group; however, statistical significance was not achieved (92.5% vs. 89.4%; $p=0.080$) (Table 3).

No significant differences were observed between the two groups with regard to 30-day and 12-month clinical outcomes. MACEs occurred in 7 patients (13.2%) in the TAPT group and 10 patients (15.6%) in the DAPT group at 30 days ($p=0.095$) and 8 patients (15.1%) in the TAPT group and 12 patients (18.2%) in the DAPT group at 12 months ($p=0.076$) (Table 4).

Improvement of left ventricular systolic function
Both mean LVESD and LVEDD significantly decreased in the TAPT group. Mean LVESD decreased, while LVEDD did not, decrease in DAPT group. LVEF was more increased in the TAPT group (ΔLVEF=17.1±9.4%, $p<0.001$), whereas it was not significantly changed in the DAPT group (ΔLVEF=8.8±6.5%, $p=0.090$), at 6 months. GLS was significantly improved in the TAPT group (ΔGLS=-9.4±4.2%, $p<0.001$). However, it was not significantly changed in the DAPT group (ΔGLS=-4.6±3.4%, $p=0.106$) (Table 5).

Independent markers for improved left ventricular systolic function
In univariate and multivariate analyses, TAPT was an independent predictor for improvement in LV systolic function (improved LVEF more than 15% compared at baseline) [odds ratio, 2.61; 95% confidence interval (CI), 1.16–5.87; $p=0.003$] (Table 6).

Safety end points
There was no significant difference in severe bleeding risk between groups. Multivariate Cox regression analysis of severe

Table 1. Baseline and Laboratory Characteristics

Variable	TAPT (n=53)	DAPT (n=66)	p value
Age (yr)	61.9±11.5	59.4±12.7	0.272
Male gender	45 (84.9)	52 (78.8)	0.479
BMI (kg/m²)	23.7±2.5	24.0±2.9	0.553
Systolic BP (mm Hg)	144.0±26.1	148.0±23.3	0.383
Diastolic BP (mm Hg)	82.0±14.4	80.0±10.7	0.406
Heart rate (bpm)	79.6±23.0	76.7±16.1	0.107
Smoking	34 (64.2)	41 (62.1)	0.526
Hypertension	32 (60.4)	34 (51.5)	0.354
Diabetes	12 (22.6)	16 (24.2)	0.251
Dyslipidemia	9 (17.0)	13 (19.7)	>0.999
Renal impairment	2 (3.8)	4 (6.1)	0.689
Cerebrovascular event	4 (7.5)	2 (3.0)	0.406
Symptom to door time (min)	118.2±56.1	109.3±63.4	0.162
Killip class on arrival to the hospital			0.328
I	12 (23.0)	17 (26.0)	
II	33 (62.0)	39 (59.0)	
III	8 (15.0)	10 (15.0)	
IV	0 (0)	0 (0)	
Echocardiographic parameters			
LVEDD (mm)	53.4±5.7	52.1±5.6	0.214
LVESD (mm)	39.4±7.7	37.4±6.7	0.152
LVEF (%)	39.4±13.2	39.1±11.0	0.900
GLS (%)	-10.5±4.1	-10.1±4.3	0.955
Laboratory parameters			
CK-MB	102.4±67.1	95.3±42.5	0.153
Troponin I	35.6±20.5	32.8±19.7	0.317
BNP (pg/mL)	185.5±616.2	202.8±474.8	0.866
Triglyceride (mg/dL)	80.8±42.5	92.2±52.0	0.220
HDL cholesterol (mg/dL)	46.9±12.7	44.9±11.7	0.375
LDL cholesterol (mg/dL)	117.9±44.1	110.9±32.1	0.340
Creatinine (mg/dL)	1.1±0.7	1.2±1.0	0.157

TAPT, triple antiplatelet therapy; DAPT, double antiplatelet therapy; BMI, body mass index; BP, blood pressure; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LVEF, left ventricular ejection fraction; GLS, global longitudinal strain; CK, creatine kinase; BNP, brain natriuretic peptide; HDL, high density lipoprotein; LDL, low density lipoprotein.
Data are expressed as a number (%) or mean±standard deviation.

bleeding showed that the TAPT group exhibited no significant increase in risk, compared to the DAPT group [TAPT vs. DAPT, hazard ratio, 0.91 (95% CI, 0.77−1.09)].

DISCUSSION

Major findings

In the present study, sarpogrelate-based TAPT did not show a difference in the rate of post-procedural complete ST-segment resolution, compared to DAPT (primary endpoint). However, TAPT trended slightly towards a higher rate of postprocedural TIMI grade 3 flow and better 30-day and 12-month clinical outcomes (secondary endpoints), compared with DAPT. Interestingly, the sarpogrelate-based TAPT group showed greater improvement in LV systolic function (LVEF and GLS, components of secondary endpoints) compared to the DAPT group after 6 months post-PCI. Also, in multivariate analyses, TAPT was an independent predictor for improvement in LV systolic function (improved LVEF more than 15%, compared to before treatment).

Recent updates to guidelines on post-PCI antiplatelet treatment for patients undergoing PCI with DES recommend administration of DAPT with aspirin and clopidogrel for at least 12 months.[16] However, previous studies have suggested that 20% to 50% of these patients do not show adequate responsiveness to aspirin or clopidogrel, posing significantly higher risks of recurrent ischemic events therein.[17-19] Müller, et al.[20] reported that an even higher loading dose (600 mg) of clopidogrel cannot sufficiently inhibit the aggregation and degranulation of

Table 2. Procedure-Related Characteristics

Variable	TAPT (n=53)	DAPT (n=66)	*p* value
Diseased vessels			0.354
1	28 (53.0)	39 (59.0)	
2	17 (32.0)	20 (30.0)	
3	8 (15.0)	7 (11.0)	
Culprit lesion			0.781
Left anterior descending	35 (66.0)	41 (62.1)	
Left circumflex	4 (7.5)	6 (9.1)	
Right coronary artery	14 (26.5)	19 (28.8)	
Left main trunk	0 (0)	0 (0)	
TIMI flow before PCI			0.768
0	48 (90.6)	59 (89.4)	
1	2 (3.8)	3 (4.5)	
2 or 3	1 (5.6)	4 (6.1)	
Procedural			
Door-to-reperfusion time (min)	93.4±140.7	107.0±71.9	0.115
Direct stenting	7 (13.2)	9 (13.6)	0.236
Thrombus aspiration	21 (39.6)	36 (54.5)	0.075
Administraion of Gp IIb/IIIa inhibitor	18 (33.9)	22 (33.3)	0.864
Total number of stents	78	86	
Type of stent			0.546
Drug-eluting stent (%)	53 (100.0)	66 (100.0)	
Paclitaxel-eluting			
Coroflex® Please	9 (17.0)	11 (16.7)	
Taxus®	12 (22.6)	15 (22.7)	
Sirolimus-eluting			
Cypher®	7 (13.2)	9 (13.6)	
Zotarolimus-eluting			
Endeavor Sprinter®	6 (11.3)	7 (10.6)	
Endeavor Resolute®	13 (24.5)	14 (21.2)	
Everolimus-eluting			
Promus®	4 (7.6)	6 (9.1)	
Xience®	2 (3.8)	4 (6.1)	
Stent diameter (mm)	3.2±0.5	3.1±0.4	
Stent length (mm)	23.7±5.6	24.1±6.5	

TAPT, triple antiplatelet therapy; DAPT, double antiplatelet therapy; TIMI, thrombolysis in myocardial infarction; PCI, percutaneous coronary intervention; Gp, glycoprotein.
Data are expressed as a number (%) or mean±standard deviation.

Table 3. Resolution of ST-Segment Elevation and TIMI Flow after PCI

Variable	TAPT (n=53)	DAPT (n=66)	*p* value
Resolution of ST-segment elevation 30 min post-PCI (%)			0.200
Absent (<30%)	9 (17.0)	13 (19.7)	
Partial (30–70%)	16 (30.2)	21 (31.8)	
Complete (>70%)	28 (52.8)	32 (48.5)	
TIMI flow at the completion of PCI (%)			0.080
0 or 1	1 (1.8)	3 (4.5)	
2	3 (5.7)	4 (6.1)	
3	49 (92.5)	59 (89.4)	

TAPT, triple antiplatelet therapy; DAPT, double antiplatelet therapy; PCI, percutaneous coronary intervention; TIMI, thrombolysis in myocardial infarction.
p values were calculated with the use of the fisher's exact test.

platelets by thrombin-related activating peptides in the setting of AMI.[20] In addition, Gawaz, et al.[21] showed that platelet reactivity significantly increased in AMI patients undergoing PCI. Meanwhile, Chen, et al.[6] showed that aggressive antiplatelet treatment with aspirin, clopidogrel, and cilostazol, compared with conventional DAPT, improved midterm clinical outcomes in acute STEMI patients who underwent primary PCI. Therefore, it is reasonable to add a potent antiplatelet agent to aspirin and clopidogrel to strengthen the effectiveness of antiplatelet therapy in patients with acute STEMI undergoing PCI with DES.

Table 4. Clinical Outcomes at 30 Days and 12 Months after PCI

Variable	TAPT (n=53)	DAPT (n=66)	Relative risk (95% CI)*	p value
MACE[†]–at 30 day	7 (13.2)	10 (15.6)	0.90 (0.58–1.13)	0.095
Cardiac death	4 (7.5)	5 (7.6)		
Myocardial infarction	1 (1.9)	2 (3.0)		
Stent thrombosis	2 (3.8)	3 (4.5)		
TVR	1 (1.9)	2 (3.0)		
Severe bleeding	2 (3.8)	3 (4.5)	0.91 (0.77–1.09)	0.230
MACE[†]–at 12 month	8 (15.1)	12 (18.2)	0.88 (0.69–1.20)	0.076
Cardiac death	5 (9.4)	7 (10.6)		
Myocardial infarction	1 (1.9)	2 (3.0)		
Stent thrombosis	2 (3.8)	3 (4.5)		
TVR	1 (1.9)	2 (3.0)		
Severe bleeding	2 (3.8)	3 (4.5)	0.91 (0.77–1.09)	0.230

PCI, percutaneous coronary intervention; MACE, major adverse cardiac events; TAPT, triple antiplatelet therapy; DAPT, double antiplatelet therapy; TVR, target vessel revascularization; CI, confidence interval.
Data are expressed as a number (%).
*Relative risk is for the TAPT group compared with the DAPT group, [†]A composite of cardiac death, myocardial infarction and stent thrombosis.

Table 5. Changes in Echocardiographic Parameters after 24 Weeks of PCI

Echocardiographic parameters	TAPT (n=47)	DAPT (n=56)	p value
LVEDD (mm)			
At baseline	53.4±5.7	52.1±5.6	0.214
At 24 weeks	50.1±5.3	51.3±5.2	0.165
ΔLVEDD (mm)	-3.3±2.9	-0.8±1.4	0.002
p value*	<0.001	0.135	
LVESD (mm)			
At baseline	39.4±7.7	37.4±6.7	0.152
At 24 weeks	36.1±6.9	34.5±5.9	0.568
ΔLVESD (mm)	-3.3±1.5	-2.9±1.8	0.432
p value*	<0.001	0.003	
LVEF (%)			
At baseline	39.4±13.2	39.1±11.0	0.900
At 24 weeks	56.5±15.2	47.9±12.3	<0.001
ΔLVEF (%)	17.1±9.4	8.8±6.5	<0.001
p value*	<0.001	0.090	
Patients with improved LV systolic function (%)[†]	22 (41.5)	10 (15.2)	0.015
GLS (%)			
At baseline	-10.5±4.1	-10.1±4.3	0.955
At 24 weeks	-19.8±5.6	-14.7±4.4	<0.001
ΔGLS (%)	-9.4±4.2	-4.6±3.4	<0.001
p value*	<0.001	0.106	

TAPT, triple antiplatelet therapy; DAPT, double antiplatelet therapy; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LVEF, left ventricular ejection fraction; LV, left ventricular; GLS, global longitudinal strain; PCI, percutaneous coronary intervention.
Data are expressed as a number (%) or mean±standard deviation.
*p value for echocardiographic parameters was calculated by paired t-test between baseline and 24 weeks, [†]Improved LVEF more than 15% compared to before treatment.

Table 6. Univariate and Multivariate Logistic Analysis for LV Functional Recovery*

Variable	Univariate analysis			Multivariate analysis		
	OR	95% CI	*p* value	OR	95% CI	*p* value
Age						
≥60	1					
<60	1.98	1.26–2.78	0.098			
Diseased vessel						
≥2	1					
1	2.11	0.95–5.72	0.071			
Culprit lesion						
LAD	1			1		
Non-LAD	1.84	1.02–3.26	0.003	1.16	0.87–2.48	0.117
Door-to-reperfusion time (min)						
≥90	1					
<90	1.02	1.00–1.05	0.105			
TIMI flow before PCI						
0	1			1		
≥1	2.69	1.78–5.12	0.019	1.85	0.97–2.78	0.095
Antiplatelet therapy						
DAPT	1			1		
TAPT	3.01	1.90–6.25	0.001	2.61	1.16–5.87	0.003

LV, left ventricle; LAD, left anterior descending artery; TIMI, thrombolysis in myocardial infarction; PCI, percutaneous coronary intervention; TAPT, triple antiplatelet therapy; DAPT, double antiplatelet therapy; OR, odds ratio; CI, confidence interval.
*Improved LV ejection fraction more than 15% compared at baseline.

Effectiveness and limitations of newer P2Y12 inhibitors

Both novel P2Y12 inhibitors, ticagrelor and prasugrel, offer us a chance to confine the reinfarction rate and stent thrombosis in interventionally treated ACS patients.[3,4] Despite these similarities, landmark clinical trials on ticagrelor and prasugrel have indicated substantial differences in outcomes when these agents were compared with clopidogrel. Ticagrelor conferred clinical advantages in the PLATO trial in a broad spectrum of ACS patients. On the other hand, dyspnea and ventricular pauses together with transient elevations in uric acid and creatinine concentrations are known adverse effects of ticagrelor. Although premature discontinuation of therapy due to dyspnea was infrequent in the PLATO trial, it occurred significantly more commonly in patients treated with ticagrelor than in those receiving clopidogrel.[22] In the same study, ventricular pauses occurred more often in ticagrelor-treated patients.[23]

Prasugrel was tested in the TRITON-TIMI 38 trial exclusively in ACS patients (moderate-to-high risk non-ST elevation ACS or STEMI) with scheduled PCI.[4] Therefore, in contrast to the PLATO trial, its findings are not applicable to medically-treated ACS patients. Furthermore, the TRILOGY ACS trial including non-ST elevation ACS patients treated conservatively failed to demonstrate any clinical benefits of prasugrel, as compared with clopidogrel.[24] Therapy with prasugrel in the TRITON-TIMI 38 trial was associated with an increased risk of major bleeding, including life-threatening bleeding and fatal bleeding, when compared with clopidogrel treatment, which have been reflected in guidelines as a contraindication to prasugrel use in higher bleeding risk group (age more than 75 years, body weight less than 60 kg, and prior history of ischemic or hemorrhagic stroke).[4]

Pleiotropic effects of sarpogrelate

Experimental animal studies have demonstrated that platelets are activated and aggregate at the sites of coronary artery stenosis and endothelial injury.[25-27] Additionally, damage to the arterial wall during angioplasty may also lead to platelet activation and thrombus formation.[28-33] Leosco, et al.[34] demonstrated that coronary stenting induces a greater release of 5-HT into the coronary circulation, probably due to the more pronounced arterial damage and platelet deposition and activation after high pressure stenting procedure. A greater release of 5-HT into the coronary circulation after coronary stenting may thus contribute to subsequent stent thrombosis and restenosis through the effects of platelet aggregation and vascular smooth muscle proliferation mediated by 5-HT$_{2A}$ receptors. These facts suggests the potential value of serotonin blockade before and after coronary intervention.

The 5-HT$_2$-receptor blocker sarpogrelate is known to exert platelet anti-aggregation effects[35] and protective effects against angina pectoris via an increase in collateral circulation.[36] Also, blockade of 5-HT$_2$-receptors was reported to improve ischemia-induced left ventricular dysfunction, even in isolated rat hearts independent of collaterals.[37] Shimizu, et al.[38] reported infarct-size reducing effects for sarpogrelate in rabbit hearts without collateral flow. Furthermore, Horibe, et al.[39] showed

that sarpogrelate improves ischemic injury after balloon inflation in a human study, suggesting that it may have a pharmacological preconditioning effect. Thus, sarpogrelate appears to elicit anti-ischemic effects via both an increase in collateral circulation and a preconditioning-like mechanism. These effects of sarpogrelate are considered to be beneficial in patients with AMI undergoing PCI.

Clinical implications

Despite anti-ischemic benefits of sarpogrelate in the AMI settings, we could not demonstrate better rate of post-procedural complete ST-segment resolution, post-procedural TIMI flow recovery, and clinical outcomes in patients received sarpogrelate-based TAPT than those with DAPT in the present study. However, the present study showed greater improvement of LV systolic function, compared to DAPT, after 6 months post-PCI. Although postulative, the pleiotropic effects of sarpogrelate (antioxidant, post-conditioning, and collateral developing effects) might play an important role in ischemia-reperfusion injury and protect against myocardial ischemic cellular damage when acute myocardial infarction occurs.

After results of large landmark trial, like the PLATO trial, clopidogrel has been largely replaced by more potent P2Y12 receptor inhibitors.[3,4] However, some side effects, such as dyspnea, elevation of serum uric acid and creatinine, and ventricular pauses, are a concern. We suggest that adding sarpogrelate, as a part of TAPT regimen, can be beneficial in patients with STEMI undergoing PCI who are not applicable with potent P2Y12 inhibitors. However, further prospective, large-scale, randomized study is needed to confirm our study results.

Study limitations

The present study has some limitations. First, this study is retrospective, single center study and included a relatively small number of subjects. Second, this study did not have sufficient power to detect differences between the two groups in the incidence of stent thrombosis or MACEs, which is a rare phenomenon. Third, although we included most confounders in the multivariable Cox regression model, it is possible that some potential confounders might have been overlooked. Fourth, we divided patients into different antiplatelet therapies on the basis of their in-hospital, discharge, and follow-up medical records. We did not collect information on other adverse reactions to sarpogrelate during the follow up period. However, we have detailed information on the major and minor bleeding events, mortality, and recurrent myocardial infarction, which also are very important components of safety profiles and can help us understand the main safety profiles of sarpogrelate. Fifth, sarpogrelate could be used as an alternative drug in patients who cannot use ticagrelor or prasugrel. However, these days, clopidogrel has been largely replaced by new potent P2Y12 inhibitors. Therefore, the clinical usefulness of this study is limited.

Conclusions

The present study showed that sarpogrelate-based TAPT had a positive effect on recovery of LV systolic function in acute STEMI patients who underwent primary PCI in the era of DES.

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