CLINICAL INVESTIGATIONS

Similar Impact of Clopidogrel or Ticagrelor on Carotid Atherosclerotic Plaque Inflammation

Minyoung Oh MD | Cheol Whan Lee MD | Hyo Sang Lee MD | Mineok Chang MD |
Jung-Min Ahn MD | Duk-Woo Park MD | Soo-Jin Kang MD | Seung-Whan Lee MD |
Young-Hak Kim MD | Dae Hyuk Moon MD | Seong-Wook Park MD, PhD |
Seung-Jung Park MD, PhD

Department of Nuclear Medicine (Oh, H.S. Lee, Moon) and Department of Medicine (C.W. Lee, Chang, Ahn, D.-W. Park, Kang, S.-W. Lee, Kim, S.-W. Park, S.-J. Park), Asan Medical Center, University of Ulsan, Seoul, Korea

This study was supported by a research grant from AstraZeneca Korea and a grant from the Asan Institute for Life Sciences, Seoul, Korea (no. 2014–217).

The authors have no other funding, financial relationships, or conflicts of interest to disclose.

Corresponding Author: Cheol Whan Lee, MD, Division of Cardiology, Heart Institute, Asan Medical Center, University of Ulsan, 88, Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Korea (cheolwlee@amc.seoul.kr)

Background: Platelets play an important role in inflammation. Inhibitors of the P2Y₁₂ receptor, which is involved in platelet activation, may have a direct effect on carotid atherosclerotic plaque inflammation.

Hypothesis: We compared the effects of clopidogrel and ticagrelor therapy for carotid atherosclerotic plaque inflammation using ¹⁸F-fluorodeoxyglucose (¹⁸FDG) positron emission tomography (PET) imaging.

Methods: Fifty patients with acute coronary syndrome and ≥ 1 ¹⁸FDG uptake in the carotid artery (target-to-background ratio [TBR] ≥ 1.6) were randomized to either clopidogrel or ticagrelor groups. Of these, 46 completed PET examinations at baseline and at 6 months. The primary endpoint was the percent change in TBR of the index vessel at the most diseased segment (MDS).

Results: Baseline characteristics were similar between the 2 groups. At 6-month follow-up, low-density lipoprotein cholesterol and C-reactive protein significantly decreased in both groups ($P < 0.001$). The TBR of the index vessel and aorta significantly decreased in both groups ($P < 0.01$). The percent change in the MDS TBR of the index vessel was numerically but not significantly lower in the clopidogrel group than in the ticagrelor group ($-9.5 \pm 14.6\%$ vs $-13.5 \pm 19.3\%$; $P = 0.427$). Likewise, the percent change in the whole-vessel TBR of the index vessel was not different between the 2 groups ($P = 0.166$). Similar findings were observed for changes in the MDS TBR ($P = 0.412$) or whole-vessel TBR of the aorta ($P = 0.363$).

Conclusions: Carotid atherosclerotic plaque inflammation significantly decreases to a similar degree following 6 months of either clopidogrel or ticagrelor treatment.

KEYWORDS

plaque inflammation, P2Y₁₂ inhibitors, Imaging, positron emission tomography, ticagrelor, clopidogrel

1 | INTRODUCTION

Platelet activation and thrombus formation at the site of plaque rupture are the underlying mechanisms responsible for acute coronary syndrome (ACS).^{1,2} The P2Y₁₂ receptor plays a key role in platelet activation,^{3,4} and clopidogrel, a P2Y₁₂ receptor blocker, is superior to aspirin for the prevention of vascular events.⁵ However, variable

responses to clopidogrel have led to the development of new P2Y₁₂ receptor blockers with superior efficacy.^{6–8} The P2Y₁₂ receptor is expressed in vascular cells as well as platelets.^{9,10} P2Y₁₂ receptor blockers reduce the levels of vascular inflammation markers and improve endothelial function, suggesting pleiotropic effects coupled with P2Y₁₂ receptor antagonism.^{11–16} We therefore speculated that P2Y₁₂ receptor blockers may have a direct effect on atherosclerotic

plaque inflammation and that ticagrelor may be superior in efficacy to clopidogrel.

In our present study, we compared the effects of clopidogrel and ticagrelor therapy to carotid atherosclerotic plaque inflammation using serial ^{18}F -fluorodeoxyglucose (^{18}FDG) positron emission tomography-computed tomography (PET/CT) imaging (<http://www.ClinicalTrials.gov> NCT01905566). This technique allows for noninvasive efficacy assessment of therapeutic interventions.^{17–20} Uptake of arterial ^{18}FDG was assessed as target-to-background ratio (TBR): (1) as a mean of standardized uptake values (SUV) of all slices of the vessel, and (2) within most diseased segment (MDS) of all vessels.^{18–20}

2 | METHODS

2.1 | Study Design

This was a prospective, single center, open-label, randomized comparison trial conducted between September 2013 and August 2015. Patients were eligible if they presented with their first ACS requiring dual antiplatelet therapy, asymptomatic carotid artery disease (diameter stenosis 20%–50%) by duplex ultrasound scanning, and ≥ 1 ^{18}FDG uptake lesion in the carotid artery (target-to-background ratio [TBR] ≥ 1.6) by ^{18}FDG PET/CT imaging. Exclusion criteria included thrombocytopenia (platelet count $<100\,000/\mu\text{L}$), P2Y₁₂ inhibitor therapy in the previous 4 weeks, cardiogenic shock, heart failure, chronic liver disease, chronic renal failure, concomitant inflammatory conditions (such as active infection, inflammatory arthritis, or connective tissue disease), type 1 diabetes mellitus, malignancies, or a contraindication to clopidogrel or ticagrelor.

Patients received a 600-mg loading dose of clopidogrel (or 180 mg ticagrelor) at the emergency room, followed by 75 mg clopidogrel once daily (or 90 mg ticagrelor twice daily) before randomization. Baseline ^{18}FDG PET/CT was performed within 2 days of coronary angiography or percutaneous coronary intervention (3–5 days after admission). Patients meeting our inclusion criteria, and none of the exclusion criteria, were randomized at a ratio of 1:1 to clopidogrel (75 mg once a day for 12 months) or ticagrelor (90 mg twice a day for 12 months) groups. All patients were treated with standard medications including aspirin and statins. A follow-up ^{18}FDG PET/CT examination at 6 months was requested for all patients. Biochemical laboratory tests were performed at admission and at the 6-month follow-up. The study protocol was approved by our institutional review committee. All patients provided written informed consent.

2.2 | ^{18}F -fluorodeoxyglucose Positron Emission Tomography/Computed Tomography Examination

Vascular ^{18}FDG PET/CT imaging was performed in accordance with standard methods.^{17–19,21} In brief, after ≥ 8 hours of fasting, patients received an intravenous administration of ^{18}FDG (5.2 MBq [0.14 mCi]/kg body weight) through the antecubital vein. Patients with diabetes mellitus were instructed to adhere to their regular schedules of

glucose-controlling drugs. Serum glucose levels were routinely measured and were maintained <130 mg/dL in all patients. Two hours after the ^{18}FDG injection, a 3-dimensional PET/CT scan was initiated. Computed tomography was performed first without the administration of contrast medium to correct photon attenuation and scattering using a continuous spiral 64-slice technique with a voltage of 140 kV, a pitch of 0.98 (39.4 mm/rotation), a slice thickness of 2.5 mm, a current of 200 mA, and a rotation speed of 0.4 s/revolution.

Positron emission tomography was performed immediately afterward, using a full-ring dedicated scanner with an axial field of view of 15.7 cm and an image reconstruction matrix of 256×256 . All examinations were performed using the time of flight-capable Discovery 690 PET/CT scanner (GE Healthcare, Waukesha, WI). Patients were imaged in the supine position using a head fixation device, which holds the patient's neck firmly with respect to the shoulders, and features an extension. Images were acquired for 10 minutes in each bed position during normal tidal breathing, with overlapping scans from the skull base to the upper chest obtained using 2 or 3 bed positions. Images were reconstructed after CT-based attenuation correction and scattering correction using the 3-dimensional ordered subsets expectation maximization reconstruction algorithm (4 iterations, 18 subsets) with time of flight reconstruction. The PET data were routinely recalculated to display images of SUVs based on the lean body mass.

2.3 | Image Analysis

Image analysis was performed on a dedicated workstation. ^{18}FDG PET was quantified after identification of the common carotid arteries and ascending aorta of the aortic arch. The PET images were subsequently visually evaluated for the presence of focal ^{18}FDG uptake by the carotid arteries and ascending aorta. Arterial ^{18}FDG uptake was determined by drawing a simple circular region of interest (ROI) around the artery on every slice of the co-registered transaxial PET/CT images. On each image slice, the maximal SUVs of ^{18}FDG in the ROI (containing the arterial wall and the lumen) were calculated as the maximal pixel activity, respectively. The SUV was the decay-corrected tissue concentration of ^{18}FDG (in kBq/g), adjusted for the injected ^{18}FDG dose and lean body mass. By averaging the SUVs of all artery slices within an arterial territory, maximal SUVs for each region were derived. The SUVs were normalized to blood ^{18}FDG activity by dividing them by the average blood ROI (calculated from ≥ 6 venous ROI measurements) estimated from the superior vena cava, which yielded an arterial TBR.

The MDS TBR was calculated by centering on the slice of the artery that demonstrated the highest ^{18}FDG uptake, then averaging 5 contiguous segments (about 1.5 cm extent), combined with the immediate inferior and superior neighbors. The whole-vessel TBR was defined as the average of the maximal TBR activity for all of the axial segments. Whole-vessel ^{18}FDG uptake (TBR) was measured in the 3 target arteries (right and left carotid and aorta) and used to indicate ^{18}FDG -defined atherosclerotic inflammation activity. Cardiac catheterization may have variable impact on ^{18}FDG uptake of the ascending aorta because of catheter-induced aorta injury, and the carotid artery with the highest ^{18}FDG uptake at baseline was chosen as the index vessel.^{19,22}

2.4 | Study Endpoints

The primary endpoint was the percent change in MDS TBR of the index vessel, defined as $(\text{MDS TBR at 6 months} - \text{MDS TBR at baseline}) / (\text{MDS TBR at baseline}) \times 100$. Secondary endpoints included changes in whole-vessel TBR within the index vessel, MDS TBR, and whole-vessel TBR of the aorta.

2.5 | Statistical Analysis

A sample size of approximately 22 patients per treatment group was needed to yield 90% power (assuming a SD of 15% in the clopidogrel group and 15% in the ticagrelor group) for detecting a difference of 15% with a significance level of 0.05, using a 2-sided test. At an anticipated dropout rate of 10%, a final sample size of 25 patients per treatment group (total, 50 patients) was specified to provide an adequate number of evaluable patients. Continuous variables were expressed as mean $\pm$ SD or median (interquartile range), whereas categorical variables were expressed as frequencies. Continuous variables were compared using the paired *t* test or Wilcoxon rank-sum test for changes in each group, and unpaired *t* test or the Mann-Whitney *U* test for differences between groups. Statistical significance was defined as a 2-sided *P* value <0.05 .

3 | RESULTS

A total of 137 patients with ACS were initially screened in our current study. Of these patients, 87 did not fulfill the criteria for randomization, and the remaining 50 patients were randomly assigned to receive either clopidogrel or ticagrelor. Exclusion was due to absence of carotid atherosclerosis ($n = 69$), enrollment of other studies ($n = 11$), and patient refusal ($n = 7$; Figure 1). Four patients did not receive PET/CT follow-up because of refusal ($n = 2$) or adverse events ($n = 2$). The remaining 46 patients (92%) completed PET/CT examination at the 6-month follow-up.

3.1 | Baseline Characteristics

The baseline characteristics were similar between the 2 groups (Table 1). The median age of the patients was 61.0 years (interquartile range, 61–70 years), and 82.4% were men. Clinical presentations at the time of admission included ST-segment elevation myocardial

TABLE 1 Baseline Clinical Characteristics

Characteristics	Clopidogrel, <i>n</i> = 25	Ticagrelor, <i>n</i> = 25	<i>P</i> Value
Age, y	62.4 $\pm$ 11.0	60.6 $\pm$ 8.8	0.535
Male sex	20 (80)	21 (84)	0.713
Current smoker	9 (36)	5 (20)	0.208
DM	5 (20)	7 (28)	0.508
HTN	12 (48)	13 (52)	0.777
Diagnosis			0.826
STEMI	11 (44)	9 (36)	
NSTE-ACS	14 (56)	16 (64)	
Culprit artery of ACS			0.743
LAD	11 (44)	12 (48)	
LCX	3 (12)	3 (12)	
RCA	11 (44)	9 (36)	
Ramus intermedius	0 (0)	1 (4)	
Culprit lesion PCI	48 (91.7)	48 (91.7)	1.0
LVEF, %	56.2 $\pm$ 7.8	59.2 $\pm$ 5.9	0.141
Medications at time of follow-up			
ASA	25 (100)	25 (100)	1.0
Statins	25 (100)	25 (100)	1.0
ACEI/ARBs	6 (24)	6 (24)	1.0
β -Blockers	21 (84)	22 (88)	0.684
Calcium channel antagonists	6 (24)	5 (20)	0.733

Abbreviations: ACEI, angiotensin-converting-enzyme inhibitor; ACS, acute coronary syndrome; ARB, angiotensin receptor blocker; ASA, aspirin; DM, diabetes mellitus; HTN, hypertension; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; LVEF, left ventricular ejection fraction; NSTE-ACS, non-ST-segment elevation acute coronary syndrome; PCI, percutaneous coronary intervention; RCA, right coronary artery; SD, standard deviation; STEMI, ST-segment elevation myocardial infarction.

Data are presented as *n* (%) or mean $\pm$ SD.

infarction in 39.2% of the patients and non-ST-segment elevation acute coronary syndrome in 60.8% of the patients. Most patients (91.8%) were treated with percutaneous coronary intervention, with 4 cases (8.2%) receiving medications.

3.2 | Laboratory Findings

Lipid and high-sensitivity C-reactive protein (hs-CRP) levels at baseline were similar between the 2 groups (Table 2). At the 6-month follow-up, total cholesterol, low-density lipoprotein cholesterol (LDL-C), and hs-CRP levels significantly decreased in both groups ($P < 0.001$), whereas high-density lipoprotein cholesterol levels significantly increased in both groups ($P < 0.01$).

3.3 | Positron Emission Tomography/Computed Tomography Findings

Representative images of improved ^{18}F FDG uptake in the carotid plaque after ticagrelor therapy are shown in Figure 2, and ^{18}F FDG PET/CT data are summarized in Table 3. Baseline measurements were similar between the 2 groups. At the 6-month follow-up, MDS TBR and TBR of the index vessel significantly decreased in both groups

FIGURE 1 Flowchart of patient enrollment. Abbreviations: CT, computed tomography; PET, positron emission tomography.

TABLE 2 Laboratory Findings

Characteristics	Clopidogrel, n = 23	Ticagrelor, n = 23	P Value
Total cholesterol, mg/dL			
Baseline	183.4 ± 42.8	180.5 ± 31.7	0.839
6 months	135.3 ± 32.2	136.8 ± 21.7	0.860
LDL-C, mg/dL			
Baseline	114.7 ± 26.4	116.8 ± 30.3	0.902
6 months	83.9 ± 24.8	86.2 ± 19.4	0.723
HDL-C, mg/dL			
Baseline	40.8 ± 10.5	40.4 ± 10.0	0.909
6 months	43.9 ± 8.1	45.6 ± 10.9	0.563
Hs-CRP, mg/L			
Baseline	3.2 ± 1.9	3.2 ± 2.8	0.995
6 months	1.4 ± 1.9	1.5 ± 2.5	0.801

Abbreviations: HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; SD, standard deviation.

Data are presented as mean ± SD.

($P < 0.01$). The percent change in MDS TBR of the index vessel (primary endpoint) was numerically but not significantly less in the clopidogrel group than in the ticagrelor group ($-9.5 \pm 14.6\%$ vs $-13.5 \pm 19.3\%$, respectively; $P = 0.427$). Likewise, the percent change in whole-vessel TBR of the index vessel was not different between the 2 groups. Compared with baseline, however, the maximal SUV of the index vessel at the 6-month follow-up significantly decreased in the ticagrelor group (2.21 ± 0.53 vs 1.89 ± 0.36 , respectively; $P = 0.004$), but not in the clopidogrel group (2.0 ± 0.23 vs 1.89 ± 0.29 , respectively; $P = 0.055$). Similar findings were observed for changes in the MDS TBR or whole-vessel TBR of the aorta. There were no significant correlations between lipid levels and percent changes in MDS TBR of the index vessel. Likewise, the hs-CRP levels did not correlate with the percent change in the MDS TBR of the index vessel.

4 | DISCUSSION

In our present study, the MDS and whole-vessel TBR of the index vessel at the 6-month follow-up significantly decreased in both clopidogrel- and ticagrelor-treated patients, and a similar degree of improvement was observed in these 2 treatment groups. Despite moderate levels of LDL-C at the 6-month follow-up, both of these antiplatelet drugs resulted in a significant reduction in ^{18}F FDG uptake in the carotid artery and aorta. These findings suggest that P2Y₁₂ inhibitors may reduce atherosclerotic plaque inflammation if they are used in addition to standard medical therapy.

In addition to their role in hemostasis and thrombosis, platelets regulate a variety of inflammatory responses.²³ In our present study, LDL-C levels modestly decreased at the 6-month follow-up, and no correlation between LDL-C levels and changes of MDS TBR was observed. However, atherosclerotic plaque inflammation significantly improved in both clopidogrel- and ticagrelor-treated patients, suggesting that P2Y₁₂ receptor blockers may have a direct effect on atherosclerotic plaque inflammation. In addition, the hs-CRP levels did not correlate with the MDS or whole-vessel TBR of the index vessel, showing poor correlations with local and systemic inflammatory markers.

In the previous Platelet Inhibition and Patient Outcomes (PLATO) trial, the cardiovascular benefits of ticagrelor outweighed those of clopidogrel, despite more spontaneous bleeds.^{24–26} These benefits may not be fully explained by platelet inhibition alone. The P2Y₁₂ receptor is present in human atherosclerotic plaques, and its level of expression is higher in patients with ACS compared with those with stable angina.²⁷ The short half-life of the clopidogrel active metabolite may prevent the drug from penetrating the vascular wall, whereas ticagrelor may be continuously available to interact with the vascular P2Y₁₂ receptor.^{10,28} In our present study, the MDS TBR values of the index vessel were not statistically different between the 2 treatment groups. However, changes in the MDS

Baseline

Post-treatment

FIGURE 2 ^{18}F FDG uptakes of the index vessel in a patient treated with ticagrelor (arrowheads). Representative CT (left), ^{18}F FDG-PET (middle), ^{18}F FDG-PET/CT (right) images at baseline (top) and at 6-month follow-up (bottom) are shown. ^{18}F FDG uptakes markedly decreased at 6-month follow-up. Abbreviations: ^{18}F FDG-PET, ^{18}F -fluorodeoxyglucose positron emission tomography; CT, computed tomography.

TABLE 3 Changes in Arterial Inflammation Activity

Characteristics	Clopidogrel, n = 23	Ticagrelor, n = 23	P Value Between Groups
MDS TBR of index carotid artery			
Baseline	2.24 ± 0.29	2.37 ± 0.65	0.379
Follow-up	1.99 ± 0.28	2.0 ± 0.29	0.90
Nominal change	-0.23 ± 0.32	-0.43 ± 0.68	0.206
P value compared with baseline	0.002	<0.001	
% change ¹	-9.5 ± 14.6	-13.5 ± 19.3	0.427
Whole-vessel TBR of index carotid artery			
Baseline	1.98 ± 0.32	2.11 ± 0.50	0.292
Follow-up	1.79 ± 0.23	1.75 ± 1.88	0.462
Nominal change	-0.19 ± 0.31	-0.40 ± 0.55	0.109
P value compared with baseline	0.009	0.002	
% change ¹	-7.9 ± 16.2	-15.1 ± 18.4	0.166
MDS TBR of aorta			
Baseline	2.65 ± 0.56	2.76 ± 0.58	0.491
Follow-up	2.27 ± 0.34	2.32 ± 0.26	0.603
Nominal change	-0.34 ± 0.45	-0.50 ± 0.59	0.30
P value compared with baseline	0.001	0.006	
% change ¹	-11.2 ± 17.3	-15.3 ± 16.5	0.412
Whole-vessel TBR of aorta			
Baseline	2.56 ± 0.52	2.67 ± 0.56	0.499
Follow-up	2.24 ± 0.34	2.27 ± 0.24	0.737
Nominal change	-0.28 ± 0.42	-0.45 ± 0.58	0.243
P value compared with baseline	0.004	0.001	
% change ¹	-9.5 ± 17.2	-14.1 ± 16.7	0.363

Abbreviations: MDS, most diseased segment; SD, standard deviation; TBR, target-to-background ratio.

Data are presented as mean ± SD.

¹ Primary endpoint.

and whole-vessel TBR of the index vessels and aorta exhibited similar trends in favor of ticagrelor. In addition, the maximal SUV of the index vessel, which may be representative of the most active spot of atherosclerotic inflammation of a specific artery,^{29–31} significantly improved after ticagrelor therapy, but not after clopidogrel therapy.

In recent years, the majority of studies prefer to use MDS TBR to evaluate the anti-inflammatory effects of specific therapies on the vessels.^{17,19,21} Compared with whole-vessel TBR, MDS TBR may be superior for investigating the effects of interventions on atherosclerotic plaque inflammation because the former assesses both diseased and healthy segments.³² However, it remains controversial as to whether MDS-based analysis is the best method for intervention studies.^{31–36} In some reports, the maximal SUV has been used because it is less affected by blood pool activity.^{31,37–39} In our current study, the hottest spot of inflamed atherosclerotic plaques showed significant improvements in ticagrelor-treated patients, but not in clopidogrel-treated patients. Taken together, both clopidogrel and ticagrelor therapy decreased ¹⁸FDG uptake of carotid atherosclerotic plaques in our study patients, with a greater reduction of maximal SUV found following ticagrelor therapy. Considering that the maximal SUV in patients with a recent stroke is the key predictor of early stroke recurrence,^{38,40} our present findings may increase our understanding of the superior outcomes in

patients treated with ticagrelor vs those treated by clopidogrel in the PLATO trial.

4.1 | Study Limitations

Several potential limitations of our current analyses need to be addressed. First, the sample size was small, which may have underpowered the detection of small differences in the MDS TBR of the index vessel. Second, our study had an open-label design, which was subject to inherent limitations. We attempted to minimize these limitations by using blind ¹⁸FDG PET/CT measurements. Third, there was no placebo arm because of ethical considerations.

5 | CONCLUSION

Our study shows that the MDS and whole-vessel TBR of the index vessel at the 6-month follow-up significantly decreased in both clopidogrel- and ticagrelor-treated patients, and a similar degree of improvement was observed in these 2 treatment groups. These findings suggest that P2Y₁₂ inhibitors may reduce atherosclerotic plaque inflammation if they are used in addition to standard medical therapy.

REFERENCES

- Valettas N, Herrmann HC. The role of platelets and platelet inhibition in acute myocardial infarction. *Coron Artery Dis*. 2003;14:357–363.
- Wenger NK. What's new in antiplatelet and anticoagulant therapy recommendations for unstable angina/non-ST-elevation myocardial infarction: 2012 focused update from the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Clin Cardiol*. 2012;35:669–672.
- Dorsam RT, Kunapuli SP. Central role of the P2Y₁₂ receptor in platelet activation. *J Clin Invest*. 2004;113:340–345.
- Cattaneo M, Gachet C. ADP receptors and clinical bleeding disorders. *Arterioscler Thromb Vasc Biol*. 1999;19:2281–2285.
- CAPRIE Steering Committee. A randomised, blinded trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet*. 1996;348:1329–1339.
- Gurbel PA, Becker RC, Mann KG, et al. Platelet function monitoring in patients with coronary artery disease. *J Am Coll Cardiol*. 2007;50:1822–1834.
- Storey RF, Angiolillo DJ, Patil SB, et al. Inhibitory effects of ticagrelor compared with clopidogrel on platelet function in patients with acute coronary syndromes: the PLATO (Platelet Inhibition and Patient Outcomes) PLATELET substudy. *J Am Coll Cardiol*. 2010;56:1456–1462.
- Reed GW, Kumar A, Guo J, et al. Point-of-care platelet function testing predicts bleeding in patients exposed to clopidogrel undergoing coronary artery bypass grafting: Verify Pre-op TIMI 45—a pilot study. *Clin Cardiol*. 2015;38:92–98.
- Shanker G, Kontos JL, Eckman DM, et al. Nicotine upregulates the expression of P2Y₁₂ on vascular cells and megakaryoblasts. *J Thromb Thrombolysis*. 2006;22:213–220.
- Wihlborg AK, Wang L, Braun OO, et al. ADP receptor P2Y₁₂ is expressed in vascular smooth muscle cells and stimulates contraction in human blood vessels. *Arterioscler Thromb Vasc Biol*. 2004;24:1810–1815.
- Quinn MJ, Bhatt DL, Zidar F, et al. Effect of clopidogrel pretreatment on inflammatory marker expression in patients undergoing percutaneous coronary intervention. *Am J Cardiol*. 2004;93:679–684.
- Angiolillo DJ, Fernandez-Ortiz A, Bernardo E, et al. Clopidogrel withdrawal is associated with proinflammatory and prothrombotic effects in patients with diabetes and coronary artery disease. *Diabetes*. 2006;55:780–784.
- Heitzer T, Rudolph V, Schwedhelm E, et al. Clopidogrel improves systemic endothelial nitric oxide bioavailability in patients with coronary artery disease: evidence for antioxidant and antiinflammatory effects. *Arterioscler Thromb Vasc Biol*. 2006;26:1648–1652.
- Warnholtz A, Ostad MA, Velich N, et al. A single loading dose of clopidogrel causes dose-dependent improvement of endothelial dysfunction in patients with stable coronary artery disease: results of a double-blind, randomized study. *Atherosclerosis*. 2008;196:689–695.
- Bonello L, Harhour K, Sabatier F, et al. Level of adenosine diphosphate receptor P2Y₁₂ blockade during percutaneous coronary intervention predicts the extent of endothelial injury, assessed by circulating endothelial cell measurement. *J Am Coll Cardiol*. 2010;56:1024–1031.
- Husted S, Storey RF, Harrington RA, et al. Changes in inflammatory biomarkers in patients treated with ticagrelor or clopidogrel. *Clin Cardiol*. 2010;33:206–212.
- Tahara N, Kai H, Ishibashi M, et al. Simvastatin attenuates plaque inflammation: evaluation by fluorodeoxyglucose positron emission tomography. *J Am Coll Cardiol*. 2006;48:1825–1831.
- Rudd JH, Myers KS, Bansilal S, et al. 18-Fluorodeoxyglucose positron emission tomography imaging of atherosclerotic plaque inflammation is highly reproducible: implications for atherosclerosis therapy trials. *J Am Coll Cardiol*. 2007;50:892–896.
- Tawakol A, Fayad ZA, Mogg R, et al. Intensification of statin therapy results in a rapid reduction in atherosclerotic inflammation: results of a multicenter fluorodeoxyglucose-positron emission tomography/computed tomography feasibility study. *J Am Coll Cardiol*. 2013;62:909–917.
- Mizoguchi M, Tahara N, Tahara A, et al. Pioglitazone attenuates atherosclerotic plaque inflammation in patients with impaired glucose tolerance or diabetes: a prospective, randomized, comparator-controlled study using serial FDG PET/CT imaging study of carotid artery and ascending aorta. *JACC Cardiovasc Imaging*. 2011;4:1110–1118.
- Fayad ZA, Mani V, Woodward M, et al. Safety and efficacy of dalce-trapib on atherosclerotic disease using novel non-invasive multimodality imaging (dal-PLAQUE): a randomised clinical trial. *Lancet*. 2011;378:1547–1559.
- Jones DN, McCowage GB, Sostman HD, et al. Monitoring of neoadjuvant therapy response of soft-tissue and musculoskeletal sarcoma using fluorine-18-FDG PET. *J Nucl Med*. 1996;37:1438–1444.
- Gawaz M, Langer H, May AE. Platelets in inflammation and atherogenesis. *J Clin Invest*. 2005;115:3378–3384.
- Wallentin L, Becker RC, Budaj A, et al; PLATO Investigators. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2009;361:1045–1057.
- Serebruany VL, Atar D. The PLATO trial: do you believe in magic? *Eur Heart J*. 2010;31:764–767.
- Fu A, Singh K, Abunassar J, et al; CAPITAL Investigators. Ticagrelor in triple antithrombotic therapy: predictors of ischemic and bleeding complications. *Clin Cardiol*. 2016;39:19–23.
- Lee CW, Hwang I, Park CS, et al. Comparison of differential expression of P2Y₁₂ receptor in culprit coronary plaques in patients with acute myocardial infarction versus stable angina pectoris. *Am J Cardiol*. 2011;108:799–803.
- Högberg C, Svensson H, Gustafsson R, et al. The reversible oral P2Y₁₂ antagonist AZD6140 inhibits ADP-induced contractions in murine and human vasculature. *Int J Cardiol*. 2010;142:187–192.
- Gholami S, Salavati A, Houshmand S, et al. Assessment of atherosclerosis in large vessel walls: a comprehensive review of FDG-PET/CT image acquisition protocols and methods for uptake quantification. *J Nucl Cardiol*. 2015;22:468–479.
- Malmberg C, Ripa RS, Johnbeck CB, et al. 64Cu-DOTATATE for noninvasive assessment of atherosclerosis in large arteries and its correlation with risk factors: head-to-head comparison with 68Ga-DOTATOC in 60 patients. *J Nucl Med*. 2015;56:1895–1900.
- Huet P, Burg S, Le Guludec D, et al. Variability and uncertainty of 18 F-FDG PET imaging protocols for assessing inflammation in atherosclerosis: suggestions for improvement. *J Nucl Med*. 2015;56:552–559.
- Elkhawad M, Rudd JH, Sarov-Blat L, et al. Effects of p38 mitogen-activated protein kinase inhibition on vascular and systemic inflammation in patients with atherosclerosis. *JACC Cardiovasc Imaging*. 2012;5:911–922.
- Chen W, Dilsizian V. PET assessment of vascular inflammation and atherosclerotic plaques: SUV or TBR? *J Nucl Med*. 2015;56:503–504.
- Noh TS, Moon SH, Cho YS, et al. Relation of carotid artery 18 F-FDG uptake to C-reactive protein and Framingham risk score in a large cohort of asymptomatic adults. *J Nucl Med*. 2013;54:2070–2076.
- Wu YW, Kao HL, Chen MF, et al. Characterization of plaques using 18F-FDG PET/CT in patients with carotid atherosclerosis and correlation with matrix metalloproteinase-1 [published correction appears in *J Nucl Med*. 2007;48:1430]. *J Nucl Med*. 2007;48:227–233.
- Arauz A, Hoyos L, Zenteno M, et al. Carotid plaque inflammation detected by 18 F-fluorodeoxyglucose-positron emission tomography: pilot study. *Clin Neurol Neurosurg*. 2007;109:409–412.
- Noh TS, Yoo J, Kim SW, et al. Effects of coverage extent and slice skipping on mean and maximum arterial 18 F-FDG uptake ratios in patients with carotid plaque. *Ann Nucl Med*. 2012;26:715–722.

38. Marnane M, Merwick A, Sheehan OC, et al. Carotid plaque inflammation on 18 F-fluorodeoxyglucose positron emission tomography predicts early stroke recurrence. *Ann Neurol*. 2012;71:709–718.
39. Ryu Y, Yoshida K, Suzuki Y, et al. Long-term changes of aortic 18 F-FDG uptake and calcification in health-screening subjects. *Ann Nucl Med*. 2013;27:239–246.
40. Kim HJ, Oh M, Moon DH, et al. Carotid inflammation on ¹⁸F-fluorodeoxyglucose positron emission tomography associates with recurrent ischemic lesions. *J Neurol Sci*. 2014;347:242–245.

How to cite this article: Oh M, Lee CW, Lee HS, Chang M, Ahn JW, Park DW, Kang SJ, Lee SH, Kim YH, Moon DH, Park SW, Park SJ. Similar Impact of Clopidogrel or Ticagrelor on Carotid Atherosclerotic Plaque Inflammation, *Clinical Cardiology*, 2016;39(11):646–652.