Early versus delayed treatment with ticagrelor on residual thrombus after percutaneous coronary intervention in patients presenting with non-ST-elevation acute coronary syndrome: an optical coherence tomography study

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Ticagrelor, a P2Y12 antagonist, is well known for its rapid, high-potent inhibition of platelet aggregation by pharmacokinetic studies [1]. In the PLATO study, ticagrelor, compared to clopidogrel, reduced the incidence of myocardial infarction, stroke, cardiovascular death and definite stent thrombosis, during 12-month follow-up in patients with acute coronary syndrome (ACS) undergoing percutaneous coronary intervention (PCI) [2,3]. To date, the effect of early ticagrelor administration versus treatment at the time of PCI has not been well studied. The ATLANTIC study demonstrated that prehospital administration of ticagrelor did not improve pre-PCI coronary reperfusion compared to in-hospital treatment [4].

We aimed to compare the effectiveness of antplatelet therapy by measuring the differences in residual thrombus burden after PCI by optical coherence tomography (OCT) between immediate and delayed initiation of ticagrelor in patients with ACS.

This was a prospective, randomized study involving eight Korean centers. Patients presented with non-ST-elevation ACS (NSTE-ACS) were screened between July 2016 and November 2017. All patients who were scheduled to undergo coronary angiography between 4 and 72 h after randomization were eligible. Patients with NYHA class III or IV heart failure or known left ventricular ejection fraction <30% and hemodynamic or electrical instability were excluded. Patients were randomized 1:1 to receive 180 mg of ticagrelor either immediately after a diagnosis of NSTE-ACS was made (early treatment group) or after diagnostic coronary angiography but prior to PCI (delayed treatment group). Patients randomized to the early treatment group received a maintenance dose of 90 mg every 12 h until the time of catheterization. Both the early treatment group and the delayed treatment group have received aspirin loading dose of 300 mg after the diagnosis of NSTE-ACS, and maintained 100 mg a day until angiography was done. After PCI, patients were maintained on ticagrelor and aspirin. Patients were followed through their index hospitalization. The study was approved by the institutional ethics committee at each participating hospital and informed consent was obtained prior to the enrollment.

The primary end point of this study was residual thrombus burden assessed by post-PCI OCT. A frequency-domain OCT system was used. Statistical analyses were performed using SPSS v. 12.5 for Windows and P < 0.05 was considered to indicate a statistically significant difference.

A total of 100 patients enrolled in the study were randomly assigned to either early treatment group (n = 50) or delayed treatment group (n = 50) (Fig. 1). There was no significant difference in baseline patient characteristics between the groups (Table 1). The degree of platelet inhibition was significantly higher in the early treatment group than in the delayed treatment group [P2Y12 reaction units (PRU), 70.6 ± 62.1 versus 227.2 ± 76.6; P < 0.001]. The median interval between the administration of ticagrelor and PCI in the early treatment group was 854 min. The primary end points of this study, thrombus area, length, volume and thrombus burden were not different between two groups (Table 1). No stent thrombosis or major bleeding occurred.

To our knowledge, this is the first study that prospectively compared the effects of early versus delayed administration of ticagrelor on residual thrombus burden after PCI with OCT in patients with NSTE-ACS. We hypothesized that early administration of ticagrelor would lead to more profound suppression of platelet reactivity at the time of PCI, and therefore, would lead to smaller residual thrombus burden. Indeed, our results showed that the early treatment group had lower values of PRU at the time of PCI; nevertheless, no significant difference in residual thrombus burden was found between the two groups. Possible explanations include the following: (1) the time difference of 14 h was not long enough to see the difference in thrombus burden. However, in real world practice, the usual time delay between presentation to
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(2) Although ticagrelor is a potent P2Y12 inhibitor, it may not be potent enough to show difference in thrombus burden. (3) The number of patients was small. Moreover, a significant number of patients did not undergo post-PCI OCT imaging.

The earliest administration of ticagrelor may be preferable to achieve early efficacy, but in cases in which NSTE-ACS is not clearly diagnosed, it should be considered to delay the loading of P2Y12 inhibitor until the angiographic lesion is observed. Prospective larger scale randomized controlled trials are needed to investigate the clinical outcomes such as myocardial infarction, cardiac death, stroke and major bleeding events.

To conclude, early administration of ticagrelor at the time of presentation showed a greater level of platelet inhibition, but did not show benefit in reduction of thrombus burden following PCI in patients presenting with NSTE-ACS.

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Conflicts of interest
There are no conflicts of interest.

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Fig. 1

Table 1 Baseline, angiographic and optical coherence tomography characteristics

|                      | Early treatment, N = 30 | Delayed treatment, N = 27 | P value |
|----------------------|-------------------------|---------------------------|---------|
| **Baseline characteristics** |                         |                           |         |
| Male, n (%)          | 20 (66.6%)              | 20 (74.0%)                | 0.542   |
| Age, years           | 63.8 ± 10.3             | 65.3 ± 10.3               | 0.596   |
| Hypertension, n (%)  | 13 (43.3%)              | 13 (48.1%)                | 0.536   |
| Diabetes mellitus, n (%) | 6 (20.0%)         | 7 (26.9%)                 | 0.594   |
| Dyslipidemia, n (%)  | 9 (30.0%)               | 8 (29.6%)                 | 0.976   |
| LVEF, %              | 58.6 ± 10.9             | 58.4 ± 7.4                | 0.944   |
| CK-MB, initial, µg/L | 19.3 ± 37.2             | 10.0 ± 12.7               | 0.222   |
| CK-MB, peak, µg/L    | 48.8 ± 67.0             | 57.6 ± 89.0               | 0.672   |
| Troponin-I, initial, µg/L | 73.1 ± 274         | 2.2 ± 5.1                 | 0.347   |
| Troponin-I, peak, µg/L | 15.7 ± 33.8         | 5.7 ± 9.2                 | 0.159   |
| PRU                   | 70.6 ± 62.1             | 227.2 ± 76.6              | <0.001  |
| **Interval between administration of ticagrelor and procedure, min** | 854.0 ± 671.0 | 0 | <0.001 |
| **Angiographic characteristics** |                         |                           |         |
| Culprit lesion, n (%) | 17 (56.6%)              | 15 (55.5%)                | 0.368   |
| Left anterior descending | 5 (16.6%)            | 8 (29.6%)                 |         |
| Left circumflex      | 8 (26.6%)               | 4 (14.8%)                 |         |
| Right coronary artery| 1 (3.3%)                | 0 (0.0%)                  |         |
| Stent length, mm     | 25.5 ± 8.2              | 24.1 ± 8.3                | 0.607   |
| Stent volume, mm³     | 1565.5 ± 57.9           | 161.7 ± 63.9              | 0.524   |
| Maximal thrombus area, mm² | 0.57 ± 0.21         | 0.45 ± 0.26               | 0.075   |
| Mean thrombus area, mm² | 0.21 ± 0.07         | 0.18 ± 0.09               | 0.185   |
| Thrombus volume, mm³  | 11.30 ± 5.57            | 9.11 ± 4.47               | 0.110   |
| Thrombus burden, %    | 1.64 ± 1.10             | 1.24 ± 0.92               | 0.143   |
| Pre-TIMI flow 0-1, n (%) | 8 (26.6%)        | 3 (11.1%)                 | 0.186   |
| Post-TIMI flow 3, n (%) | 29 (96.6%)           | 27 (100%)                 | 1.000   |

CK-MB, creatine kinase myocardial band; LVEF, left ventricular ejection fraction; PRU, P2Y12 reaction units, TIMI, thrombolysis in myocardial infarction.

a hospital and catheterization in patients with NSTE-ACS is 22 h [5]. (2) Although ticagrelor is a potent P2Y12 inhibitor, it may not be potent enough to show difference in thrombus burden. (3) The number of patients was small. Moreover, a significant number of patients did not undergo post-PCI OCT imaging.
Necessity of back-up pace maker support during acetylcholine testing as a safe method
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Introduction
Intracoronary acetylcholine (ACh) testing was first reported by Yasue and Okumura in 1986 [1]. According to the Japanese Circulation Society (JCS) guidelines, temporary pacing is necessary when performing intracoronary ACh spasm provocation tests [2]. Ong et al. reported the ACh testing for over 3 min administration without pace maker (PM) [3]. In this article, we examined the necessity of back-up PM supports during intracoronary ACh spasm provocation test based on the JCS guidelines.

Methods
From October 2012 to November 2017, we tried to perform ACh spasm provocation tests in 315 patients (male: 242 patients, mean age of 67.5 ± 10.9 year) whenever possible. As show in Table 1, ischemic heart disease (IHD) was observed in 237 patients, whereas non-IHD was found in 78 patients. We classified these 315 patients into two groups consisting of with and without back-up PM support during ACh testing. We defined positive provoked spasm as ≥90% transient narrowing and usual chest pain or ischemic ECG changes.

All drugs except for nitroglycerine were discontinued for ≥24 h before the study. A temporary PM was inserted into the right ventricle of each patient and the pacing rate was set at 40 beats/min. We defined positive back-up PM support as any pacing during ACh testing. ACh chloride was injected in incremental doses of 20, 50 and 80 μg into the right coronary artery (RCA) and of 20, 50, 100 and 200 μg into the left coronary artery (LCA) over 20’s with at least a 3-min interval between each injection [4,5]. The study protocol complied with the Declaration of Helsinki. Written informed consent about performing the ACh spasm provocation tests was obtained from all patients and the protocol of this study was in agreement with the guidelines of the ethical committee at our institution.

Statistical analysis
Data analysis was carried out with SPSS (version 22.0, IBM Japan, Ltd., Tokyo, Japan). All data were presented as the mean ± 1 SD and analyzed by the Fisher’s exact test with correction or the Mann–Whitney test. P < 0.05 was considered significant.

Results
We used the 5 French temporary PM. Brachial vein approach was employed n 252 patients (80%), while femoral vein was used in the remaining 63 patients (20%).

Table 1  Clinical characteristics in all patients

|               | Total   | With back-up PM | Without back-up PM |
|---------------|---------|-----------------|--------------------|
| Number        | 315     | 293             | 22                 |
| Male (%)      | 242 (76.8%) | 224 (76.5%) | 18 (85.0%)         |
| Age (year)    | 67.5 ± 10.9 | 68.0 ± 10.8 | 61.7 ± 10.8*       |
| Organic stenosis | 41 (13.0%) | 39 (13.3%) | 2 (9.1%)           |
| History of smoking | 226 (71.7%) | 211 (72.0%) | 15 (68.2%)        |
| Hypertension  | 185 (58.7%) | 173 (59.0%) | 12 (54.5%)        |
| Dyslipidemia  | 196 (62.2%) | 183 (62.5%) | 13 (59.1%)        |
| Diabetes mellitus | 107 (34.0%) | 97 (33.1%) | 10 (45.4%)        |
| Ischemic heart disease | 237 (75.2%) | 224 (76.5%) | 13 (59.1%)        |
| Effort        | 29 (9.2%) | 27 (9.2%) | 2 (9.1%)           |
| Effort and effort | 23 (7.3%) | 22 (7.5%) | 1 (4.5%)           |
| Healed myocardial infarction | 9 (2.9%) | 9 (3.1%) | 0                 |
| Postpercutaneous coronary intervention | 93 (29.5%) | 88 (30.0%) | 5 (22.7%)        |
| Nonischemic heart disease | 78 (24.8%) | 69 (23.5%) | 9 (40.9%)         |
| Atypical chest pain | 22 (7.0%) | 19 (6.5%) | 3 (13.6%)         |
| Dilated cardiomyopathy | 18 (5.7%) | 13 (4.4%) | 5 (22.7%)**       |
| Congestive heart failure | 3 (1.0%) | 3 (1.0%) | 0                 |
| Hypertrophic cardiomyopathy | 2 (0.6%) | 2 (0.7%) | 0                 |
| Valvular heart disease | 13 (4.1%) | 13 (4.4%) | 0                 |
| Other         | 20 (6.3%) | 19 (6.5%) | 1 (4.5%)           |
| Proved spasm  | 206 (65.4%) | 195 (66.6%) | 11 (50.0%)        |
| In the right coronary artery | 148 (47.0%) | 141 (48.1%) | 7 (31.8%)         |
| In the circumflex artery | 84 (26.7%) | 79 (27.0%) | 5 (22.7%)         |
| In the left anterior descending artery | 162 (51.4%) | 152 (51.9%) | 10 (45.4%)       |
| Single vessel spasm | 76 (24.1%) | 71 (24.2%) | 5 (22.7%)         |
| Double vessel spasm | 72 (22.9%) | 71 (24.2%) | 1 (4.5%)          |
| Triple vessel spasm | 58 (18.4%) | 53 (18.1%) | 5 (22.7%)         |

PM, pace maker.
*P < 0.05 and **P < 0.001 vs. with back-up PM.