# Cilostazol Addition to Aspirin could not Reduce the Neurological Deterioration in TOAST Subtypes: ADS Post-Hoc Analysis

Junya Aoki, MD,[*,†] Yasuyuki Iguchi, MD,[‡] Takao Urabe, MD,[§] Hiroshi Yamagami, MD,[¶] Kenichi Todo, MD,[¶] Shigeru Fujimoto, MD,[#] Koji Idomari, MD,[||] Nobuyuki Kaneko, MD,[||] Takeshi Iwanaga, MD,[**] Tadashi Terasaki, MD,[††] Ryota Tanaka, MD,[‡‡] Nobuaki Yamamoto, MD,[§§] Akira Tsujino, MD,[¶¶] Koichi Nomura, MD,[##] Koji Abe, MD,[||||] Masaaki Uno, MD,[***] Yasushi Okada, MD,[†††] Hideki Matsuoka, MD,[‡‡‡] Sen Yamagata, MD,[§§§] Yasumasa Yamamoto, MD,[¶¶¶] Toshiro Yonehara, MD,[###] Takeshi Inoue, MD,[||||||] Yoshiki Yagita, MD,[†] and Kazumi Kimura, MD[*,†], on behalf of the ADS investigators

*Background:* Our previous trial acute dual study (ADS) reported that dual antiplatelet therapy (DAPT) using cilostazol and aspirin did not reduce the rate of short-term neurological worsening in non-cardioembolic stroke patients. Present post-hoc analysis investigated whether the impact of combined cilostazol and aspirin differed among stroke subtypes and factors associated with neurological deterioration and/or stroke recurrence. *Methods:* Using the ADS registry, the rate of neurological deterioration, defined as clinical worsening and/or recurrent stroke, including transient ischemic attack was calculated. Stroke subtypes included large-artery atherosclerosis (LAA), small vessel occlusion (SVO), other determined etiology (Others), and undetermined etiology of stroke (Undetermined). *Results:* Data of 1022 patients were analyzed. Deterioration was seen in 104 (10%) patients, and the rates were not markedly different between patients treated with DAPT vs. aspirin in any stroke subtypes: LAA, 19% vs. 11%, ($p = 0.192$); SVO, 10% vs. 10% ($p = 1.000$); Others, 6% vs. 6% ($p = 1.000$); Undetermined, 11% vs. 8% ($p = 0.590$). Diabetes mellitus was the independent factor associated with deterioration (odds ratio 4.360, 95% confidence

From the *Department of Neurological Science, Nippon Medical School Graduate School of Medicine, 1-1-5, Sendagi, Bunkyo-ku, Tokyo 113-8602, Japan; †Department of Stroke Medicine, Kawasaki Medical School, Kurashiki, Japan; ‡Department of Neurology, Jikei University School of Medicine, Tokyo, Japan; §Department of Neurology, Juntendo University Urayasu Hospital, Chiba, Japan; ¶Department of Neurology, Stroke Center, Kobe City Medical Center General Hospital, Hyogo; #Department of Cerebrovascular Medicine, Stroke Center, Steel Memorial Yawata Hospital, Fukuoka, Japan; ||Department of Stroke Medicine, Okinawa Kyodo Hospital, Okinawa, Japan; **Department of Stroke Medicine, Okayama Red Cross Hospital, Okayama, Japan; ††Department of Neurology, Japanese Red Cross Kumamoto Hospital, Kumamoto, Japan; ‡‡Department of Neurology, Juntendo University Faculty of Medicine, Tokyo, Japan; §§Department of Clinical Neurosciences, Institute of Biomedical Sciences, Tokushima University, Tokushima, Japan; ¶¶Department of Neurology and Strokology, Nagasaki University Hospital, Nagasaki, Japan; ##Department of Neurology, Shioda Hospital, Chiba, Japan; ||||Department of Neurology, Okayama University Medical School. Okayama, Japan; ***Department of Neurosurgery, Kawasaki Medical School, Okayama, Japan; †††Department of Cerebrovascular Medicine and Neurology, Clinical Research Institute, National Hospital Organization, Kyushu Medical Center, Fukuoka, Japan; ‡‡‡Department of Cerebrovascular Medicine, NHO Kagoshima Medical Center, Kagoshima, Japan; §§§Department of Neurosurgery, Kurashiki Central Hospital, Okayama, Japan; ¶¶¶Department of Neurology, Kyoto Second Red Cross Hospital, Kyoto, Japan; ###Department of Neurology, Stroke Center, Saiseikai Kumamoto Hospital, Kumamoto, Japan; and ||||||Department of Stroke Medicine, Kawasaki Medical School General Medical Center, Kawasaki Medical School, Okayama, Japan.

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Address correspondence to Junya Aoki, MD, Department of Neurological Science, Nippon Medical School Graduate School of Medicine, 1-1-5, Sendagi, Bunkyo-ku, Tokyo 113-8602, Japan. E-mail: aokijy@gmail.com.

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interval 1.139−16.691, $p = 0.032$) in the LAA group. Age (1.030 [1.004−1.057], $p = 0.026$), systolic blood pressure (1.012 [1.003−1.022], $p = 0.010$), and infarct size (2.550 [1.488−4.371], $p = 0.001$) were associated with deterioration in SVO group, and intracranial stenosis/occlusion was associated with it in the Undetermined group (3.744 [1.138−12.318], $p = 0.030$). *Conclusions:* Combined cilostazol and aspirin did not reduce the rate of short-term neurological deterioration in any clinical stroke subtype. The characteristics of patients whose condition deteriorates in the acute period may differ based on the stroke subtypes.

**Key Words:** Ischemic stroke—Antiplatelet drug—Stroke management—Clinical outcome



## Introduction

Antiplatelet therapy is a central pillar for patients with acute non-cardioembolic stroke. The safety and efficacy of dual antiplatelet therapy (DAPT) with aspirin and clopidogrel has been confirmed by recent clinical trials.[1,2] In addition, particularly in the Asian population, cilostazol has been predicted to be effective as an alternative antiplatelet drug.

Cilostazol, a reversible phosphodiesterase type 3 enzyme inhibitor, promotes vasodilation and inhibits of platelet activation and aggregation by increasing cyclic adenosine monophosphate levels.[3] Evidence suggests that cilostazol can prevent secondary stroke in patients with mild neurological deficits.[4,5] In our previous study, we reported the final results of our acute aspirin plus cilostazol dual therapy study (ADS) that evaluated the safety and efficacy of this therapy in non-cardioembolic stroke.[6] We could not prove the efficacy of this DAPT; however, we showed that this DAPT is a safe treatment option. Here, we have reported detailed information on our ADS to provide valuable data for clinical practice.

The Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification, initially introduced by Adams et al in 1993, is the most valid and reliable stroke classification worldwide.[7,8] According to the TOAST criteria, ischemic stroke is divided into five subgroups: large artery atherosclerosis (LAA), small vessel occlusion (SVO), cardioembolic stroke (CES), other determined etiology (Others), and undetermined etiology (Undetermined). Since the pathology, epidemiology, risk factors, and clinical symptoms vary among stroke subtypes, it is important to classify strokes into these subgroups based on the TOAST classification in order to administer the most appropriate intervention and improve the early and long-term outcomes.

We hypothesized that the impact of antiplatelet therapy differs among the stroke subtypes. Therefore, we conducted this post-hoc analysis to investigate whether the impact of cilostazol addition to aspirin differs among stroke subtypes and which factors are associated with neurological deterioration and/or stroke recurrence to identify therapeutic targets.

## Methods

### Patient registry

This post-hoc study extracted the patient data from the ADS registry, a multicenter, prospective, randomized, open-label trial that evaluated the safety and efficacy of acute aspirin plus cilostazol dual therapy in patients with non-cardioembolic stroke within 48 h of symptom onset. The ADS trial was performed between May 2011 and June 2017 and involved 34 centers in Japan. Patients were randomly allocated to either the DAPT group or the aspirin group. The DAPT group was treated with cilostazol (200 mg/day) and aspirin (80−200 mg/day) for 14 days, while the aspirin group was treated with only aspirin (80−200 mg/day) for 14 days. Concomitant anticoagulant therapy with heparin and argatroban was permitted since it was widely used in clinical practice in Japan during the study period.

In the ADS, the following primary outcomes were evaluated: neurological worsening, transient ischemic attack (TIA), and stroke recurrence within 14 days. The inclusion criteria were as follows: age ≥18 years, non-cardioembolic stroke, presentation within 48 h of symptom onset, neurological deficits with a National Institutes of Health Stroke Scale (NIHSS) score <20, and a pre-morbid modified Rankin Scale score of 0−2. Patients with cardioembolic stroke on admission with a high-risk source defined according to the TOAST criteria; those treated with antiplatelet agents, including cilostazol, aspirin ≥200 mg, clopidogrel, ticlopidine or any anticoagulants, before stroke onset; and those who had undergone or were planning to undergo thrombectomy were excluded from the ADS. This study was approved by the institutional review board of our institutions. The results demonstrated that DAPT with cilostazol and aspirin did not reduce the rate of short-term neurological worsening.[6]

### Study purpose

This study aimed to investigate whether the impact of cilostazol addition to aspirin differs among stroke subtypes and which factors are associated with neurological deterioration and/or stroke recurrence in each stroke subtype.

Neurological deterioration included neurological progression with an NIHSS score of ≥2 and recurrent ischemic stroke or TIA within 14 days, as defined in the ADS.

**Inclusion and exclusion criteria for this retrospective analysis**

In this post-hoc analysis, only patients with ischemic stroke patients who had successfully continued the allocated therapy and received the 14-day assessment were included. Therefore, patients who were unable to continue the therapy for reasons including side effects and allergic reactions and those who did not receive the 14-day assessment were excluded. Stroke etiologies were re-classified based on the TOAST criteria by a certified vascular neurologist (J.A), and only patients who were diagnosed with ischemic stroke due to LAA, SVO, Others, or Undetermined etiologies were analyzed. Patients diagnosed with CES or other neurological diseases at discharge were also excluded.

*Collected variables*

Age, gender, neurological deficits scored using the NIHSS, previous medical history, time from onset to admission, blood pressure, acute combination therapy, neuro-image on admission, and clinical outcomes were reviewed. Previous medical histories included hypertension, diabetes mellitus (DM), and dyslipidemia. Aspirin therapy before onset was also evaluated. Neuroimaging findings on magnetic resonance image (MRI), MR angiography (MRA), and ultrasound examination a on admission included number of infarcts (multiple, single, or none), infarct site (cortex, subcortical white matter, internal capsule, cerebellum, thalamus, midbrain/medullar, pontine, other), infarct size (≤1.5 cm, 1.5−3.0 cm, or >3.0 cm), arterial lesion including the symptomatic intracranial and carotid stenosis/occlusion (≥50%). Periventricular hyperintensity was grade from 0 to 4. Laboratory data on creatinine, glucose, low density lipoprotein (LDL), and hemoglobin A1c (HbA1c) were also collected.

*Statistical analyses*

First, the clinical characteristics and imaging findings were compared among the stroke subtypes. The impact of DAPT on the neurological deterioration was then compared among the four stroke subtypes. Next, data on each stroke subtype were divided into deterioration and no-deterioration groups based on the presence of neurological deterioration. The clinical characteristics and image findings were then compared between these two groups for each subtype. Finally, a multivariate regression analysis was conducted to evaluate the independent parameters related to neurological deterioration in each TOAST subtype. The Mann−Whitney U test was used to analyze differences in continuous variables, and Fisher's exact test and Pearson chi-square were used to analyze differences in categorical variables. The data are presented as median values (interquartile range [IQR]) or frequencies (%). Variables identified on univariate analyses with p values <0.1 as well as the age and gender were entered into the multivariate analysis. The relative risks of complete recanalization at 24 h were expressed as odds ratios (OR) with 95% confidence intervals (CIs). All statistical analyses were performed using the SPSS software program, version 22 (SPSS Japan, Inc., Tokyo, Japan). Results were considered statistically significant at $p<0.05$.

## Results

Between February 2011 and March 2017, 1208 patients were enrolled in the ADS trial. Seven patients withdrew their consent after the study started, 10 patients were lost to follow-up at 14 days, and 125 patients discontinued the allocated therapy. Of the remaining 1066 patients, 1022 (686 [67%] men; median age [interquartile range], 69 [60−77] years old; initial NIHSS score, 2 [1-4]) with non-cardioembolic stroke were analyzed.

*Subtype analysis to evaluate the detailed effects of DAPT*

Table 1 shows the clinical backgrounds based on the stroke subtypes. In total, 164 (16%), 630 (62%), 70 (7%), and 158 (15%) patients were diagnosed with ischemic stroke due to LAA, SVO, Other, and Undetermined etiologies, respectively. Patients in the SVO group and those in the LAA group were younger and older, respectively, than those in other groups ($p=0.001$). Dyslipidemia was less frequent in the Undetermined group than in others ($p=0.047$). Systolic and diastolic blood pressures were the highest in the SVO group ($p=0.003$ and $p=0.001$, respectively). The proportion of aspirin therapy before stroke was the highest in the LAA group ($p=0.032$).

Table 2 presents the neuroimaging findings on admission. Multiple and single infarcts were more frequent in the LAA and SVO groups, respectively, than in other groups ($p<0.001$ and $p<0.001$, respectively). The location of ischemic lesion also differed among the stroke subtypes; cortical and subcortical lesions were dominant in the LAA group, followed by the Others, Undetermined, and SVO groups (both $p<0.001$). The cerebellum was the most frequent site in the Others group ($p<0.001$), while the internal capsule, thalamus, and pontine were the most frequent sites in the SVO group ($p<0.001$, 0.043, <0.001, respectively). The proportion of midbrain/medulla lesions was lower in in the SVO group compared to that in other groups ($p=0.001$).

Fourteen days after stroke onset, 104 (10%) of the 1022 patients showed neurological deterioration—53 (11%) patients in the DAPT group and in 51 (10%) patients in the aspirin group ($p=0.469$). According to stroke subtypes, 24 (15%) of the 164 patients in the LAA group, 61 (10%) of the 630 patients in the SVO group, 4 (6%) of the 70 in the Others group, and 15 (10%) of the 158 in the Undetermined

**Table 1.** *Clinical characteristics of the enrolled patients based on the stroke subtypes.*

| | LAA $n = 164$ | SVO $n = 630$ | Others $n = 70$ | Undetermined $n = 158$ | $p$ |
|---|---|---|---|---|---|
| Age | 71 (63–79) | 67 (59–76) | 68 (61–74) | 70 (61–78) | 0.001 |
| Male, n (%) | 114 (70) | 406 (64) | 52 (74) | 114 (72) | 0.116 |
| Aspirin and cilostazol therapy | 75 (46) | 310 (49) | 36 (51) | 63 (40) | 0.168 |
| NIHSS score | 2 (1–5) | 2 (1–4) | 2 (1–4) | 2 (1–4) | 0.282 |
| Hypertension, n (%) | 138 (84) | 487 (77) | 52 (74) | 121 (77) | 0.201 |
| Diabetes mellitus, n (%) | 59 (36) | 204 (32) | 28 (40) | 42 (27) | 0.157 |
| Dyslipidemia, n (%) | 92 (56) | 298 (47) | 38 (54) | 66 (42) | 0.047 |
| Onset to admission, minutes | 660 (249–1318) | 726 (300–1260) | 478 (255–1241) | 537 (269–1080) | 0.101 |
| Systolic blood pressure, mmHg | 160 (146–180) | 163 (148–185) | 159 (132–170) | 157 (141–175) | 0.003 |
| Diastolic blood pressure, mmHg | 88 (78–100) | 91 (82–104) | 87 (76–100) | 88 (78–99) | 0.001 |
| Aspirin therapy before onset | 25 (15) | 49 (8) | 8 (11) | 15 (10) | 0.032 |
| Periventricular hyperintensity, grade | 1 (0–2) | 1 (0–2) | 1 (0–1) | 1 (1–2) | 0.49 |
| Laboratory findings | | | | | |
| Creatinine, mg/dl | 0.75 (0.61–0.90) | 0.74 (0.61–0.88) | 0.74 (0.63–0.93) | 0.75 (0.62–0.90) | 0.865 |
| Glucose, mg/dl | 123 (103–157) | 116 (100–152) | 125 (104–175) | 118 (101–144) | 0.155 |
| Low density lipoprotein | 125 (96–149) | 122 (97–148) | 121 (100–140) | 115 (100–138) | 0.484 |
| HbA1c, % | 5.9 (5.5–6.9) | 5.8 (5.4–6.6) | 5.9 (5.4–6.8) | 5.7 (5.4–6.4) | 0.118 |

group showed neurological deterioration ($p = 0.149$). We then evaluated whether the impact of DAPT on neurological deterioration differed among stroke subtypes. As shown in Fig. 1, addition of cilostazol to aspirin did not prevent short-term neurological deterioration in any stroke subtype ($p = 0.192$ in the LAA, 1.000 in the SVO and Others, and 0.590 in the Undetermined groups).

*Parameters related to neurological deterioration in each TOAST subtype*

The clinical characteristics based on the presence of neurological deterioration among stroke subtypes are shown in Table 3. The NIHSS score ($p = 0.010$), systolic blood pressure ($p = 0.008$), and HbA1c ($p = 0.044$) differed significantly between the deterioration and no-deterioration groups in the LAA subgroup. In the SVO group, the age ($p = 0.002$), systolic blood pressure ($p = 0.015$), and periventricular hyperintensity ($p = 0.016$) were found to be related to neurological deterioration. In the others group, dyslipidemia (p = 0.039) and the systolic blood pressure ($p = 0.047$) differed between the deterioration and no-deterioration groups. There were no clinical background parameters associated with neurological deterioration in the Undetermined group.

**Table 2.** *Parameters regarding the initial neurological images of patients based on the stroke subtypes.*

| | LAA $n = 164$ | SVO $n = 630$ | Others $n = 70$ | Undetermined $n = 158$ | $p$ |
|---|---|---|---|---|---|
| Number of infarcts | | | | | |
| Multiple | 81 (49) | 16 (3) | 29 (41) | 57 (36) | <0.001 |
| Single | 78 (48) | 599 (95) | 39 (56) | 98 (62) | <0.001 |
| None | 4 (2) | 15 (2) | 2 (3) | 3 (2) | 0.973 |
| Location | | | | | |
| Cortex | 79 (50) | 4 (1) | 23 (34) | 54 (35) | <0.001 |
| Subcortical | 78 (49) | 150 (24) | 29 (43) | 61 (39) | <0.001 |
| Internal capsule | 22 (14) | 246 (40) | 10 (15) | 27 (17) | <0.001 |
| Cerebellum | 11 (7) | 3 (1) | 10 (15) | 18 (12) | <0.001 |
| Thalamus | 13 (8) | 80 (13) | 4 (6) | 11 (7) | 0.043 |
| Midbrain/Medulla | 5 (3) | 10 (2) | 5 (7) | 11 (7) | 0.001 |
| Pontine | 18 (11) | 137 (22) | 3 (4) | 9 (6) | <0.001 |
| Size | | | | | <0.001 |
| <1.5cm | 83 (52) | 524 (85) | 47 (69) | 91 (59) | <0.001 |
| 1.5-3.0 cm | 48 (30) | 85 (14) | 15 (22) | 47 (30) | <0.001 |
| >3.0cm | 28 (18) | 6 (1) | 6 (9) | 17 (11) | <0.001 |
| Intracranial stenosis/occlusion | 123 (75) | 0 (0) | 14 (20) | 31 (20) | <0.001 |
| Cervical stenosis/occlusion | 52 (32) | 0 (0) | 4 (6) | 3 (2) | <0.001 |

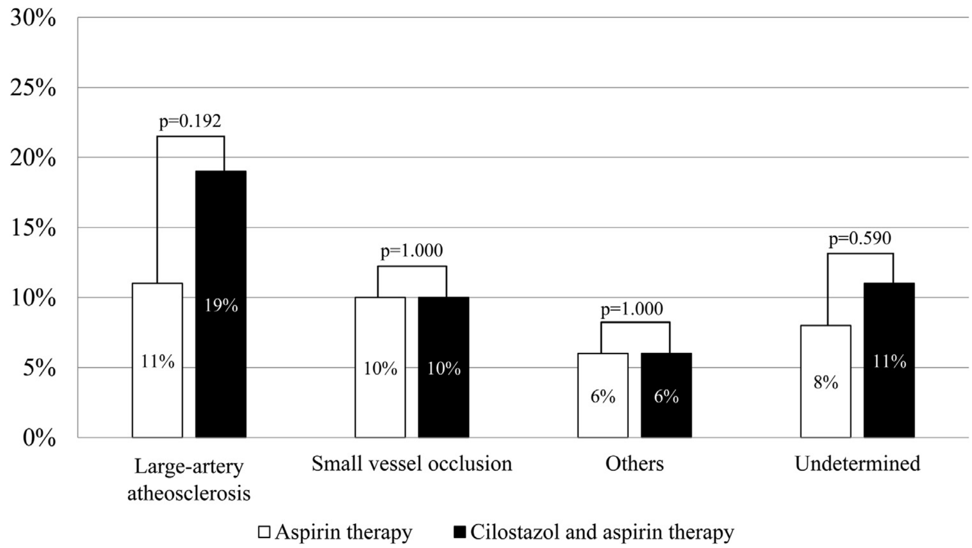


**Fig. 1.** *Differences in the rates of neurological deterioration between the aspirin and the cilostazol and aspirin groups among stroke subtypes.*

The neuroimaging findings are presented in Table 4. In the LAA group, pontine infarct ($p = 0.008$) and cervical stenosis/occlusion ($p = 0.032$) were associated with neurological deterioration. In the SVO group, thalamic infarct was less frequent ($p = 0.046$), and the infarct size was larger ($p < 0.001$) in the deterioration group than in the no-deterioration group. The infarct size was also related to the neurological deterioration in the others ($p = 0.028$) and Undetermined subgroups ($p = 0.048$), but not in the LAA subgroup ($p = 0.904$).

Finally, we conducted a multivariate regression analysis to investigate the independent parameters related to the neurological deterioration in the LAA, SVO, Others, and Undetermined groups (Table 5). Age, gender, and parameters associated with neurological deterioration with $p < 0.1$ were included in the analysis. DM was the only independent factor related to the neurological deterioration in the LAA group (OR, 4.360; 95% CI, 1.139−16.691; $p = 0.032$). In the SVO group, age (OR, 1.030; 95% CI, 1.004−1.057; $p = 0.026$), systolic blood pressure (OR, 1.012; 95% CI, 1.003−1.022; $p = 0.010$), and infarct size (OR, 2.550; 95% CI, 1.488−4.371; $p = 0.001$) were independently associated with neurological deterioration. There were no relevant independent factors in the Others group. In the Undetermined group, intracranial stenosis/occlusion was the only factor related to neurological deterioration (OR, 3.744; 95% CI, 1.138−12.318; $p = 0.030$).

## Discussion

This post-hoc analysis of ADS data demonstrated two major findings. First, addition of cilostazol to aspirin did not alter the rate of neurological deterioration, regardless of the stroke subtype. Second, the independent parameters associated with neurological deterioration differed when mild stroke was classified based on the TOAST criteria.

In our previous primary analysis, which was conducted on an intention-to-treat basis, there was no significant difference in the frequency of symptom progression between treatment the DAPT and aspirin groups (11% vs. 11%).[6] The current study only included patients who successfully continued the randomized treatment for 14 days and received a prescribed evaluation. The obtained findings were similar to those of the previous study, showing no significant difference in the rate of deterioration between the DAPT and aspirin groups (11% vs. 10%). We also showed that DAPT did not have superior efficiency to aspirin monotherapy in any stoke subtype.

We initially hypothesized that the efficacy of this DAPT might vary according to the TOAST subtypes, based on the fact that the pathology and mechanism of stroke differ among stroke subtypes. Previous studies on LAA have indicated that DAPT prior to treatment for cervical artery stenosis can prevent cerebral infarction.[9] In the SVO subtype, there are many causes of stroke, including hypertension, arteriosclerosis, lipohyalinosis, microatheroma, branch atheromatous disease, embolus, and blood coagulation abnormalities.[10,11] The disease type "Others" includes various conditions, such as aortogenic and paradoxical embolism along with vascular dissection, which are difficult to diagnosis on admission.[12-15] In addition, in a chronic phase trial, the combination of cilostazol and aspirin or clopidogrel reduced the incidence of ischemic stroke recurrence in high-risk patients.[5] Furthermore, in addition to antiplatelet effects, cilostazol has been reported to have various effects, such as vasodilation and neurogenesis.[16,17] However, our study findings showed that the neurological deterioration rate with DAPT using cilostazol and aspirin is unlikely to vary according to the stroke subtypes. Therefore, routine DAPT using cilostazol and aspirin for non-cardioembolic stroke may not lead to the suppression of short-term exacerbation.

**Table 3.** *Comparison of clinical and laboratory findings between patients with/without deterioration in each stroke subtypes.*

| | LAA | | | SVO | | | Others | | | Undetermined | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Deterioration (-) | Deterioration (±) | | Deterioration (-) | Deterioration (±) | | Deterioration (-) | Deterioration (±) | | Deterioration (-) | Deterioration (±) | |
| | *n* = 140 | *n* = 24 | *p* | *n* = 569 | *n* = 61 | *p* | *n* = 66 | *n* = 4 | *p* | 143 | 15 | p |
| Age | 71 (62–78) | 76 (66–81) | 0.353 | 66 (59–76) | 74 (64-80) | 0.002 | 69 (61–75) | 67 (65–69) | 0.761 | 69 (61–78) | 73 (67–78) | 0.414 |
| Male, n (%) | 99 (71) | 15 (63) | 0.474 | 370 (65) | 36 (59) | 0.399 | 49 (74) | 3 (75) | 1.000 | 104 (73) | 10 (67) | 0.762 |
| NIHSS score | 2 (1–4) | 5 (2–6) | 0.010 | 2 (1–4) | 3 (2–4) | 0.115 | 2 (1–4) | 4 (1–14) | 0.197 | 2 (1–4) | 3 (2–5) | 0.170 |
| Hypertension, n (%) | 119 (85) | 19 (79) | 0.544 | 439 (77) | 47 (77) | 1.000 | 48 (73) | 4 (100) | 0.556 | 110 (77) | 11 (73) | 0.753 |
| Diabetes mellitus, n (%) | 46 (33) | 13 (54) | 0.064 | 184 (32) | 20 (33) | 1.000 | 25 (38) | 3 (75) | 0.264 | 29 (37) | 3 (20) | 0.761 |
| Dyslipidemia, n (%) | 78 (56) | 14 (58) | 1.000 | 273 (48) | 25 (41) | 0.345 | 38 (58) | 0 (0) | 0.039 | 60 (42) | 6 (40) | 1.000 |
| Onset to admission, minutes | 660 (242–1318) | 633 (281–1331) | 0.950 | 748 (322–1260) | 645 (230–1320) | 0.404 | 478 (268–1267) | 534 (27–1029) | 0.390 | 530 (264–1051) | 585 (360–1660) | 0.684 |
| Systolic blood pressure, mmHg | 158 (144–178) | 176 (162–186) | 0.008 | 162 (147–183) | 169 (158–191) | 0.015 | 156 (132–170) | 170 (168–221) | 0.047 | 157 (140–174) | 166 (146–203) | 0.127 |
| Diastolic blood pressure, mmHg | 87 (78–100) | 96 (80–108) | 0.169 | 90 (82–104) | 94 (81–109) | 0.304 | 84 (76–100) | 94 (91–119) | 0.111 | 88 (78–98) | 95 (78–110) | 0.257 |
| Aspirin therapy before onset, n (%) | 23 (16) | 2 (8) | 0.537 | 43 (8) | 6 (10) | 0.458 | 7 (11) | 1 (25) | 0.392 | 15 (11) | 0 (0) | 0.364 |
| Periventricular hyperintensity, grade | 1 (0–1) | 1 (1–2) | 0.271 | 1 (0–2) | 1 (1–2) | 0.016 | 1 (0–1) | 1 (0–1) | 0.631 | 1 (1–2) | 1 (0–2) | 0.718 |
| Laboratory findings | | | | | | | | | | | | |
| Creatinine, mg/dl | 0,75 (0.60–0.90) | 0.70 (0.62–0.89) | 0.818 | 0.74 (0.61–0.88) | 0.73 (0.56–0.93) | 0.692 | 0.74 (0.62–0.93) | 0.84 (0.74–1.31) | 0.201 | 0.74 (0.62–0.90) | 0.77 (0.59–0.96) | 0.845 |
| Glucose, mg/dl | 122 (102–151) | 134 (114–246) | 0.050 | 116 (101–152) | 115 (98–143) | 0.678 | 120 (103–170) | 158 (117–190) | 0.342 | 118 (101–144) | 117 (102–144) | 0.836 |
| Low density lipoprotein, mg/dl | 122 (95–149) | 136 (110–176) | 0.097 | 121 (97–147) | 130 (98–153) | 0.258 | 116 (99–140) | 139 (132–218) | 0.085 | 115 (99–137) | 114 (101–150) | 0.956 |
| HbA1c, % | 5.8 (5.5–6.7) | 6.6 (5.5–7.7) | 0.044 | 5.8 (5.4–6.6) | 5.8 (5.3–6.4) | 0.911 | 5.9 (5.4–6.7) | 6.3 (5.4–8.5) | 0.580 | 5.7 (5.4–6.3) | 5.8 (5.2–6.4) | 0.917 |

**Table 4.** *Comparison of image findings between patients with/without deterioration in each stroke subtypes.*

| | LAA | | | SVO | | | Others | | | Undetermined | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Deterioration (-) | Deterioration (±) | | Deterioration (-) | Deterioration (±) | | Deterioration (-) | Deterioration (±) | | Deterioration (-) | Deterioration (±) | |
| | *n* = 140 | *n* = 24 | *p* | *n* = 569 | *n* = 61 | *p* | *n* = 66 | *n* = 4 | *p* | 143 | 15 | p |
| Number of infarcts, n (%) | | | | | | | | | | | | |
| Multiple | 71 (51) | 10 (42) | 0.509 | 16 (3) | 0 (0) | 0.387 | 28 (42) | 1 (25) | 0.637 | 50 (35) | 7 (47) | 0.404 |
| Single | 64 (46) | 14 (58) | 0.276 | 538 (95) | 61 (100) | 0.062 | 37 (56) | 2 (50) | 1.000 | 90 (63) | 8 (53) | 0.578 |
| None | 4 (3) | 0 (0) | 1.000 | 15 (3) | 0 (0) | 0.383 | 1 (2) | 1 (25) | 0.112 | 3 (2) | 0 (0) | 1.000 |
| Location | | | | | | | | | | | | |
| Cortex | 71 (53) | 8 (33) | 0.120 | 4 (1) | 0 (0) | 1.000 | 21 (32) | 2 (67) | 0.263 | 51 (36) | 3 (20) | 0.262 |
| Subcortical | 67 (50) | 11 (46) | 0.826 | 131 (24) | 19 (31) | 0.210 | 28 (43) | 1 (33) | 1.000 | 52 (37) | 9 (60) | 1.000 |
| Internal capsule | 20 (15) | 2 (8) | 0.533 | 218 (39) | 28 (46) | 0.337 | 10 (15) | 0 (0) | 1.000 | 22 (16) | 5 (33) | 0.142 |
| Cerebellum | 8 (6) | 3 (13) | 0.374 | 3 (1) | 0 (0) | 1.000 | 9 (14) | 1 (33) | 0.384 | 18 (13) | 0 (0) | 0.219 |
| Thalamus | 13 (10) | 0 (0) | 0.220 | 77 (14) | 3 (5) | 0.046 | 4 (6) | 0 (0) | 1.000 | 10 (7) | 1 (7) | 1.000 |
| Midbrain/Medulla | 3 (2) | 2 (8) | 0.164 | 8 (1) | 2 (3) | 0.260 | 5 (8) | 0 (0) | 1.000 | 9 (6) | 2 (13) | 0.288 |
| Pontine | 11 (8) | 7 (29) | 0.008 | 125 (23) | 12 (20) | 0.746 | 3 (5) | 0 (0) | 1.000 | 9 (6) | 0 (0) | 0.601 |
| Size | | | 0.904 | | | <0.001 | | | 0.028 | | | 0.048 |
| <1.5cm | 71 (53) | 12 (50) | 0.828 | 483 (87) | 41 (67) | <0.001 | 47 (72) | 0 (0) | 0.027 | 86 (61) | 5 (33) | 0.052 |
| 1.5-3.0 cm | 41 (30) | 7 (29) | 1.000 | 67 (12) | 18 (30) | 0.001 | 13 (20) | 2 (67) | 0.120 | 41 (29) | 6 (40) | 0.389 |
| >3.0cm | 23 (17) | 5 (21) | 0.771 | 4 (1) | 2 (3) | 0.112 | 5 (8) | 1 (33) | 0.245 | 13 (9) | 4 (27) | 0.064 |
| Intracranial stenosis/occlusion | 104 (74) | 19 (79) | 0.800 | 0 (0) | 0 (0) | - | 12 (18) | 2 (50) | 0.176 | 24 (17) | 7 (47) | 0.012 |
| Cervical stenosis/occlusion | 49 (35) | 3 (13) | 0.032 | 0 (0) | 0 (0) | - | 4 (6) | 0 (0) | 1.000 | 3 (2) | 0 (0) | 1.000 |

**Table 5.** *Multivariate regression analysis investigating for the parameters related to the neurological deterioration in each stroke subtype.*

| | odds ratio | 95% CI | *p* |
|---|---|---|---|
| LAA[a] | | | |
| Diabetes mellitus | 4.360 | 1.139-16.691 | 0.032 |
| SVO[b] | | | |
| Age | 1.030 | 1.004-1.057 | 0.026 |
| Systolic blood pressure, mmHg | 1.012 | 1.003-1.022 | 0.010 |
| Size | 2.550 | 1.488-4.371 | 0.001 |
| Others[c] | | | |
| No independent parameter | | | |
| Undetermined[d] | | | |
| Intracranial arterial lesion | 3.744 | 1.138-12.318 | 0.030 |

[a]adjusted for NIHSS score, systolic blood pressure, pontine lesion, cervical lesion, age, gender, glucose, LDL, and HbA1c.
[b]adjusted for periventricular hyperintensity, thalamus lesion, and gender.
[c]adjusted for age, gender, systolic blood pressure, infarct size, ACA lesion, and LDL.
[d]adjusted for age, gender, and infarct size.

A history of DM was an independent factor related to neurological deterioration superior to age and the initial NIHSS score in LAA group only. This finding is partly in agreement with those of previous studies. DM has been shown to be an independent and significant predictor for the presence of middle cerebral artery stenosis,[18] stenosis progression,[19] restenosis after angioplasty,[20] and carotid artery restenosis[21] due to neointima enhanced by the promotion of inflammatory cell recruitment and abnormal extracellular matrix production, all of which promote unfavorable outcomes. In contrast, DM is generally associated with a poor clinical outcome after ischemic stroke, regardless of the stroke mechanism.[22,23] In the Secondary Prevention of Small Subcortical Strokes randomized trial, DM independently doubled the risk of recurrent stroke.[24] In our study, the impact of DM differed among stroke subtypes possibly because of the influence of the study design, patient cohort, and methodological manner, especially considering the use of a first-line neuroimaging tool. In the ADS, all patients received MRA; if patients with clinical lacuna syndrome had been examined with computed tomography only, the status of the arterial lesion would have remained unknown. Therefore, there is a possibility that some patients in previous studies who had mild stroke due to a major artery lesion were classified into the SVO group and not the LAA group. We should therefore play close attention to patients who have a history of DM, especially those with arterial stenosis/occlusion, even when they have only mild stroke on admission.

In the SVO group, aging and elevated blood pressure were important parameters related to neurological deterioration. The definitive association between age and mortality has been established,[25] and aging is known to influence the stroke subtypes. Atrial fibrillation is the most prevalent arrhythmia in elderly patients, occluding the intracranial major artery.[26,27] Atherosclerosis also progresses with age. Even in the SVO subtype, aging has been shown to be associated with neurological deterioration in the acute phase.[28,29] In addition, aging is also associated with susceptibility to infection, malignancy, dementia, and delirium. The Copenhagen Stroke Study found that age influences certain activities of daily living-related aspects, but not the neurological recovery.[30] Acute elevated blood pressure was observed in >60−80% of stroke patients who presented to the emergency room.[31,32] The pathology is represented as a stroke-specific mechanism, presumed to be the result of increased sympathoadrenal tone and reduced parasympathetic activity,[33] although there seems to be no definite correlation with the ischemic lesion size or location.[34] In the SVO subtype, patients defined by age and blood pressure parameters, may have a higher rate of neurological deterioration than those defined by DM and dyslipidemia parameters

Infarct size was another factor associated with neurological deterioration in the SVO group, and the association between infarct volume and clinical outcome has been studied extensively. The initial infarct volume before acute therapy[35,36] and volume expansion after therapy[37] directly influences the clinical outcome in patients with SVO stroke. In the present study, the onset-to-admission time was not significantly different, but the infarct size on initial imaging was important for predicting neurological deterioration in the acute period. This finding implies that, rather than stroke progression, occlusion of the relatively large perforating artery is the mechanism underlying neurological deterioration, even in patients with stroke due to SVO etiology. A previous aggressive study successfully visualized occlusion of the lenticulostriate arteries using 1.5-,[38], 3.0-[39] and 7.0-T MRI.[40] The accumulation of further evidence on the status of small artery occlusion, including the number, diameter, and length of the perforating artery, will help predict the clinical outcome in patients with stroke due to SVO etiology.

The Undetermined group includes heterogeneous patient characteristics, such as cases with two or more causes identified, a negative evaluation, and an incomplete evaluation. There are many situations in clinical practice when physicians specializing in stroke find it difficult to classify patients based on the TOAST criteria. In such situations, intracranial artery stenosis/occlusion is the determinant of neurological deterioration. Previously, even in cases of infarction in the territory of the perforating artery, parent large artery stenosis was reported to be a major clinical determinant.[41] A post-hoc analysis of a multicenter randomized trial indicated that the rate of recurrent stroke was higher in minor stroke or high-risk TIA patients with intracranial artery stenosis than in those without it.[42]

Therefore, a comprehensive assessment of the intracranial artery status on admission seems to be essential for predicting the clinical outcome, even in patients with acute minor stroke, regardless of the etiology.

Several limitations associated with the present study warrant mention. First, this was a retrospective analysis of a prospective multicenter trial. Second, the study cohort mainly consisted of patients with mild stroke. Third, concomitant anticoagulant therapy with argatroban and heparin was permitted, and detailed information on the concomitant therapy was not always available. In addition, our cohort was examined using routine MRI and MRA, which minimized the number of patients with stroke mimics; this may have led to overestimation of the number of arterial lesions. Finally, we were unable to identify independent parameters related to neurological deterioration in the Others group, partly due to the small sample size.

In conclusion, DAPT with cilostazol and aspirin did not reduce the rate of short-term neurological worsening in any stroke subtype. The predictors of neurological deterioration may depend on TOAST calcifications.

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## Declaration of Competing Interest

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