Uninterrupted Direct Oral Anticoagulants Without a Change in Regimen for Catheter Ablation for Atrial Fibrillation Is an Acceptable Protocol

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Background: In patients undergoing catheter ablation (CA) for atrial fibrillation (AF), the use of uninterrupted direct oral anticoagulants (DOACs) is the current protocol. This study evaluated bleeding complications following the uninterrupted use of 4 DOACs in patients undergoing CA for AF without any change in the dosing regimen. Moreover, we assessed differences between once- and twice-daily DOAC dosing in patients undergoing CA for AF who continued on DOACs without any change in the dosing regimen.

Methods and Results: This study was a retrospective single-center cohort study of consecutive patients. All patients continued DOACs without interruption or changes to the dosing schedule, even in the case of morning procedures. The primary endpoint was the incidence of major bleeding events within the first 30 days after CA. In all, 710 consecutive patients were included in the study. Bleeding complications were less frequent in the uninterrupted twice-than once-daily DOACs group. However, the incidence of cardiac tamponade across all DOACs was low (0.98%; 7/710), suggesting that uninterrupted DOACs without changes to the dosing regimen may be an acceptable strategy. The rate of total bleeding events, including minor bleeding (12/710; 1.6%), was also satisfactory.

Conclusions: Uninterrupted DOACs without any change in dosing regimen for patients undergoing CA for AF is acceptable. Bleeding complications may be less frequent in patients receiving DOACs twice rather than once daily.

Key Words: Atrial fibrillation; Catheter ablation; Complication; Direct oral anticoagulants; Twice-daily administration
However, in some of these trials, patients received once-daily DOACs in the evening of the day of the procedure, not in the morning.\textsuperscript{15,16} In Japan, most patients receive once-daily DOACs in the morning. Therefore, the safety of uninterrupted DOACs without any change in dosing regimen in patients undergoing CA for AF, particularly if the once-daily DOAC is received in the morning, remains unclear. In this study we evaluated bleeding complications in consecutive patients who underwent CA for AF without any change in the DOAC dosing regimen throughout all procedures.

**Methods**

CA for AF was performed without discontinuation of DOACs, even if they were taken in the morning on the day of the procedure, in all consecutive cases. Moreover, all once-daily DOACs were administrated in the morning before CA and were not shifted to the evening on the day of CA. This study is a retrospective single-center cohort study of consecutive patients who underwent AF ablation. All data were collected from electronic medical records.

**Anticoagulant Management**

All consecutive patients who underwent CA for AF took DOACs unless they had severe renal dysfunction which is a contraindication for DOACs. The type of DOAC was decided by individual attending physicians. All patients were on anticoagulants for >4 weeks before CA. The once-daily DOACs (rivaroxaban and edoxaban) were taken in the morning, not in the evening, by all patients. Left atrial thrombi were evaluated before ablation by transesophageal echocardiography or computed tomography in all patients whose CHADS\textsubscript{2} scores were >1. Thrombi were evaluated in PeAF and long-standing PeAF (LSPeAF) patients even if their CHADS\textsubscript{2} scores were 0.

Off-label underdosing of dabigatran was defined in the present study as a dose <220 mg/day. This definition of off-label underdosing of dabigatran included the 150-mg/day on-label dose in the US.

A bolus of 5,000 IU heparin was administered before transseptal puncture, just after puncture of the femoral vein. Patient were also given a continuous infusion of heparin 1,000 IU/h. During the procedure, the activated clotting time was maintained at 300–350 s. After ablation was completed, protamine sulfate was administered to reverse the effects of heparin.

After each procedure, the same kind of anticoagulant was administered for at least 4 weeks. Therefore, 4 weeks before and after CA, including on the day of the procedure, all patients continued to take the same kind of DOAC in the morning (and evening in the case of patients taking DOACs twice daily).

None of the patients in the present study switched to another kind of DOACs during the observation periods. There was no significant difference in periprocedural anticoagulant management among different DOAC types.

**Ablation Procedure**

In cases of radiofrequency CA, extensive encircling pulmonary vein isolation (PVI) guided by intracardiac echocardiography and contact force was performed. If PVI was insufficient to sustain sinus rhythm, linear ablation (mitral isthmus linear ablation, left atrium [LA] roof linear ablation, or LA anterior linear ablation), ablation of complex fractionated atrial electrocardiograms, ganglionic plexi ablation, and/or superior vena cava isolation was added. In patients with PeAF or LSPeAF, if AF was not terminated, electric cardioversion was performed to restore sinus rhythm.

In cases of balloon ablation, including cryoballoon, hot balloon, and laser balloon, the 4 pulmonary veins (PVs) were isolated one by one. Touch-up ablation with radiofrequency was added if the isolation was not achieved after 2 sessions of balloon ablation.

ATP and isoproterenol were administered to disclose dormant conduction of the PV and non-PV triggers.

**Adverse Events**

All adverse events throughout the periprocedural period and within the first 30 days after CA were recorded and analyzed. Adverse events included bleeding, defined as greater than Type 3 bleeding based on the Bleeding Academic Research Consortium (BARC), cardiac tamponade, and ischemic events. Bleeding included overt bleeding plus a decrease in hemoglobin >3 g/dL, overt bleeding requiring transfusion, intracerebral hemorrhage detected by imaging or during autopsy, and bleeding requiring surgical intervention.

Ischemic events included ischemic stroke, non-central nervous system systemic embolism, and myocardial infarction. Stroke was defined as the sudden onset of a focal neurologic deficit in a consistent location with the territory of the major cerebral artery. Systemic embolism was defined as acute vascular occlusion of an extremity or organ detected by imaging or surgery.

**Statistical Analysis**

All continuous variables are expressed as the mean±SD and were assessed using the Mann-Whitney U test. Categorical data are presented as frequencies and percentages, and the significance of differences between groups was evaluated using Chi-squared or Fisher’s exact tests. Two-sided P<0.05 was considered to be statistically significant. Multivariate analysis was used to assess and collect statistical data to explain the relationship between different variables associated with a result.

**Ethical Considerations**

The study protocol conformed to the Declaration of Helsinki and was reviewed and approved by the Institutional Review Board of The University of Tokyo (No. 2650).

**Results**

**Baseline Characteristics**

In all, 710 patients with AF underwent CA (Table 1). The mean age was 65.1±11.9 years. At baseline, the edoxaban group had a smaller percentage of female patients (20.1%) compared with the other groups (dabigatran, 29.5%; rivaroxaban, 32.0%; apixaban, 31.4%; P=0.041). The apixaban group had a higher age, specifically a higher percentage of elderly (>75 years old) patients (32.8%) than in the other groups (dabigatran, 14.7%; rivaroxaban, 17.3%; edoxaban, 16.5%; P<0.0001). Because of a higher percentage of elderly patients and a higher percentage of patients with a history of stroke/transient ischemic attack (TIA), the apixaban group had a CHA\textsubscript{2}-DS\textsubscript{2}-VASC score. Conversely, there were no significant differences in the HAS-BLED score among groups. There was a higher frequency of bal-
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| Table 1. Baseline Characteristics According to DOAC Used |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Age (years)                     | Dabigatran (n=88) | Rivaroxaban (n=237) | Apixaban (n=216) | Edoxaban (n=169) | P value         |
|                                | 63.4±10.8        | 64.4±11.7        | 66.9±11.8        | 64.1±12.6        | 0.019           |
| Female sex                      | 26 (29.5)        | 77 (32.4)        | 68 (31.4)        | 34 (20.1)        | 0.035           |
| PAF                             | 53 (60.2)        | 110 (46.4)       | 104 (48.1)       | 70 (41.4)        | 0.039           |
| PeAF                            | 22 (25.0)        | 73 (30.8)        | 69 (31.9)        | 61 (36.0)        | 0.330           |
| LSPeAF                          | 4 (4.5)          | 21 (8.8)         | 18 (8.3)         | 14 (8.2)         | 0.634           |
| AT/AFF                          | 9 (10.2)         | 33 (13.9)        | 25 (11.5)        | 24 (14.2)        | 0.711           |
| Body weight (kg)                | 65.3±11.3        | 65.5±12.9        | 64.0±12.3        | 66.3±13.4        | 0.428           |
| Operator experience ≥5 years    | 85 (96.5)        | 220 (92.8)       | 197 (91.2)       | 146 (86.3)       | 0.031           |
| AM procedure                    | 41 (46.5)        | 101 (42.6)       | 121 (56.2)       | 87 (51.4)        | 0.033           |
| Time from DOAC to procedure (h) | 4.3±2.3          | 4.4±2.2          | 3.8±2.1          | 4.0±2.2          | 0.031           |

DOAC dose

|                                | Dabigatran (n=88) | Rivaroxaban (n=237) | Apixaban (n=216) | Edoxaban (n=169) | P value         |
|                                | 83 (94.4)         | 212 (89.5)         | 196 (90.8)       | 145 (85.8)       | 0.003           |
|                                | 5 (5.6)           | 25 (10.5)          | 20 (9.2)         | 24 (14.2)        | 0.170           |
|                                | 83 (94.4)         | 170 (71.7)         | 164 (75.9)       | 101 (59.7)       | 0.003           |
|                                | 2.2±1.61          | 2.09±1.37          | 2.61±1.75        | 2.23±1.64        | 0.005           |
|                                | 12 (13.6)         | 32 (13.5)          | 42 (19.4)        | 31 (18.3)        | 0.278           |
|                                | 51 (57.9)         | 126 (53.1)         | 124 (57.4)       | 105 (62.1)       | 0.350           |
|                                | 13 (14.7)         | 41 (17.3)          | 71 (32.8)        | 28 (16.5)        | <0.001          |
| Diabetes                       | 15 (17.0)         | 39 (16.4)          | 44 (20.3)        | 37 (21.8)        | 0.494           |
|                                | 10 (11.3)         | 14 (5.9)           | 28 (12.9)        | 13 (7.6)         | 0.052           |
| Vascular disease               | 12 (13.6)         | 20 (8.4)           | 31 (14.3)        | 21 (12.4)        | 0.234           |
| HAS-BLED score                 | 1.39±0.12         | 1.33±0.99          | 1.55±1.05        | 1.5±1.13         | 0.127           |
| Abnormal renal/liver function  | 5 (5.68)          | 18 (7.59)          | 18 (8.33)        | 9 (5.33)         | 0.564           |
|                                | 2 (2.27)          | 7 (2.95)           | 2 (0.93)         | 6 (3.55)         | 0.350           |
|                                | 10 (11.3)         | 17 (7.1)           | 32 (14.8)        | 25 (14.7)        | 0.041           |
|                                | 62.9±9.3          | 62.5±10.2          | 60.9±12.1        | 60.2±13.3        | 0.160           |
| LAD (mm)                       | 40.7±7.87         | 40.6±6.31          | 40.9±6.59        | 40.7±6.57        | 0.975           |
| CKD                            | 29 (32.9)         | 81 (34.1)          | 77 (35.6)        | 56 (33.1)        | 0.951           |
| eGFR                           | 67.9±15.7         | 66.3±15.6          | 65.5±15.7        | 66.7±17.1        | 0.696           |
| Balloon ablation               | 16 (18.1)         | 19 (8.02)          | 17 (7.87)        | 16 (9.47)        | 0.030           |

Values are presented as the mean±SD or n (%). AM, ante meridiem; AT/AFL, atrial tachycardia/atrial flutter; CKD, chronic kidney disease; DOAC, direct oral anticoagulant; LAD, left atrial diameter; LSPeAF, long-standing persistent atrial fibrillation; LVEF, left ventricular ejection fraction; PAF, paroxysmal atrial fibrillation; PeAF, persistent atrial fibrillation; TIa, transient ischemic attack.

loon ablation in the dabigatran group than in the other groups (P=0.0304).

Comparing patients receiving twice-daily DOACs (dabigatran and apixaban; n=304) and those receiving once-daily DOACs (rivaroxaban and edoxaban; n=406) revealed a significantly higher CHA2DS2-VASc score in the twice- than once-daily group (2.49±1.72 vs. 2.15±1.49, respectively; P=0.0085) due to the higher percentage of elderly patients and the higher frequency of stroke history (Table 2). There were no significant differences in other characteristics, including the timing of the procedure, appropriate dose ratio, and off-label underdosing ratio.

Complications

There were no fatal events or intracranial bleeding events in any group. There was a low frequency of cardiac tamponade among all patients (0.99%; 7/710). Cardiac tamponade occurred in 4 (1.6%) patients in the rivaroxaban group and in 3 (1.7%) patients in the edoxaban group; it did not occur in either the dabigatran or apixaban groups (P=0.13; Table 3). Other bleeding complications, including pericardial effusion, puncture site hematoma, and intraperitoneal hemorrhage requiring blood transfusion due to a drop in hemoglobin >3 mg/dL, occurred in 1 (0.4%) patient in the apixaban group and in 4 (2.3%) patients in the edoxaban group. None of these bleeding complications were recorded in either the dabigatran or rivaroxaban groups (P=0.035). In total, bleeding complications occurred in 4 (1.6%) patients in the rivaroxaban group, in 1 (0.4%) patient in the apixaban group, and in 7 (4.1%) patients in the edoxaban group. There were bleeding complications in the dabigatran group (P=0.022). Stroke and TIa occurred in 1 (0.4%) patient in the rivaroxaban group and in 2 (1.1%) patients in the edoxaban group; there were no events of stroke/TAa recorded in either the dabigatran or apixaban groups (P=0.306; Table 3). Other ischemic events, including non-central nervous system systemic embolism and myocardial infarction, were not reported. There were significant differences in overall complications among the 4 groups, as indicated in Table 3.

Comparing the twice- and once-daily DOACs groups revealed that cardiac tamponade occurred in 7 (1.7%) patients in the once-daily group, but not at all in the twice-daily group (P=0.022). There was a significantly higher incidence of total bleeding events in the once- than twice-daily group (11 [2.7%] vs. 1 [0.3%], respectively; P=0.016;
Table 2. Baseline Characteristics According to Twice- or Once-Daily DOAC Dosing

|                          | Twice-daily dosing (n=304) | Once-daily dosing (n=406) | P value |
|--------------------------|----------------------------|---------------------------|---------|
| Age (years)              | 66.0±11.7                  | 64.1±12.2                 | 0.0462  |
| Female sex               | 94 (30.9)                  | 110 (27.0)                | 0.315   |
| PAF                      | 157 (51.6)                 | 180 (44.3)                | 0.057   |
| PeAF                     | 91 (29.9)                  | 134 (33.0)                | 0.415   |
| LSPeAF                   | 22 (7.2)                   | 35 (8.6)                  | 0.577   |
| AT/AFL                   | 34 (11.1)                  | 57 (14.0)                 | 0.307   |
| Body weight (kg)         | 64.4±12.1                  | 65.7±13.1                 | 0.177   |
| Operator experience >5 years | 282 (92.7)                  | 366 (90.1)                | 0.23    |
| AM procedure             | 162 (53.2)                 | 188 (46.3)                | 0.069   |
| Time from DOAC to procedure (h) | 4.0±2.2                   | 4.2±2.2                   | 0.082   |

DOAC dose
- Appropriate dose
- Off-label underdose
- CHA2DS2-VASc score
- Heart failure
- Hypertension
- Age ≥75 years
- Diabetes
- Previous stroke/TIA
- Vascular disease
- HAS-BLED score
- Abnormal renal/liver function
- Previous bleeding
- Antiplatelet therapy or alcohol
- LVEF (%)
- LAD (mm)
- CKD
- eGFR
- Balloon ablation

Values are presented as the mean±SD or n (%). Abbreviations as in Table 1.

Table 3. Complications According to Direct Oral Anticoagulant Used

|                          | Dabigatran (n=88) | Rivaroxaban (n=237) | Apixaban (n=216) | Edoxaban (n=169) | P value |
|--------------------------|-------------------|---------------------|------------------|------------------|---------|
| Total bleeding complications | 0 (0)             | 4 (1.6)             | 1 (0.4)          | 7 (4.1)          | 0.0224  |
| Cardiac tamponade        | 0 (0)             | 4 (1.6)             | 0 (0)            | 3 (1.7)          | 0.1307  |
| Other bleeding complications | 0 (0)             | 0 (0)               | 1 (0.4)          | 4 (2.3)          | 0.0356  |
| Stroke/transient ischemic attack | 0 (0)            | 1 (0.4)             | 0 (0)            | 2 (1.1)          | 0.306   |
| Total no. complications  | 0 (0)             | 5 (2.1)             | 1 (0.4)          | 9 (5.3)          | 0.0043  |

Values are presented as n (%).

Table 4. Bleeding and Stroke Complications According to Twice- or Once-Daily Direct Oral Anticoagulant Dosing

|                          | Twice-daily dosing (n=304) | Once-daily dosing (n=406) | P value |
|--------------------------|----------------------------|---------------------------|---------|
| Total bleeding complications | 1 (0.3)                  | 11 (2.7)                  | 0.016   |
| Cardiac tamponade        | 0 (0)                      | 7 (1.7)                   | 0.0221  |
| Other bleeding complications | 1 (0.3)                  | 4 (0.9)                   | 0.398   |
| Stroke/transient ischemic attack | 0 (0)                    | 3 (0.7)                   | 0.264   |
| Total no. complications  | 1 (0.3)                    | 11 (2.7)                  | 0.016   |

Values are presented as n (%).
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Table 4. There was no significant difference in ischemic events between these 2 groups (Table 4). Overall complications tended to occur more frequently in the once- than twice-daily group (P=0.0016; Table 4). Details of each case of complications are presented in Table 5.

Multivariate analysis revealed that once-daily DOAC was the only independent predictor of complications (Table 6).

Discussion

There is no doubt that uninterrupted DOACs have been used in AF ablation. However, decisions as to how the DOAC regimen is handled on the day of CA for AF are left to the discretion of medical staff. There is question as to whether once-daily DOACs should be shifted to the evening on the day of the procedure.

In this study, there was no change in the timing of administration and the type of DOAC from 4 weeks before to 4 weeks after CA, including on the day of the procedure.

Table 5. Details of Patients With Complications

| Age (years) | Sex | Type of AF | Type of DOAC | Appropriate dose | Off-label underdosing | Procedure | Procedure timinga | CHA2-DSCVASc |
|-------------|-----|------------|--------------|------------------|-----------------------|-----------|-------------------|---------------|
| 85          | F   | PAF       | Apixaban     | 1                | 0                     | RFCA (PVI+CTI) | PM (9)            | 3             |
| 49          | M   | PeAF      | Edoxaban     | 1                | 0                     | RFCA (PVI+linear) | AM (2)           | 0             |
| 56          | F   | PeAF      | Rivaroxaban  | 0                | 1                     | RFCA (PVI+linear) | PM (8)           | 3             |
| 72          | M   | PeAF      | Edoxaban     | 0                | 1                     | RFCA (PVI+linear+CTI) | PM (6)        | 3             |
| 61          | M   | PAF       | Edoxaban     | 0                | 1                     | RFCA (PVI+CTI)  | PM (6)           | 2             |
| 57          | M   | PAF       | Edoxaban     | 1                | 0                     | RFCA (PVI)     | PM (6)           | 0             |
| 72          | M   | PAF       | Edoxaban     | 1                | 0                     | RFCA (PVI)     | AM (2)           | 4             |
| 59          | M   | PAF       | Edoxaban     | 1                | 0                     | RFCA (PVI+SVCI+CTI) | AM (2)      | 0             |
| 83          | F   | PAF       | Edoxaban     | 1                | 0                     | RFCA (PVI)     | PM (10)          | 7             |
| 73          | F   | PAF       | Rivaroxaban  | 1                | 0                     | Balloon ablation+CTI | AM (2)      | 2             |
| 81          | M   | PAF       | Edoxaban     | 1                | 0                     | RFCA (PVI)     | PM (7)           | 6             |
| 72          | M   | PAF       | Edoxaban     | 1                | 0                     | RFCA (PVI+CTI) | PM (6)           | 1             |
| 67          | F   | PAF       | Rivaroxaban  | 0                | 1                     | RFCA (PVI)     | PM (6)           | 3             |
| 71          | M   | PAF       | Rivaroxaban  | 1                | 0                     | RFCA (PVI+CTI) | AM (2)           | 1             |

Table 6. Multivariate Analysis of Predictors of Complications

|                          | P value |
|--------------------------|---------|
| Twice-daily dosing       | 0.0269  |
| Age >75 years            | 0.882   |
| Female sex               | 0.864   |
| Operator experience >5 years | 0.4     |
| AM procedure             | 0.92    |
| Appropriate dose         | 0.81    |
| Off-label underdosing    | 0.22    |
| Hypertension             | 0.125   |
| Diabetes                 | 0.787   |
| Previous stroke/TIA      | 0.696   |
| Antiplatelet therapy or alcohol consumption | 0.502 |
| Chronic kidney disease   | 0.664   |
| Balloon ablation         | 0.935   |

*The procedure-started timings are shown as AM (in the morning) or PM (afternoon), with the duration (h) between DOAC administration and the procedure. AF, atrial fibrillation; CI, cerebral infarction; CT, cardiac tamponade; CTI, cavotricuspid isthmus ablation; DOAC, direct oral anticoagulant; F, female; M, male; N, no; PVI, pulmonary vein isolation; RFCA, radiofrequency catheter ablation; SVCi, superior vena cava isolation; TIA, transient ischemic attack; Y, yes.
Specifically, all consecutive patients continued to take the same sort of DOAC they had been receiving in the morning (and evening in the case of twice-daily DOACs). There is a neutralizing antibody, idarucizumab, available for dabigatran, and it is highly effective in bleeding events, as shown by some studies. Therefore, the switch to dabigatran from other kinds of DOACs may be potentially safer. However, a change in the kind of DOAC during the perioperative period may increase the risk of human error, such as erroneous administration. Therefore, we did not change the kinds of DOACs or their administration.

Cardiac tamponade, a major life-threatening complication, has been evaluated as a representative bleeding event in previous uninterrupted DOAC with CA studies. In those studies, the frequency of cardiac tamponade under CA for AF with uninterrupted DOAC ranged from 0% (0/123) to 1.6% (1/64), with a mean of 0.66% (22/3,323). Currently, an incidence of cardiac tamponade of <1% seems to be acceptable during CA for AF. Considering the results of the previous studies and the complication rate of 0.98% (7/710, Table 4) in the present study, the uninterrupted use of DOACs without any change in the dosage regimen during CA for AF may be acceptable.

However, cardiac tamponade and bleeding events were significantly lower in the twice-than once-daily group (Table 3). Fortunately, all patients with these complications recovered without any aftereffects with appropriate treatment, including observation only, epicardial drainage, or cardiac surgery. Thus, we do not expect to prevent administration of once-daily DOACs in the morning on the day of CA for AF.

The mean age and the proportion of patients >75 years of age were higher in the apixaban group (Table 1). Age is one of the risk factors for cardiac tamponade during ablation. Bleeding complications were not increased in the apixaban group, suggesting the safety and effectiveness of uninterrupted apixaban. There were no complications, including bleeding events and ischemic events, in the dabigatran group. However, the frequency of balloon ablation in the dabigatran group was significantly higher than in the other groups. Balloon ablation can reduce cardiac tamponade compared with radiofrequency ablation; therefore, we cannot directly conclude that uninterrupted dabigatran is safe and effective, based on the findings of the present study.

The baseline CHA2DS2-VASc score differed between the once- and twice-daily groups because of the higher frequency of elderly patients and history of stroke in the latter group. However, bleeding complications were significantly less frequent in the twice-daily DOAC group. Moreover, even after multivariate analysis, once-daily DOAC use was an independent predictor of bleeding complications. Therefore, twice-daily DOAC may be safer than once-daily DOACs in the context of CA for AF.

The specific feature of blood concentrations may be one reason why the once-daily DOAC regimen was associated with a higher incidence of complications. There is a significant difference in blood concentrations between peak and baseline with once-daily DOACs. The high peak concentration of once-daily DOACs might be associated with the higher rate of complications.

Study Limitations

One limitation of this study is that it was a retrospective study. In addition, the subjects in this study were exclusively Japanese, and the dosage of DOACs in Japan differs compared with other countries. Therefore, randomized double-blind multicenter trials are required to prove whether there is a difference between the 4 DOACs in terms of their effectiveness and safety.

Conclusions

The uninterrupted use of DOACs without any changes in the dosage in patients undergoing CA for AF was acceptable. However, bleeding complications may be less frequent in the patients receiving twice-daily DOACs than in those receiving once-daily DOACs.

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IRB Information

This study was approved by the Institutional Review Board of The University of Tokyo (Reference no. 2659).

Data Availability

The deidentified participant data will not be shared.

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