Original Article

Results of Mechanical Thrombectomy 6 Hours after Stroke Onset: Analysis of Multiple Stroke Centers in Fukushima Prefecture

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Objective: The purpose of this study was to examine the efficacy and safety of mechanical thrombectomy in patients with acute occlusion of a large cerebral artery in the anterior circulation beyond 6 hours of the time last known to be well using the real-world clinical data collected from non-urban areas of Japan.

Methods: We analyzed a retrospective multicenter database collected at 10 thrombectomy capable primary stroke centers in Fukushima Prefecture. In all, 188 patients were presenting a large cerebral artery occlusion in the anterior circulation, that is, internal carotid and middle cerebral artery (M1 and M2 segment). In all, 158 patients received mechanical thrombectomy within 6 hours from symptom onset (early time window), and 30 patients exceeded 6 hours (late time window). We compared the patient background, outcomes, and safety variables between the two groups. The modified Rankin Scale (mRS) score of 0–2 at 90 days after treatment and the incidence of symptomatic intracranial hemorrhage were compared between groups to evaluate treatment efficacy and safety.

Results: There was no significant difference in the proportion of mRS score 0–2 at 90 days after treatment (51.3 vs. 46.7%: P = 0.644). However, symptomatic intracranial hemorrhage was more frequent in the late time window group (7.0 vs. 16.7%: P = 0.081). Symptomatic intracranial hemorrhage was a significant factor of a poor functional outcome in the late time window group (P = 0.022).

Conclusion: This study reflects the real-world results of mechanical thrombectomy in the non-urban areas of Japan. The treatment efficacy in the late time window patients was equivalent to that in the early time window patients. On the other hand, the incidence of symptomatic intracranial hemorrhage showed a trend to high in patients beyond 6 hours, which was a significant factor related to a poor functional outcome.

Introduction

Mechanical thrombectomy for patients with acute ischemic stroke caused by a large cerebral artery occlusion in the proximal anterior circulation within 6 hours of symptom onset has been proved its efficacy and safety in randomized controlled trials (RCTs) and meta-analyses.[1–5] Additional clinical trials demonstrated its effectiveness in

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selected patients using imaging-based criteria beyond 6 hours of the time last known to be well,[6,7] and was recommended in the 2018 Guidelines for the Early Management of Patients with Acute Ischemic Stroke (American Heart Association [AHA]/American Stroke Association [ASA] guideline 2018).[8] However, only a small number of studies based on real-world clinical practice have reported the results of mechanical thrombectomy in patients beyond 6 hours of the time last known to be well.[9–11]

Fukushima Prefecture is located at the south end of the Tohoku District, being within a 300-km distance from Tokyo. Its area is the third largest in Japan and divided into six medical administrative areas (set for regional health and medical care). According to the RESCUE Japan Project nationwide survey,[12] the number of mechanical thrombectomy sessions per 100,000 populations in Fukushima Prefecture was 8.20 in 2018. Still, each medical administrative area has a limited number of institutions responsible for this treatment.

The purpose of this study was to examine the efficacy and safety of mechanical thrombectomy in a large cerebral artery occlusion in the anterior circulation patients beyond 6 hours of the time last known to be well using the clinical data collected from non-urban areas of Japan.

Materials and Methods

This study was implemented at 10 mechanical thrombectomy capable primary stroke centers in Fukushima Prefecture. We retrospectively collected patients who met the following criteria—acute ischemic stroke patients age 18 years or older with an independent state before symptom onset. Patients who hospitalized within 24 hours of the time last known to be well and a large cerebral artery occlusion in the anterior circulation (internal carotid artery [ICA], M1/M2 middle carotid artery [MCA]) confirmed by CTA, MRA, or cerebral angiography. Patients with intraoperative stroke onset or recurrent acute cerebral artery occlusion were excluded. The medical records of each patient were reviewed to collect information, including baseline characteristics, imaging and procedural results, and clinical outcomes. The research protocol was approved by the Fukushima Medical University and each participating institutional ethics committee and written informed consent was waived because of the retrospective design.

Patients were divided into two groups according to the timing of treatment. For patients who started treatment within 6 hours were assigned as early time window (Group E),

and beyond 6 hours were assigned as late time window (Group L), respectively.

The treatment efficacy was evaluated using the post-treatment modified Thrombolysis in Cerebral Infarction (mTICI) grading and the modified Rankin Scale (mRS) score at 90 days after treatment. An mTICI 2b or 3 recanalization was regarded as effective recanalization, and an mRS score of 0–2 was defined as a good functional outcome. The treatment safety was evaluated with the presence of symptomatic intracranial hemorrhage and death within 90 days after treatment. Patients with at least 4-point deterioration of the National Institutes of Health Stroke Scale (NIHSS) score in comparison with neurological findings immediately before treatment, and the hemorrhage was related to the clinical deterioration were regarded as having a symptomatic intracranial hemorrhage. For the assessment of intracranial hemorrhage, the Heidelberg Bleeding Classification[13] was used. Class 1 refers to the hemorrhagic transformation of infarcted brain tissue. Class 1 is classified into three subclasses. Class 1a: scattered small petechiae without mass effect, Class 1b: confluent petechiae without mass effect, and Class 1c: hematoma within infarcted tissue occupying <30% without substantive mass effect. Class 2 refers to intracerebral hemorrhage occupying 30% or more of the infarcted tissue with obvious mass effect. Class 3 refers to intracerebral hemorrhage outside the infarcted brain tissue or intracranial-extracerebral hemorrhage. Class 3 is classified into four subclasses. Class 3a: parenchymal hematoma remote from infarcted brain tissue, Class 3b: intraventricular hemorrhage, Class 3c: subarachnoid hemorrhage, Class 3d: subdural hemorrhage.

A certified neuroendovascular physician in Japan performs mechanical thrombectomy. There were three ways of patients access to the treatment. Direct method was regarded as patient transfer directly to a mechanical thrombectomy capable primary stroke center. Transfer method was considered as a patient transfer to a mechanical thrombectomy capable primary stroke center from a local primary stroke center. Trip and Treat method transfer certified physicians to a local primary stroke center for mechanical thrombectomy.

Reperfusion therapy for acute ischemic stroke was performed following the Japanese guidelines.[14] CT and CTA were used for diagnostic imaging, and the Alberta Stroke Program Early CT Score (CT-ASPECTS) was calculated to assess the extent of ischemia. Some institutes preceded MRI, including diffusion-weighted imaging (DWI). In Group L, MRI was performed in addition to CT to evaluate
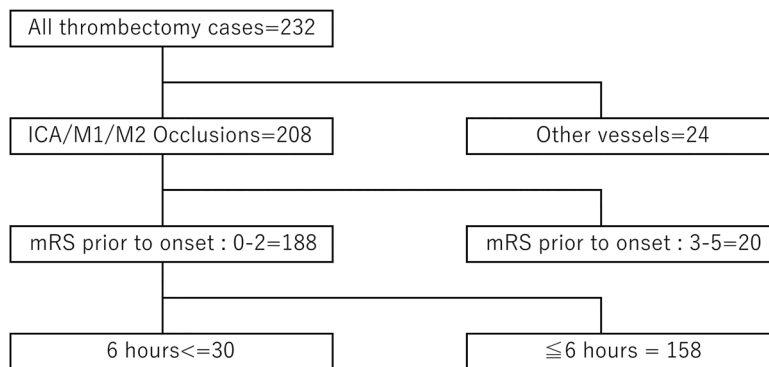
Fig. 1 The patient flowchart in the present study. ICA: internal carotid artery; M1: middle cerebral artery M1 segment; M2: middle cerebral artery M2 segment; mRS: modified Rankin Scale

a clinical-ASPECTS mismatch. Intravenous recombinant tissue plasminogen activator (IV-rtPA) was conducted on all patients for whom this therapy was indicated, and the dose approved in Japan (0.6 mg/kg) was used. There was no restriction for the selection of procedures and devices, depending upon local preference and experience. Both second-generation stent retrievers and catheter aspiration devices were used for mechanical thrombectomy.

SPSS Statistics version 26 (IBM, Armonk, NY, USA) software was used for statistical analysis. The Mann–Whitney U-test and Chi-square test were used to compare categorical variables. P value of <0.05 was regarded as statistically significant.

Results

We collected 232 patients who underwent mechanical thrombectomy between January 2016 and December 2018. Of these, we investigated 188 patients with anterior circulation occlusion. They were divided into two groups: 158 patients as Group E and 30 patients as Group L (**Fig. 1**). Baseline characteristics are summarized in **Table 1**. In Group L, the mean age was 79.3 ± 8.3 years, the median baseline NIHSS score was 15 (interquartile range: 9–19), and 27 patients (90.0%) were directly transferred to a mechanical thrombectomy capable primary stroke center. The median time from symptom onset to start of mechanical thrombectomy was 755 (interquartile range: 497–965) minutes. The location of occlusion was ICA for 7 patients (22.3%), M1 for 20 patients (66.7%), and M2 for 3 patients (10.0%). Significant differences in baseline characteristics between Group L and Group E were age (79.3 vs. 74.2 years), IV-rtPA treatment (3.3% vs. 63.9%), and symptom onset to start of mechanical thrombectomy (755 vs. 161

minutes). Baseline NIHSS showed a low tendency in Group L (15 vs. 18). Although there were no statistical significances, the rate of patients with an mRS score of 0 before symptom onset (76.7% vs. 65.8%) and an atherothrombotic stroke subtype (23.3% vs. 10.8%) were slightly high in Group L compared to Group E.

The results of the clinical outcomes are summarized in **Table 2**. There were no significant differences in the rate of patients achieving effective recanalization and that of patients with a good functional outcome 90 days after symptom onset. The incidence of symptomatic intracranial hemorrhage showed a higher tendency in Group L (16.7% vs. 7.0%).

We conducted a univariate analysis of variables related to a good functional outcome in Group L (**Table 3**). The incidence of symptomatic intracranial hemorrhage was a significant variable for a good functional outcome (0% vs. 31.3%, P = 0.022).

The detailed information on five patients with symptomatic intracranial hemorrhage in Group L is described in **Table 4**. The classification of bleeding events after ischemic stroke was evaluated as Class 1 in one patient, Class 2 in two, and Class 3 in two, according to the Heidelberg Bleeding Classification. In Case 1, petechiae (Heidelberg Class 1a) involving an infarcted area of the basal ganglia reached the internal capsule, presenting paralysis. In Cases 2 and 3, intracerebral hemorrhages were consistent with Heidelberg Class 2. In Case 3, carotid artery stenting was performed for the cervical ICA and MCA tandem occlusion, and antiplatelet therapy was started immediately after treatment, which may have caused an increase in hematoma size. In Case 4, subarachnoid hemorrhage localized in the Sylvian fissure was observed immediately after treatment due to the procedural-related injury of a perforating branch (Heidelberg Class 3a). Still, a hematoma serially

Table 1 Baseline characteristics and treatment

	≤6 hr	6 hr<	P value
N	158	30	
Age, mean (SD)	74.2 (11.8)	79.3 (8.3)	0.041
Female, (%)	68 (43)	15 (50)	0.481
Past history, no(%)			
Hypertension	91 (57.6)	20 (66.7)	0.354
Diabetes mellitus	27 (17.1)	8 (26.7)	0.217
Dyslipidemia	37 (23.4)	9 (30.0)	0.442
Smoking	41 (25.9)	7 (23.3)	0.763
Atrial fibrillation	76 (48.1)	17 (56.7)	0.390
Pre-onset antithrombotic therapy,no.(%)			
Antiplatelet agent	28 (17.7)	5 (16.7)	0.889
Anticoagulant agent	38 (24.1)	4 (13.3)	0.196
None	95 (60.1)	21 (70.0)	0.308
In-hospital stroke, no.(%)	23 (14.6)	3 (10)	0.507
Treatment modality,no.(%)			
Direct	118 (74.5)	27 (90)	
Transfer	12 (7.6)	2 (6.7)	0.124
Trip & Treat	28 (17.7)	1 (3.3)	
Pre-onset mRS, no.(%)			
0	104 (65.8)	23 (76.7)	
1	36 (22.8)	2 (6.7)	0.119
2	18 (11.4)	5 (16.7)	
NIHSS, median [IQR]	18 [13–21]	15 [9–19]	0.065
CT-ASPECTS, median [IQR]	9 [8–10]	9 [8–10]	0.903
Occlusion site,no.(%)			
ICA	57 (36)	7 (22.3)	
M1	76 (48)	20 (66.7)	0.176
M2	25 (16)	3 (10)	
Onset to puncture, min, median [IQR]	160.5 (115–202.5)	754.5 (497–965.25)	<0.01
Stroke cause, no.(%)			
Cardiogenic embolism	129 (81.6)	23 (76.7)	
Atheroscleorosis	17 (10.8)	7 (23.3)	0.140
Other	7 (4.4)	0	
Undetermined	5 (3.2)	0	
IV-rtPA,no. (%)	101 (63.9)	1 (3.3)	<0.001

CT-ASPECTS: CT-Alberta Stroke Program Early Computed Tomography Scores; ICA: internal carotid artery; IV-rtPA: intravenous thrombolysis recombinant tissue plasminogen activator; mRS: modified Rankin Scale; M1: 1st segment of the middle cerebral artery; M2: 2nd segment of the middle cerebral artery; NIHSS: National Institutes of Health Stroke Score

Table 2 Clinical outcomes

	≤6 hr	6 hr<	P value
N	158	30	
TICI,no. (%)			
2b≤	137 (86.7)	23 (76.7)	0.157
3	78 (49.4)	11 (36.7)	0.202
Good functional outcome,no.(%)	81 (51.3)	14 (46.7)	0.644
Cerebrovascular complications,no.(%)			
Intracranial hemorrhage	40 (25.3)	10 (33.3)	0.362
Symptomatic intracranial hemorrhage	11 (7.0)	5 (16.7)	0.081
Death at 90 days,no.(%)	21 (13.3)	2 (6.7)	0.310

TICI: Thrombolysis in Cerebral Infarction

Table 3 Comparison of demographic and clinical characteristics between a good functional outcome and a poor functional outcome group in late time window patients.

	Good outcome	Poor outcome	P value
N	14	16	
Age, mean (SD)	78.2 (9.3)	80.3 (7.6)	0.552
Female, no.(%)	7 (50.0)	8 (50.0)	1.000
Hypertention, no.(%)	10 (71.4)	10 (62.5)	0.605
Diabetes mellitus, no.(%)	8 (57.1)	9 (56.3)	0.961
Dyslipidemia, no.(%)	3 (21.4)	5 (31.3)	0.544
Smoking, no.(%)	3 (21.4)	6 (37.5)	0.338
Atrial fibrillation, no.(%)	4 (28.6)	3 (18.8)	0.526
Pre-onset antithrombotic therapy, no.(%)	3 (21.4)	6 (37.5)	0.338
NIHSS, median [IQR]	15 [7–17]	15.5 [10.5–20]	0.313
DWI-ASPECT, median [IQR]	7 [5.5–8.5]	7 [5.5–8.0]	0.833
Onset to puncture, min, median [IQR]	665 [494–890]	862 [579–968.5]	0.240
TICI 2b≤, no.(%)	10 (71.4)	12 (75)	0.825
TICI 3, no.(%)	6 (42.9)	5 (31.3)	0.510
Intracranial hemorrhage,no.(%)	3 (21.4)	7 (43.8)	0.196
Symptomatic intracranial hemorrhage,no.(%)	0 (0.0)	5 (31.3)	0.022

DWI-ASPECTS: DWI-Alberta Stroke Program Early Computed Tomography Scores; M1: middle cerebral artery M1 segment; M2: middle cerebral artery M2 segment; mRS: modified Rankin Scale; NIHSS: National Institutes of Health Stroke Score; TICI: Thrombolysis in Cerebral Infarction

increased in size, leading to an intracerebral hematoma connecting from the Sylvian fissure and causing consciousness disturbance. In Case 5, cerebral infarction occurred during conservative treatment for minor traumatic subarachnoid hemorrhage. There was no procedural-related complication but presented extensive subarachnoid hemorrhage (Heidelberg Class 3c) the day after mechanical thrombectomy. The possibility that traumatic subarachnoid hemorrhage increased in size was unable to be excluded, but bleeding may also have newly developed. All five patients presented a poor functional outcome at 90 days after symptom onset.

Discussion

In 2015, the results of RCTs demonstrated the efficacy of mechanical thrombectomy in patients with a large cerebral artery occlusion in the proximal anterior circulation within

Table 4 Summary of symptomatic intracranial hemorrhagic cases in late time window patients

Case	Age	Antithrombic therapy	mRS prior to onset	NIHSS	DWI-ASPECTS	Occlusion site	Onset to puncturte (min)	TICI	Heidelberg bleeding classification	mRS at 90 days
1	83	None	0	9	NA	M1	1227	3	1a	4
2	83	Antiplatelet	2	19	8	M2	864	2b	2	5
3	72	None	0	10	9	ICA	490	2b	2	5
4	82	DOAC	0	13	9	M1	498	3	3a	5
5	74	Warfarin	0	14	8	M1	779	2b	3c	6

DOAC: direct oral anticoagulants; DWI-ASPECTS: DWI-Alberta Stroke Program Early Computed Tomography Scores; ICA: internal carotid artery; M1: middle cerebral artery M1 segment; M2: middle cerebral artery M2 segment; mRS: modified Rankin Scale; NIHSS: National Institutes of Health Stroke Score; TICI: Thrombolysis in Cerebral Infarction

6 hours after symptom onset.[1–5] The Japanese Guidelines for the Management of Stroke 2015 and supplement version 2019 recommended this treatment as grade A,[14] and the number of treatment sessions has rapidly increased in Japan.[12] Several studies reported that mechanical thrombectomy was effective even in patients with occlusion at the M2 segment of the MCA,[15,16] those with posterior circulation occlusion,[17,18] mild-status patients,[19] and those with extensive ischemic changes.[20] In particular, two RCTs concerning patients with an interval beyond 6 hours of the time last known to be well were published in 2018. The DAWN trial demonstrated the efficacy of mechanical thrombectomy for acute ischemic stroke patients caused by an ICA or M1-MCA-occlusion with an interval of 6–24 hours from the time last known to be well and a mismatch between the clinical deficit and infarct volume (clinical-imaging mismatch).[6] A clinical imaging mismatch was defined according to the following criteria. (1) a score of 10 or higher on the NIHSS score and had an infarct volume of less than 21 ml (for patients 80 years of age or older), (2) a score of 10 or higher on the NIHSS score and had an infarct volume of less than 31 mL or a score of 20 or higher on the NIHSS score and had an infarct volume of 31 to less than 51 mL (for patients younger than 80 years of age). The DEFUSE 3 trial demonstrated the efficacy of mechanical thrombectomy for ICA or M1-MCA-occlusion with an interval of 6–16 hours from the time last known to be well and a target mismatch.[7] A target mismatch was defined according to the following criteria. (1) an initial infarct volume of less than 70 mL and (2) a ratio of the volume of ischemic tissue to initial infarct volume of 1.8 or more. In both trials, automated software processing of DWI-MRI or CT perfusion imaging (RAPID software, iSchemaView) measured estimates of the infarct and penumbra volume. Based on these results, the AHA/ASA guidelines 2018 recommended mechanical thrombectomy for patients beyond

6 hours of the time last known to be well if patients met the DAWN/DEFUSE 3 trial criteria.[8] The Japanese Guidelines for the Proper Use of Percutaneous Transluminal Cerebral Thrombus Retrieval Devices recommended mechanical thrombectomy as Grade A for patients with an interval of 6–16 hours from the time last known to be well.[21] The score of 10 or higher on the NIHSS score and an infarct volume of less than 25 mL were both required (corresponding to DWI-ASPECTS of 7 or higher[22]). In this research period, an automated software processing the infarct volume was not widely applied in Japan, so it was necessary to decide the indication of mechanical thrombectomy in individual patients by combining the DWI-ASPECTS threshold,[23] which is associated with the ischemic core volume, with clinical signs (NIHSS). We reviewed the indication of mechanical thrombectomy in individual patients using a Clinical-ASPECTS Mismatch. Clinical-ASPECTS Mismatch version 1 (CAM1) was defined according to the following criteria. (1) a score of 10 or higher on the NIHSS score and an ASPECTS of 8 or higher (for patients 80 years of age or older). (2) a score of 10 or higher on the NIHSS score and ASPECTS of 8 or higher (for patients younger than 80 years of age), (3) a score of 20 or higher on the NIHSS score and an ASPECTS of 6–8 (for patients younger than 80 years of age).[24] CAM1 reported having a case-selecting capacity similar to the clinical-imaging mismatch in the DAWN trial. In the present research, the NIHSS score 10 or higher in Group L was 22 patients. Of these, 17 patients (77.3%) met the CAM1 criteria, which represent proper patient selection.

The rates of patients with a favorable outcome 90 days after symptom onset were 49% in the DAWN trial and 45% in the DEFUSE 3 trial. Our result with late time window patients was 46.7%. In comparison with previous trials, the efficacy seems to be similar. There were no significant differences between groups for the proportion of an effective recanalization and a

good functional outcome 90 days after symptom onset. Although there was no significant difference, the percentage of patients with an mRS score of 0 before symptom onset was high, and the baseline NIHSS score was low in Group L. These findings suggested a selection bias of mild-stroke symptom patients with high-degree daily living independence before symptom onset. Also, the rate of patients with atherothrombotic stroke subtype was slightly higher. This stroke subtype may include patients with rich collateral pathway in comparison with the cardioembolic stroke subtype.

The incidence of symptomatic intracranial hemorrhage showed a trend toward high in Group L and was a significant factor for a poor functional outcome 90 days after symptom onset. Several predictive factors were reported for symptomatic intracranial hemorrhage after mechanical thrombectomy such as time of symptom onset to start of mechanical thrombectomy,[25,26] poor development of a collateral pathway,[26] extensive cerebral infarction with ASPECTS of less than 6,[26] numbers of procedures (three or more passes),[26] diabetes mellitus,[25] and atrial fibrillation.[25] Additional attention may be necessary, such as avoid multiple procedures and conduct mild postoperative antithrombotic therapy.

Previous observational research involving local participating institutions in the Tama district of Tokyo reported the efficacy of mechanical thrombectomy.[27] The Tama district has a population of 4300000 persons, and its area is 1160 km^2. There are 13 mechanical thrombectomy capable institutions. Transfer patients accounted for 19%, and there was no Trip and Treat patients. Of all patients, 94% were transported to institutions within 10 km away from the place of symptom onset. The effective recanalization rate was 78.8%, and the rate of patients with a good functional outcome 90 days after symptom onset was 39.6%. In our research, we investigated three medical administrative areas in Fukushima Prefecture. The population is 1140000 persons, and its area is 5900 km^2 (materials: census population, Ministry of Internal Affairs and Communications, October 1, 2015).[28] There are 10 institutions at which it was possible to accept acute ischemic stroke patients and perform mechanical thrombectomy. The northern and middle medical administrative areas involve core cities with a population of approximately 300000 persons (Fukushima City and Koriyama City). A rotational on-call system for patient acceptance is established in these areas (five institutes in the northern area and four institutes in the middle area). However, the Soso medical administrative area remains a single institution and responsible for an extensive medical area due to the influence of the Great East Japan earthquake. Certified neuroendovascular physicians belong to six institutions (three in the northern area, two in the middle area, and one in the Soso area). Of these institutions, more than two certified neuroendovascular physicians are employed only at two institutions. The population density is approximately 22 times lower than that in the Tama district. Consequently, the distance of patient transfer is long. Trip and Treat method was more common than Transfer method (29 patients, 15.4% vs. 14 patients, 7.4%). As the background, an angiography room is shared among several departments in most institutions, and acute ischemic stroke patients cannot always be housed under such an environment. Also, all institutions have an angiography room, and cerebral angiography can be performed by the local physician who is responsible for setting up the device, arterial puncture, and guiding-catheter placement.

We acknowledge that there are several limitations to this research. First, there were missing data regarding items collected, such as transfer distance, frequency of the procedure, and details of devices. Second, each institution was responsible for patient selection and treatment indication. Third, we compared our results with early time window patients because of the lack of a medical control arm. These are the weak points of a retrospective observational study.

Conclusion

We examined the efficacy and safety of mechanical thrombectomy in large cerebral artery occlusion in the anterior circulation patients beyond 6 hours of the time last known to be well using the clinical data collected from multiple primary stroke centers in Fukushima Prefecture. The results reflect the status of mechanical thrombectomy in the non-urban areas of Japan. The treatment efficacy in the late time window patients was equivalent to that in the early time window patients. On the other hand, the incidence of symptomatic intracranial hemorrhage showed a trend to high in patients beyond 6 hours, which was a significant factor related to a poor functional outcome.

Disclosure Statement

The authors declare no conflict of interest.

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