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Letter to the Editor

Hemorrhagic Complications Following Endovascular Treatment for Atherothrombotic Large Vessel Occlusion

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Dear Sir:

Approximately 15% of large vessel occlusions (LVOs) treated with endovascular treatment (EVT) are classified as atherothrombotic stroke-related LVOs (AT-LVOs), which encompass two underlying etiologies: tandem and intracranial atherosclerotic occlusions.[1] EVT for AT-LVOs commonly necessitates the intraoperative or early postoperative addition of antithrombotic drugs, even after thrombolytic therapy,[2] thereby increasing the risk of hemorrhagic complications. Herein, we investigated the differences in the incidence and characteristics of hemorrhagic complications following EVT for AT-LVOs according to etiology.

We conducted a *post hoc* analysis of the Recovery by Endovascular Salvage for Cerebral Ultra-acute Embolic and Athero-

Table 1. Comparison of patient characteristics between the tandem and intracranial groups

Characteristic	Total (n=635)	Tandem group (n=254)	Intracranial group (n=381)	*P*	N
Age (yr)	73.1±10.7	74.5±9.3	72.1±11.5	<0.01	635
Male sex	456 (71.8)	212 (83.4)	244 (64.0)	<0.01	635
mRS score before onset	0 (0–1)	0 (0–0)	0 (0–1)	0.29	634
mRS score before onset of 0–1	528 (83.3)	216 (85.0)	312 (82.1)	0.33	634
Body mass index (kg/m^2)	22.8±3.6	22.4±3.4	23.1±3.6	<0.01	634
Comorbidities					
Hypertension	407 (64.1)	166 (65.4)	241 (63.3)	0.59	635
Diabetes mellitus	194 (30.6)	86 (33.9)	108 (28.3)	0.14	635
Transient ischemic attack	5 (0.9)	2 (0.9)	3 (0.9)	0.99	554
Ischemic stroke	98 (15.4)	35 (13.8)	63 (16.5)	0.35	635
Cerebral hemorrhage	16 (2.5)	4 (1.6)	12 (3.2)	0.21	635
Coronary artery disease	55 (8.7)	31 (12.2)	24 (6.3)	0.01	635
Atrial fibrillation	29 (4.6)	12 (4.7)	17 (4.5)	0.88	635
Any smoking habit	365 (63.7)	171 (72.8)	194 (56.3)	<0.01	573
Dyslipidemia	193 (30.4)	87 (34.3)	106 (27.8)	0.08	635
Medications before admission					
Warfarin	14 (2.2)	7 (2.8)	7 (1.3)	0.19	628
DOACs	15 (2.4)	7 (2.8)	8 (2.1)	0.59	628
Antiplatelets	123 (19.6)	54 (21.6)	69 (18.0)	0.33	627
Dual antiplatelet therapy	17 (2.7)	10 (4.0)	7 (1.9)	0.11	627
Statin	122 (19.4)	63 (25.2)	59 (15.8)	<0.01	628
Systolic blood pressure (mm Hg)	160 (140–181)	160 (138–181)	161 (142–181)	0.38	621
Diastolic blood pressure (mm Hg)	87 (76–97)	85 (73–96)	88 (78–98)	0.01	618
NIHSS on admission	14 (8–19)	15 (10–21)	12 (7–18)	<0.01	626
ASPECTS on admission	8 (7–9)	7 (6–9)	8 (7–9)	<0.01	635
Laboratory values					
LDL cholesterol (mg/dL)	123±41	117±41	126±41	0.03	474
HDL cholesterol (mg/dL)	49±15	48±15	50±15	0.17	452
Glucose (mg/dL)	124 (108–156)	126 (110–153)	122 (107–157)	0.26	600
Creatinine (mg/dL)	0.82 (0.67–1.0)	0.86 (0.71–1.02)	0.81 (0.65–0.99)	0.01	626
CRP (mg/dL)	0.18 (0.08–0.72)	0.2 (0.08–0.83)	0.17 (0.08–0.66)	0.54	612
Hemoglobin (g/dL)	13.9 (12.7–15.2)	13.9 (12.4–15.1)	13.9 (12.7–15.4)	0.47	629
Intracranial occlusion site				<0.01	635
Intracranial ICA	150 (23.6)	76 (29.9)	74 (19.4)		
M1 segment of MCA	379 (59.7)	121 (47.6)	258 (67.7)		
M2 segment of MCA	106 (16.7)	57 (22.4)	449 (12.8)		
Involving cervical ICA occlusion	NA	149 (58.7)	NA	NA	254
Involving cervical ICA stenosis	NA	105 (41.3)	NA	NA	254
t-PA administration	198 (31.2)	89 (35.0)	109 (28.6)	0.09	635
Onset to door time (min)	155 (61–423)	133 (60–317)	179 (63–513)	0.06	576
Onset to puncture time (min)	264 (145–560)	227 (143–440)	300 (145–643)	<0.01	576
Intraoperative addition of antiplatelets	394 (62.0)	164 (64.6)	230 (60.3)	0.29	635

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Table 1. Continued

	Total (n=635)	Tandem group (n=254)	Intracranial group (n=381)	*P*	N
EVT procedures					
Carotid artery					
Stenting	NA	166 (65.3)	NA	NA	254
Thrombectomy	NA	22 (8.7)	NA	NA	254
Balloon angioplasty	NA	117 (46.1)	NA	NA	254
Intracranial artery					
Stenting	65 (10.2)	9 (3.5)	56 (14.7)	<0.01	635
Thrombectomy	474 (74.6)	207 (81.5)	267 (70.1)	<0.01	635
Balloon angioplasty	223 (35.1)	18 (7.1)	205 (53.8)	<0.01	635
Local intraarterial fibrinolysis	17 (2.7)	4 (1.6)	13 (3.4)	0.16	635
mTICI grade of 2b–3	542 (85.4)	236 (92.9)	306 (80.3)	<0.01	635
Puncture to recanalization time (min)	54 (33–92)	68 (45–105)	47 (30–76)	<0.01	635

Values are presented as mean±standard deviation, median (interquartile range), or n (%).
mRS, modified Rankin Scale; DOACs, direct oral anticoagulants; NIHSS, National Institutes of Health Stroke Scale; ASPECTS, Alberta Stroke Program Early CT Score; LDL, low density lipoprotein; HDL, high density lipoprotein; CRP, C-reactive protein; ICA, internal carotid artery; MCA, middle cerebral artery; t-PA, tissue plasminogen activator; EVT, endovascular treatment; mTICI, modified Thrombolysis in Cerebral Infarction.

thrombotic Stroke with Large Vessel Occlusion (RESCUE AT-LVO), that enrolled 783 patients who underwent EVT for AT-LVOs at 51 centers across Japan between January 2017 and December 2019.[3] AT-LVOs were defined as follows: (1) residual stenosis of ≥50% on final angiography during EVT, and (2) residual stenosis <50% with the appearance of a tapered sign and/or flow impairment during EVT.[4] We further included patients with anterior circulation AT-LVOs, excluding those with (1) a non-atherosclerotic etiology, (2) multiple acute infarctions in multiple vascular territories, and (3) an unknown onset time. According to the etiology of intracranial artery occlusion, patients with artery-to-artery embolism from tandem extracranial atherosclerosis were classified into the tandem group, while those with *in situ* occlusion of intracranial atherosclerosis were classified into the intracranial group. The primary outcome was any intracranial hemorrhage (ICH), while secondary outcomes included ICH subtypes, symptomatic ICH (a worsening of ≥4 on the National Institutes of Health Stroke Scale [NIHSS]),[5] decompressive craniectomy, and all-cause mortality within 90 days. ICH was assessed by brain computed tomography or magnetic resonance imaging 24±8 hours following EVT, and categorized into hemorrhagic infarction, parenchymal hematoma, and subarachnoid hemorrhage.[6] We further constructed Firth's bias-reduced logistic regression model to estimate the adjusted odds ratios (aORs) and 95% confidence intervals (CIs). Considering the substantial differences in patient backgrounds, we further calculated the propensity score and performed a comparison between the two groups using inverse probability of treatment weighting. Details of the statistical analyses are presented in the Supplementary Table 1.

We analyzed 635 patients (mean age, 73.1 yr; 72% male); of these, 254 (40%) were classified into the tandem group, of whom 166 (65%) underwent carotid stenting. Regarding treatment of the intracranial artery, thrombectomy was performed in 474 (75%) patients, while stenting was performed in 65 (10%) patients (Table 1). A comparison of the characteristics of the two groups is presented in Table 1. ICH after EVT was observed in 53 (8.3%) patients, with a significantly higher incidence in the tandem group compared to the intracranial group (11.8% vs. 6.0%, aOR, 1.94; 95% CI, 1.08–3.48) (Table 2). The distribution of hemorrhagic complications revealed significant differences between the two groups (Figure 1), with a higher proportion of parenchymal hematomas (6.3% vs. 0.8%, aOR, 6.71; 95% CI, 2.03–22.2) (Table 2). The tandem group had a higher incidence of symptomatic ICH (6.3% vs. 1.3%, aOR, 4.93; 95% CI, 1.80–13.6). There were no significant differences in the incidences of hemorrhagic infarction, subarachnoid hemorrhage, decompressive craniotomy, or all-cause mortality within 90 days (Table 2). Similar trends were observed in additional analyses (Supplementary Table 2).

The incidence of ICH following EVT for AT-LVOs has been reported in previous studies conducted in various settings. However, tandem and intracranial atherosclerotic occlusions have typically been discussed separately, while the differences in ICH between these two etiologies have not been studied. Our study is unique in that it examined the differences in the incidence and subtypes of hemorrhagic complications after EVT for AT-LVOs according to the two etiologies using a large-scale registry. There are several possible reasons for different types of ICH following

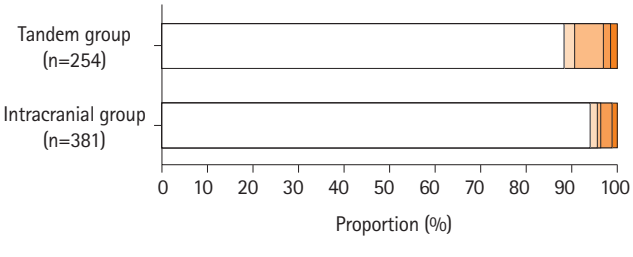
Table 2. Differences in type of ICH following endovascular treatment for AT-LVO

	Total (n=635)	Tandem group (n=254)	Intracranial group (n=381)	Crude OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*
ICH	53 (8.3)	30 (11.8)	23 (6.0)	2.08 (1.18–3.68)	0.01	1.94 (1.08–3.48)	0.03
Hemorrhagic infarction	12 (1.9)	6 (2.4)	6 (1.6)	1.51 (0.48–4.74)	0.48	1.07 (0.35–3.31)	0.91
Parenchymal hematoma	19 (3.0)	16 (6.3)	3 (0.8)	8.47 (2.44–29.4)	<0.01	6.71 (2.03–22.2)	<0.01
Subarachnoid hemorrhage	13 (2.1)	4 (1.6)	9 (2.4)	0.66 (0.20–2.17)	0.49	0.78 (0.24–2.51)	0.68
Symptomatic ICH	21 (3.3)	16 (6.3)	5 (1.3)	5.06 (1.83–14.0)	<0.01	4.93 (1.80–13.6)	<0.01
Decompressive craniotomy	5 (0.8)	4 (1.6)	1 (0.3)	6.08 (0.68–54.7)	0.07	5.17 (0.77–34.6)	0.09
All-cause mortality within 90 days	28 (4.4)	16 (6.3)	12 (3.2)	2.07 (0.96–4.45)	0.06	1.82 (0.82–4.05)	0.14

Values are presented as n (%) unless otherwise indicated. We constructed a Firth's bias-reduced logistic regression model to estimate the adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for the outcomes. The variables adjusted in the model were age, sex, and the occlusion site (ICA, M1, or M2), which were selected for consistency with biological plausibility and pre-existing knowledge.
OR, odds ratio; CI, confidence interval; ICH, intracranial hemorrhage; AT-LVO, atherothrombotic stroke-related large vessel occlusion.

EVT in patients with AT-LVOs. For example, patients in the intracranial group may have better collateral circulation at the distal site of the acute occlusion, facilitated by chronic atherosclerotic stenosis, compared to acute occlusion caused by an embolus, as demonstrated in a prior study.[6] This may mitigate ischemic damage, and consequently lower the risk of parenchymal hematoma formation that could become symptomatic. Indeed, the ASPECTS scores on admission tended to be higher in the intracranial group. Further, our results underscore the importance of managing ICH risk during EVT and recognizing differences based on the diagnosed etiologies, even within the same category of AT-LVOs. While there is currently no robust evidence suggesting that additional antiplatelet or thrombolytic therapies adversely affect outcomes after EVT for AT-LVOs, antithrombotic medications may be a concern for ICH. Our results indicate that strategies to reduce the risk of ICH, particularly in cases of tandem occlusion, may be important for improving the outcomes of patients with AT-LVOs. Indeed, a weighted analysis of a registry study of patients with tandem occlusion showed that patients who underwent carotid stenting had a higher incidence of any and symptomatic ICH than those who did not undergo stenting.[7] While considering the risk of re-occlusion, skipping stenting during emergent EVT or staged angioplasty to avoid hyperperfusion, which may lead to hemorrhagic complications,[8] could be a useful option.

This study had several limitations. Firstly, this multicenter registry study did not include eligibility criteria or a predefined protocol for EVT in AT-LVOs; as such, selection bias was unavoidable. Second, our analysis did not consider some potential confounding factors between post-EVT hemorrhage and AT-LVOs etiology, due to the small number of events. Several factors, such as the skill level of the operator, EVT procedures, collateral state or ischemic volume assessed on perfusion images, and changes in blood pressure during EVT, may all have influenced the occurrence of ICH. Third, the number of patients who developed ICH was relatively small; therefore, although we used what we considered to be the most appropriate analytical method, caution is required when interpreting the results. Finally, the findings from our registry may not be generalizable to other settings.



	No ICH	HI	PH	SAH	Other ICH	*P*
Tandem group (n=254)	224 (88)	6 (2.4)	16 (6.3)	4 (1.6)	4 (1.6)	0.002
Intracranial group (n=381)	358 (94)	6 (1.6)	3 (0.8)	9 (2.4)	5 (1.3)	

Figure 1. Intracranial hemorrhages following endovascular treatment for AT-LVO. AT-LVO, atherothrombotic stroke-related large vessel occlusion; ICH, intracranial hemorrhage; PH, parenchymal hematoma; HI, hemorrhagic infarction; SAH, subarachnoid hemorrhage.

In conclusion, the frequency and subtypes of ICH following EVT for AT-LVOs vary according to the underlying etiology. Perioperative management based on awareness of differences in ICH risk may be beneficial for further improving the outcomes of AT-LVOs.

Supplementary materials

Supplementary materials related to this article can be found online at https://doi.org/10.5853/jos.2024.01935.

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Conflicts of interest

The disclosures of conflicts of interest of all authors are provided in Appendix 1.

Author contribution

Conceptualization: SF, KU. Study design: SF, KU, TO, HY, KT (Kazunori Toyoda), KT (Kenichi Todo), FS, MS, SY, NS. Methodology: KU, SF. Data collection: all authors. Investigation: SF, KU. Statistical analysis: SF, KU. Writing—original draft: SF, KU. Writing—review & editing: SF, KU, TO, HY, KT (Kazunori Toyoda), KT (Kenichi Todo), KT (Kanta Tanaka), FS, MS. Approval of final manuscript: all authors.

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Supplementary Table 1. Comparison between propensity score-matched cohorts

Characteristics	Total (n=1,131)	Tandem group (n=574)	Intracranial group (n=557)	SMD	N
Age (yr)	72.3±16.0	71.8±18.3	72.7±14.2	0.06	1,131
Male sex	796 (70.4)	395 (68.8)	401 (72.0)	0.07	1,131
mRS score before onset	0.5±1.6	0.5±1.7	0.6±1.5	0.06	1,131
mRS score before onset of 0–1	957 (84.6)	493 (85.9)	464 (83.3)	0.08	1,131
Body mass index (kg/m^2)	22.7±5.1	22.6±5.7	22.8±4.6	0.04	1,131
Comorbidities					
Hypertension	742 (65.6)	386 (67.2)	357 (64.1)	0.06	1,131
Diabetes mellitus	350 (30.9)	187 (32.6)	163 (29.3)	0.08	1,131
Transient ischemic attack	8 (0.8)	3 (0.6)	5 (0.9)	0.04	1,006
Ischemic stroke	181 (16.0)	97 (16.9)	84 (15.1)	0.06	1,131
Cerebral hemorrhage	29 (2.6)	15 (2.6)	14 (2.6)	0.00	1,131
Coronary artery disease	91 (8.1)	45 (7.9)	46 (8.3)	0.02	1,131
Atrial fibrillation	38 (3.3)	18 (3.2)	20 (3.5)	0.02	1,131
Any smoking habit	758 (67.0)	388 (67.6)	371 (66.6)	0.02	1,131
Dyslipidemia	344 (30.4)	175 (30.5)	169 (30.3)	0.00	1,131
Medications before admission					
Warfarin	20 (1.8)	14 (2.4)	6 (1.0)	0.11	1,122
DOACs	24 (2.1)	13 (2.2)	11 (2.0)	0.01	1,122
Antiplatelets	214 (19.1)	108 (18.9)	105 (19.0)	0.00	1,122
Dual antiplatelet therapy	31 (2.7)	19 (3.3)	12 (2.2)	0.07	1,122
Statin	218 (19.4)	126 (22.1)	92 (16.6)	0.13	1,122
Systolic blood pressure (mm Hg)	161±40	159±48	162±34	0.07	1,120
Diastolic blood pressure (mm Hg)	87±26	86±32	89±21	0.11	920
NIHSS on admission	14±11	15±13	13±10	0.17	1,126
ASPECTS on admission	8±2.7	7±3.3	8±2.2	0.36	1,131
Laboratory values					
LDL cholesterol (mg/dL)	124±59	122±69	125±53	0.05	991
HDL cholesterol (mg/dL)	50±21	50±24	50±19	0.00	973
Glucose (mg/dL)	139±71	140±74	139±70	0.01	1,103
Creatinine (mg/dL)	0.89±0.8	0.88±1.0	0.94±1.0	0.06	1,122
CRP (mg/dL)	1.02±3.7	1.06±4.3	0.98±3.3	0.02	1,111
Hemoglobin (g/dL)	13.7±3.1	13.6±3.3	13.9±3.0	0.10	1,125
Intracranial occlusion site				0.28	1,128
Intracranial ICA	266 (23.6)	159 (27.7)	107 (19.3)		
M1 segment of MCA	658 (58.3)	284 (49.6)	375 (67.6)		
M2 segment of MCA	203 (18.0)	130 (22.7)	73 (13.2)		
Involving cervical ICA occlusion	NA	347 (60)	NA	NA	574
Involving cervical ICA stenosis	NA	227 (40)	NA	NA	574
t-PA administration	338 (30)	198 (35)	140 (25)	0.18	1,131
Onset to door time (min)	313±690	264±842	393±776	0.16	1,075
Onset to puncture time (min)	480±1,068	408±1,336	622±1,217	0.17	1,075
Intraoperative addition of antiplatelets	690 (61.2)	355 (61.9)	335 (60.1)	0.03	1,128

Supplementary Table 1. Continued

Characteristics	Total (n=1,131)	Tandem group (n=574)	Intracranial group (n=557)	SMD	N
EVT procedures					
Carotid artery					
Stenting	NA	368 (64.1)	NA	NA	574
Thrombectomy	NA	57 (9.9)	NA	NA	574
Balloon angioplasty	NA	258 (44.9)	NA	NA	574
Intracranial artery					
Stenting	95 (8.4)	17 (2.9)	78 (14.0)	0.56	1,131
Thrombectomy	868 (76.7)	484 (84.3)	384 (68.9)	0.12	1,131
Balloon angioplasty	328 (29.0)	31 (5.4)	297 (53.3)	0.57	1,131
Local intraarterial fibrinolysis	33 (2.9)	12 (2.0)	22 (3.9)	0.05	1,131
mTICI grade of 2b–3	977 (86.4)	524 (91.3)	453 (80.8)	0.07	1,131
Puncture to recanalization time (min)	70±71	80±85	60±57	0.28	1,131

Values are presented as mean±standard deviation or n (%).
mRS, modified Rankin Scale; DOACs, direct oral anticoagulants; NIHSS, National Institutes of Health Stroke Scale; ASPECTS, Alberta Stroke Program Early CT Score; CRP, C-reactive protein; ICA, intracarotid artery; MCA, middle cerebral artery; t-PA, tissue plasminogen activator; EVT, endovascular treatment; mTICI, modified Thrombolysis in Cerebral Infarction; SMD, standard mean difference.

Supplementary Table 2. Comparison of outcomes between propensity score-matched cohorts

Outcomes	Total (n=1,131)	Tandem group (n=574)	Intracranial group (n=557)	OR (95% CI)	*P*
ICH	104 (9.2)	69 (12.0)	35 (6.2)	2.07 (1.35–3.17)	<0.01
Hemorrhagic infarction	21 (1.9)	11 (2.0)	10 (1.8)	1.11 (0.47–2.14)	0.81
Parenchymal hematoma	36 (3.2)	29 (5.1)	7 (1.3)	4.08 (1.80–9.25)	<0.01
Subarachnoid hemorrhage	19 (1.7)	8 (1.4)	11 (2.0)	0.68 (0.28–1.70)	0.41
Symptomatic ICH	36 (3.2)	30 (5.2)	6 (1.1)	4.99 (2.07–12.0)	<0.01
Decompressive craniotomy	8 (0.7)	8 (1.3)	0 (0)	NA	<0.01
All-cause mortality within 90 days	44 (3.9)	31 (5.5)	13 (2.3)	2.49 (1.28–4.84)	<0.01

Values are presented as n (%) unless otherwise indicated. We constructed multivariable logistic regression models to calculate the propensity score with the following variables: age, sex, body mass index, history of coronary artery disease, smoking habit, dyslipidemia, cerebral infarction, and intracranial hemorrhage. Using the propensity score, patients in the Tandem and Intracranial groups were weighted by the Inverse Probability of Treatment Weighting method.
ICH, intracranial hemorrhage; OR, odds ratio; CI, confidence interval.

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Appendix 1. Disclosure of conflicts of interest

Drs. Fujiwara, Ohara, Kawamoto, Hayakawa, Ota, Morimoto, Tanaka, and Kakita declare no conflicts of interest.

Dr. Uchida reports receiving lecturer fees from Daiichi Sankyo, Bristol-Myers Squibb, Stryker, and Medtronic.

Dr. Ohta reports receiving lecturer fees from Medtronic, Daiichi-Sankyo, Johnson & Johnson, Terumo, Stryker Japan, Tokai Medical, Otsuka, Takeda, Eisai, Kaneka, Bristol-Myers Squibb, AstraZeneca, Japan Lifeline, Kowa, Nipro, Century Medical, and Idorsia, and a consulting fee from Johnson & Johnson and Tokai Medical outside the submitted work.

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Dr. Toyoda received lecture fees from Bayer, Daiichi Sankyo, Otsuka, Janssen, and Bristol Myers Squibb.

Dr. Matsumaru received lecture fees from Medtronic, Stryker, Terumo, Johnson, Johnson, Kaneka, and Jimro.

Dr. Matsumoto received lecturer fees from Kaneka, Medico's Hirata, Fuji Systems, GE Healthcare, Otsuka, Takeda, Century Medical, Terumo, Medtronic, and Stryker.

Dr. Todo received lecture fees from Pfizer, Bristol-Myers Squibb, and Daiichi Sankyo.

Bayer, Stryker, Medtronic, AstraZeneca, Otsuka Pharmaceutical, Kyowa Kirin, Takeda Pharmaceutical, and Amgen.

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Dr. Takeuchi received lecturer fees from Stryker, Daiichi Sankyo, Johnson, and Johnson.

Dr. Imamura reports lecturer fees from Medtronic, Daiichi Sankyo, Stryker, Terumo, Johnson & Johnson, and Asahi Intecc.

Dr. Ikeda received lecture fees from Medtronic, Daiichi Sankyo, and Terumo.

Dr. Ishihara received lecture fees from Daiichi Sakyo and Stryker.

Dr. Sano received lecture fees from Stryker.

Dr. Araki received lecture fees from Pfizer, Bristol-Myers Squibb, Daiichi Sankyo, Johnson & Johnson, Medico's Hirata, Asahi-Intec, and Medtronic.

Dr. Nomura has received lecture fees from Oben, Daiici Sankyo, Bayer, Wakamoto Seiyaku, Idorsia Pharma, Stryker, Medtronic, Kaneka, Johnson, and Johnson.

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Dr. Shirakawa received lecturer fees from Stryker, Medtronic, Terumo, Johnson, Johnson, and Kaneka.

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