Distinction in Prevalence of Atherosclerotic Embolic Sources in Cryptogenic Stroke With Cancer Status

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BACKGROUND: Cerebrovascular diseases are common comorbidities in patients with cancer. Although active cancer causes ischemic stroke by multiple pathological conditions, including thromboembolism attributable to Trousseau syndrome, the relationship between stroke and inactive cancer is poorly known. The aim of this study was to elucidate the different underlying pathogeneses of cryptogenic stroke in active and inactive patients with cancer, with detailed investigation by transesophageal echocardiography.

METHODS AND RESULTS: CHALLENGE ESUS/CS (Mechanisms of Embolic Stroke Clarified by Transesophageal Echocardiography for Embolic Stroke of Undetermined Source/Cryptogenic Stroke) registry is a multicenter registry including data of patients initially diagnosed as having cryptogenic stroke and undergoing transesophageal echocardiography. Patients were divided into active cancer, inactive cancer, and noncancer groups, and their clinical features were compared. Of the total 667 enrolled patients (age, 68.7±12.8 years; 455 men), 41 (6.1%) had active cancer, and 51 (7.5%) had a history of inactive cancer. On multinomial logistic regression analysis, infarctions in multiple vascular territories (odds ratio [OR], 2.73; 95% CI, 1.39–5.40) and CRP (C-reactive protein) (OR, 1.10; 95% CI, 1.01–1.19) were independently associated with active cancer, whereas age (OR, 1.05; 95% CI, 1.01–1.08), contralateral carotid stenosis from the index stroke lesion (OR, 4.05; 95% CI, 1.60–10.27), calcification of the aortic valve (OR, 2.10; 95% CI, 1.09–4.05), and complicated lesion of the aortic arch (OR, 2.13; 95% CI, 1.11–4.10) were significantly associated with inactive cancer.

CONCLUSIONS: Patients with cancer were not rare in cryptogenic stroke. Although patients with active cancer had more multiple infarctions, patients with inactive cancer had more atherosclerotic embolic sources potentially causing arteriogenic strokes.

REGISTRATION: URL: https://www.umin.ac.jp/ctr/; Unique identifier: UMIN000032957.
with cancer are definitely diverse. As examples, direct invasion of tumor cells, concurrent coagulopathy, coexisting and de novo atrial fibrillation, and atherosclerotic change could be possible culprits in patients with cancer-associated stroke. In particular, thromboembolism attributable to coagulopathy, called Trousseau syndrome, was regarded as a major component of ischemic stroke associated with active cancer. On the contrary, detailed investigation of transesophageal echocardiography elucidated that the patients with cryptogenic stroke with inactive cancer had more potential atherosclerotic embolic sources for their stroke.

What Are the Clinical Implications?
- Infarctions in multiple vascular territories of patients with active cancer might suggest the coexistence of intravascular coagulopathy regarded as Trousseau syndrome.
- Meanwhile, atherosclerosis of patients with inactive cancer could be partly related to antineoplastic treatment, such as chemotherapy and radiation.
- Differences in mechanisms identified in patients with active compared with inactive cancer may result in different secondary stroke prevention strategies in individual patients.

Nonstandard Abbreviations and Acronyms

| ACL  | aortic complicated lesion |
|------|---------------------------|
| CS   | cryptogenic stroke        |
| ESUS | embolic stroke of undetermined source |
| TEE  | transesophageal echocardiography |

In addition, a pragmatic concept of CS, embolic stroke of undetermined source (ESUS), which also includes covert nonbacterial thrombotic endocarditis and tumor emboli from occult cancer as essential possible embolic sources of CS, has been advocated. During multidisciplinary antineoplastic treatment have increased the survival rate of patients with cancer, cardiovascular death among cancer survivors has increased. Thus, it is an urgent priority to elucidate the pathophysiological features of stroke associated with not only active, but also inactive, cancers in the era of cancer survivors.

In the present study, a multicenter registry with a comprehensive database of patients initially classified as having CS and undergoing transesophageal echocardiography (TEE) to elucidate their latent embolic causes was created. Using this multicenter TEE registry, the aim of this study was to clarify the frequency and clinical features of patients with active and inactive cancer with CS. In addition, the latent pathological differences, especially in embolic origins, were investigated in patients with CS with active and inactive cancers.

METHODS
The data sets used and analyzed during the current study are available from the corresponding author on reasonable request.

Study Population
The CHALLENGE ESUS/CS (Mechanisms of Embolic Stroke Clarified by Transesophageal Echocardiography for Embolic Stroke of Undetermined Source/Cryptogenic Stroke) registry,
a retrospective, multicenter registry enrolling consecutive patients originally diagnosed as having CS and undergoing TEE in 8 hospitals in Japan between April 2014 and December 2016, was constructed. Inclusion criteria for this registry were as follows: (1) within 7 days of stroke onset; (2) nonlacunar stroke on neuroradiological imaging; (3) absence of arterial stenosis ≥50% or occlusion in a corresponding large artery; (4) absence of major embolic cardiac diseases; and (5) absence of other determined stroke causes. As exclusion criteria, the diagnostic criteria of ESUS recommended cardiac monitoring for >24 hours; therefore, atrial fibrillation that was detected at <24 hours after admission was excluded from the CHALLENGE ESUS/CS registry. Institutional review boards in all 8 participating centers approved the protocol. Clinical information was obtained from medical records, and the need to obtain written, informed consent from each patient was therefore waived in this retrospective study. The present study was registered at http://www.umin.ac.jp/ctr/ (UMIN000032957).

**TEE Study**

Subjects were awake and had fasted for at least 4 hours before TEE. Lidocaine spray was given, but no premedication was given. To investigate the heart and aortic arch, a multiplane probe was manipulated to provide appropriate views, including axial and sagittal images. An atrial septal aneurysm was diagnosed when the atrial septum extended into the left or right atrium, or both. The presence of a right-to-left shunt was assessed by injecting agitated saline and making subjects perform the Valsalva maneuver, and then the numbers of microbubbles with and without contrast agent were compared. The number of microbubbles passing from the right atrium to the left atrium was also counted. A patent foramen ovale was diagnosed when microbubbles were visualized in the left atrium within 3 cardiac cycles after the Valsalva maneuver. A pulmonary arteriovenous fistula was diagnosed when microbubbles were visualized in the left atrium >3 cardiac cycles after the Valsalva maneuver or when microbubbles were visualized without the Valsalva maneuver. Plaque thickness ≥4 mm, mobile plaque seen swinging on their peduncle, or ulcerative plaque with width and maximum depth of at least 2 mm each was defined as aortic complicated lesion (ACL). Examinations were performed by 2 or 3 experienced sonographers in each facility.

**Magnetic Resonance Imaging Sequences**

Magnetic resonance imaging scans were performed at each institution on 1.5- or 3-T scanners during hospitalization. Sequences included axial diffusion-weighted imaging, fluid-attenuated inversion recovery imaging, magnetic resonance angiography, and the gradient-recalled echo (GRE) T2* sequence. Diffusion-weighted imaging (repetition time/echo time=3000–8000/60–91 ms) was used to assess the size and distribution of the index stroke lesion. A large infarct was defined as >3 cm in diameter. The distribution of the index lesions was divided into single and multiple vascular territories among bilateral anterior, middle, and posterior cerebral arteries, and cortical and subcortical lesions. Fluid-attenuated inversion recovery imaging (repetition time/echo time=9000–12 000/94–120 ms) was used to evaluate the degree of deep and subcortical white matter hyperintensity and periventricular hyperintensity and classified as Fazekas grades 0 to 3. Magnetic resonance angiography (repetition time/echo time=19–37/2.8–7.5 ms) was used to detect intracranial stenosis >50%, principally not relevant to the infarction area. GRE T2* (repetition time/echo time=410–740/12–20 ms) was used to identify cerebral microbleeds, defined as a rounded area of signal loss with diameter <10 mm. The size and distribution of stroke lesions, the degree of deep and subcortical white matter hyperintensity and periventricular hyperintensity, the existence of intracranial stenosis, and the presence of cerebral microbleeds were all assessed by several experienced neurologists in each institution.

**Data Collection and Analyses**

Baseline clinical information, including cardiovascular risk factors, history and status of cancer, laboratory and radiological data on admission, echocardiographic findings, and clinical course on admission, was collected by hospital chart or database reviews during the study period from May 2017 to July 2019. The definitions of cardiovascular risk factors were described in our previous work. Covert atrial fibrillation >24 hours after admission was detected by continuous cardiac monitoring, 24-hour Holter electrocardiography, or, infrequently, an insertable cardiac monitor. Baseline characteristics, radiological and laboratory data, echocardiographic findings, including potential embolic diseases, and clinical courses were compared by cancer status (none, active, or inactive).

On the basis of previous studies, active cancer was defined as cancer diagnosed or under treatment within 6 months before index stroke onset or detected on imaging examination and newly diagnosed during hospitalization. On the other hand, inactive cancer was defined as cancer treated within >6 months before stroke onset, and remission or complete recovery was confirmed at the time of admission without any evidence of active cancer on imaging investigation during the hospital stay.
**Statistical Analysis**

Numerical values are reported as means±SD or medians with interquartile range. Data were analyzed using the Kruskal-Wallis test for nonparametric analyses and the χ² test and Fisher exact test for categorical variables, as appropriate. All variables related to baseline clinical characteristics and imaging and laboratory data with values of P<0.05 on univariate analyses were entered into multinomial logistic regression analyses to identify independent variables related to the pathophysiological status of cancer. A 2-sided probability value of P<0.05 was considered significant. All data were analyzed using SPSS for Macintosh version 26.0 software (SPSS, Chicago, IL).

**RESULTS**

A total of 677 patients initially classified as having CS were enrolled in the present study. Their mean age was 68.7±12.8 years, and 455 men were

| Table 1. Baseline Characteristics, Cardiovascular Risks, MRI and TEE Findings, and Laboratory Data of Patients With Active and Inactive Cancers |
|---------------------------------------------------------------|
| **Variable** | **Noncancer group (n=585; 86.4%)** | **Active cancer group (n=41; 6.1%)** | **Inactive cancer group (n=51; 7.5%)** | **P value** |
| Age, y | 68.0±13.0 | 70.7±11.1 | 75.7±6.6 | <0.001 |
| Men | 391 (66.8) | 24 (58.5) | 40 (78.4) | 0.114 |
| Premorbid mRS score 0–2 | 553 (94.5) | 41 (100.0) | 46 (90.2) | 0.100 |
| Hypertension | 417 (71.3) | 28 (68.3) | 39 (76.5) | 0.857 |
| Diabetes | 146 (25.0) | 12 (29.3) | 14 (27.5) | 0.780 |
| Dyslipidemia | 295 (50.4) | 19 (46.3) | 31 (60.8) | 0.303 |
| CKD | 221 (37.8) | 12 (29.3) | 19 (37.3) | 0.552 |
| Ischemic heart disease | 61 (10.4) | 2 (4.9) | 5 (9.8) | 0.520 |
| Previous stroke | 104 (17.8) | 7 (17.1) | 12 (23.5) | 0.583 |
| History of smoking | 288 (49.2) | 18 (43.9) | 31 (60.8) | 0.211 |
| Prior antiplatelet agents | 149 (25.5) | 5 (12.2) | 14 (27.5) | 0.148 |
| Prior anticoagulants | 14 (2.4) | 3 (7.3) | 0 (0.0) | 0.102 |
| NIHSS score on admission | 2 (1–5) | 3 (2–4.5) | 3 (1–7) | 0.115 |
| DWI lesion size >3 cm* | 172 (29.6) | 15 (36.6) | 14 (28.6) | 0.622 |
| Cortical infarction* | 460 (79.0) | 36 (87.8) | 43 (87.8) | 0.153 |
| Infarctions in multiple vascular territories* | 145 (24.9) | 21 (51.2) | 15 (30.6) | 0.001 |
| DSWMH* | 198 (34.0) | 17 (41.5) | 13 (26.5) | 0.327 |
| PVH* | 208 (35.7) | 17 (41.5) | 24 (49.0) | 0.152 |
| CMBs* | 181 (31.7) | 10 (24.4) | 18 (36.7) | 0.453 |
| Intracranial artery stenosis* | 61 (10.5) | 5 (12.2) | 6 (12.2) | 0.884 |
| Contrast carotid artery stenosis | 23 (3.9) | 2 (4.9) | 8 (15.7) | 0.004 |
| Right-to-left shunt† | 270 (47.8) | 23 (56.1) | 19 (39.6) | 0.297 |
| ACL in the aortic arch§ | 207 (35.5) | 14 (34.1) | 33 (64.7) | <0.001 |
| Covert atrial fibrillation | 58 (9.9) | 1 (2.4) | 5 (9.8) | 0.304 |
| Calcification of aortic valve† | 122 (21.0) | 7 (17.1) | 24 (47.1) | <0.001 |
| Calcification of mitral valve‖ | 57 (10.6) | 5 (13.5) | 7 (14.6) | 0.618 |
| WBC count, /µL | 727±2683 | 748±2876 | 719±2717 | 0.874 |
| CRP, mg/dL* | 0.61±2.33 | 1.83±2.72 | 0.60±1.45 | <0.001 |
| D-dimer, µg/mL | 2.47±16.5 | 11.4±20.9 | 2.22±2.64 | <0.001 |

Data are presented as number (percentage), mean±SD, or median (interquartile range). ACL indicates aortic complicated lesion; CKD, chronic kidney disease; CMB, cerebral microbleed; CRP, C-reactive protein; DSWMH, deep and subcortical white matter hyperintensity; DWI, diffusion-weighted imaging; MRI, magnetic resonance imaging; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; PVH, periventricular hyperintensity; TEE, transesophageal echocardiography; and WBC, white blood cell.

* n=5 missing values.
† n=16 missing values.
‡ n=23 missing values.
§ n=2 missing values.
– n=3 missing values.
‖ n=53 missing values.
¶ n=47 missing values.
enrolled. TEE showed that 254 (37.6%) patients had ACL in the aortic arch, 312 (47.7%) had a right-to-left shunt, and 153 (22.7%) had aortic valve calcification, whereas only 2 patients had nonbacterial thrombotic endocarditis. Of the 677 patients with CS, 41 (6.1%) had active cancer, and 51 (7.5%) had a history of inactive cancer.

Cancer Status and Baseline Characteristics, Including Potential Embolic Sources

Baseline characteristics of the 3 groups according to cancer status are shown in Table 1. Whereas the inactive cancer group was the oldest of the 3 groups (noncancer versus active cancer versus inactive cancer, 68.0±13.0 versus 70.7±11.1 versus 75.7±8.6 years; \( P<0.001 \)), other clinical patient background characteristics, including cardiovascular risk factors, were not significantly different among the 3 groups.

As for the imaging examinations, brain magnetic resonance imaging showed that multiple lesions in multiple vascular territories were the most frequent in the active cancer group compared with the other 2 groups (noncancer versus active cancer versus inactive cancer, 24.9% versus 51.2% versus 30.6%; \( P=0.001 \)). Carotid duplex ultrasonography showed that contralateral carotid stenosis from the index stroke lesion was the most common in the inactive cancer group (noncancer versus active cancer versus inactive cancer, 3.9% versus 4.9% versus 15.7%; \( P=0.004 \)) compared with the other 2 groups. In addition, on TEE, ACL in the aortic arch (noncancer versus active cancer versus inactive cancer, 35.5% versus 34.1% versus 64.7%; \( P<0.001 \)) and calcification of the aortic valve (noncancer versus active cancer versus inactive cancer, 21.0% versus 17.1% versus 47.1%; \( P<0.001 \)) were the most frequent in the inactive cancer group.

Laboratory examinations showed that CRP (C-reactive protein) (noncancer versus active cancer versus inactive cancer, 0.61±2.33 versus 1.83±2.72 versus 0.60±1.45 mg/dL; \( P<0.001 \)) and D-dimer (noncancer versus active cancer versus inactive cancer, 2.47±16.5 versus 11.4±20.9 versus 2.22±2.64 mg/dL; \( P<0.001 \)) were the highest in the active cancer group.

On multinomial logistic regression analysis, multiple lesions in multiple vascular territories (odds ratio [OR], 2.73; 95% CI, 1.39–5.40) and CRP (OR, 1.10; 95% CI, 1.01–1.19) were independently associated with active cancer. Age (OR, 1.05; 95% CI, 1.01–1.08), contralateral carotid stenosis (OR, 4.05; 95% CI, 1.60–10.27), ACLs in the arch (OR, 2.13; 95% CI, 1.11–4.10), and calcification of the aortic valve (OR, 2.10; 95% CI, 1.09–4.05) were significantly associated with inactive cancer (Table 2).

Therapy and Clinical Course After Admission

The treatment and prognosis of the 3 groups according to cancer status are presented in Table 3. As secondary prevention, antiplatelet therapy was the least frequent (noncancer versus active cancer versus inactive cancer, 70.1% versus 43.9% versus 76.5%; \( P=0.001 \)), whereas anticoagulant therapy was the most common (noncancer versus active cancer versus inactive cancer, 33.0% versus 56.1% versus 27.5%; \( P=0.006 \)), in the active cancer group. In addition, 2 patients with active cancer died during their hospital stays (noncancer versus active cancer versus inactive cancer, 0% versus 4.9% versus 0%; \( P=0.004 \)).

Primary Lesion, Histological Type, Clinical Stage, and Treatment of Active and Inactive Cancers

First, primary lesions of active and inactive cancers are shown in Figure 1. In both active and inactive cancers, lung cancer was the most prevalent cancer. Prostate cancer was more frequent in the active cancer group, whereas bladder cancer was more common in the

| Variable | Active cancer vs none | Inactive cancer vs none |
|----------|-----------------------|-------------------------|
| OR       | 95% CI                | \( P \) value           |
| Age (per 1 y) | 1.03 | 1.00–1.06 | 0.067 |
| Infarctions in multiple vascular territories | 2.73 | 1.39–5.40 | 0.004 |
| Contralateral carotid artery stenosis | 0.97 | 0.21–4.41 | 0.966 |
| ACL in the aortic arch | 0.84 | 0.41–1.73 | 0.643 |
| Calcification of aortic valve | 0.65 | 0.27–1.59 | 0.347 |
| CRP | 1.10 | 1.01–1.19 | 0.029 |
| D-dimer | 1.01 | 0.99–1.02 | 0.354 |

ACL indicates aortic complicated lesion; CRP, C-reactive protein; and OR, odds ratio.
inactive cancer group. One patient in the active cancer group and 5 patients in the inactive cancer group had double cancers.

Information on cancer histological type and clinical stage were available in 15 (37%) and 20 (49%) cases in the active cancer group, respectively, and 14 (27%) and 10 (20%) cases in the inactive cancer group, respectively (Figure 2). Compared with inactive cancers, adenocarcinoma tended to be more frequent in active cancers. For clinical stage, active cancers were in a more advanced stage, whereas inactive cancers were in an earlier stage. Treatment histories, such as surgery, chemotherapy, and radiotherapy, were available for 28 (68%), 28 (68%), and 23 (56%) patients with active cancer, respectively, and 40 (78%), 17 (33%), and 17 (33%) patients with inactive cancer, respectively (Figure 2).

**DISCUSSION**

In the present study, the CHALLENGE ESUS/CS registry showed that 6.1% of patients originally diagnosed as having CS had comorbid active cancer, and 7.5% had a history of inactive cancer. Compared with patients with CS who did not have cancer, patients with comorbid active cancer had more infarctions in multiple vascular territories, whereas patients with a history of inactive cancer had more atherosclerotic embolic sources causing arteriogenic strokes.

![Figure 1. Primary lesions of active and inactive cancers.](image)
The numbers of patients for each primary lesion of active and inactive cancers are presented.
Previous studies suggested that ≈4% to 12% of patients with ischemic stroke have comorbid active cancer.\textsuperscript{15,20} In particular, the frequency of active cancer in CS was more common, but ranged from 8% to 47%.\textsuperscript{15,20,21} Because the present registry enrolled patients with CS who underwent TEE, a semi-invasive and avoidable examination for cancers involving the gastrointestinal tract, those patients in this study were presumed to be small in number. Some studies reported that the ischemic stroke of patients with active cancer presented with multiple infarctions in multiple vascular territories.\textsuperscript{4,22} Moreover, this imaging feature was associated with recurrence of stroke,\textsuperscript{23} together with elevation of D-dimer levels,\textsuperscript{3,4,15} CRP,\textsuperscript{24} and several tumor markers of adenocarcinoma.\textsuperscript{25} In the present study as well, the presence of infarctions in multiple vascular territories and elevation of CRP were independently associated with active cancer. Although arteriogenic embolism, especially in strokes attributable to emboli from complex aortic plaque, showed multiple infarctions,\textsuperscript{26} the present data indicated that infarction in multiple vascular territories was more closely related to active cancer-associated stroke, which was well concordant with the concept of Trousseau syndrome.\textsuperscript{9,22,24} D-dimer levels in the present study were not independently associated with active cancer, contrary to previous reports, because the subjects of the present study were limited to patients with CS who had relatively high average D-dimer levels related to a variety of potential embolic mechanisms.

This study had another notable finding, that a history of inactive cancer was significantly related to some atherosclerotic embolic sources, such as contralateral carotid stenosis, ACL in the aortic arch, and aortic valve calcification. It was shown that these pathologic processes coexisted in CS or ESUS,\textsuperscript{27,28} and not only ACL in the arch, but aortic valve calcification was regarded as a substantial embolic source of ESUS and CS.\textsuperscript{14} As for atherosclerotic burden in cancer, autopsy studies in the 1950s suggested that atherosclerotic changes were rather inconspicuous in patients with cancer.\textsuperscript{29,30} Although recent progress in treatment has increased the survival rate of patients with cancer, cardiovascular death has instead increased among them.\textsuperscript{12,13} Not only mutual physiological factors, such as chronic inflammation and oxidative stress,\textsuperscript{6,31} but recent advances of treatments themselves could accelerate the atherosclerotic burden in patients with cancer.\textsuperscript{1,12,13} In particular, chemotherapy induces endothelial dysfunction, thrombophilia, and alteration of mitochondrial metabolism, whereas radiotherapy evokes degeneration and persistent inflammation in vascular endothelium, which last for years and arise over time.\textsuperscript{12} Thus, it is possible that atherosclerotic embolic sources in some of the patients with stroke who have inactive cancer are related to past treatment for their malignancy.

**Figure 2.** Histological type, clinical stage, and treatment for active and inactive cancers. The proportions of patients by histological type, clinical stage, and treatment details (surgery, chemotherapy, and radiation) of active and inactive cancers are presented.
Although the follow-up data were limited to the acute stage hospitalization in the present study, recurrence rates of stroke in patients with active cancer and childhood cancer survivors were generally high.\textsuperscript{15,32,33} Consequently, it is crucial to elucidate exact embolic sources and pathological features of patients with stroke with active and inactive cancers for the purpose of providing optimal secondary prevention. Antiplatelets are typically used for secondary stroke prevention after stroke attributable to atheroembolism. The optimal treatment for cancer-associated embolic stroke affecting multiple vascular territories is not clear, although previous studies have demonstrated the effectiveness of anticoagulation cancer-associated venous thromboembolism.\textsuperscript{19,34,35} Thus, it could be a beneficial implication for medical management to investigate and understand the mechanism of stroke in patients with active and inactive cancer.

There were some limitations to this study. First, this study was retrospective, which might have affected the accuracy of CS diagnosis; the methods to detect covert atrial fibrillation during hospitalization, the protocols for TEE and magnetic resonance imaging, and the interpretation of these findings differed by institute; and there was a lack of standardization. Furthermore, evaluation of intraobserver and interobserver reliabilities was not performed in the current multicenter study. Second, there was a selection bias to perform TEE, a semi-invasive and avoidable examination. In particular, we had no data for the proportion of patients who originally met the criteria of CS but could not undergo TEE in each institution. Third, for the presence and history of cancers, the interpretations of medical records depended on each institution’s board, and detailed information of cancer was limited in the present multicenter stroke registry. Regrettably, there was little specific information on the details and periods of chemoradiation therapy for cancers. Last, the follow-up period, limited to the acute stage of hospitalization, was not sufficient to estimate the prognosis of this population with CS. The most important mission of this registry will be to gather longer follow-up data.

CONCLUSIONS

Active and inactive cancers in patients who were originally classified as having CS in the CHALLENGE ESUS/CS registry were not rare, and all patients who underwent TEE had genuinely diverse embolic sources. In the present study, patients with comorbid active cancer had more infarctions in multiple vascular territories, whereas patients with a history of inactive cancer had more atherosclerotic embolic sources potentially causing arteriogenic strokes.

APPENDIX

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Received April 21, 2021; accepted September 7, 2021.

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Sources of Funding

None.

Disclosures

Dr Ueno received personal fees from OHARA Pharmaceutical Co, Ltd, and grants from Bristol-Myers Squibb, outside the submitted work. Dr Takakawa received grants from Pfizer Japan Inc and Daiichi Sankyo Co, Ltd, outside the submitted work. MK received honoraria from Bayer and Daiichi Sankyo; consultant fee from Ono Pharmaceutical Co, LTD; and research funds from Takeda, Daiichi Sankyo, Nippon Boeringer Ingelheim, Astellas, and Shinongi. Dr Kamiya received personal fees from Daiichi Sankyo Co Ltd and grants from Bristol-Myers Squibb Co Ltd and Nippon Boeringer Ingelheim Co Ltd, outside the submitted work. Dr Hara received grants from Shimadzu Corporation, Otsuka Pharmaceutical, and Panasonic Corporation, and personal fees from Daiichi Sankyo Co, Ltd, Eisai Co Ltd, and Bayer Pharmaceutical Co, outside the submitted work. Dr Hirata received personal fees from MSD Co, Ltd, Eisai Co Ltd, Otsuka Pharmaceutical Co, Ltd, Takeda Pharmaceutical Co, Ltd, Pfizer Japan Inc, Novartis Pharma K.K., AbbVie GK, Kyowa Hakko-Kirin Co, Eli Lilly Japan K.K., Argen K.K., Lundbeck Japan K.K., and grants from Eisai Co, Ltd, Pfizer Japan Inc, Novartis Pharma K.K., Takeda Pharmaceutical Co, Ltd, TaiYO Co, Ltd, Kyowa Minami Hospital, Shirasawa Hospital, Shiobara Onsen Hospital, Utsunomiya Chuo Hospital, Nishikata Hospital, and Moka Hospital, outside the submitted work. Dr Hasagawa received personal fees from Bayer Pharmaceutical Co and Nippon Boeringer Ingelheim, Co, Ltd, during the conduct of the study. Dr Hattori was an advisory member of Dai-Nippon Sumitomo Pharma Co, Ltd, Hisamitsu Pharmaceutical Co, Inc, Biogen Idec Japan Ltd, received lecture fees from Dai-Nippon Sumitomo Pharma Co, Ltd, Otsuka Pharmaceutical, Co, Ltd, Takeda Pharmaceutical Co, Ltd, Kyowa Hakko-Kirin Co, Ltd, FP Pharmaceutical Corporation, Eisai Co, Ltd, Novartis Pharma K.K., and AbbVie, and received departmental endowments by commercial entities from Kyowa Hakko-Kirin Co, Ltd, Nippon Boeringer Ingelheim, Co, Ltd, AbbVie GK, FP Pharmaceutical Corporation, Otsuka Pharmaceutical, Co, Ltd, Dai-Nippon Sumitomo Pharma Co, Ltd, Eisai Co, Ltd, Nihon Medi-physics Co, Ltd, Asahi Kasei Medical Co, Ltd, Ono Pharmaceutical Co, Ltd, Miz Co, Ltd, AbbVie GK, OHARA Pharmaceutical Co, Ltd, Nihon Pharmaceutical Co, Ltd, Mitsubishi Tanabe Pharma Corporation, Boston Scientific Corporation, and Medtronic Inc. Dr Urabe received lecture fees from Daiichi Sankyo Co, Ltd, Boehringer Ingelheim, Otsuka Pharmaceutical Co, Ltd, Bayer Pharmaceutical Co, and AstraZeneca K.K., and research funds from Otsuka Pharmaceutical Co, Ltd, and AbbVie GK.
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