










ORIGINAL RESEARCH

Dual Antiplatelet Therapy Using Cilostazol in Patients With Stroke and Intracranial Arterial Stenosis

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BACKGROUND: Long-term benefit of dual antiplatelet therapy (DAPT) over single antiplatelet therapy (SAPT) for the prevention of recurrent stroke has not been established in patients with intracranial arterial stenosis. We compared the efficacy and safety of DAPT with cilostazol and clopidogrel or aspirin to those of SAPT with clopidogrel or aspirin in patients with intracranial arterial stenosis, who were recruited to the Cilostazol Stroke Prevention Study for Antiplatelet Combination trial, a randomized controlled trial in high-risk Japanese patients with ischemic stroke.

METHODS AND RESULTS: We compared the vascular and hemorrhagic events between DAPT and SAPT in patients with ischemic stroke and symptomatic or asymptomatic intracranial arterial stenosis of at least 50% in a major intracranial artery. Patients were placed in two groups: 275 were assigned to receive DAPT and 272 patients SAPT. The risks of ischemic stroke (hazard ratio [HR], 0.47; 95% CI, 0.23–0.95); and composite of stroke, myocardial infarction, and vascular death (HR, 0.48; 95% CI, 0.26–0.91) were lower in DAPT than SAPT, whereas the risk of severe or life-threatening bleeding (HR, 0.72; 95% CI, 0.12–4.30) did not differ between the 2 treatment groups.

CONCLUSIONS: DAPT using cilostazol was superior to SAPT with clopidogrel or aspirin for the prevention of recurrent stroke and vascular events without increasing bleeding risk among patients with intracranial arterial stenosis after stroke.

REGISTRATION: URL: <https://www.clinicaltrials.gov>; Unique identifier: NCT01995370.

Key Words: antiplatelet therapy ■ cilostazol ■ intracranial artery ■ stroke ■ vascular event

Intracranial arterial stenosis (ICAS) is more common in Asian people than in White people,^{1–3} and the risk of first-ever and recurrent stroke is high in patients with ICAS.^{4–6} Based on the results of clinical trials including the WASID⁷ (Warfarin-Aspirin Symptomatic Intracranial Disease) and SAMPRIS⁸ (Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis) trials, the American Heart Association/American Stroke Association guidelines recommend short-term dual antiplatelet therapy (DAPT)

plus aggressive risk factor management in patients with severe ICAS in the vascular territory of ischemic stroke or transient ischemic attack.⁹ According to a meta-analysis of clopidogrel plus aspirin versus aspirin alone for acute ischemic stroke or high-risk transient ischemic attack, that included the CHANCE¹⁰ (Clopidogrel in High-risk Patients With Acute Non-disabling Cerebrovascular Events) and POINT¹¹ (Platelet-Oriented Inhibition in New TIA [Transient Ischemic Attack] and Minor Ischemic Stroke) trials, the risk

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For Sources of Funding and Disclosures, see page 6.

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CLINICAL PERSPECTIVE

What Is New?

- Dual antiplatelet therapy with cilostazol was superior to aspirin or clopidogrel alone for the long-term prevention of recurrent stroke and vascular events without increasing bleeding risk in patients with ischemic stroke and intracranial arterial stenosis.

What Are the Clinical Implications?

- Dual antiplatelet therapy with cilostazol can be a therapeutic option for the long-term prevention of recurrent stroke and vascular events without concern for increased bleeding in patients with symptomatic or asymptomatic intracranial arterial stenosis of at least 50% after ischemic stroke.

Nonstandard Abbreviations and Acronyms

CSPS.com	Cilostazol Stroke Prevention Study for Antiplatelet Combination
DAPT	dual antiplatelet therapy
ICAS	intracranial arterial stenosis
SAPT	single antiplatelet therapy

of recurrent stroke was reduced by DAPT only for the first 10 days, there was no benefit at 22 to 90 days after the initiation, and the risk of bleeding increased until 90 days.¹² In addition, clopidogrel resistance in association with CYP2C19 polymorphisms is more common in East Asian people including the Japanese population, than in White people.¹³ In reality, according to the genetic analysis of CHANCE trial, the use of clopidogrel plus aspirin, as compared with aspirin alone, reduced the risk of recurrent stroke only in the subgroup of patients who were not carriers of the CYP2C19 loss-of-function alleles.¹⁴

We previously conducted the CSPS.com (Cilostazol Stroke Prevention Study for Antiplatelet Combination) trial, a randomized controlled trial that compare DAPT using cilostazol and single antiplatelet therapy (SAPT) with aspirin or clopidogrel in high-risk Japanese patients with ischemic stroke, including those with ICAS.¹⁵ The results showed that recurrent stroke and vascular events were significantly fewer in the DAPT group than in the SAPT group, whereas serious or life-threatening bleeding was comparable between both groups.¹⁶

Based on this background, we conducted a subgroup analysis of ICAS in patients recruited in the

CSPS.com trial to compare DAPT with cilostazol and aspirin or clopidogrel and SAPT with aspirin or clopidogrel in high-risk patients with ischemic stroke.⁷

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

The CSPS.com trial was a multicenter, open-label, randomized controlled trial that involved patients who were recruited from 292 hospitals across Japan. The design and main results on CSPS.com were described previously.⁷ The study was approved by the institutional review board in each participating site and the patients gave written informed consent before being randomly assigned to treatment. Eligible patients were aged between 20 and 85 years, had developed a noncardioembolic ischemic stroke identified on magnetic resonance imaging between 8 and 180 days before the start of the protocol treatment, and were taking either aspirin (81 or 100 mg/day) or clopidogrel (50 or 75 mg/day) alone as antiplatelet therapy when providing informed consent. The patients were required to meet at least 1 of the 3 following criteria indicating a high risk for stroke recurrence: at least 50% stenosis of a major intracranial artery (to the level of A2 [the post-communicating segment of the anterior cerebral artery], M2 [the Sylvian segment of the middle cerebral artery], or P2 [the ambient segment of the posterior cerebral artery]), at least 50% stenosis of an extracranial artery (the common carotid artery, internal carotid artery, vertebral artery, brachiocephalic artery, or subclavian artery); and 2 or more of the following risk factors including age of 65 years or older, hypertension, diabetes, chronic kidney disease, peripheral artery disease, history of ischemic stroke, history of ischemic heart disease, and current cigarette smoking. Among the recruited patients who met these criteria, those with 50% or more ICAS in a major intracranial artery were selected for this subgroup analysis. Patients were randomly allocated to either the cilostazol group (200 mg/day, 100 mg twice daily) or noncilostazol group. The observation periods lasted for at least a year.

The background characteristics in patients with ICAS included sex, age, body mass index, cigarette smoking, hypertension, diabetes, dyslipidemia, chronic kidney disease, peripheral artery disease, extracranial arterial stenosis, history of stroke, and history of ischemic heart disease. Vascular events included any stroke, ischemic stroke, hemorrhagic stroke (intracerebral hemorrhage and subarachnoid hemorrhage),

and composite vascular events (stroke, myocardial infarction, and vascular death). Hemorrhagic events included any hemorrhagic events and severe or life-threatening bleeding.

STATISTICAL ANALYSIS

Differences in background characteristics between patients with DAPT and SAPT were analyzed using the Wilcoxon rank sum test for continuous variables and the chi-square test for binary variables. The log-rank test was used for comparison between the 2 treatment groups, and the hazard ratios (HRs) and 95% CIs were calculated using the Cox-proportional hazard model. Cumulative event rates in the 2 treatment groups were expressed using the Kaplan-Meier's plot and compared using the log-rank test. Vascular events were analyzed in the intention-to-treat population, and hemorrhagic events were analyzed in patients who had received study treatment at least once during the trial. Data with missing values for variables necessary in the analyses were excluded from the analysis data set. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

A total of 155 patients were excluded from the overall intention-to-treat population ($n=1879$) because of missing ICAS data (Figure 1). Among the remaining 1724 patients, the numbers of patients with ICAS and without ICAS were 547 (31.7%) and 1177 (68.3%), respectively. Aspirin was used in 198 (36.2%) patients, and clopidogrel was used in 349 (63.8%) patients with ICAS. The median duration of follow-up was 1.4 years (interquartile range: 0.8–2.2). Finally, 275 patients were assigned to receive DAPT, and 272 to SAPT. Clopidogrel was similarly used between DAPT (58.2%) and SAPT (59.3%) groups ($P=0.6575$).

The background characteristics were comparable between the 2 treatment groups, except for chronic kidney disease, which was more common in DAPT than SAPT (Table 1). The risk of any stroke (HR, 0.47; 95% CI, 0.24–0.93), ischemic stroke (HR, 0.47; 95% CI, 0.23–0.95), and composite vascular events (HR, 0.48; 95% CI, 0.26–0.90) were lower in the DAPT group, whereas the risk of major or life-threatening bleeding (HR, 0.72; 95% CI, 0.12–4.30) was comparable between 2 groups (Table 2). After

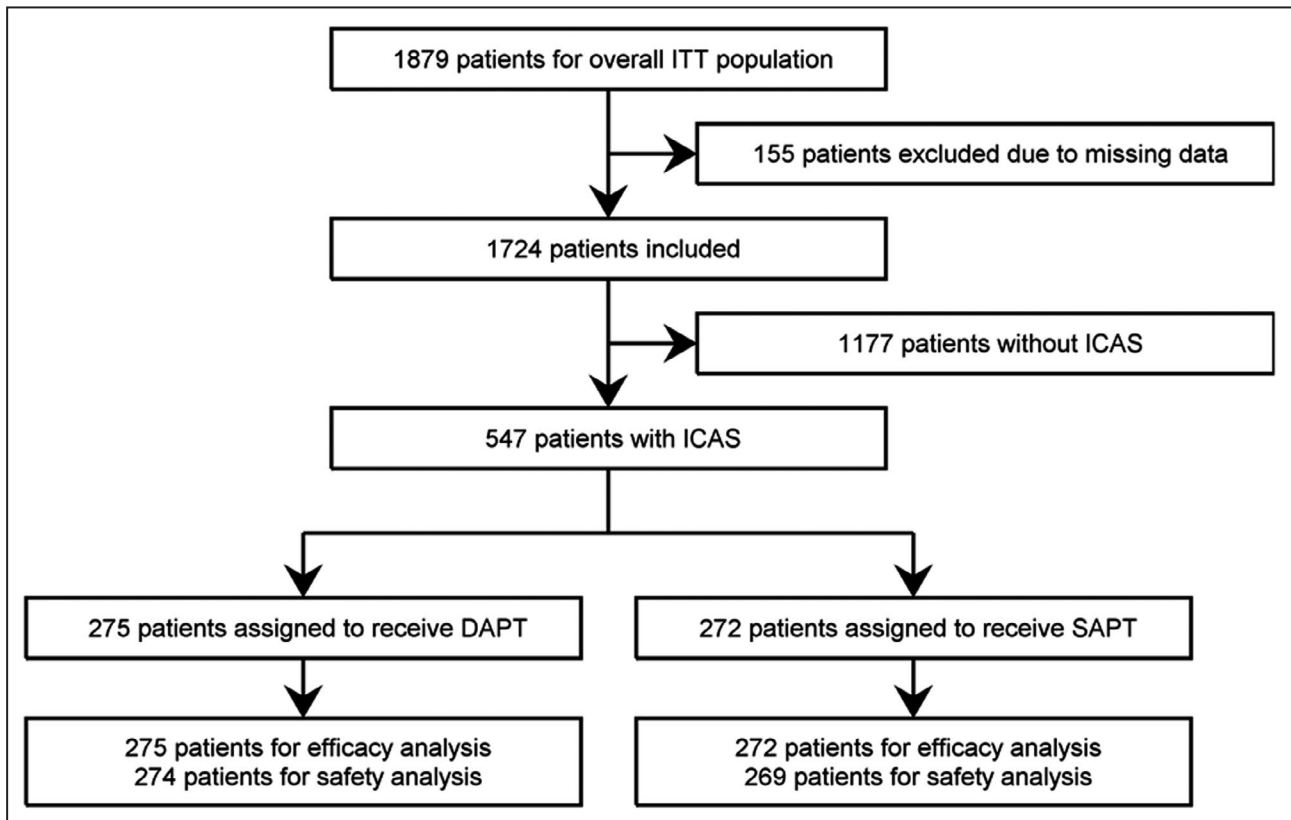


Figure 1. Flow chart of patients.

Efficacy analysis was conducted for vascular events including any stroke, ischemic stroke, and composite vascular events of stroke, myocardial infarction, and vascular death in all randomized patients. Safety analysis was conducted for any bleeding and severe or life-threatening bleeding in patients excluding those who never received a dose (1 in the DAPT group and 3 in the SAPT group). DAPT indicates dual antiplatelet therapy; ICAS, intracranial arterial stenosis; ITT, intention to treat; and SAPT, single antiplatelet therapy.

Table 1. Background Characteristics of Patients Treated With Dual Antiplatelet Therapy 458 With Cilostazol and Aspirin or Clopidogrel and Those Treated With Single Antiplatelet Therapy With Aspirin or Clopidogrel Among Patients With Intracranial Arterial Stenosis After Ischemic Stroke

	DAPT* (n=275)	SAPT† (n=272)	P value
Sex, female	101 (36.7%)	79 (29.0%)	0.056
Age, y, median (IQR*,‡)	70 (65–76)	70 (65–76)	0.74
Body mass index, median (IQR*,‡)	23.4 (21.6–25.9)	23.4 (21.6–25.5)	0.52
Current cigarette smoking	62 (22.5%)	68 (25.0%)	0.50
Hypertension	219 (79.6%)	216 (79.4%)	0.95
Diabetes	114 (41.5%)	102 (37.5%)	0.34
Dyslipidemia	171 (62.4%)	162 (59.6%)	0.49
Chronic kidney disease	28 (10.2%)	9 (3.3%)	0.0014
Extracranial arterial stenosis	53 (20.8%)	49 (19.8%)	0.77
Coronary artery disease	16 (5.8%)	16 (5.9%)	0.97
Peripheral artery disease	8 (2.9%)	2 (0.7%)	0.058
History of ischemic stroke	29 (10.5%)	29 (10.7%)	0.96

DAPT indicates dual antiplatelet therapy; IQR, interquartile range; and SAPT, single antiplatelet therapy.

*Dual antiplatelet therapy with cilostazol and aspirin or clopidogrel.

†Single antiplatelet therapy with clopidogrel or aspirin.

‡Interquartile range.

adjusting for chronic kidney disease, the risk of any stroke (HR, 0.47; 95% CI, 0.24–0.94; $P=0.033$), ischemic stroke (HR, 0.47; 95% CI, 0.23–0.95; $P=0.036$), and the composite vascular events (HR, 0.47; 95% CI, 0.25–0.90; $P=0.022$) remained lower in the DAPT group than in the SAPT group, whereas the risk of major or life-threatening bleeding (HR, 0.59; 95% CI, 0.09–3.78; $P=0.58$) remained comparable between the 2 treatment groups in patients with ICAS. Figure 2 shows the Kaplan-Meier curves to the first events.

There were no interactions for vascular and hemorrhagic events between ICAS/no ICAS and DAPT/SAPT treatment; $P=0.8169$, 0.9540 , 0.7458 , 0.8067 , 0.4128 , and 0.8445 for any stroke, ischemic stroke, composite vascular events, any bleeding, and severe or life-threatening bleeding, respectively.

DISCUSSION

Among patients with stroke or transient ischemic attack associated with ICAS, the risk of recurrent stroke remains high despite adherence to the current guidelines.^{2–6} Two randomized clinical trials were conducted to compare DAPT and SAPT in symptomatic ICAS among Asian patients. In the TOSS trial (Trial of Cilostazol in Symptomatic Intracranial Stenosis), involving 135 Korean patients with acute symptomatic ICAS, the progression of ICAS was less in DAPT with aspirin and cilostazol than aspirin alone, and there was no stroke recurrence in either group during the observation period of 6 months.¹⁴ In the CATHARSIS trial (Cilostazol-Aspirin Therapy against Recurrent Stroke with Intracranial Artery Stenosis), involving 165 Japanese patients with symptomatic ICAS>50%, we

Table 2. Vascular and Hemorrhagic Events in Patients With Intracranial Arterial Stenosis After Ischemic Stroke, Who Were Either in Dual Antiplatelet Therapy or Single Antiplatelet Therapy

	Dual antiplatelet therapy	Single antiplatelet therapy	HR (95% CI)	P value
Vascular events	n=275	n=272		
Any stroke	12 (4.4%)	27 (9.9%)	0.47 (0.24–0.93)	0.027
Ischemic stroke	11 (4.0%)	25 (9.2%)	0.47 (0.23–0.95)	0.031
Hemorrhagic stroke	1 (0.4%)	2 (0.7%)	0.55 (0.05–6.03)	0.620
Composite of stroke, myocardial infarction and vascular death	14 (5.1%)	31 (11.4%)	0.48 (0.26–0.90)	0.020
Hemorrhagic events	n=274	n=269		
Any bleeding	12 (4.4%)	7 (2.6%)	1.83 (0.72–4.65)	0.20
Severe or life-threatening bleeding	2 (0.7%)	3 (1.1%)	0.72 (0.12–4.30)	0.72

DAPT indicates dual antiplatelet therapy; HR, hazard ratio; and SAPT, single antiplatelet therapy.

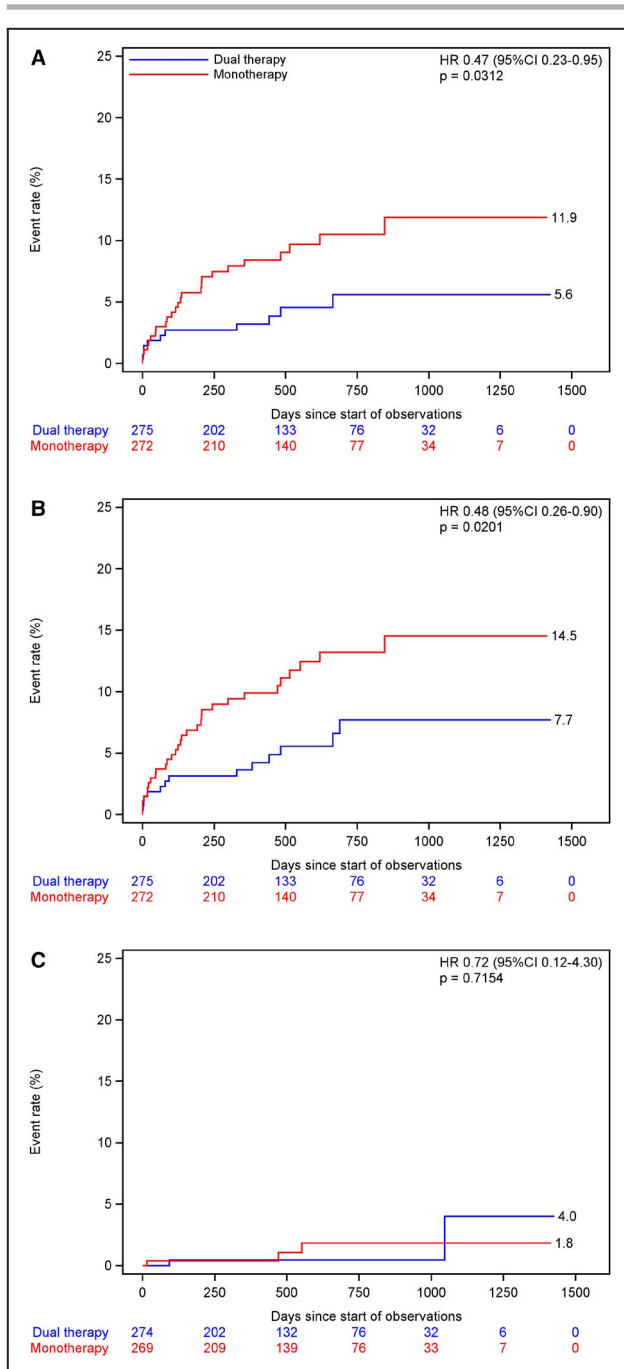


Figure 2. The Kaplan-Meier curves for the time to the first event of ischemic stroke (A), composite of stroke, myocardial infarction, and vascular death (B), and severe or life-threatening bleeding (C). Intention-to-treat analysis for (A) and (B) and safety analysis for (C). HR indicates hazard ratio.

failed to prevent the progression of ICAS, which was the primary end point, whereas the composite of all vascular events and silent brain infarcts, which was the secondary end point, was lower in DAPT with aspirin and cilostazol than aspirin alone during a 2-year observation period.¹⁵

In this CSPS.com subgroup analysis, the risks of stroke, ischemic stroke, and vascular events were less than half in DAPT using cilostazol than SAPT with aspirin or clopidogrel, whereas the bleeding risk did not differ. Stroke rate in this study was lower than those in WASID,⁷ SAMPRIS,⁸ and other studies⁵ including only patients with symptomatic ICAS, partly because CSPS.com also included asymptomatic ICAS. According to the results of the Oxford Vascular Study, asymptomatic ICAS did not increase the short- or medium-term risk of distal recurrent ischemic stroke for patients receiving standard medical treatment.¹⁶ A difference in the definition of stenosis in ICAS between this study and previous trials^{7,8} would also affect the different stroke rates.

Cilostazol, a phosphodiesterase inhibitor, is known to have pleiotropic effects such as antiplatelet, vasodilating, anti-inflammatory, and antiatherogenic effects, and protective effects on endothelial function.¹⁷⁻¹⁹ These effects might contribute to the long-term stroke prevention and help to avoid bleeding risk.^{20,21} The long-term effect of cilostazol combined with clopidogrel or aspirin on recurrent stroke is similar to the effect of dipyridamole combined with aspirin.²² Interestingly, the Kaplan-Meier curves for the ischemic stroke diverged gradually. Thus, effects of cilostazol might be delayed and presumably more related to the pleiotropic effects rather than direct antiplatelet effects.

This study had some limitations. First, the sample size was relatively small and the evidence level was limited. Second, it remains uncertain whether the present results can be generalized to other ethnicities than Japanese and to patients with acute stroke within 7 days after onset. Third, one cannot tell from these data whether DAPT is preventing recurrent stroke related to ICAS or just preventing stroke in any territory related to other mechanisms of stroke in patients with asymptomatic ICAS.

CONCLUSIONS

DAPT with cilostazol and clopidogrel or aspirin would be superior to clopidogrel or aspirin alone for the long-term prevention of stroke and vascular events without increasing bleeding risk in patients with symptomatic or asymptomatic ICAS after ischemic stroke.

ARTICLE INFORMATION

Received May 21, 2021; accepted July 26, 2021.

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Sources of Funding

Japan Cardiovascular Research Foundation received trial funding from Otsuka Pharmaceutical Co, Ltd. Otsuka did not directly contribute to the trial design, data management, or statistical analysis. Statistical analysis of this article was performed in the Department of Data Science, National Cerebral and Cardiovascular Center. This study was funded mainly by the Japan Agency for Medical Research and Development (AMED, 211k0201094h0003 and 211k0201109h0002; PI, Toyoda).

Disclosures

Uchiyama reports grant support, honoraria, advisory board fees, and lecture fees from Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Takeda, Healios, Otsuka, Sanofi, and the Japan Cardiovascular Research Foundation. Toyoda reports honoraria from Bayer, Bristol-Myers Squibb, Daiichi Sankyo, Takeda, and Boehringer Ingelheim. T Yamaguchi reports honoraria from Bristol-Myers Squibb, Daiichi Sankyo, and Pfizer. Kimura reports lecture fees and research funding from Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Medtronic, Pfizer, and Teijin. Hoshino reports honoraria from Daiichi Sankyo and Pfizer. Sakai reports grant support and lecture fees from Asahi-Intec, Daiichi Sankyo, Medtronic, NeuroVasc, Stryker, and Terumo. Houkin reports honoraria as trial principal investigator from Healios. K Yamaguchi reports lecture fee from Daiichi Sankyo. Minematsu reports honoraria from Bayer, Bristol-Myers Squibb, CSL Behring, Daiichi Sankyo, EPS Corporation, Fujii Film Pharma, Healios, Mitsubishi Tanabe, Nippon Chemiphar, Otsuka, Pfizer, Sanofi, and Stryker. Terayama reports grant support, consulting fees, and honoraria from Boehringer Ingelheim, Bristol-Myers Squibb, and Daiichi Sankyo. Yasuda reports grant support, lecture fees, and clinical trial fees from Abbott, Bristol-Myers Squibb, Daiichi Sankyo, and Takeda. The remaining authors have no disclosures to report.

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