Assessment of Sirolimus-Eluting Coronary Stent Implantation With Aspirin Plus Low Dose Ticlopidine Administration

— One Year Results From CYPHER Stent Japan Post-Marketing Surveillance Registry (J-PMS) —

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on behalf of the J-PMS study group

Background: Clinical data of sirolimus-eluting stent (SES) implantation are under investigation in Japan.

Methods and Results: The CYPHER stent Japan Post-Marketing Surveillance Registry (J-PMS) was conducted at 50 medical centers to assess the results of SES in daily clinical practice exclusively under aspirin plus low dose ticlopidine (200 mg/day). A total of 2,459 lesions in 2,054 patients were treated with 3,285 SES. The mean age was 67.1 ± 10.1 years, 75.6% were men and 43.3% were diabetics. Intravascular ultrasound was used in 77.2%. The 8-month angiographic and 1-year clinical follow-up data were available in 85.4% and 96.8%, respectively. Quantitative coronary angiography showed the reference vessel diameter and percentage diameter stenosis at baseline were 2.47 ± 0.58 mm and 72.0 ± 16.1 %. The 8-month late loss was 0.20 ± 0.50 mm. The major adverse cardiovascular events at 1 year was 7.3%; cardiac death: 1.1%, myocardial infarction (MI): 1.2%, and target lesion revascularization (TLR): 4.2%. The rates of definite and probable stent thrombosis at 1 year were 0.30% and 0.10%, respectively. Hemodialysis was the strongest predictor of death/MI or TLR.

Conclusions: J-PMS showed the effectiveness of SES implantation under aspirin plus low dose ticlopidine administration at 1 year, although further studies are necessary to demonstrate the safety. (Circ J 2009; 73: 1038–1044)

Key Words: Antiplatelet therapy; Coronary disease; Drug-eluting stents; Thrombosis

A lot of clinical results of sirolimus-eluting stent (SES) (CYPHER stent; Johnson & Johnson-Cordis Corp, Warren, NJ, USA) have been reported in many randomized control trials and registries under thienopyridine therapy in combination with aspirin.^{1–9} Ticlopidine was commonly used for bare metal stent implantation, but clopidogrel has been considered a favorable thienopyridine for drug-eluting stent (DES) implantation.^{10–14} Thus, most patients enrolled in the above studies had taken clopidogrel. Although dual antiplatelet therapy has become the mainstay to reduce the risk of stent thrombosis, several factors contribute to premature cessation of thienopyridine, including economic reasons.¹⁵ Therefore, use of ticlopidine might improve compliance as a result of its lower cost. However, effectiveness with aspirin plus ticlopidine for SES implantation has not been established because sufficiently large data set is not available.

Since clopidogrel had not been approved to use for

percutaneous coronary intervention (PCI) in Japan until recently, we had to use ticlopidine for SES implantation. In addition, the approved dose of ticlopidine was 200 mg/day not 500 mg/day. We herein report the real world registry data of SES including off-label and complex cases under aspirin plus low dose ticlopidine (200 mg/day) administration.

Methods

Study Design and Patient Enrollment

CYPHER stent Japan Post-Marketing Surveillance Registry (J-PMS) is a post-marketing surveillance registry that was mandated by the Japanese government to fulfill one of the regulatory approval conditions. The primary objective is to assess the results of SES in daily clinical practice under aspirin plus ticlopidine. The secondary objective is to evaluate the efficacy of SES in Japanese patients with angiographic evaluation of late loss and binary restenosis, thus angiographic follow-up at 8 months was mandated. A total of 2,000 cases implanted with SES were planned to enroll consecutively from September 2004 through September 2005 at 50 community-based and university hospitals that are representative of clinical environment nationwide in Japan. Total enrollment at each site was targeted to be 20–80 patients in proportion to the annual scale of PCI procedures. The indications for stent implantation were left to the discretion of each cardiologist participating in the registry, including off-label use.

(Received September 4, 2008; revised manuscript received January 7, 2009; accepted January 12, 2009; released online April 14, 2009)

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Table 1. Baseline Clinical Characteristics

No. of patient	2,051
Age, years	67.1±10.1
Male sex	1,550 (75.6)
Angina pectoris	
Unstable angina	277 (13.5)
Stable angina	1,096 (53.4)
CCS Classification III or IV	115 (5.6)
MI	411 (20.0)
Acute MI (≤72 h)	88 (4.3)
Recent MI	54 (2.6)
Old MI	269 (13.1)
Silent ischemia	255 (12.4)
Others	12 (0.6)
Elective cases	1,883 (91.8)
Ejection fraction <50%*	435 (25.1)
Previous MI	778 (37.9)
Previous coronary angioplasty	1,153 (56.2)
Previous CABG surgery	166 (8.1)
Hyperlipidemia	1,164 (56.8)
Hypertension	1,429 (69.7)
Diabetes	889 (43.3)
Insulin treatment	207 (10.1)
Current smoker	905 (44.1)
Dialysis	105 (5.1)
Cerebrovascular disease	160 (7.8)
Peripheral vascular disease	130 (6.3)
No. of diseased vessel	
1-vessel disease	1,206 (58.8)
2-vessel disease	563 (27.5)
3-vessel disease	282 (13.7)
Use of glycoprotein IIb/IIIa inhibitor	0 (0.0)
Use of ticlopidine	2,020 (98.5)

Value are mean±SD or n (%).

CCS, Canadian Cardiovascular Society; MI, myocardial infarction; CABG, coronary artery bypass graft.

*Denominator=1,733.

Antiplatelet Therapy

To reduce risk of stent thrombosis, it was recommended that aspirin (81–200 mg daily) should be administered pre-procedure and continued indefinitely, and ticlopidine (200 mg daily) should be administered concomitantly with aspirin and for a period of 3 months post-procedure in Japan. However, the management of antiplatelet therapy; initiation and discontinuation, including unavoidable ticlopidine discontinuation due to side effects or surgical operation, was left to the discretion of each cardiologist at participating study sites.

Data Collection and Management

The post-marketing surveillance databases were developed by Johnson & Johnson K.K. in Japan. Detailed demographics, clinical, angiographic and procedural information including complications were gathered for each patient. The data have been entered into case report forms by participating sites and collected by Johnson & Johnson K.K. Follow-up data were collected at 3, 8, 12 months and will be collected yearly up to 5 years. Angiographic data on 1,063 of 2,459 lesions were analyzed by an independent core laboratory (Cardiocore, Tokyo, Japan) and the remaining angiograms were analyzed by on-site quantitative coronary angiography (QCA). An independent safety and efficacy evaluation committee adjudicated all reported and suspected major adverse cardiovascular events (MACE) defined as death, myocardial infarction (MI) and target lesion revascularization (TLR) by PCI or by coronary artery bypass

Table 2. Lesion Characteristics

No. of lesions	2,459
Target coronary artery	
Right coronary artery	751 (30.5)
Left anterior descending artery	1,075 (43.7)
Left circumflex artery	522 (21.2)
Left main coronary artery	95 (3.9)
HL	16 (0.7)
ACC/AHA Classification*	
Type B2/C	1,981 (80.9)
Lesion characteristics	
De novo	1,946 (79.1)
In-stent restenosis	363 (14.8)
Moderate/severe calcification	426 (17.3)
Ostial lesion	511 (20.8)
Right coronary artery ostial lesion	110 (4.5)
Left coronary artery ostial lesion	69 (2.8)
Total occlusion	276 (11.2)
CTO (less than 3 months)	101 (4.1)
CTO (more than 3 months)	111 (4.5)
Unknown	64 (2.6)
No. of lesions	2,459
No. of stents	3,285
Direct stenting	538 (21.9)
Intravascular ultrasound using	1,776 (77.2)
Maximum deployment pressure	16.0±3.5
Stents/patient ratio	1.6±0.9
Stents/lesion ratio	1.3±0.6
Post dilatation	1,142 (46.4)
Post dilatation maximum pressure	17.4±4.5

Value are mean±SD or n (%).

HL, high lateral branch; ACC/AHA, American College of Cardiology/American Heart Association; CTO, chronic total occlusion.

*Denominator=2,449.

graft surgery (CABG); stent thromboses; and target vessel revascularization (TVR) by PCI or CABG. The adjudications were based on the information contained in the case report form and on the responses to queries addressed to the participating study sites.

Deaths were classified as cardiac or non-cardiac based on SIRIUS trial protocol definition, so unidentified death, that was any death in which a cardiac cause could not be excluded was classified as cardiac in this study. MI were classified as Q wave and non-Q wave by the physicians' discretions on the basis of ECG changes and/or a rise in creatine kinase enzyme concentration above twice the upper normal limit. If no information to judge classification of MI was available, it was classified as unidentified. TLR were based on the SIRIUS trial protocol definition and, all reported re-interventions inside the implanted stent or within 5 mm proximal or distal to the stent were classified as TLR. Repeated PCI in the same vessel was recorded as non-target lesion TVR (non-TL TVR). Stent thrombosis was classified based on Academic Research Consortium (ARC) definition as 'definite' or 'probable', and 'early' (0–30 days after implantation) or 'late' (31–360 days after implantation).

Statistical Analysis

Data were expressed as mean±SD for continuous variables and as frequencies for the categorical variables. Categorical variables that were significant on univariate analysis to determine their independent relation to TLR, were analyzed by the Fisher's exact test. Statistical significance was declared if the 2-sided probability value was <0.05. Event-free (death free, death+MI free, MACE free) and administration of ticlopidine during the 12 months follow-up period

Table 3. Major Adverse Cardiac Events

	Total number of the patients		On-label use only
	3 months follow-up	12 months follow-up	12 months follow-up
No. of patients	2,037 (99.3)	1,986 (96.8)	618
Major adverse cardiac events	28 (1.4)	145 (7.3)	34 (5.6)
Death	16 (0.8)	48 (2.4)	13 (2.1)
Cardiac	8 (0.4)	21 (1.1)	2 (0.3)
Non-cardiac	8 (0.4)	27 (1.4)	11 (1.8)
MI	11 (0.5)	24 (1.2)	4 (0.7)
Q-wave	3 (0.1)	5 (0.3)	2 (0.3)
Non Q-wave	5 (0.2)	14 (0.7)	2 (0.3)
Unknown/undetermined	3 (0.1)	5 (0.3)	0 (0.0)
Emergency CABG	0 (0.0)	3 (0.2)	0 (0.0)
TLR	5 (0.2)	83 (4.2)	17 (2.8)
TL-PCI	5 (0.2)	75 (3.8)	15 (2.5)
TL-CABG	0 (0.0)	9 (0.5)	2 (0.3)
TVR	13 (0.6)	159 (8.0)	38 (6.2)
Non-TL TVR	9 (0.4)	92 (4.6)	26 (4.3)
TV/non-TL-PCI	8 (0.4)	87 (4.4)	25 (4.1)
TV/non-TL-CABG	1 (0.05)	7 (0.4)	1 (0.2)
Target vessel failure	24 (1.2)	184 (9.3)	43 (7.1)

Values are n (%).

TLR, target lesion revascularization; TL, target lesion; PCI, percutaneous coronary intervention; TVR, target vessel revascularization.

Other abbreviation see in Table 1.

Figure. (A) Kaplan-Meier event free curve. MI, myocardial infarction; MACE, major adverse cardiac events including death, MI and target lesion revascularization. (B) Administration of ticlopidine.

were analyzed by the Kaplan–Meier method. Statistical analysis was performed with SAS ver 8.2 (SAS Institute, Cary, NC, USA).

Results

Patients and Follow-up Compliance

A total of 2,054 cases/2,464 lesions were enrolled. The mean age was 67.1 ± 10.1 , 75.6% were men, and 43.3% were diabetics including 10.1% with insulin treatment. Glycoprotein IIb/IIIa inhibitors were not used because they were unavailable in Japan. The baseline characteristics are detailed in **Table 1**. Note that this study included 1,401 cases (68.3%) that could be considered high risk, so called ‘off-label use’. This included acute MI treatment, unprotected left main coronary artery, bifurcation, ostial, restenotic lesion, non-native vessel, chronic total occlusion or long lesions over 30 mm.

Lesion Characteristics

A total of 3,279 SES were implanted into 2,458 lesions during the index procedure. Delivery failure of SES was observed in 5 lesions, and thus the initial success rate of implantation of SES was 99.8% (2,453/2,458 lesions). The stent lengths were 13 to 33 mm and diameters between 2.5 and 3.5 mm. Lesion characteristics are shown in **Table 2**. It is noteworthy that the average of maximum deployment pressure of SES was high, post-dilatation was performed with another balloon in 46.4%, intravascular ultrasound (IVUS) was used in 77.2% of the procedure.

Clinical Follow-up

Follow-up data were available for 2,037 patients at 3 months, and 1,986 patients at 1 year, representing 99.3% and 96.8% compliance, respectively. Follow-up data are listed in **Table 3**. Event free survival curves are shown in **Figure**.

Angiographic Follow-up

Angiographic follow-up data at 8 months were available

Table 4. Results of Quantitative Coronary Analysis at Baseline and at 8 Months Follow-up (Core Lab)

	In-lesion (n)	Proximal-margin (n)	In-stent (n)	Distal-margin (n)
Lesion length, mm	16.40±9.89 (904)	—	—	—
Reference diameter, mm				
Before procedure	2.47±0.58 (950)	—	—	—
After procedure	2.50±0.51 (951)	2.92±0.50 (740)	2.63±0.49 (951)	2.45±0.48 (942)
At 8 months	2.60±0.49 (949)	2.93±0.52 (743)	2.67±0.49 (948)	2.50±0.47 (937)
MLD, mm				
Before procedure	0.70±0.45 (952)	—	—	—
After procedure	1.83±0.51 (951)	2.37±0.58 (740)	2.29±0.43 (951)	1.88±0.54 (942)
At 8 months	1.79±0.58 (952)	2.35±0.62 (745)	2.09±0.60 (952)	1.98±0.56 (939)
%DS				
Before procedure	72.0±16.1 (952)	—	—	—
After procedure	26.8±13.4 (951)	19.0±12.8 (740)	12.6±9.3 (951)	23.7±14.1 (942)
At 8 months	30.9±18.5 (952)	19.8±15.4 (745)	21.5±18.8 (952)	21.1±14.6 (939)
Acute gain, mm	1.13±0.53 (951)	—	1.59±0.50 (951)	—
Late loss, mm	0.04±0.49 (951)	—	0.20±0.50 (951)	—
Late loss index, mm	0.08±2.48 (948)	—	0.13±0.49 (951)	—
Binary restenosis	13.1% (125/952)	4.8% (36/745)	8.0% (76/952)	2.8% (26/939)

Value are mean±SD or %. This table shows only the core lab analysis data.

MLD, minimum lumen diameter; %DS, percent diameter stenosis.

Table 5. Sub-Analysis of Predictors for Death Plus MI or TLR

Predictor	Yes	No	P value	OR (95%CI)
Death + MI				
Dialysis	12.9% (13/101)	3.0% (56/1,885)	<0.001	4.825 (2.544–9.152)
Previous MI	5.4% (41/759)	2.3% (28/1,227)	<0.001	2.445 (1.499–3.989)
Hyperlipidemia	2.3% (26/1,128)	5.0% (43/858)	0.001	0.447 (0.273–0.734)
Cerebrovascular disease	7.6% (12/157)	3.1% (57/1,829)	0.004	2.573 (1.350–4.904)
Age >74 years old	5.3% (26/489)	2.9% (43/1,497)	0.012	1.899 (1.154–3.124)
Previous PCI	3.8% (43/1,123)	3.0% (26/863)	0.326	1.282 (0.781–2.103)
Diabetes	3.0% (26/860)	3.8% (43/1,126)	0.339	0.785 (0.479–1.288)
Current smoking	4.0% (15/377)	3.4% (54/1,609)	0.553	1.193 (0.666–2.138)
Hypertension	3.4% (47/1,389)	3.7% (22/597)	0.737	0.915 (0.547–1.533)
Peripheral vascular disease	4.0% (5/126)	3.4% (64/1,860)	0.755	1.160 (0.458–2.935)
Multivessel disease	3.5% (29/817)	3.4% (40/1,169)	0.878	1.039 (0.639–1.690)
Previous CABG	3.7% (6/163)	3.5% (63/1,823)	0.880	1.068 (0.455–2.506)
Female	3.5% (17/487)	3.5% (52/1,499)	0.982	1.007 (0.576–1.757)
TLR rate				
Dialysis	15.8% (16/101)	3.6% (67/1,885)	<0.001	5.881 (3.410–10.140)
Mod./severe calcification	6.7% (27/406)	3.1% (62/1,972)	0.001	2.195 (1.378–3.495)
Lesion length >30 mm	7.0% (18/258)	3.1% (62/1,973)	0.004	2.313 (1.346–3.975)
RVD <2.5 mm	4.8% (53/1,101)	2.6% (31/1,181)	0.007	1.876 (1.195–2.945)
Diabetes	5.6% (48/860)	3.1% (35/1,126)	0.009	1.985 (1.287–3.062)
Ostial	5.7% (23/401)	3.3% (66/1,977)	0.029	1.762 (1.082–2.868)
Multivessel disease	5.4% (44/817)	3.3% (39/1,169)	0.030	1.256 (0.822–1.918)
Restenosis	5.4% (27/498)	3.3% (62/1,880)	0.033	1.681 (1.058–2.671)
Previous PCI	5.0% (56/1,123)	3.1% (27/863)	0.042	1.482 (0.951–2.310)
Bifurcation	4.6% (36/784)	3.3% (53/1,594)	0.135	1.254 (0.673–2.337)
ACC/AHA B2/C	4.0% (77/1,919)	2.7% (12/449)	0.215	1.400 (0.908–2.156)
Total occlusion	4.5% (12/265)	3.6% (77/2,113)	0.490	1.522 (0.821–2.822)
Previous MI	4.0% (30/759)	4.3% (53/1,227)	0.730	0.845 (0.542–1.317)

OR, odds ratio; CI, confidence interval; RVD, reference vessel diameter. Other abbreviations see in Tables 1–3.

in 1,752 patients (85.4%), which included 812 patients enrolled for core laboratory analysis (**Table 4**). The in-segment binary restenosis rate was 9.0% (187/2,087 lesions) in overall QCA data. The core-lab QCA data showed the in-stent binary restenosis rate and late loss were 8.0% (76/952 lesions) and 0.20±0.50 mm.

Predictors of TLR

Predictors of TLR are shown in **Table 5**. Significant predictors of TLR were multiple vessel disease, diabetes, dialysis, restenotic lesions, small reference vessel, long lesion and calcified lesions. The result of univariate analy-

sis indicated dialysis was the most significant predictor of TLR in this study.

Antiplatelet Drugs and Stent Thrombosis

Aspirin was administrated continuously to 1 year after stent implantation. Meanwhile the use of ticlopidine decreases significantly approximately 3 months partly as shown in **Figure B** because the recommendation of administration period for ticlopidine was at least 3 months after implantation in the SES instruction for use in Japan. The reasons for discontinuation of ticlopidine were as follows: 42.3% secondary to ticlopidine side effects, 38.9% judg-

Table 6. Stent Thrombosis Rate Based on Academic Research Consortium Definition

Stent thrombosis	Early (0–30 days)	Late (31–360 days)	Total
No. of patients	2,037	1,986	1,986
Definite	1 (0.05)	5 (0.25)	6 (0.30)
Probable	0* (0.00)	2 (0.10)	2 (0.10)
Possible	0 (0.00)	14 (0.70)	14 (0.70)
Definite + probable	1 (0.05)	7 (0.35)	8 (0.40)
Total	1 (0.05)	21 (1.06)	22 (1.11)

Values are n (%).

*Exclude one case with procedure failure (MI occurred during PCI procedure).

Abbreviations see in Tables 1, 3.

ment of full-term, 4.7% from complications other than ticlopidine side effects, 3.4% non-compliance or errors in description, 2.7% due to surgical operations, and 8.1% for unknown reasons. Detailed data of ticlopidine side effects were as follows: 24.2% hepatic disorder, 10.1% skin rash, 7.3% any abnormal biochemical test, 0.3% deterioration of renal function and 0.3% agranulocytosis. No thrombotic thrombocytopenic purpura was reported in this study.

In this situation, the rates of 'definite' and 'definite or probable' thrombosis within 1 year were 0.30% and 0.40%, respectively (Table 6). In the total of 8 patients, 2 patients took dual antiplatelet drugs, 1 took only aspirin, and the remaining patients discontinued dual APT (unknown, 3, 6, 55 and 149 days before thrombosis occurred, respectively).

Discussion

The J-PMS is a unique study because the initial dual antiplatelet regimen was aspirin plus low dose ticlopidine for all patients without exception. Clopidogrel had not been approved for use in Japan during the conduct of this study. There were no data to confirm the efficacy of ticlopidine as an antiplatelet drug for DES implantation. Additionally, there was a concern about the risk of severe ticlopidine side effects. Thus, the J-PMS was mandated by the government.

Pharmacologic studies show there is a linear increase in antiplatelet effects an increasing dose of ticlopidine. The 90% of maximal effect is seen approximately 200 to 250 mg and it is almost a plateau with only a small increase up to 500 mg.^{16–18} Thus, the usual dose selection was 500 mg, which was almost doubling the dose for reaching plateau. In China, 250 mg/day ticlopidine therapy was suggested to prevent side effects.¹⁹ In Japan, ticlopidine was approved at the dose of 300 mg/day in the 1980s but the Japanese physicians reduced the dose to 200 mg/day due to frequent side effects of hepatic disorder. This dose has been used in daily practice for more than 1 decade.

Only limited amounts of data were available comparing ticlopidine 200 mg and clopidogrel 75 mg. There is a double-blind randomized study comparing ticlopidine 200 mg and clopidogrel 75 mg.²⁰ The study did not show any significant difference in the prevention of strokes between the 2 groups; however, the frequency of side effects almost doubled in the ticlopidine group as in the clopidogrel group. The REACH registry in Japan arm showed the event rate using ticlopidine 200 mg/day was similar to other countries.²¹ These observations suggest that the antiplatelet effect of ticlopidine 200 mg/day was sufficient to prevent thrombotic events in Japan with lower side effect rate of ticlopidine.^{22,23}

A benefit of this study is the limited case selection bias because no other DESs were available during the study period in Japan. On the contrary, there were several Japan-specific risk factors such as small reference vessel diameter (the average was 2.47 mm), high percent of diabetics (43.3%) and off-label use (68.3%), including 11.2% total occlusion. Despite treating high risk lesions with low dose ticlopidine, J-PMS data showed event rates are equal to or lower than other studies in other countries^{2–5,7,8,24–33} The rates at 1 year of definite and probable stent thrombosis, MACE and target vessel failure: 0.40%, 7.3% and 9.3% are acceptable because other registry studies showed these results ranged from 0.4%³ to 1.3%;²² 5.8%⁷ to 15%;²³ and 9.8%³ to 12%²¹ respectively.^{2–5,7,8,24–32} Before the launch of the CYPHER stent in Japan, educational instruction courses were conducted all over the country to teach high maximal inflation pressure^{34–37} and confirmation of stent full expansion with IVUS, if possible.^{38–41} J-PMS showed high rate of IVUS usage (77.2%) and high inflation pressure (16.0±3.5 atm). These courses could have helped to achieve the current favorable results, even with the high percentage of off-label use.⁴²

Predictors of hard endpoints (death plus MI) and TLR were shown in Table 5. We found that dialysis was the strongest predictor of not only TLR but also death plus MI. This study included 5.1% dialysis patients which was a higher rate compared to other studies. Results of DESs for dialysis patients have not been clarified but data from this study might suggest we need to focus on the data of dialysis patients.⁴³

Limitations of this study are as follows: these were interim results of J-PMS study with 1 year follow-up rate 96.8%. The study is mandated up to 5-year follow-up, so the data will be updated and finalized by completing follow-up with all patients. Platelet reaction to drugs might be different in other races and the data should be confirmed in other countries. QCA was performed in only half of the patients at the independent core laboratory. In conclusion, this study showed acceptable results with SES with aspirin plus low dose of ticlopidine (200 mg/day) compared to other registry studies with aspirin plus clopidogrel^{2–5,7,8,24–33} although approximately half of the patients quit ticlopidine within 1 year mainly due to side effects. Low dose of ticlopidine administration might be a cost-effective substitute of clopidogrel after SES implantation in Japanese populations.

Acknowledgments

The following investigators and institutions participated in CYPHER stent Japan Post-Marketing Surveillance: Safety and Efficacy Evaluation Committee Board—Y. Ikari, Tokai University School of Medicine; M. Nakamura, Toho University Ohashi Medical Center; H. Yokoi, Kokura Memorial Hospital; E. Kyo, Kusatsu Heart Center; J. Kotani, Osaka University Hospital. Clinical Site—Y. Hamazaki, Showa University Hospital; T. Tamura, Itabashi Chuo Medical Center; Y. Hiasa, Tokushima Red Cross Hospital; T. Shibata, Miyazaki Medical Association Hospital; K. Hirata, Okinawa Chubu Hospital; Y. Nagai, Rinku General Medical Center; M. Tanaka, Osaka Red Cross Hospital; S. Nakamura, Kyoto-Katsura Hospital; R. Hamada, Hokuto Cardiovascular Hospital; Y. Katsuta, Fukuoka City Medical Association Hospital; T. Isshiki, Teikyo University Hospital; T. Hirabayashi, Sunagawa City Medical Center; M. Iwabuchi, Kokura Memorial Hospital; K. Hara, Mitsui Memorial Hospital; R. Asano, Sakakibara Heart Institute; S. Saito, Shonan Kamakura General Hospital; H. Nonogi, National Cardiovascular Center; T. Kimura, Kyoto University Hospital; H. Kanno, Katta Hospital; K. Inoue, South Miyagi Medical Center; M. Nakamura, Toho University Ohashi Medical Center; Y. Ota, Saiseikai Kurihashi Hospital; N. Komatsu, Ohta General Hospital Foundation, Ohta Nishinouchi Hospital; M. Kijima, Hoshi General Hospital; J. Hirose, Comfort Hospital; Y. Fujimoto, Kimitsu Central Hospital; K. Tamaki,

Iwate Prefectural Central Hospital; Y. Hayashi, Tsuchiya General Hospital; T. Oie, National Hospital Organization Oita Medical Center; H. Ogawa, Tokuyama Central Hospital; K. Mitsudo, Kurashiki Central Hospital; K. Ueda, Otowa Hospital; K. Kosuga, Shiga Medical Center for Adults; S. Ishiwata, Toranomon Hospital; H. Fujita, Kyoto Second Red Cross Hospital; K. Fukui, Kanagawa Cardiovascular and Respiratory Center; H. Oda, Niigata City General Hospital; Y. Noguchi, Tsukuba Medical Center Hospital; I. Michishita, Yokohama Sakae Kyosai Hospital; S. Nanto, Kansai Rosai Hospital; H. Hirayama, Nagoya Daini Red Cross Hospital; M. Watarai, Anjo Kosei Hospital; H. Takashima, Aichi Medical University; A. Takizawa, Shizuoka City Shizuoka Hospital; N. Tanaka, Toyohashi Heart Center; M. Kashida, International Medical Center of Japan; T. Hayashi, Himeji Cardiovascular Center; T. Ota, Matsue City Hospital; T. Kataoka, Osaka City University Hospital; I. Kubo, Metropolitan Bokuto Hospital; Y. Ikari, Tokai University, School of Medicine.

Funding Sources

Funding was provided from Johnson & Johnson Cordis Corp (Warren, NJ, USA).

Disclosures

All authors reported no conflict of interests.

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