BRIEF REPORT

Efficacy and Safety of Landiolol in Patients With Ventricular Tachyarrhythmias With or Without Renal Impairment
— Subanalysis of the J-Land II Study —

Tsuyoshi Shiga, MD, PhD; Takanori Ikeda, MD, PhD; Wataru Shimizu, MD, PhD;
Koichiro Kinugawa, MD, PhD; Atsuhiro Sakamoto, MD, PhD; Ryozo Nagai, MD, PhD;
Takashi Daimon, PhD; Kaori Oki; Haruka Okamoto; Takeshi Yamashita, MD, PhD

Background: Post hoc analysis was used to investigate the effects of renal function on the efficacy and safety of landiolol using data from the J-Land II study, which evaluated landiolol in patients with hemodynamically unstable ventricular tachycardia (VT) or ventricular fibrillation (VF) who were refractory to Class III antiarrhythmic drugs.

Methods and Results: Patient data from the J-Land II study (n=29) were stratified by renal function (estimated glomerular filtration rate [eGFR] <45 and ≥45 mL/min/1.73 m^2) and analyzed. Continuous landiolol infusion (1 μg/kg/min, i.v.) was initiated after VT/VF was suppressed with electrical defibrillation; subsequent dose adjustments were made (1–40 μg/kg/min). The primary efficacy endpoint was the proportion of patients free from recurrent VT/VF during the assessment period. Safety endpoints were also assessed. In the eGFR <45 and ≥45 mL/min/1.73 m^2 groups, the median doses of landiolol during the assessment period were 9.44 and 8.97 μg/kg/min, the proportions of patients free from recurrent VT/VF were 69.2% and 81.8%, and adverse events occurred in 9 and 10 of 13 patients in each group, respectively. There were no apparent differences in the efficacy or safety of landiolol between the 2 groups.

Conclusions: The data suggest that renal function may not affect the efficacy and safety of landiolol for hemodynamically unstable VT or VF.

Key Words: Beta-blocker; Landiolol; Renal impairment; Ventricular arrhythmias

H emodynamically unstable ventricular tachycardia (VT) and ventricular fibrillation (VF) are life-threatening ventricular arrhythmias that require emergency treatment and are the primary causes of sudden cardiac death.[1] Renal impairment is a known risk factor for arrhythmias; the incidence of sudden cardiac death has been reported to increase as the severity of renal impairment increases,[2] and, in a retrospective study of dialysis patients using a wearable defibrillator, 80% of all cardiac arrest cases were attributed to VT or VF.[3] However, the treatment of ventricular arrhythmias in patients with renal impairment poses several challenges. It has been reported

that in patients at high risk of VT/VF who have an implantable cardioverter defibrillator (ICD), renal impairment is a risk factor for interference with ICD therapy.[4] In addition, some Class III antiarrhythmic drugs used in the treatment of ventricular arrhythmias in patients with moderate to severe renal impairment require pharmacokinetic or pharmacodynamic dose adjustment or have limited uses. Nifekalant and sotalol are excreted by the kidneys and require dose reduction and careful monitoring in patients with severe renal impairment; amiodarone, which does not require dosage reduction in patients with non-dialysis renal impairment, is not dialyzable;[2,5] and,

Figure 1. Patient disposition. eGFR, estimated glomerular filtration rate; VF, ventricular fibrillation; VT, ventricular tachycardia.

although β-blockers can be used in patients with severe renal impairment, these drugs require careful administration and dose titration. In patients requiring emergency treatment for hemodynamically unstable VT or VF, an injectable formulation with easily adjustable dosing is required. Thus, there is a demand for antiarrhythmic drugs that can be used safely and effectively in patients requiring emergency treatment for hemodynamically unstable VT or VF, regardless of the presence of renal impairment.

Landiolol is an ultra-short-acting $β_1$-adrenergic receptor antagonist that was developed in Japan and can be used to treat atrial fibrillation or flutter and ventricular arrhythmias in patients with reduced cardiac function.[6,7] Landiolol is an intravenously administered drug and has a short half-life of approximately 4 min, meaning that its dose can be easily adjusted. The JCS/JHRS 2020 Guideline on Pharmacotherapy of Cardiac Arrhythmias recommends starting intravenous landiolol at a low dose and titrating the dose while monitoring hemodynamics and controlling heart rate in the acute phase of tachycardiac atrial fibrillation with reduced cardiac function (left ventricle ejection fraction between 25% and <40%).[8] The guideline also recommends using intravenous landiolol for repetitive VT, VF, and pulseless VT associated with organic heart disease refractory to antiarrhythmic drugs such as amiodarone and nifekalant.[8] Similarly, the 2017 American Heart Association (AHA)/American College of Cardiology (ACC)/Heart Rhythm Society (HRS) guidelines recommend using intravenous β-blockers for polymorphic VT or a VT/VF storm secondary to myocardial infarction.[9] Landiolol

is mainly metabolized in the plasma and liver, and its urinary excretion rate is low. Thus, dose adjustments related to the severity of renal impairment are not necessary, which makes landiolol suitable for use in dialysis patients.[10,11]

In a subgroup analysis of the J-Land study, which investigated the efficacy and safety of landiolol for the treatment of atrial fibrillation or flutter in patients with reduced cardiac function, patients with severe renal impairment (estimated glomerular filtration rate [eGFR] between 15 and <30 mL/min/1.73 m²) in the landiolol group showed a lower incidence of adverse events (AEs) than those in the digoxin group, as well as more rapid regulation of heart rate.[12] However, whether the efficacy and safety of landiolol in VT or VF patients are affected by the presence or absence of renal impairment remains unknown. We previously reported the safety and efficacy of landiolol treatment in patients with hemodynamically unstable VT or VF who were refractory to Class III antiarrhythmic drugs in the J-Land II study: landiolol showed a preventive effect against the recurrence of VT or VF in approximately 80% of patients and was well tolerated.[7] Herein, we conducted a post hoc analysis using data from the J-Land II study[7] to investigate the effect of renal impairment on the efficacy and safety of landiolol in patients with hemodynamically unstable VT or VF who were refractory to Class III antiarrhythmic drugs.

Table 1. Baseline Patient Characteristics

	Safety analysis set		
	Total	**eGFR (mL/min/1.73 m²)**	
		<45	**≥45**
No. patients	26	13	13
Age (years)	66.5±9.7	70.8±6.2	62.2±10.8
No. males/females	21/5	12/1	9/4
Body weight (kg)	61.08±11.34	60.92±9.99	61.24±12.95
ICD/CRT-D (n)	19	10	9
NYHA Class III/IV (n)	11	4	7
LVEF (%)	30.9±15.9	29.8±14.6	32.0±17.7
LVEF groups (n)			
<25%	9	3	6
≥25%–<50%	13	9	4
≥50%	4	1	3
BNP (pg/mL)ᴬ	509.7 [180.8–1,115.9]	642.2 [212.5–1,625.1]	307.6 [95.1–919.0]
eGFR (mL/min/1.73 m²)	48.7±21.1	32.2±11.0	65.2±14.6
Creatinine (mg/dL)	1.462±1.073	2.035±1.280	0.890±0.226
Na (mEq/L)	137.2±4.6	138.5±3.1	135.9±5.6
K (mEq/L)	4.31±0.54	4.54±0.51	4.08±0.48
Cl (mEq/L)	101.7±5.3	103.9±4.1	99.5±5.6
Ca (mEq/L)	4.19±0.35	4.28±0.36	4.11±0.35
Mg (mEq/L)	1.84±0.39	1.75±0.32	1.93±0.44
Class III antiarrhythmic drugsᴮ (n)			
Amiodarone (i.v.)	10	3	7
Amiodarone (p.o.)	11	7	4
Nifekalant (i.v.)	4	2	2
Sotalol (p.o.)	5	3	2

Unless indicated otherwise, data are given as the mean±SD or the median [interquartile range]. ᴬB-Type natriuretic peptide (BNP) was measured in 23, 12, and 11 patients in the total safety analysis set and in groups with estimated glomerular filtration rate (eGFR) <45 and ≥45 mL/min/1.73 m², respectively. ᴮTreatments used prior to the start of landiolol; there was some overlap. CRT-D, cardiac resynchronization therapy defibrillator; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

Methods

Study Design and Patients
The detailed study design of the J-Land II study has been published previously.[7] Briefly, the J-Land II study was an open-label uncontrolled multicenter study in 29 patients with recurrent hemodynamically unstable VT or VF who were refractory to Class III antiarrhythmic drugs.

The major inclusion criteria for the J-Land II study were patient hospitalization at the time the study drug was administered, recurrent VT or VF with hemodynamic instability despite treatment with oral or intravenous Class III antiarrhythmic drugs (amiodarone, nifekalant, or sotalol) within 24h prior to informed consent, and a stable maximum dose for at least 1 month in the case of the oral antiarrhythmic drugs. Patients were excluded from the study if they had temporal reperfusion VT or VF during percutaneous transluminal coronary angioplasty or temporal VT or VF after coronary obstruction or stenosis, cardiogenic shock or systolic blood pressure <90mmHg despite pressure-raising treatment, diabetic ketoacidosis or metabolic acidosis, bradyarrhythmia such as atrioventricular block (greater than second degree) or sick sinus syndrome, right cardiac failure due to pulmonary arterial hypertension, untreated pheochromocytoma, progressive malignant neoplasm, a high risk of death (for reasons other than cardiac disease), a ventricular assist device, or a history of serious allergy or treatment with landiolol, or if they were undergoing surgery.

The present study was approved by the institutional review boards of each participating center and was performed in accordance with the Declaration of Helsinki, the Pharmaceuticals and Medical Devices Law, and the Japanese Ministerial Ordinance on Good Clinical Practice for Drugs. Written informed consent was obtained from all patients. This study is registered with Japan Pharmaceutical Information Center – Clinical Trials Information (JapicCTI; ID: JapicCTI-152956).

Treatment
Continuous intravenous infusion of landiolol was started at an initial dose of 1 μg/kg/min. The dose was increased in a stepwise manner from 1 to 2.5, 5, and 10 μg/kg/min within the first hour (titration period), according to the dose-escalation procedure. The maintenance dose was kept at ≤10 μg/kg/min during the efficacy assessment period (1–49h from the start of administration). At VT or VF recurrence, dose escalation up to a maximum of 40 μg/kg/min was permitted (if tolerated). A 49-h period from the start of administration was defined as the essential treatment period (1-h titration period plus a 48-h efficacy assessment period); landiolol could be administered at the discretion
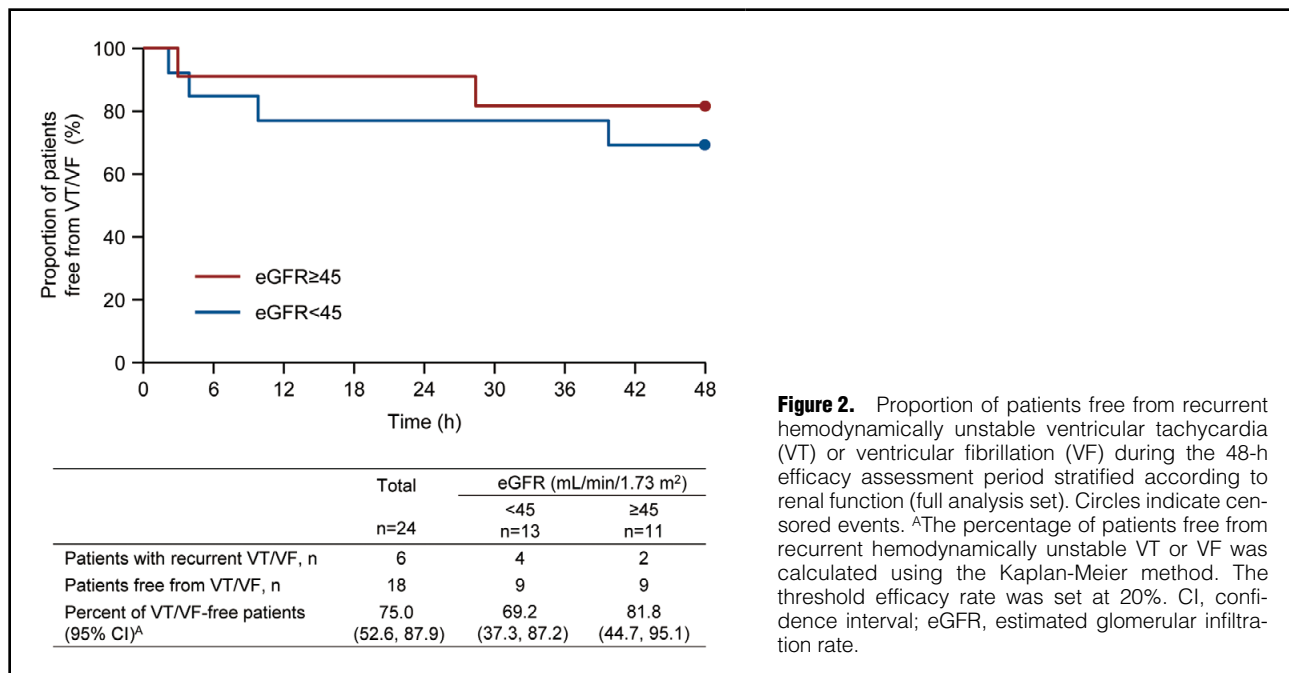
Figure 2. Proportion of patients free from recurrent hemodynamically unstable ventricular tachycardia (VT) or ventricular fibrillation (VF) during the 48-h efficacy assessment period stratified according to renal function (full analysis set). Circles indicate censored events. [A]The percentage of patients free from recurrent hemodynamically unstable VT or VF was calculated using the Kaplan-Meier method. The threshold efficacy rate was set at 20%. CI, confidence interval; eGFR, estimated glomerular infiltration rate.

	Total	eGFR (mL/min/1.73 m²)	
		<45	≥45
	n=24	n=13	n=11
Patients with recurrent VT/VF, n	6	4	2
Patients free from VT/VF, n	18	9	9
Percent of VT/VF-free patients (95% CI)[A]	75.0 (52.6, 87.9)	69.2 (37.3, 87.2)	81.8 (44.7, 95.1)

of the study investigators for a maximum of 5 days (120 h). In addition, the following drugs were permitted (with a consistent dose regimen) during landiolol treatment (titration period and efficacy assessment period; up to 49 h): Class III antiarrhythmic drugs (amiodarone, nifekalant, and sotalol), oral β-blockers (carvedilol and bisoprolol), and adrenergic agents.

Endpoints

In this study, the data of patients from the J-Land II study[7] were stratified by baseline eGFR into 2 groups: one with moderate to severe renal impairment (eGFR <45 mL/min/1.73 m²) and the other with mild renal impairment or normal renal function (eGFR ≥45 mL/min/1.73 m²). Hereafter, these groups are referred to as the "eGFR <45" and "eGFR ≥45" groups, respectively. After stratification, the data were analyzed further. The primary efficacy endpoint was the proportion of patients free from recurrent hemodynamically unstable VT or recurrent VF during the 48-h efficacy assessment period. Secondary endpoints (safety assessments) were the incidences of AEs, adverse drug reactions (ADRs), hypotension (the most common AE in the J-Land II study, including blood pressure decrease), and bradycardia. AEs were assessed in terms of severity and relationship with the study drug using MedDRA/J version 20.1.

Statistical Analysis

The sample size for the J-Land II study was not determined statistically because of the rarity of the disease; the details of sample size determination were reported previously.[7] In the present study, summary data are presented as the number of patients, the mean±SD, or as the median and range. In this analysis, the safety analysis set (SAF) was defined as patients who were administered landiolol at least once during the study period and for whom creatinine measurements prior to administration of landiolol were available. The full analysis set (FAS), which was used for the analysis

of efficacy, was defined as patients in the SAF who did not have VT or VF recurrence during the titration period, were administered landiolol continuously during the titration period, and had at least 1 efficacy assessment during the efficacy evaluation period.

The Kaplan-Meier method was used for efficacy endpoint analysis (the proportion of patients free from recurrent VT or VF during the 48-h efficacy assessment period), and 95% confidence intervals (CIs) for proportions were calculated using Greenwood's formula. Summary statistics were calculated using SAS version 9.3 for Windows (SAS Institute, Cary, NC, USA). No statistical tests were performed.

Results

Patients

Patient disposition is shown in **Figure 1**. In the J-Land II study, 39 patients were screened, 29 of whom received landiolol.[7] Of these, 3 were excluded from the SAF of the present study because creatinine was not measured prior to landiolol administration; the remaining 26 patients were included in the SAF of present study. The SAF consisted of 13 patients each in the eGFR <45 and eGFR ≥45 groups. Of the 26 patients in the SAF, 24 were included in the FAS; two patients were excluded due to VT or VF recurrence during the titration period (1 h). The FAS comprised 13 patients in the eGFR <45 group and 11 in the eGFR ≥45 group.

Baseline patient characteristics are given in **Table 1**. The mean age tended to be higher in the eGFR <45 than eGFR ≥45 group (70.8±6.2 vs. 62.2±10.8 years, respectively). Mean left ventricular ejection fraction was 29.8±14.6% and 32.0±17.7% in the eGFR <45 and eGFR ≥45 groups, respectively.

Treatment Exposure

The median dose of landiolol at the end of the titration

Table 2. Subgroup Analysis of the Incidence of AEs and ADRs

	Safety analysis set		
	Total	eGFR (mL/min/1.73 m²)	
		<45	≥45
No. patients	26	13	13
AEs	19	9	10
ADRs	10	4	6
Hypotension^A (ADR)	6	2	4
Bradycardia (ADR)	1	0	1

Data show the number of patients in the total safety analysis set and in groups with estimated glomerular filtration rate (eGFR) <45 and ≥45 mL/min/1.73 m². If a patient presented with the same adverse event (AE) more than once, it was counted as 1 patient having that event. ^AIncludes a decrease in blood pressure. ADR, adverse drug reaction.

period was 10.0 μg/kg/min in both groups. The median dose of landiolol during the period from the start of landiolol treatment to the end of the efficacy assessment period (0–49 h) was 9.44 and 8.97 μg/kg/min in the eGFR <45 and eGFR ≥45 groups, respectively.

Efficacy
Results for the primary efficacy endpoint, stratified by renal function, are shown in **Figure 2**. To assess the preventive effect of landiolol on VT or VF recurrence, the proportion of patients free from recurrent hemodynamically unstable VT and recurrent VF during the 48-h efficacy assessment period was calculated. For the entire study population, the proportion of patients free from VT or VF recurrence was 75.0% (18/24 patients; 95% CI 52.6–87.9); in the eGFR <45 and eGFR ≥45 groups, 69.2% (9/13 patients; 95% CI 37.3–87.2) and 81.8% (9/11 patients; 95% CI 44.7–95.1) of patients were free from VT or VF recurrence, respectively.

Safety
The results for the secondary (safety) endpoints, stratified by renal function, are given in **Table 2**. AEs occurred in 19 of 26 patients in the entire study population, in 9 of 13 patients in the eGFR <45 group, and in 10 of 13 patients in the eGFR ≥45 group. ADRs occurred in 10, 4, and 6 patients in the entire study population and eGFR <45 and eGFR ≥45 groups, respectively. The most common ADR, hypotension, occurred in 6, 2, and 4 patients in the study population and eGFR <45 and eGFR ≥45 groups, respectively. Bradycardia occurred in 1 patient in the entire study population, and that patient was in the eGFR ≥45 group. Both hypotension and bradycardia were mild or moderate in severity and resolved with either dose reduction or discontinuation of landiolol.

Discussion
Analysis of data from the J-Land II study after stratification by renal function revealed that the proportion of patients free from recurrent hemodynamically unstable VT or recurrent VF was comparable between the 2 groups (69.2% and 81.8% in the eGFR <45 and eGFR ≥45 groups, respectively). In both groups, the proportion was greater than the efficacy rate threshold of 20%, which had been set before the start of the J-Land II study. These data suggest that landiolol is effective for VT or VF regardless of renal impairment. Safety assessments revealed that the incidence

of AEs and ADRs was comparable between the 2 groups. Furthermore, the incidences of hypotension and bradycardia, both of which are important considerations for the use of landiolol, were also comparable between the 2 groups. This suggests that landiolol is tolerated by patients with renal impairment.

The results of the present post hoc analysis of the results from the J-Land II study agree with the results of subgroup analysis in the J-Land study investigating the efficacy and safety of landiolol for atrial fibrillation or flutter. In the J-Land study, no apparent differences that could be attributed to the severity of renal impairment were observed in the proportion of patients with a heart rate of <110 beats/min and those with a ≥20% decrease in heart rate from baseline 2 h after the start of landiolol treatment (the primary efficacy endpoint of the J-Land study).[12] In the present analysis, the incidence of AEs was similar between the 2 groups, stratified according to the severity of renal impairment.

The present analysis showed no apparent differences in the efficacy and safety of landiolol for hemodynamically unstable VT or VF according to the presence or absence of renal impairment. These results are consistent with the results obtained for atrial fibrillation or flutter.[12] The lack of apparent differences may be explained by the pharmacokinetic profile of landiolol. In general, drugs that primarily undergo renal excretion require dose reduction in patients with renal impairment and cannot be used in some patients who are on dialysis. Moreover, because patients with severe renal impairment or patients on dialysis have reduced hepatic metabolism, some drugs that are predominantly metabolized by the liver require dose adjustments.[13] Landiolol is rapidly metabolized by cholinesterase in the plasma and liver, with a low renal excretion rate.[11] These characteristics of landiolol may explain why renal impairment did not seem to affect the efficacy and safety of landiolol in relation to atrial fibrillation or flutter and VT or VF.

Study Limitations
The limitations of this study included its open-label uncontrolled study design (a control group was not included because of the rarity and seriousness of the diseases) and the fact that the subgroup analysis was performed post hoc. In addition, because no dialysis patients were included in the J-Land study, the present study was unable to evaluate the efficacy and safety of landiolol in patients with end-stage renal disease who required dialysis. Although the sample size of this study was not large enough for sub-

group analysis, analysis of the safety and efficacy of landiolol stratified by renal function is considered to be clinically important given the rarity and seriousness of the disease.

Conclusions

The results from the present post hoc analysis suggest that the efficacy and safety of intravenously administered landiolol for the prevention of VT and VF may not differ between patients with moderate to severe renal impairment and those with mild renal impairment or normal renal function, suggesting that drug safety and efficacy may be less affected by renal function. Landiolol should be considered as a new treatment option for VT or VF patients, regardless of renal function.

Disclosures

T.S. has received lecture fees from Bristol Myers Squibb, Daiichi Sankyo, and Ono Pharmaceutical; research funding from Daiichi Sankyo; and scholarship funds from Ono Pharmaceutical. T.I. has received lecture fees from Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Daiichi Sankyo, and Ono Pharmaceutical; and scholarship funds from Daiichi Sankyo, Japan Lifeline, and Medtronic. W.S. has received lecture fees from Bristol Myers Squibb. K.K. has received lecture fees, manuscript fees, and research funding from Ono Pharmaceutical, and is a member of *Circulation Reports*' Editorial Team. T.Y. has received lecture fees from Bayer, Bristol Myers Squibb, Daiichi Sankyo, Ono Pharmaceutical, and Toa Eiyo; manuscript fees from Bristol Myers Squibb and Daiichi Sankyo; and research funding from Bayer, Bristol Myers Squibb, and Daiichi Sankyo. K.O. and H.O. are employees of Ono Pharmaceutical. The remaining authors have no conflicts of interest to disclose.

IRB Information

The present study was approved by the institutional review boards of the following participating centers: Toho University Omori Medical Center (Reference no. 15-06), Showa University Hospital (Reference no. 1511011), Tokyo Women's Medical University Hospital (Reference no. N2015030), Nippon Medical School Hospital (Reference no. 127018), Yokohama City University Medical Center (Reference no. 115-296), Tosei General Hospital (Reference no. H270902ONO-1101), Aichi Medical University Hospital (Reference no. 2708), National Cerebral and Cardiovascular Center Hospital (Reference no. #901), Kurume University Hospital (Reference no. 215022), and St. Mary's Hospital (Reference no. 2015-08-28).

Data Availability

The deidentified participant data will not be shared. For more information on Ono Pharmaceutical's policy regarding the disclosure of clinical study data, please refer to https://www.ono.co.jp/eng/rd/policy.html (accessed June 11, 2020).

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Appendix

Investigators and site staff who participated in the J-Land II study are listed below, along with study sites.
Investigators and Study Sites:
Takanori Ikeda, Toho University Omori Medical Center; Yoichi Kobayashi, Showa University Hospital; Tsuyoshi Shiga, Tokyo Women's Medical University Hospital; Wataru Shimizu, Nippon Medical School Hospital; Kengo Kusano, National Cerebral and Cardiovascular Center Hospital; Hideki Tashiro, St. Mary's Hospital; Masayoshi Ajioka, Tosei General Hospital; Tetsuya Amano, Aichi Medical University Hospital; Kazuo Kimura, Yokohama City University Medical Center; Yoshihiro Fukumoto, Kurume University Hospital
Ono Pharmaceutical Core Team:
Tatsuaki Okamura, Akira Ichikawa, Chiaki Minamoto, Masaki Kubota, Yoshimi Hosoya, Ryoko Fujimaki, Mikiko Takagi, Makiko Yamashita, Daisuke Matsuura, Eiichiro Morishima