Japanese Randomized Trial for Investigation of a Combined Therapy of Amiodarone and Implantable Cardioverter Defibrillator in Patients With Ventricular Tachycardia and Fibrillation

—The Nippon ICD Plus Pharmacologic Option Necessity (NIPPON) Study Design—

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Background Implantable cardioverter-defibrillators (ICDs) are the most effective therapy in reducing the mortality of patients with life-threatening ventricular tachyarrhythmias. However, the ICD cannot prevent the recurrence of tachycardia attacks and that limits the clinical usefulness of them. The Nippon ICD Plus Pharmacologic Option Necessity (NIPPON) trial was designed as the first prospective randomized study to test the hypothesis whether amiodarone could improve the patient's clinical outcome by reducing the amount of ICD therapy in the Japanese patient population.

Methods and Results Approximately 400 patients with organic heart disease and spontaneous episode(s) of sustained ventricular tachycardia/fibrillation (VT/VF) will be randomly assigned to one of 2 groups; the amiodarone group and non-amiodarone group. Both groups of patients will be followed at least for 24 months. The end-point committee will adjudicate events in a blinded fashion. The primary end-points of this study are determination of the appropriate therapy from the ICD and alteration of the assigned treatment because of its harmful effects and/or frequent ICD therapies.

Conclusion The NIPPON study is expected to confirm our understanding of the prognostic and therapeutic usefulness of adjuvant amiodarone therapy for patients with an ICD and with a history of sustained VT/VF. (Circ J 2006; 70: 316–320)

Key Words: Amiodarone; Implantable cardioverter defibrillator; Ventricular fibrillation; Ventricular tachycardia

Implantable cardioverter-defibrillators (ICDs) are the most effective therapy in reducing the mortality of patients who have a history of life-threatening ventricular tachyarrhythmias when compared with the effects

of antiarrhythmic drugs!^{1–7} However, the ICD cannot prevent the recurrence of ventricular tachycardia/fibrillation (VT/VF) attacks and potential loss of consciousness and that limits the clinical usefulness of it.

An important rationale for an adjuvant therapy with antiarrhythmic drugs in patients with ICDs is that defibrillators do not provide absolute protection against death from arrhythmias. Approximately 2 percent of VT/VF episodes were reported to be refractory to appropriate ICD therapy; the condition is known as 'electrical storm' or 'pulse-less electrical activity'.⁸ Recent studies suggest that episodes of VF, even ones that are successfully terminated by an ICD, may increase the risk of myocardial and cerebral ischemic injury.^{9–11} The avoidance of frequent shocks by the use of antiarrhythmic agents may be crucial for the safety and quality of life (QOL) of patients with ICDs. Another aim for the use of a combination drug therapy with the ICD is to reduce shock therapies not only by inhibiting ventricular tachyarrhythmias, per se, but also by converting rapid VT/VF to hemodynamically stable VT, which may not only be more responsive to anti-tachycardia pacing but can also avoid loss of consciousness of the patient.¹² Further-

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Fig 1. Diagram of the Nippon ICD Plus Pharmacologic Option Necessity (NIPPON) study design. Randomization would be performed before ICD implantation. ICD, implantable cardioverter-defibrillator; DFT, defibrillation threshold.

more, an inappropriate ICD therapy may also be prevented by antiarrhythmic drugs through the suppression of supraventricular tachyarrhythmias.

In contrast, the combined use of antiarrhythmic agents with ICDs might lead to adverse responses such as an unacceptable increase in the defibrillation threshold (DFT) and under-detection of VT/VF because of a prolongation of an arrhythmia cycle length beyond the programmed detection interval, and potential proarrhythmias or extracardiac toxicity.^{13–15} The Nippon ICD Plus Pharmacologic Option Necessity (NIPPON) pre-study demonstrated that the VT/VF event rate in ICD patients with class I agent adjunctive therapy was significantly higher than that in patients with amiodarone.¹⁶ Furthermore, no fatal side-effect of amiodarone was observed in the NIPPON pre-study.

Sotalol has been proven to be safe and efficacious in reducing the risk of death and frequency of defibrillator shocks.^{17–19} Amiodarone is the most frequently prescribed drug for ICD patients in Japan, but its efficacy to suppress VT/VF episodes in ICD patients has not yet been substantiated.^{16,19} The Cardiac Arrest in Seattle: Conventional Versus Amiodarone Drug Evaluation (CASCADE) trial demonstrated that amiodarone prevents potentially lethal arrhythmias in patients resuscitated from cardiac arrest compared with conventional antiarrhythmic drug therapy guided by electrophysiological study or Holter monitoring.²⁰ However, that study was not designed to confirm the efficacy of anti-arrhythmic drugs in reducing VT/VF recurrences in patients with a history of VT/VF and with ICD therapy.

The NIPPON trial was designed to be the first prospective randomized study to test the hypothesis that amiodarone could improve the patient's clinical outcome by reducing ICD therapy deliveries required for prompt termination of VT/VF in the Japanese patient population.

Methods

Patient Population

The patients entering this trial will meet the following entry criteria: (1) all patients will have spontaneous epi-

sode(s) of sustained VT or VF; (2) all patients will have organic heart disease as documented either by electrocardiography, echocardiography, cardiac catheterization, nuclear scintigraphy, computed tomography or magnetic resonance imaging; (3) all patients will correspond to the guidelines for ICD therapy determined by the Ministry of Health, Labor and Welfare, in Japan; (4) all patients will be free of any class I or class III drugs at the time of the ICD implantation, and all anti-arrhythmic drugs (except for β -blockers) will be discontinued at least 5 half-lives before the implantation. Beta-blockers will be allowed to be prescribed when appropriate.

The exclusion criteria for this study are when patients have the following: (1) idiopathic VT/VF; (2) Brugada syndrome; (3) congenital long QT syndrome; (4) an incessant form of VT/VF; (5) VT/VF resulting from a transient or reversible disorder such as acute myocardial infarction, electrolyte imbalance or drugs; (5) are aged less than 20 years old; (6) are taking class I or class III drugs (including amiodarone), which cannot be discontinued; (7) a life expectancy less than 2 years; (8) congestive heart failure with a New York Heart Association (NYHA) cardiac function class IV or are candidates for cardiac transplantation; (9) bradycardia less than 50 beats/min.; (10) second- or third-degree atrioventricular block; (11) corrected QT interval ($QT_c = QT \sqrt{RR/1000}$) equal to or longer than 480 ms; (12) significant pulmonary disease such as interstitial pneumonitis, pulmonary fibrosis, diffusion capacity of the lung for carbon monoxide (DLco) <60% or high molecular weight mucin-like antigen (KL-6) >1,000 U/ml; (13) severe dysfunction of the liver, kidney or thyroid; (14) more than 2 episodes of hemodynamically unstable sustained VT or VF per month before the ICD implantation; (15) are candidates for curative procedures for VT/VF such as catheter ablation or cryosurgery; (16) unstable angina pectoris; (17) DFT at the ICD implantation of more than 20 J; and (18) are pregnant (or have the possibility of), or are breast feeding.

Fig 2. Diagram of the defibrillation test during ICD implantation. An almost exact defibrillation threshold (DFT) will be determined by inducing VF 3 times. ICD, implantable cardioverter-defibrillator; Success, successful defibrillation; Non-success, unsuccessful defibrillation; VF, ventricular fibrillation. This diagram is designed for a device with a maximum shock output of 30 J.

Fig 3. Diagram of the defibrillation threshold (DFT) measurements after ICD implantation. A series of deliverable shock energies will be programmed individually according to the DFT during ICD implantation. A decrease in the DFT will not be assessed by using this protocol. ICD, implantable cardioverter defibrillator; Success, successful defibrillation; Non-success, unsuccessful defibrillation; VF, ventricular fibrillation; Defib, defibrillation. This diagram is designed for a device with a maximum shock output of 30 J.

End-Points

Primary End-Points The NIPPON study will investigate the efficacy of amiodarone in reducing the appropriate ICD therapy deliveries and in improving the QOL in patients with spontaneous VT/VF episodes caused by organic heart disease. The primary end-points of this study are: (1) an appropriate ICD therapy; and (2) an alteration of the assigned treatment because of its harmful effect and/or frequent ICD therapy deliveries (more than 3 sessions of ICD first therapy within 24h). The latter one includes termination of amiodarone or a transition to an alternative antiarrhythmic drug (class I or class III) in the amiodarone group, addition of class I or class III drugs in the control group, or curative interventions such as catheter ablation or cryosurgery in either group.

Secondary End-Points

The secondary end-points of this study are: (1) total

death; (2) arrhythmic death; (3) cardiac death; (4) re-hospitalization aiming to control VT/VF; (5) impairment of patient's QOL; (6) deterioration of heart failure (worsening of NYHA class or unplanned admission to the hospital because of heart failure); (7) abnormal increase in the DFT (less than a 10 J safety margin); (8) inappropriate ICD therapy; or (9) occurrence of side-effects from amiodarone.

Study Design

The NIPPON study is a multicenter randomized, no-treatment concurrent controlled study to access the efficacy of amiodarone in patients with an ICD.

After obtaining written informed consent, patients will be randomly assigned to one of 2 groups; amiodarone group and non-amiodarone group. An ICD (basically, dual chamber types) will be implanted as soon as possible after randomization (Fig 1). At least a 10-J safety margin for defibrillation will be determined by inducing VF 3 times

under the protocol (Fig 2). As a general rule, amiodarone will be started on the next day after the ICD implantation with a loading dose of 400 mg/day. Two weeks after the loading dose period, amiodarone will be reduced to a maintenance dose of 200 mg/day. The defibrillation ability will be reassessed 2–4 weeks after the ICD implantation in both groups (Fig 3). The aim of the second test is to recognize at least a 10-J safety margin for defibrillation, and therefore, an improvement of the DFT will not be evaluated. Any patients, in whom the DFT has increased to a level where the safety margin is less than 10 J during the second test, will be excluded. All patients will be followed up for at least 2 years in cases where the patient is still alive.

Discontinuation of amiodarone will be considered if the following conditions are observed: (1) a marked QT interval prolongation (QTc interval >550 ms); (2) symptoms suggestive of pulmonary intoxication; (3) newly developed infiltration on the chest X-ray; (4) a DLco of less than 60% for the absolute value or a 20% decrease in the control value; or (5) other adverse effects from amiodarone such as frequent VT/VF, congestive heart failure.

The patient's QOL will be evaluated by a questionnaire comprised of general health-related questions and also ICD-specific questions. The general health-related questions are based on the SF-36.²¹ Furthermore, several additional questions concerned with arrhythmias and the ICD implantation have been specially designed by the NIPPON committee, and those consist of only 4 questions asking about the patient's anxiety and restrictions on daily living related to the VT/VF itself and the assigned treatment of ICD implantation with or without amiodarone.

Patient Follow-up

All patients will be followed up at the ICD clinic in each participating institution every 3 months, and the therapy recordings retrieved from the ICD will be analyzed in terms of heart rate, heart rate variability, arrhythmia morphology and temporal relation between the atrial and ventricle electrograms. The side-effects of amiodarone will be assessed by symptoms, chest X-ray, DLco, and KL-6 level every 3 months;²² and the QOL will be evaluated before randomization and at 12 and 24 months after the initiation of the treatment.

Recommendations for the ICD System and Optimal Programming

Although the selection of the ICD system will be left to the judgment of the physician, a dual chamber ICD approved by the Ministry of Health, Labor and Welfare, of Japan, at the time of the implantation will be recommended, because the dual chamber device provides much more exact information for the discrimination of the tachycardia and an appropriate back-up pace.

The device will be programmed to maximize its ability for the detection and termination of the tachyarrhythmias. The detection interval for VT will be programmed according to the slowest VT with a safety margin of more than 60 ms combined with an algorithm for the discriminative criteria of atrio-ventricular dissociation, cycle length variation and acceleration of the tachycardia.^{23,24} The detection interval for VF will be programmed equal to or more than 300 ms, and the maximum shock energy will be selected for all defibrillation therapies.

The DDI mode for backup pacing will be programmed to provide a relatively long A-V delay, hence allowing the

atrioventricular propagation of the atrial impulse to avoid asynchronous contractions because of artificial right ventricular pacing.²⁵

Data Analysis and Sample Size

The primary analysis will be made on an unadjusted intention-to-treat comparison between groups for the time to any part of the composite primary end-point (appropriate therapy from the ICD or alteration of the assigned treatment) and secondary end-point (total death, arrhythmic death, cardiac death or re-hospitalization aiming to control VT/VF) by using the Kaplan–Meier survival curve and log-rank test. As part of the secondary end-point, a questionnaire for the assessment of the patient's QOL will be collected from each group, and the absolute values for each question will be used to calculate the mean value, SD, number of cases, and median value (as required) per question per group. The inter-group difference will be assayed at each measurement point by using the unpaired Student's t-test or Mann–Whitney U-test. Differences between the groups and over time in the absolute values of the measurement points will be investigated by repeated ANOVA. Items that cannot be appropriately assessed and analyzed by absolute values will be subjected to separate analysis by the most appropriate method. The patient background factors and other observational items will be aggregated by group, and any inter-group differences will be analyzed by methods corresponding to the nature of the data.

Two hundred patients in each group (a total 400 patients) will be enrolled at more than 40 Japanese centers over a 3-year period with the minimum follow-up of 2 years. Therefore, we plan for this study to last a total of 5 years. The target number of cases has been established by our estimation of the primary end-point incidence.²⁶ The projected incidence of appropriate ICD therapy in the non-amiodarone group is estimated to be 40% over 3.5 years, and the expected event decrease rate in the amiodarone group is estimated to be 30%; these were presumed based on the CASCADE and NIPPON pre-study.^{16,20} By using these outcome rates, and assuming an α error of 0.05, we will have a power of above 0.80 for demonstrating this outcome if a total of 400 patients are randomized. Assuming further that approximately 10% of patients will be found ineligible after randomization, the total sample size needed in this trial is 440 patients.

Steering Committee

This committee will be responsible for developing and monitoring the implementation of the protocol. The committee is supported by a statistician, independent of the sponsor, and is responsible for ensuring the timely publication of the results.

Adverse Event and End-Point Committee

This committee will be responsible for classifying all deaths that could potentially contribute to an end-point or adverse event. When accuracy of the ICD therapy during the tachycardia is inconclusive, retrieved electrograms from the device will be analyzed by the committee. All these events will be adjudicated in a blinded manner.

Data Safety Monitoring Board (DSMB)

The DSMB will be responsible for monitoring patient safety and will recommend that the trial be stopped prematurely if a pre-defined increase in all-cause mortality occurs

in the amiodarone arm or if a 3-standard deviation in the benefit in all-cause mortality, on a log rank test, is observed.

Randomization

Randomization of patients will be through a centralized, concealed, minimization process implemented by an independent statistician.

Expected Implications

The NIPPON study is expected to confirm our understanding of the prognostic and therapeutic usefulness of adjuvant amiodarone therapy for patients with an ICD, and with a history of sustained VT/VF. There are 4 supplemental features in this trial to be addressed. First, this trial will allow us to use amiodarone based on a more scientific background than an individual's anecdotal experience, thus should help our clinical strategy aiming to reduce the VT/VF recurrence and improve the mortality and/or QOL. Second, the efficacy and feasibility, as well as safety, of a relatively low dose of amiodarone, which has been traditionally preferred in Japan, will be properly assessed. Third, this trial will enable the evaluation of the role of KL-6 in the early detection of pulmonary intoxication. Finally, the study will generate the first large database of Japanese ICD patients, which can be used for subgroup analysis, and provide further information for investigating the peculiar characteristics of VT/VF patients in Japan.

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