Amiodarone Therapy in Patients Implanted With Cardioverter-Defibrillator for Life-Threatening Ventricular Arrhythmias

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Background Whether amiodarone can improve the patient’s clinical outcome by reducing implantable cardioverter-defibrillator (ICD) therapy deliveries for ventricular tachycardia or fibrillation (VT/VF) has not been clearly evaluated.

Methods and Results A total of 507 patients with VT/VF due to organic heart disease who had ICDs implanted were enrolled in this study. The patients were divided into 3 groups: Amiodarone (n=247), Class I antiarrhythmic drug (n=103) and Control (n=157) groups, and the total cause mortality and arrhythmic event free survival rates were evaluated between the groups. The mean follow-up period was 38±27 months. The left ventricular ejection fraction was significantly decreased in the Amiodarone group (Amiodarone: 37±16%; Class I: 44±17%). The mortality and arrhythmic events were significantly higher in the Class I group than the Amiodarone group (p<0.05), but there was no significant difference between the Amiodarone and Control groups (arrhythmic event free rate at 5 years: Amiodarone: 53%; Class I: 35%; Control: 48%; 5 year survival: 86%, 74% and 77%, respectively). Side effects from amiodarone were found in 12% of the patients, but no fatal events were observed.

Conclusions The present study could not demonstrate the benefit of amiodarone in ICD patients, probably due to a significant clinical bias exerted in selecting this drug. 

Key Words: Amiodarone; Implantable cardioverter-defibrillator; Prognosis; Ventricular arrhythmia

An implantable cardioverter-defibrillator (ICD) is the most effective therapy in improving the mortality in patients with a history of life-threatening ventricular tachyarrhythmias as compared with antiarrhythmic drugs. However, still an essential problem remains with ICD therapy in that it cannot prevent the recurrence of ventricular arrhythmic attacks. Patients with ICDs sometimes receive shock therapy and even inappropriate shocks. Further, about 2% of ventricular tachycardia or fibrillation (VT/VF) episodes were reported to be refractory to appropriate ICD therapy; this condition is known as an “electrical storm” or “pulse-less electrical activity”. Defibrillators do not provide absolute protection against death from arrhythmias.

The aim of adjunctive drug therapy with ICDs is to reduce both appropriate shocks triggered by ventricular tachyarrhythmias and inappropriate shocks from supraventricular tachycardia. The avoidance of frequent shocks through the use of antiarrhythmic agents may be crucial for the safety and quality of life (QOL) in patients with ICDs. At the present time, d,l-sotalol is the only antiarrhythmic drug that has been proven to reduce the incidence of VT/VF recurrence after an ICD implantation.

Amiodarone, which prolongs the action potential duration and refractoriness of cardiac tissue, has emerged as the antiarrhythmic agent of choice for treating life-threatening ventricular arrhythmias in Japan. Previous prospective randomized studies have suggested that amiodarone prevents the recurrence of VT, VF and unexpected death, and reduces the total mortality in patients with ventricular tachyarrhythmias.

On the other hand, the combined use of antiarrhythmic agents with ICDs might lead to adverse responses such as an unacceptable increase in the defibrillation threshold, under-detection of VT/VF due to a prolongation of the arrhythmia cycle length beyond the programmed detection interval or potential proarrhythmias or extracardiac toxicity. Amiodarone is widely used as an adjunct drug therapy with ICDs, especially in Japan; however, there are few randomized placebo-control trials to evaluate whether amiodarone is beneficial or not in patients with an ICD and structural heart disease.

The Nippon ICD Plus Pharmacologic Option Necessity (NIPPON) study is prepared to be the first prospective ran-
Pre-NIPPON Questionnaire

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<td>At Implantation</td>
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<td>%</td>
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<td>Model of ICD</td>
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<td>Prescribed Drug</td>
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<td>Outcome</td>
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<tr>
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<td>yy/mm/dd</td>
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<tr>
<td>Date of latest follow-up</td>
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Fig 1. The questionnaire used in the present study; NIPPON, The Nippon ICD Plus Pharmacologic Option Necessity; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association functional class; ICD, implantable cardioverter-defibrillator; VT, ventricular tachycardia; VF, ventricular fibrillation; ATP, anti-tachy pacing.

Randomized study to test whether amiodarone can improve the patient’s clinical outcome by reducing the ICD therapy deliveries for ventricular tachyarrhythmias. The NIPPON pre-study (retrospective multi-center registry) was performed to compare the outcome of an empirical adjunctive drug therapy in Japanese patients with ICDs, and also to evaluate the rationale and feasibility of the NIPPON study.

Methods

Questionnaire

The committee of NIPPON pre-study, which was established by the Japanese Society of Electrocardiology, compiled a simple questionnaire for clinical and arrhythmic data from patients with an ICD implantation who had a history of life-threatening ventricular tachyarrhythmias caused from structural heart disease. Idiopathic VF, Brugada syndrome and congenital long QT syndrome were excluded from the present study. The questionnaire included the following patient characteristics; age, gender, New York Heart Association (NYHA) cardiac function classification, left ventricular ejection fraction (LVEF), type of clinically documented tachyarrhythmias, antiarrhythmic agents prescribed, date of the ICD implantation, date of the first appropriate or inappropriate ICD therapy delivery, type of the ICD therapy delivery (anti-tachycardia pacing or shock), efficacy of the ICD therapy, history of electrical storm (more than 3 events during 24h), side effects from amiodarone if prescribed and their prognosis (Fig 1). As an additional analysis, we collected more detailed information, especially pulmonary intoxication, using an additional questionnaire in case adverse events from amiodarone occurred (Fig 2), because the pulmonary intoxication is a fatal side effect for patients who have been prescribed amiodarone.

Participating Hospitals

We sent the questionnaires to 7 Japanese centers and compiled data from all patients meeting the enrolment criteria. These centers were authorized as cardiac arrhythmia specialist institutions by the committee of the NIPPON pre-study.

Collection of Questionnaires (Fig 3)

We collected 738 case questionnaires from the 7 centers from April 2004 to May 2004. From those, we excluded 66...
cases in which indispensable items (age, gender, structural heart disease, LVEF, antiarrhythmic agents prescribed, date of the ICD implantation, date of the first appropriate ICD therapy delivery, side effects from amiodarone and outcome) had not been correctly completed in the questionnaire. We further omitted those patients with a combination of class I and class III (amiodarone n=87, sotalol n=1) therapies (n=88) in order to clarify the effects of the antiarrhythmic drugs on the outcome, and also those patients having received d,l-sotalol because it was prescribed only to a small number of patients (n=49). We also excluded those patients in whom the antiarrhythmic agents were changed or discontinued during the follow-up (amiodarone; n=20, class I drugs; n=3, and no drug; n=5). In total, we enrolled 507 patients in the present study.

Patient Population
The patients enrolled consisted of 400 males and 107 females, and their ages ranged from 15 to 86 years old with an average age of 58±13 at the time of the ICD implantation. The anti-arrhythmic drugs prescribed were class I drugs in 103 patients (class Ia: 49; class Ib: 50; and class Ic: 13), amiodarone in 247 patients and -blockers in 221 patients, which were used either solely in 88 patients or in combination with class I drugs (35 patients) or amiodarone (98 patients).

We divided the 507 patients into the 3 groups according to the adjunctive anti-arrhythmic drug therapy: the Class I group (n=103), Amiodarone group (n=247) and Control group (n=157, 88 with -blockers in 221 patients, which were used either solely in 88 patients or in combination with class I drugs (35 patients) or amiodarone (98 patients).

Data Analysis
The primary endpoint was death from any cause and first arrhythmic event defined as the appropriate ICD therapy for VT or VF. An analysis of the therapy recording retrieved from the ICD was performed on the device-derived data including the heart rate, variability of the rate, morphological findings and relationship between the atrial and ventricular electrograms in cases with a dual chamber ICD.

The observation period lasted until the patients’ death or until 1 April 2004 when the patient was alive and could be followed-up.

Additionally, the adverse effects of amiodarone were analyzed in all 354 patients prescribed amiodarone, including patients with a combination of class I and class III drugs that we excluded from the analysis of patient outcomes.

Statistical Analysis
All statistical analysis were calculated using statistical software (JMP, SAS institute Japan). All measured data are shown as the mean±standard deviation. The ANOVA or chi-square test was used to analyze the differences between more than 2 groups. The unpaired t-test was used for comparisons between 2 groups corrected using honestly significant difference Tukey-Kramer analysis. The Kaplan-Meier analysis was used for the examination of the survival and event free rate. Differences in survival rate or arrhythmic event free rate were assessed by the log-rank test. A 2-sided p<0.05 was considered to indicate statistical significance.

Results
Patient Characteristics (Table 1)
The LVEF evaluated by left ventriculography, echocardiography or radionuclide imaging was 39±16%.

There were no significant differences between the 3 groups in terms of the age, gender and NYHA class. However, the LVEF and administration of -blockers were significantly higher in the Control group as compared to the Amiodarone and Class I groups (LVEF: 44% vs 37%, 39%, respectively, p<0.05, administration of -blockers: 56% vs 40%, 34%, respectively, p<0.05), and the proportion of ischemic heart disease was significantly lower in the Class I group as compared to the Amiodarone and Control group (32% vs 48%, 38%, respectively; p<0.05).

Arrhythmic Events and ICD Therapy (Table 2)
There were no significant differences in the follow-up period (Amiodarone: 37±26 months; Class I: 42±29 months;
and Control: 37±26 months, respectively), mean period from the implantation to the first appropriate therapy delivery (Amiodarone: 324±407 days; Class I: 307±349 days; and Control: 408±487 days, respectively), type of arrhythmia (VT or VF) (Amiodarone: VT/VF =74/9; Class I: 44/10; and Control: 37/6), loss of consciousness during the first therapy delivery (Amiodarone: 30%; Class I: 26%; and Control: 32%) and frequency of electrical storms (Amiodarone: 13%; Class I: 22%; and Control: 11%) between the 3 groups. Interestingly, inappropriate therapy deliveries in the Amiodarone group were significantly lower as compared to the Class I and Control groups (7%, vs 18% and 27%; p<0.001) and there were no unsuccessful appropriate ICD therapy deliveries in the Amiodarone group (Amiodarone: 0%; Class I: 5%; and Control: 4%).

Mortality and Arrhythmic Event-Free Rate
The analysis of the Kaplan-Meier curves plotted with the survival rate for the 3 groups indicated a significantly higher survival rate in the Amiodarone group than in the Class I group (86% vs 74% at 5 years, p<0.05, Fig 4). However, there was no significant difference in the mortality between the Amiodarone and Control groups (86% vs 77% at 5 years, NS), and Class I and Control groups (74% vs 77% at 5 years, NS).

The arrhythmic event-free (appropriate ICD therapy)
Amiodarone and Implantable Cardioverter-Defibrillator

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The cumulative survival rate in the 3 groups. An analysis using Kaplan-Meier curves plotted with the survival rates among the 3 groups indicated a significant lower mortality in the Amiodarone group (solid line) than in the Class I group (large dotted line). Furthermore, there was no significant difference in the mortality between Amiodarone and the Control group (small dotted line), and Class I and the Control group using the log-rank test. The survival rates at 5 years were 86% in the Amiodarone group, 74% in the Class I group and 77% in the Control group, respectively.

The cumulative arrhythmic event free rate in the 3 groups. The arrhythmic event free rate was significantly higher in the Amiodarone group (solid line) as compared with the Class I group (large dotted line) (53% vs 35% at 5 years; p<0.05). However, there was no significant difference between the Amiodarone group and Control group (small dotted line) (53% vs 48% at 5 years, NS).

Adverse Effects of Amiodarone

Adverse effects of amiodarone were observed in 41 out of 354 patients (12%), including patients taking a combination of amiodarone and class I drugs. Thyroid function abnormalities were observed in 16 patients (4.5%), pulmonary intoxication (including an asymptomatic decrease in the DLCO: Diffusing capacity of the lungs for carbon monoxide) in 22 (6.2%), pro-arrhythmic effects in 2 (0.5%) and a worsening of congestive heart failure in 1 (0.3%).

Pulmonary intoxication occurred in 11 patients from drug-induced pulmonary infiltrations (3.1%) and 11 had an asymptomatic decrease in the DLCO (3.1%, Table 3). The dosage of the amiodarone in the patients with adverse effects ranged from 100 mg to 400 mg per day (average 210 mg). The average interval between the administration of the amiodarone and the onset of the pulmonary intoxica-

_rate was significantly higher in the Amiodarone group as compared with the Class I group (68% vs 49% at 2 years, 53% vs 35% at 5 years; p<0.05, Fig 5). However, there was no significant difference between the Amiodarone and Control groups (68% vs 68% at 2 years, 53% vs 48% at 5 years, NS).

Subgroup analysis focusing on the patients with an LVEF of less than 35% revealed a lower mortality in the Amiodarone group as compared with the Class I and Control groups (68% vs 68% at 2 years, 53% vs 48% at 5 years, NS).

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The pulmonary toxicity was 19 months (ranging from 1 to 84 months). All pulmonary toxicities improved with the termination of the drug (n=16; 73%), reduction in the dosage (n=4; 18%) and administration of corticosteroid therapy (n=2; 10%). Furthermore, of importance, there were no deaths caused by the adverse effects of amiodarone during the follow-up period.

### Discussion

**Efficacy of Amiodarone**

The present retrospective study demonstrated that the total mortality was lower and arrhythmic events were less with amiodarone as compared to class I drugs, but the benefits of amiodarone disappeared when compared with Control group patients. The harmful effects of class I drugs may account for this result. However, in spite of the sicker background of the amiodarone patients, their outcome was slightly better (but not statistically significant) than the control patients, which suggests some beneficial effects from amiodarone. A significant clinical bias, which could have resulted in a trend of amiodarone being prescribed in sicker patients, might have led to an underestimation of the drug effect. Furthermore, the relatively low incidence of adverse effects and the lack of any fatal events during the amiodarone therapy indicated that adjunctive amiodarone therapy with an ICD implantation is considered to be acceptably safe. The incidence of discontinuation of treatment was higher than those of other groups (Amiodarone in 20 cases, Class I group in 3, and Control in 5). These data could overestimate the effect of amiodarone therapy in the present study. To evaluate the efficacy of amiodarone more precisely in the patients with a history of VT/VF and with an ICD, a randomized prospective study such as the NIPPON study is strongly required.

An important rationale for an adjuvant therapy with anti-arrhythmic drugs in patients with an ICD is that defibrillators do not provide absolute protection against death from arrhythmias. About 2 per cent of VT/VF episodes were reported to be refractory to appropriate defibrillator therapy deliveries. Recent studies suggest that episodes of VF, even ones that were successfully terminated by an ICD, may increase the risk of myocardial and cerebral ischemic injury. The avoidance of frequent shocks is crucial for the safety and QOL of patients with an ICD. An important complication of appropriate or inappropriate shocks delivered by implantable defibrillators is that they may evoke serious psychological reactions in up to one third of the patients. If the combined use of amiodarone with an ICD is tested prospectively, it is expected that the drug reduces the total mortality and improves the patient's QOL by inhibiting the electrical therapy from the ICDs.

Another benefit of the combination of anti-arrhythmic agents and ICDs may be to reduce the number of appropriate shocks by converting VF to hemodynamically stable VT and to provide an improved efficacy of anti-tachy pacing (ATP) for the termination of hemodynamically stable VT. Furthermore, the adjuvant drug therapy with an ICD can reduce inappropriate shocks by preventing supraventricular tachycardia. Because the questionnaire in the present study included only the items concerning the first ICD

### Table 3 Pulmonary Toxicity (n=22)

<table>
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<tr>
<td>Reduction of %DLco</td>
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<tr>
<td>Dose of amiodarone (mg/day)</td>
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<tr>
<td>100</td>
<td>2</td>
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<tr>
<td>200</td>
<td>18</td>
</tr>
<tr>
<td>400</td>
<td>2</td>
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<tr>
<td>Dosing period (months)</td>
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<td>Therapy</td>
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<td>Termination</td>
<td>16</td>
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<td>Reduction of dosage</td>
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<td>Prednisone</td>
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</tr>
<tr>
<td>Improvement</td>
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DL, diffusing capacity of the lungs for carbon monoxide.
therapy delivery, it was not adequate for evaluating the pronounced efficacy of the ATP from the amiodarone administration. However, the significantly reduced inappropriate ICD therapy deliveries in the amiodarone group in the present study suggest its favorable effects in preventing supraventricular tachycardias.

Adverse Effects of Antiarrhythmic Agents

It has been reported that antiarrhythmic drugs such as class I drugs and amiodarone may potentially make ICD therapy for VT/VF unsuccessful by either increasing the defibrillation threshold or by increasing the cycle length of the VT/VF above the programmed detection criteria. In the present study, there were no unsuccessful episodes in the amiodarone group, whereas there were 5% in the Class I group and 4% in the Control group (p=NS). This also indicates that amiodarone is a safe drug to use in ICD patients with respect to the interaction between the drug and the device. There was a relatively higher incidence of unsuccessful episodes in the Class I group and that may relate to their poor outcome. However, the efficacy of ICD therapy was not available in 5% of patients in Class I group and 25% in Control group. Therefore it is possible that these data led to an overestimation of the number of unsuccessful ICD episodes in both groups.

As shown in the CAST and MUSTT studies, the higher recurrence rate of VT/VF in the Class I group in the present study may reflect a higher incidence of the proarrhythmic effects of the agent. Sodium-channel blockers induce a significant conduction delay in diseased myocardium by facilitating the formation of reentrant circuits. In the present study, class Ie and class Ia drugs, both of which have a strong blocking effect on sodium channels, were prescribed in >50% of the patients in the Class I group. Another possible adverse effect of class I drugs is the negative inotropic effect. Suppression of the inward sodium current decreases the intracellular calcium level, and relates to a decreased contraction of the myocardium. Due to the simplification of the questionnaire, we could not investigate the incidence of symptomatic congestive heart failure. However, this might be related to the poor prognosis of the Class I group in the present study.

On the other hand, amiodarone increases the refractory period without affecting the conduction velocity. The CASCADE trial demonstrated the significant superiority of amiodarone as compared to the conventional therapy guided by electrophysiological testing or Holter monitoring in preventing potentially lethal arrhythmias in patients resuscitated from cardiac arrest. CAMIAT and EMIAT demonstrated the beneficial effects of amiodarone on arrhythmic death in patients with post-myocardial infarction. The amiodarone meta-analysis, which accumulated 6,500 patients from 13 randomized trials and tested the efficacy of amiodarone, showed an improvement in the total mortality in patients with amiodarone. According to these trials, amiodarone is considered to be effective when used not only for secondary prevention, but also for primary prevention. However, the newest randomized mega-trial, SCD-HeFT, which accessed the efficacy of amiodarone and ICDs in patients with congestive heart failure, failed to suggest any significant beneficial effect of amiodarone on the total mortality in patients with NYHA III heart failure. Therefore, the efficacy and feasibility of the combined use of amiodarone with an ICD in patients with a high risk for sudden cardiac death remains undetermined.

Implication of a Randomized Prospective Study

The number of patients included in the randomized study will be determined on the basis of the estimation of the sample size needed to identify a significant difference in the primary end point of the study. On the basis of the present study, the projected incidence of appropriate ICD therapy in the non-amiodarone group was estimated to be 30% at 2 years. We assumed a relative risk reduction of 30% after amiodarone therapy. A sample size of 400 patients (200 patients per group) will be required to ensure the detection of the difference between the groups with a 2-sided p value of 0.05 and a power of 80% in the NIPPON study.

The SCD-HeFT trial revealed complications in 10% of the patients with amiodarone at the time of the last follow-up visit. Similarly, adverse effects were demonstrated in 12% of patients with amiodarone; however, no fatal side effects from amiodarone was observed in the present study. A decrease of DLco was not routinely performed and was observed in only non-symptomatic patients; therefore, we might have overestimated the rate of pulmonary deficiency caused by amiodarone. This indicates that when amiodarone is used under closer observation, the risk of conjunctive amiodarone therapy will be sufficiently low to promote the NIPPON study.

Limitations

Because the present study was retrospectively investigated, it contains several limitations. First, there was an irremovable clinical bias such that amiodarone tended to be administered in the more critical patients. The LVEF in the amiodarone group was significantly lower than that in the Control group in the present study. This bias may have led to an underestimation of the effects of amiodarone. Second, because we made the questionnaire as simple as possible, the information, especially regarding the cause of death, was lacking, and thus the cause of the poor prognosis in the Class I group was unclear. Also we could not determine precisely when there was a change or discontinuation of anti-arrhythmia drugs, especially in patients without ICD events. Third, the registration of patients depended on efforts of the each investigator. There were inadequate data in considerable numbers of questionnaires, such as in the number of electrical storms and inappropriate therapy; therefore, these data might allow for over- or under-estimation in this analysis.

Conclusions

The present study could not demonstrate the benefit of amiodarone in ICD patients due to a significant clinical bias exerted in selecting this drug. Randomized administration of amiodarone is feasible and safe under close observation. To evaluate the efficacy of amiodarone more precisely in the patients with a history of VT/VF and with an ICD, a randomized prospective study such as NIPPON study is strongly required.

References


Appendix 1

NIPPON Pre-Study Investigators

In addition to the authors, the following investigators also participated in this study:

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