A Prospective Study on the Risk-Stratification for Patients With Non-Sustained Ventricular Tachycardia Using a Novel Algorithm

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Background The therapeutic strategy for non-sustained ventricular tachycardia (NSVT), considered as a risk-stratifier for sudden cardiac death (SCD), still remains undetermined.

Methods and Results In the present study 222 of 4,079 patients (5.4%) hospitalized with NSVT during 2002 to 2004 were prospectively evaluated using an algorithm for risk-stratification according to each type of structural heart disease. The algorithm comprises the left ventricular ejection fraction, signal-averaged electrocardiography, programmed ventricular stimulation and the family history of SCD. Of the 222 patients, 151 (68.0%) were successfully risk-stratified and 32 patients consequently received an implantable cardioverter defibrillator (ICD) (21.2%; algorithm-ICD group). The remaining 119 patients without an ICD (algorithm-observation group) were observed. During 27.7±11.4 months of follow-up, the patients in the algorithm-ICD group had a significantly higher prevalence of tachyarrhythmic events than did those in the algorithm-observation group (9/32 vs 1/119; p<0.05). In the algorithm-ICD group, 2, 1 and 6 patients experienced an SCD, aborted SCD and appropriate ICD intervention, respectively, while there was only 1 SCD in the algorithm-observation group.

Conclusions The proposed algorithm for risk-stratification of patients with NSVT may be feasible for appropriate selection of high-risk patients and candidates for prophylactic ICD implantation. (Circ J 2007; 71: 1107–1114)

Key Words: Algorithm; Electrophysiologic study; Non-sustained ventricular tachycardia; Prophylactic ICD implantation

Recent clinical trials demonstrated that implantable cardioverter-defibrillators (ICDs) were superior to medical therapy, including amiodarone, for primary1–5 as well as secondary6,7 prevention of sudden cardiac death (SCD) in high-risk populations. However, a prophylactic study found that the prevalence of arrhythmic events, including ICD shock deliveries, was unpredictably low and the absolute cost effectiveness was very poor, suggesting that it is necessary to establish a reasonable method of risk-stratification to identify the genuine high-risk patients, who are likely to receive appropriate shock deliveries.

Non-sustained ventricular tachycardia (NSVT), defined commonly as 3 or more consecutive beats of a ventricular origin lasting less than 30 s, occurs in various clinical settings in anyone from patients with or without structural heart disease to healthy individuals8 Previous studies have demonstrated that the occurrence of NSVT has prognostic significance for subsequent lethal ventricular tachyarrhythmias and SCD in patients with structural heart disease9–12. Currently in Japan, there are clinical guidelines for prophylactic ICD implantation in patients with NSVT, which was developed by a working group of the Japanese Circulation Society (JCS) and published in 200113. Together with these and the results of recent clinical randomized trials, we constructed an algorithm using the left ventricular ejection fraction (LVEF), signal-averaged electrocardiography (SAECG), programmed ventricular stimulation (PVS) and family history of SCD for risk-stratification of these patients. The aim of the present study was to evaluate the usefulness of our algorithm in a selection of high-risk patients with and without structural heart disease, by prospective enrollment of patients with NSVT and then follow-up.

Methods

Study Population

This study was approved by the Institutional Review Board of Nippon Medical School. We enrolled 229 patients (5.6%) with NSVT detected by 24-h Holter monitoring and without any documented sustained ventricular tachyarrhythmias or syncope, out of a total 4,079 consecutive patients who were admitted to the cardiology section during the period of January 2002 to December 2004. NSVT was defined as 3 or more consecutive beats of ventricular origin, with a rate of more than 120 beats/min and lasting less than 30 s. Each type of underlying heart disease was diagnosed by the generally accepted criteria using echocardiography, radionuclide imaging and coronary angiography. Any patients with a recording of NSVT occurring during the 2-week period following the onset of an acute myocardial infarction, or exacerbation of congestive heart failure, were
excluded from the study. Demographic data, including age, sex, and underlying heart disease, were collected for all patients, as well as the following clinical data for patients with NSVT: (1) follow-up period, (2) New York Heart Association (NYHA) functional class, (3) basic rhythm (sinus rhythm, atrial fibrillation, or pacing rhythm), (4) number of premature ventricular complexes per 24 h, number of consecutive ventricular beats and the cycle length of the NSVT, (5) echocardiographic parameters including left ventricular diastolic dimension (LVDd) and LVEF, (6) level of serum brain natriuretic peptide (BNP), and (7) administration of angiotensin-converting enzyme inhibitors, angiotensin-II receptor blockers, β-blockers, amiodarone or sotalol. A family history of SCD, defined as SCD in a first-degree relative, was elicited from the patients with hypertrophic cardiomyopathy (HCM).

**Algorithm**

An algorithm was constructed for each of the following underlying heart diseases (Fig 1).

**Ischemic Heart Disease (IHD) With NSVT** Recent multicenter clinical trials have demonstrated that sustained ventricular tachyarrhythmias induced by PVS are associated with an increased risk of mortality in patients with LVEF ≤40%. Although the clinical role of PVS has not been well established in patients with preserved ejection fraction (LVEF >40%), SAECG has been shown to have potential in selecting high-risk patients. Therefore, in the present study patients with an LVEF ≤40% or >40% and positive late potentials (LPs), underwent PVS and the reproducible induction of sustained ventricular tachyarrhythmias was confirmed before ICD implantation.

**Nonischemic Cardiomyopathy (NICM) With NSVT** NICM is defined as the cardiac dysfunction (both systolic and diastolic) of the left ventricle (LV) because of non-ischemic causes such as dilated cardiomyopathy (DCM), valvular heart disease, and hypertensive heart disease. Because impaired LV systolic function has been shown to be a very powerful and reliable marker for predicting SCD in NICM, we excluded any patients with an LVEF >40% from further risk-stratification. Although the role of SAECG is still undetermined in this condition, we assessed the arrhythmia substrate using SAECG before using PVS, because tachycardia induction has been shown to be well-correlated with the presence of LPs. The role of PVS in risk-stratification for NICM still remains unclear, however, we decided to use this invasive tool according to JCS guidelines for ICD implantation in patients with NSVT. Because the efficacy of prophylactic antiarrhythmic treatment using amiodarone still remains undetermined in this patient population, it was inferred that the efficacy of amiodarone should be evaluated before implantation of an ICD.

**HCM With NSVT** The recognized risk factors for SCD, such as NSVT, thickened ventricular wall etc, have had a low positive predictive value independently below 30%, and a positive family history has had the highest (28%). Furthermore, no family history, and positive LPs, which are reported to reflect the electrical and textural substrate of ventricular tachycardia (VT) in HCM, had a high incidence of a clinical ventricular tachyarrhythmia. In addition, 2 or more risk factors raised the risk of SCD and the annual sudden death rate by 3%. Therefore, it was decided that patients with 2 risk factors (ie, NSVT and a positive family history or NSVT and positive LP), should undergo PVS, because inducibility has been reported to predict clinical tachyarrhythmias. Inducible ventricular tachyarrhythmias necessitated ICD implantation.

**No Structural LV Disease With NSVT** Atrial septal defect and ventricular septal defect with low shunt ratio, not associated with LV dysfunction, were included in this category. They were examined without the use of any invasive or non-invasive tests or specific antiarrhythmic drugs, based on the findings of recent reports that NSVT in patients with no structural heart disease is not associated with any adverse prognosis.

The greatest prophylactic use of ICDs using this algorithm, other than in 2 IHD patients with an LVEF ≤40%, positive LPs and inducible PVS, corresponded to the Class IIa or IIb recommendations of the JCS guidelines for the primary prevention of SCD.
Three orthogonal leads (X, Y, Z) were amplified and filtered with R-wave triggering through a bi-directional bandpass filter (50–250 Hz) and then combined and expressed as a vector magnitude ($X^2+Y^2+Z^2$). The following 3 signal-filtering were used: (1) the duration of the signal-averaged, high-frequency filtered QRS complex (f-QRS), (2) the duration of the low amplitude signal <40μV in the terminal portion of the f-QRS (LAS40), and (3) the root mean square voltage of the terminal 40 ms of the f-QRS (RMS40). A LP was considered to be positive if 2 of the following 3 criteria were met: (1) f-QRS >120 ms, (2) LAS40 >38 ms, and (3) RMS40 <20μV, or otherwise, classified as negative. Patients with bundle branch block or a ventricular paced rhythm did not undergo an SAECG study and were assumed to have a similarly poor prognosis as those with a positive test, thus proceeding to the next examination of the algorithm.

**SAECG**

A high-resolution electrogram was obtained using the Sanei Signal Processor DP 1100 (NEC Co, Tokyo, Japan). Three orthogonal leads (X, Y, Z) were amplified and filtered with R-wave triggering through a bi-directional bandpass filter (50–250 Hz) and then combined and expressed as a vector magnitude ($X^2+Y^2+Z^2$). The following 3 signal-averaged parameters were calculated: (1) the duration of the signal-averaged, high-frequency filtered QRS complex (f-QRS), (2) the duration of the low amplitude signal <40μV in the terminal portion of the f-QRS (LAS40), and (3) the root mean square voltage of the terminal 40 ms of the f-QRS (RMS40). A LP was considered to be positive if 2 of the following 3 criteria were met: (1) f-QRS >120 ms, (2) LAS40 >38 ms, and (3) RMS40 <20μV, or otherwise, classified as negative. Patients with bundle branch block or a ventricular paced rhythm did not undergo an SAECG study and were assumed to have a similarly poor prognosis as those with a positive test, thus proceeding to the next examination of the algorithm.

**PVS**

After obtaining written informed consent, an electrophysiologic study was performed while the patient was fasted and sedated with midazolam. Any antiarrhythmic agents were not discontinued before the study. PVS of up to triple extrastimuli with 2 basic pacing cycle lengths and from 2 different sites in the right ventricle was performed, and repeated under isoproterenol infusion if a sustained ventricular tachyarrhythmia was not induced. The pacing pulse width and amplitude were 1 ms and twice the diastolic threshold, respectively. Each extrastimulus was delivered in incrementally shorter coupling intervals by steps of 10 ms down to the effective refractory period of the right ventricle or a coupling interval of 180 ms in order to avoid any non-specific induction. In patients with NICM, if any significant ventricular tachyarrhythmias were induced, PVS was repeated after 2 weeks of treatment with amiodarone. The sinus node function and atrioventricular conduction properties were also evaluated simultaneously in all patients. The surface ECGs and intracardiac electrograms were continuously monitored and recorded using an EP Workmate system (EPMed System, West Berlin, NJ, USA). Reproducible induction of sustained VT with up to triple extrastimuli or ventricular fibrillation (VF) with up to double extrastimuli was considered to be significant because inducible VF by triple extrastimuli has a low prognostic significance in patients without prior documentation of any clinical ventricular tachyarrhythmias.

**NSVT**

Non-sustained ventricular tachycardia; LVEF, left ventricular ejection fraction; HHD, ischemic heart disease; NICM, non-ischemic cardiomyopathy; DCM, dilated cardiomyopathy; VHD, valvular heart disease; HHD, hypertensive heart disease; HCM, hypertrophic cardiomyopathy; LV, left ventricle.

**Clinical Characteristics of the Patients With NSVT**

<table>
<thead>
<tr>
<th>Clinical Characteristics</th>
<th>NSVT patients (n=229)</th>
<th>LVEF (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>M/F</strong></td>
<td>183/46</td>
<td></td>
</tr>
<tr>
<td>No. of patients with structural heart disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HHD</td>
<td>98</td>
<td>41±18</td>
</tr>
<tr>
<td>NICM</td>
<td>61</td>
<td>37±19</td>
</tr>
<tr>
<td>DCM</td>
<td>38</td>
<td>29±12</td>
</tr>
<tr>
<td>VHD</td>
<td>16</td>
<td>50±22</td>
</tr>
<tr>
<td>HHD</td>
<td>7</td>
<td>42±21</td>
</tr>
<tr>
<td>HCM</td>
<td>29</td>
<td>63±20</td>
</tr>
<tr>
<td>No structural LV disease</td>
<td>41</td>
<td>57±14</td>
</tr>
</tbody>
</table>

*One patient with atrial septal defect and 2 with ventricular septal defect were categorized as “No structural LV disease” because they were not associated with LV dysfunction.

**NSVT**, non-sustained ventricular tachycardia; LVEF, left ventricular ejection fraction; HHD, ischemic heart disease; NICM, non-ischemic cardiomyopathy; DCM, dilated cardiomyopathy; VHD, valvular heart disease; HHD, hypertensive heart disease; HCM, hypertrophic cardiomyopathy; LV, left ventricle.

### Risk-Stratification of NSVT Using a Novel Algorithm

The prophylactic implantation of an ICD was carried out according to the results of the risk-stratification. Both single-chamber and dual-chamber ICDs were used in accordance with the basic rhythm and sinus/atrioventricular nodal function of each patient. The detection zone of the VT and VF, anti-tachycardia pacing therapy, and cardioversion and defibrillation parameters were programmed individually based on the findings of the electrophysiologic study.

### Clinical Follow-up

The NSVT patients were followed via routine visits to hospital or outpatient clinic up to December 2005. The stored ICD data were obtained every 4 months. Any episodes of spontaneous VT or VF, ICD interventions, SCDs and the reason for admission or death were recorded. SCD was defined as a witnessed death within 1 h of the onset of new symptoms or a nocturnal death with no antecedent history of worsening symptoms, provided that any apparent cerebrovascular disease was excluded. Death because of congestive heart failure was defined as a death in the hospital with findings of progressive heart failure, including cardiogenic shock, and no evidence of ventricular tachyarrhythmias. For the patients who were lost during follow-up, telephone interviews and letters to them or their relatives were used to investigate their clinical condition. The follow-up period was started on the day the patients were risk-stratified using the algorithm and the therapeutic strategy was decided.

### Statistical Analysis

Data are presented as the mean ± standard deviation. Student’s t-test was performed on the different sets of data. Kaplan-Meier curves were used to estimate the rate of tachyarrhythmic events and were compared with using log-rank statistics. Differences were considered significant when the p-value was <0.05. Descriptive statistical analyses were calculated with SPSS software (Chicago, IL, USA).
Results

Clinical Characteristics

Of the 4,079 patients, 252 (6.2%) had NSVT on 24-h Holter monitoring during their hospitalization, without a history of documented sustained ventricular tachyarrhythmias. Of them, 23 patients had a history of syncope and were excluded from the study. Consequently, there were 229 patients (5.6% IHD, 12.3% NICM, 22.0% HCM, 2.4% without structural LV disease) who had NSVT without any documented sustained ventricular tachyarrhythmias or syncope (Table 1). Their mean age was 65±13 years.

Algorithm-ICD, Algorithm-Observation and No-Algorithm Groups

Four NSVT patients died of either congestive heart failure (3 patients) or a cerebrovascular disorder (1 patient) before discharge. Three patients who were diagnosed with idiopathic VF after a routine evaluation, were excluded from the study. Consequently, a total of 222 patients with NSVT were prospectively followed and of them 151 (68.0%) were successfully risk-stratified and treated according to the algorithm (algorithm group) and 71 patients (no-algorithm group) dropped out for various reasons; such as refusing further examination, impaired systemic condition or being very elderly. The results of the risk-stratification assessed by the algorithm are shown in Fig 1. In the algorithm group, 32 patients were eventually judged to be at high risk for SCD and ICD implantation was carried out (algorithm-ICD group). Nine single-chamber ICDs (2: GEMIIVR; Medtronic Inc, St Paul, MN, USA; 7: VENTAK MINIIV; Guidant Inc, Minneapolis, MN, USA) and 23 dual-chamber ICDs (12: GEMIIDR; Medtronic and 11: VENTAK PRIZMII; Guidant) were used. No major complications occurred during the implantation procedures. The remaining 119 patients were observed with and without antiarrhythmic drugs (algorithm-observation group). Tables 2 and 3 show the baseline characteristics and clinical data of the algorithm-ICD and algorithm-observation groups.

Table 2 Clinical Characteristics of the Algorithm-ICD and Algorithm-Observation Groups

<table>
<thead>
<tr>
<th></th>
<th>Algorithm-ICD (n=32)</th>
<th>Algorithm-observation (n=119)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>64±12</td>
<td>61±13</td>
<td>NS</td>
</tr>
<tr>
<td>M/F</td>
<td>28/4</td>
<td>90/29</td>
<td>NS</td>
</tr>
<tr>
<td>No. of patients with structural heart disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IHD</td>
<td>16</td>
<td>27</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>NICM</td>
<td>10</td>
<td>40</td>
<td>NS</td>
</tr>
<tr>
<td>DCM</td>
<td>10</td>
<td>21</td>
<td>NS</td>
</tr>
<tr>
<td>VHD</td>
<td>0</td>
<td>13</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>HHD</td>
<td>0</td>
<td>6</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>HCM</td>
<td>6</td>
<td>15</td>
<td>NS</td>
</tr>
<tr>
<td>No structural LV disease</td>
<td>0</td>
<td>37</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IHD</td>
<td>31±11</td>
<td>47±13</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>NICM</td>
<td>27±9</td>
<td>43±20</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>DCM</td>
<td>27±9</td>
<td>33±12</td>
<td>NS</td>
</tr>
<tr>
<td>VHD</td>
<td>56±20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HHD</td>
<td>50±24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCM</td>
<td>59±20</td>
<td>70±12</td>
<td>NS</td>
</tr>
<tr>
<td>No structural LV disease</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ICD, implantable cardioverter defibrillator. Other abbreviations see in Table 1.

Table 3 Clinical Data From the Algorithm-ICD and Algorithm-Observation Groups

<table>
<thead>
<tr>
<th></th>
<th>Algorithm-ICD (n=32)</th>
<th>Algorithm-observation (n=119)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA class</td>
<td>1.7±0.7</td>
<td>1.4±0.6</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Basic rhythm (SR/AF/pacing)</td>
<td>27/4/1</td>
<td>93/24/2</td>
<td></td>
</tr>
<tr>
<td>No. of consecutive NSVT beats</td>
<td>12±9</td>
<td>13±24</td>
<td>NS</td>
</tr>
<tr>
<td>CL of the NSVT (ms)</td>
<td>382±75</td>
<td>355±79</td>
<td>NS</td>
</tr>
<tr>
<td>Total VPC count/day</td>
<td>5,513±7,910</td>
<td>5,473±10,804</td>
<td></td>
</tr>
<tr>
<td>Brain natriuretic peptide level (pg/ml)</td>
<td>309±204</td>
<td>355±483</td>
<td>NS</td>
</tr>
<tr>
<td>LVDd (mm)</td>
<td>62±12</td>
<td>55±10</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>38±20</td>
<td>52±18</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>No. of patients with an LVEF ≤40%</td>
<td>25</td>
<td>26</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>No. of patients with an LVEF ≤30%</td>
<td>17</td>
<td>20</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Positive LP</td>
<td>12/14</td>
<td>14/68</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Bundle branch block</td>
<td>6</td>
<td>4</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Inducible mVT/pVT/VF</td>
<td>19/9/4</td>
<td>0/0/1</td>
<td></td>
</tr>
<tr>
<td>ACE inhibitors or ARBs (%)</td>
<td>88</td>
<td>67</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>β-blockers (%)</td>
<td>81</td>
<td>61</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>AMD or sotalol (%)</td>
<td>47</td>
<td>15</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

NYHA, New York Heart Association; SR, sinus rhythm; AF, atrial fibrillation; CL, cycle length; VPC, ventricular premature contraction; LVDd, left ventricular diastolic dimension; LP, late potential; mVT, monomorphic ventricular tachycardia; pVT, polymorphic ventricular tachycardia; VF, ventricular fibrillation; ACE, angiotensin-converting enzyme; ARB, angiotensin-II receptor blocker; AMD, amiodarone. Other abbreviations see in Tables 1, 2.
algorithm-observation groups. The patients in the algorithm-ICD group had a significantly higher NYHA class and more enlarged LVDd than those in the algorithm-observation group. The parameters of Holter monitoring and level of BNP did not differ between the 2 groups. Angiotensin converting enzyme inhibitors/angiotensin-II receptor blockers and Î²-blockers were more frequently used in the algorithm-ICD group than in the algorithm-observation group (88 vs 67% and 81 vs 61%, respectively). The mean age and NYHA class were 71±12 and 1.9±0.7, respectively, in the no-algorithm group, which were slightly higher than in the other 2 groups, but was not statistically significant.

Follow-up
During a mean follow-up period of 27.7±11.4 months (range 3–48), 9 patients (28.1%) in the algorithm-ICD group had tachyarrhythmic events, including 6 patients with spontaneous VT/VF followed by appropriate ICD intervention, 2 SCDs and 1 aborted SCD, whereas only 1 patient (0.8%) in the algorithm-observation group had a tachyarrhythmic event (p<0.05) (Table 4). The 2 SCDs were not witnessed and no stored ICD data were available. The patient with an aborted SCD was resuscitated in the emergency department after 2 consecutive ICD shocks for VF and subsequent electromechanical dissociation. The patient with the tachyarrhythmic event in the algorithm-observation group died suddenly at night alone. The rate of patients with tachyarrhythmic events in the algorithm-ICD group was 28.1% compared with 0.8% in the algorithm-observation group (p<0.001; Fig 2). One SCD and 1 spontaneous VT occurred in the no-algorithm group and for the latter patient, an ICD was implanted. Inappropriate ICD interventions for 2 sinus tachycardia episodes and 4 atrial fibrillation episodes were observed in 6 (18.8%) of the 32 patients in the algorithm-ICD group. One patient in the algorithm-ICD

<table>
<thead>
<tr>
<th></th>
<th>Algorithm-ICD (n=32)</th>
<th>Algorithm-observation (n=119)</th>
<th>p value</th>
<th>No-algorithm (n=71)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total tachyarrhythmic events</strong></td>
<td>9 (3/5/1/0)</td>
<td>1 (0/1/0/0)</td>
<td>&lt;0.05</td>
<td>2 (2/0/0/0)</td>
</tr>
<tr>
<td><strong>SCD</strong></td>
<td>2 (0/2/0/0)</td>
<td>1 (0/1/0/0)</td>
<td>NS</td>
<td>1 (1/0/0/0)</td>
</tr>
<tr>
<td><strong>Aborted SCD</strong></td>
<td>1 (1/0/0/0)</td>
<td>0</td>
<td>NS</td>
<td>0</td>
</tr>
<tr>
<td><strong>Spontaneous VT/VF</strong></td>
<td>6 (2/2/1/0)</td>
<td>0</td>
<td>&lt;0.05</td>
<td>1 (1/0/0/0)</td>
</tr>
<tr>
<td><strong>Appropriate ICD intervention</strong></td>
<td>6 (2/2/1/0)</td>
<td>0</td>
<td>NS</td>
<td>1 (1/0/0/0)</td>
</tr>
<tr>
<td><strong>ATP</strong></td>
<td>2 (2/1/0/0)</td>
<td>0</td>
<td>NS</td>
<td>0</td>
</tr>
<tr>
<td><strong>DC</strong></td>
<td>5 (2/2/1/0)</td>
<td>0</td>
<td>NS</td>
<td>0</td>
</tr>
</tbody>
</table>

Numbers in parentheses indicates the number of patients with IHD, NICM, HCM and no structural LV disease, respectively. SCD, sudden cardiac death; VT, ventricular tachycardia; ATP, anti-tachycardia pacing; DC, direct-current cardioversion. Other abbreviations see in Tables 1–3.

Fig. 2. Kaplan-Meier estimates of the rate of tachyarrhythmic events stratified for the algorithm-implantable cardioverter defibrillator (ICD) group vs the algorithm-observation group. The algorithm-ICD group had a higher prevalence of tachyarrhythmic events than the algorithm-observation group (28.1% vs 0.8%, p<0.001).

Fig. 3. Comparison of the tachyarrhythmic event rate in the algorithm-implantable cardioverter defibrillator (ICD) patients and presumed event rate in patients extracted from our patient population with nonsustained ventricular tachycardia (NSVT) and left ventricular (LV) ejection fraction (EF) ≤30%, 35% or 40%, irrespective of other variables, with regard to ischemic heart disease (IHD) and nonischemic cardiomyopathy (NICM). The rate of tachyarrhythmic events was significantly higher in the algorithm-ICD group than in the patients with NSVT and an LVEF ≤40% (p<0.05) and had a greater trend (vs an LVEF ≤30%: p=0.08, vs an LVEF ≤35%: p=0.06).
group, 2 in the algorithm-observation group, and 9 in the no-algorithm group died of congestive heart failure. During the follow-up period, bi-ventricular pacing devices were additionally implanted in 2 patients (IHD and DCM) in the algorithm-ICD group and newly implanted in 2 patients (DCM and the dilated phase of HCM) in the no-algorithm group. None of the patients crossed over to another group during the follow-up period.

Comparison of the Follow-up Results Among the Structural Heart Diseases

When the prevalence of arrhythmic events was compared for each basic heart disease, 3 (18.8%) of the 16 patients with IHD in the algorithm-ICD group had tachyarrhythmic events, whereas no events occurred in the 27 patients in the algorithm-observation group (p<0.05). In the patients with NICM and HCM, there were 5 (50%) (p<0.05) and 1 patient (16.7%), respectively, with tachyarrhythmic events in the algorithm-ICD group, but only 1 and none, respectively, in the algorithm-observation group.

Comparison of the Results of the ICD Indications for NSVT and LVEF in the IHD and NICM Patients

In the patients with IHD and NICM, the rate of tachyarrhythmic events in the algorithm-ICD group was significantly higher than that in the patients extracted from our patient population who had an LVEF ≤40% and NSVT, irrespective of the results of other risk assessments (p<0.05) and had a higher trend (vs LVEF ≤30%: p=0.08, vs LVEF ≤35%: p=0.06) (Fig 3).

Clinical Data and Induced Tachyarrhythmias in the Patients With Tachyarrhythmic Events in the Algorithm-ICD Group

Table 5 shows the clinical and electrophysiological data for the patients in the algorithm-ICD group who had tachyarrhythmic events during the follow-up. The LVEF in these patients was <40%, except for the HCM patient. Amiodarone was not administered in the 3 IHD patients or 1 HCM patient. There was no similarity between the cycle lengths of the NSVT for the induced tachyarrhythmias and spontaneous tachyarrhythmias except in 2 patients (case nos. 87 and 2499).

Discussion

The major finding in this study is that our proposed algorithm for the risk-stratification of patients with NSVT could reasonably identify those patients at high-risk for SCD and the candidates for prophylactic ICD implantation. There is scant information systematically risk-stratifying NSVT patients with various types of underlying structural heart disease, so we constructed an algorithm that consisted of SAECG, LVEF, PVS and family history of SCD, based on the JCS guidelines13 and recent clinical studies.

Construction of the Algorithm

The results of our novel method, which integrated the Japanese guidelines, suggest the need for greater emphasis on the role of PVS in primary prevention in patients with NSVT.

For patients with IHD, a low LVEF and NSVT, the results of the MADIT1 and MUSTT2 trials showed that PVS played a key role in detecting high-risk patients. Our eligible patients with IHD comprised an almost similar population to those studies, and PVS is also emphasized in our algorithm, resulting in significant identification of the high-risk patients. Our finding was consistent with the results of the MUSTT sub-study, which demonstrated that ventricular tachyarrhythmias induced by PVS predict a greater occurrence of subsequent arrhythmic death and cardiac arrest.1 Therefore, PVS is an important tool for risk-stratification of IHD patients with a low LVEF and NSVT. We also performed PVS not only in patients with an LVEF ≤40% but also in those with an LVEF >40% with positive LPs, on the basis of the finding that positive LPs are possibly associated with a high rate of inducible ventricular tachyarrhythmias and poor prognosis.14 However, 2 patients with an LVEF >40%, positive LPs and inducible ventricular tachyarrhythmias, who underwent ICD implantation, had no tachyarrhythmic events during the follow-up. Thus, because of the small number of patients the clinical significance of NSVT in IHD patients with an LVEF >40% remains unclear from the present results.

In contrast to IHD, the importance of PVS in the prediction of the risk of arrhythmic events in patients with NICM and HCM is still controversial because of conflicting data and lack of large randomized trials.18-20,27,28 However, in our observation, 5 (50%) and 1 (16.6%) of 10 and 6 ICD recipients with NICM and HCM, respectively, had tachyarrhythmic events during the follow-up as a result of the risk-stratification using this algorithm with its emphasis on SAECG and subsequent PVS study. SAECG has been reported as useful for screening high-risk patients with NICM33 and for detecting electrical instability in those with HCM.25 Therefore, in patients with NICM and HCM, a SAECG study may be useful for selecting the candidates for PVS. In the JCS guidelines for the prevention of SCD updated in 2005,34 as well as in those developed in 2001, PVS was the main diagnostic tool for deciding whether a prophylactic ICD was needed not only for patients with

### Table 5 Data From the Patients With Tachyarrhythmic Events in the Algorithm-ICD Group

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Age (years)</th>
<th>Structural heart disease</th>
<th>Event/CL (ms)</th>
<th>EF (%)</th>
<th>LP</th>
<th>AMD</th>
<th>NSVT beats/CL (ms)</th>
<th>Arrhythmia induced by PVS/CL (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1907</td>
<td>58</td>
<td>IHD</td>
<td>Aborted SCD</td>
<td>29</td>
<td>(+)</td>
<td>(+)</td>
<td>7/360</td>
<td>nVT/240</td>
</tr>
<tr>
<td>87</td>
<td>73</td>
<td>IHD</td>
<td>VT (ATP, DC)/360</td>
<td>25</td>
<td>(+)</td>
<td>(+)</td>
<td>15/420</td>
<td>nVT/400</td>
</tr>
<tr>
<td>2442</td>
<td>61</td>
<td>IHD</td>
<td>VT (DC)/300</td>
<td>35</td>
<td>(+)</td>
<td>(+)</td>
<td>10/480</td>
<td>pVT/250</td>
</tr>
<tr>
<td>4009</td>
<td>28</td>
<td>DCM</td>
<td>SCD</td>
<td>10</td>
<td>(+)</td>
<td>(+)</td>
<td>11/440</td>
<td>nVT/320</td>
</tr>
<tr>
<td>2105</td>
<td>71</td>
<td>DCM</td>
<td>SCD</td>
<td>29</td>
<td>(+)</td>
<td>(+)</td>
<td>15/460</td>
<td>nVT/267</td>
</tr>
<tr>
<td>2468</td>
<td>52</td>
<td>DCM</td>
<td>VT (DC)/360</td>
<td>31</td>
<td>(+)</td>
<td>(+)</td>
<td>14/440</td>
<td>nVT/250</td>
</tr>
<tr>
<td>562</td>
<td>63</td>
<td>DCM</td>
<td>VT (DC)/290</td>
<td>28</td>
<td>(+)</td>
<td>(+)</td>
<td>26/420</td>
<td>nVT/272</td>
</tr>
<tr>
<td>2499</td>
<td>70</td>
<td>DCM</td>
<td>VT (ATP)/370</td>
<td>34</td>
<td>Pacing (+)</td>
<td>9/400</td>
<td>nVT/360</td>
<td></td>
</tr>
<tr>
<td>3413</td>
<td>67</td>
<td>HCM</td>
<td>VF (DC)</td>
<td>56</td>
<td>(+)</td>
<td>(+)</td>
<td>12/360</td>
<td>nVT/280</td>
</tr>
</tbody>
</table>

EF, ejection fraction; PVS, programmed ventricular stimulation; LBBB, left bundle branch block. Other abbreviations see in Tables 1–4.
Risk-Stratification of NSVT Using a Novel Algorithm

IHD, but also for those with NICM or HCM. Further investigation with a larger number of subjects is necessary to conclude the usefulness of this algorithm including PVS for NICM and HCM patients with NSVT.

Clinical Necessity of Risk-Stratifiers in Addition to LVEF

The MADIT-II and SCD-HEFT trials, which were 2 large randomized clinical trials, proposed broader criteria for the prophylactic implantation of ICDs without any evaluation of invasive and non-invasive electrophysiological markers, and used only LVEF ≤30% in IHD and LVEF ≤35% with a NYHA class II or III heart failure in ischemic and nonischemic patients. On the basis of those trials, the ACC/AHA/ESC 2006 guidelines included a class-I indication for prophylactic ICD therapy with a low LVEF and moderate heart failure in patients with IHD or NICM. However, only 21 patients (4.3%) of the 490 in the MADIT-II conventional therapy group had lethal ventricular arrhythmias that required ICD implantation during an average follow-up of 20 months, and 177 (21%) of 829 patients in the SCD-HEFT ICD group had appropriate ICD shocks during a median follow-up of 45.5 months. In Japan, it has been reported that only 6 (6.7%) of 90 patients with similar backgrounds to the MADIT-II inclusion criteria had clinical VTs or SCDs during 3 years of follow-up. In the present study, the incidence of lethal VTs or SCDs during PVS and spontaneous VT that occurred clinically during the follow-up period was much higher than did the ICD indications for NSVT and a LVEF ≤40%, 35% or 30% (Fig 3). This observation suggests the usefulness of combining risk-stratifiers, such as our algorithm, with the LVEF in patients with NSVT for predicting tachyarrhythmic events and SCD.

Characteristics of the Clinical, Induced, and Non-Sustained Ventricular Arrhythmias

As shown in Table 5, there was no similarity between the cycle lengths of the NSVT on Holter monitoring, induced tachyarrhythmias during PVS and spontaneous VT that occurred clinically during the follow-up period. These findings are consistent with a recent report that induced tachyarrhythmias depended on the decision of each attending physician. Therefore elderly patients or those with a higher NYHA class tended to be assigned to the no-algorithm group, resulting in high rates of death from congestive heart failure in that group. As described earlier, the 2 IHD patients with NSVT, an LVEF >40%, positive LPs and inducible ventricular tachyarrhythmias never underwent ICD therapy during 27.7±11.4 months of follow-up. Further evaluation is needed in this patient population. (3) Microvolt T-wave alternans testing, known as an important tool for noninvasive arrhythmia risk stratification, was attempted in the initial 20 patients, but was discontinued because 14 patients had indeterminate results because of insufficient elevation in the heart rate and frequent prema-

ture ventricular complexes, which may, in part, be related to the continuation of the use of β-blockers. (4) The study population was too small to determine the efficacy of our proposed algorithm for risk-stratification of SCD in patients with NSVT.

Clinical Implications

This study revealed a higher prevalence of tachyarrhythmic events in high-risk patients assessed using our algorithm than in the low-risk patients. Our algorithm for risk-stratification of patients with NSVT may be feasible for the appropriate selection of high-risk patients and candidates for prophylactic ICD implantation.

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References


