Safety and Efficacy of Subcutaneous Cardioverter Defibrillator in Patients at High Risk of Sudden Cardiac Death — Primary Japanese Experience —

Shingo Sasaki, MD, PhD; Hirofumi Tomita, MD, PhD; Takuo Tsurugi, MD; Yuji Ishida, MD, PhD; Yosshihiro Shoji, MD; Kimitaka Nishizaki, MD, PhD; Takahiko Kinjo, MD, PhD; Tomohide Endo, MD, PhD; Fumio Nishizaki, MD, PhD; Kenji Hanada, MD, PhD; Kenichi Sasaki, MD, PhD; Daisuke Horiuchi, MD, PhD; Masaomi Kimura, MD, PhD; Takumi Higuma, MD, PhD; Hideharu Okamatsu, MD; Yasuaki Tanaka, MD; Junjiroh Koyama, MD; Ken Okumura, MD, PhD

Background: The entirely subcutaneous implantable cardioverter defibrillator (S-ICD) was introduced as a new alternative to conventional transvenous ICD (TV-ICD) in Japan in February 2016, but its safety and efficacy are unclear.

Methods and Results: A total of 60 patients (48 men, median age, 60 years; IQR, 44–67 years; primary prevention, n=24) underwent S-ICD implantation between February 2016 and August 2017. The device pocket was formed in the intermuscular space between the serratus anterior muscle and the latissimus dorsi muscle, and the parasternal S-ICD lead was placed according to pre-implant screening. Defibrillation test was performed in 56 patients (93%). Ventricular fibrillation (VF) was induced in 55 patients and terminated by a single 65-J shock in all patients. The median time to shock therapy was 13.4 s (IQR, 12.1–14.9 s) and the median post-shock impedance of the S-ICD lead was 64 Ω (IQR, 58–77 Ω). There were no operation-related complications or subsequent infectious complications. During follow-up (median, 275 days; IQR, 107–421 days), 1 patient (1.7%) had appropriate shock for VF with successful termination, whereas 5 patients (8.3%) had inappropriate shock due to oversensing of myopotential (n=3) or T-wave (n=1), and detection of supraventricular tachycardia (n=1).

Conclusions: S-ICD is a safe and effective alternative to conventional TV-ICD. The long-term safety and efficacy of the S-ICD need further investigation.

Key Words: Subcutaneous cardioverter defibrillator; Sudden cardiac death; Transvenous implantable cardioverter defibrillator
The S-ICD system is placed after the S-ICD system is placed, the S-ICD assesses the optimal vector for sensing, and the vector with the greatest distinction between the QRS and the T-wave is chosen. Defibrillation test was performed subsequently and we confirmed termination of ventricular fibrillation (VF) by a 65-J shock delivered by the S-ICD. When this 65-J shock was not effective, the defibrillation energy was increased to 80J and applied. If these 2 shocks failed to terminate VF, external defibrillation using 200J of biphasic energy was planned. After defibrillation test, the S-ICD was programmed with 2 zones of tachycardia detection: a conditional shock zone and a non-conditional (shock) zone. In the present case, threshold heart rate for the conditional shock zone and non-conditional shock zone was programmed at 190 beats/min and 240 beats/min respectively. Shock energy was set to 80J for both tachycardia detection zones.

### Statistical Analysis
Data are expressed as median (IQR) or n (%). Continuous data were compared using Mann-Whitney U-test. Categorical variables are summarized as frequencies and percentages and compared using Fisher’s exact test. Rates of freedom from appropriate shock and inappropriate shock were analyzed using the Kaplan-Meier method. Statistical analysis was performed using JMP 13 (SAS, Cary, NC, USA).

### Results

#### Clinical Characteristics
To clarify the characteristics of the patients who were eligible for S-ICD, we compared the clinical characteristics between S-ICD and TV-ICD patients treated in the 2 hospitals from February 2016 to August 2017 (Table 1). Of the 107 consecutive patients, 60 were treated with S-ICD (56%) and the other 47 were treated with TV-ICD (44%). Median age was significantly younger in the S-ICD group than in the TV-ICD group (60 years; IQR, 44–67 years vs. 69 years; IQR, 58–79 years, P=0.0001). Approximately 70–80% were male in both groups. The median body mass index (BMI) in S-ICD patients was 24.4 kg/m² with the lowest of 14.3 kg/m² and highest of 42.5 kg/m², and there was no difference between the 2 groups. Median LVEF on echocardiography was significantly lower in S-ICD group than in TV-ICD group (58% (39–66) vs. 35% (28–57), P=0.0003). Secondary prevention was more frequent in S-ICD group than in TV-ICD group (36 (60%) vs. 21 (45%), P=0.12).

#### Table 1. Clinical Characteristics vs. Device Status

|                      | S-ICD  | TV-ICD  | P-value |
|----------------------|--------|---------|---------|
| Age (years)          | 60 (44–67) | 69 (58–79) | 0.0001  |
| Male gender          | 48 (80)  | 35 (74)  | 0.64    |
| BMI (kg/m²)          | 24.4 (20.9–27.0) | 23.5 (22.1–26.6) | 0.98    |
| Device infection or lead failure | 9 (15)  | 0        | 0.004   |
| Atrial fibrillation  | 4 (7)    | 8 (17)   | 0.12    |
| LVEF (%)             | 58 (39–66) | 35 (28–57) | 0.0003  |
| ≤55                  | 14 (23)  | 23 (49)  | 0.004   |
| ≥50                  | 31 (52)  | 14 (30)  | 0.004   |
| History of VT/VF     |         |         |         |
| Primary prevention   | 24 (40)  | 26 (55)  | 0.12    |
| Secondary prevention | 36 (60)  | 21 (45)  |         |

Data given as median (IQR) or n (%). BMI, body mass index; LVEF, left ventricular ejection fraction; S-ICD, subcutaneous implantable cardioverter defibrillator; TV-ICD, transvenous implantable cardioverter defibrillator; VF, ventricular fibrillation; VT, ventricular tachycardia.
Primary Japanese Experience of S-ICD

A. S-ICD (n=60)

- DCM (n=6, 10%)
- HCM (n=7, 12%)
- Prior MI (n=22, 37%)
- J-wave (n=2, 3%)
- LVF (n=7, 12%)
- Brugada syndrome (n=10, 17%)
- Amyloidosis (n=1)
- ARVC (n=1)
- Sarcoidosis (n=1)

B. TV-ICD (n=47)

- DCM (n=10, 21%)
- Prior MI (n=14, 30%)
- HCM (n=10, 21%)
- LQTS (n=1)
- Brugada syndrome (n=1)
- ARVC (n=1)
- Sarcoidosis (n=4)

Defibrillation Test

Defibrillation test was performed in 56 patients (56/60; 93%) during the procedure. Three patients did not undergo defibrillation test because of the presence of intracardiac thrombi, which were detected in the left atrial appendage (LAA) due to long-standing atrial fibrillation (AF) in 2 patients and in the left ventricular apex due to prior MI in 1 patient. Defibrillation test was avoided due to low LVEF in the remaining 1 patient. VF was induced in 55 patients during the procedure and successfully terminated by a single 65-J shock in all patients. Induced VF was detected appropriately by the S-ICD and no external defibrillation was needed. The median time to shock therapy was 13.4 s (IQR, 12.1–14.9 s) and the median post-shock impedance of the S-ICD lead was 64 Ω (IQR, 58–77 Ω). None of them...
A representative example of inappropriate shock is given in Figure 3. After inappropriate shock occurred, 4 patients were forced to change a sensing vector from the initial sensing vector to another vector that did not detect the myopotential during exercise test, and there was no recurrence of inappropriate shock after this change. In the remaining 1 patient, inappropriate shock was caused by supraventricular tachycardia (SVT), the average ventricular rate of which exceeded the detection rate of VF. For this patient, radiofrequency catheter ablation was performed and then there was no recurrence of inappropriate shock.

Discussion

Major Findings

In the present study, we have provided information on S-ICD use in Japanese patients who were all indicative of ICD implantation and not of either pacing therapy or CRT indication. There were no implantation-related complications nor subsequent infectious complication. VF required revision of position of the pulse generator or parasternal tunneling after defibrillation test.

Implantation-Related Complications and Follow-up

There were no implantation-related complications such as infection, pocket erosion, hematoma, or inadequate/prolonged healing of incision site, although 32 patients (53%) were on anti-thrombotic medication. There was no suboptimal position of pulse generator and/or parasternal S-ICD lead requiring re-implantation.

During a median follow-up of 275 days (IQR, 107–421 days), 1 patient (1.7%) with chronic renal failure (male, 66 years old) had appropriate shock for VF and it was successfully terminated, whereas 5 patients (8.3%) had inappropriate shock. The median time from S-ICD implantation to first inappropriate shock was 381 days (IQR, 112–423 days). The Kaplan-Meier estimates of appropriate and inappropriate shocks are shown in Figure 2. In 4 of the 5 patients, inappropriate shock was caused by oversensing of myopotential (n=3) and T-wave (n=1; Table 2). A

| Patient age (years)/Sex | Primary heart disease | Days from implant | Reason for inappropriate shock | Situation at the time of shock | Sensing vector at the time of shock |
|-------------------------|-----------------------|-------------------|-------------------------------|-------------------------------|----------------------------------|
| 69/M Prior MI           | 416                   | T-wave oversensing | Sleeping                      | Primary                       |
| 46/M BrS               | 76                    | Myopotential      | Doing yard work               | Secondary                     |
| 56/M Prior MI           | 147                   | Myopotential      | Upper limb lifting work       | Secondary                     |
| 34/M BrS               | 430                   | SVT               | Shampooing hair               | Secondary                     |
| 17/M IVF               | 381                   | Myopotential      | Shampooing hair               | Alternate                     |

BrS, Brugada syndrome; IVF, idiopathic ventricular fibrillation; MI, myocardial infarction; SVT, supraventricular tachycardia.

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Figure 2. Inappropriate Shock: Patient Characteristics

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Figure 3. Representative example of subcutaneous implantable cardioverter defibrillator (S-ICD) electrocardiogram in a patient with inappropriate shock. The secondary sensing vector was automatically chosen as the optimal sensing vector by the S-ICD at implantation. Periodic interference of myopotentials was followed by detection in the ventricular fibrillation zone. Black arrow, shock (80-J) delivery by S-ICD. Oversensing of myopotentials caused inappropriate shock delivery. C, charging; N, noisy beat; S, sensed beat; T, tachy detection.
was induced in 55 patients during the procedure and successfully terminated by a single 65-J shock in all patients. One patient had appropriate shock therapy for VF and it was successfully terminated by first shock therapy, whereas 5 patients had inappropriate shocks due to oversensing of myopotential or T-wave and detection of SVT. This study has shown that S-ICD is a safe and effective alternative to TV-ICD for Japanese patients at high risk of SCD.

S-ICD Use in Japan: Patient Characteristics

The safety and effectiveness of the S-ICD has been established in Europe and the USA. A pooled analysis of the IDE study and EFFORTLESS registry include a wide variety of younger patients (median age, 50 years), 70% of whom had primary prevention indication. This tendency was also seen in the S-ICD Post-Approval Study, which enrolled 1,637 patients who underwent S-ICD implantation at 86 US centers. In contrast, the majority (60%) of the present patients had a secondary prevention indication for TV-ICD and had preserved LVEF, characteristic of the present report compared with reports from Western countries. This suggests a Japanese trend in patient selection for S-ICD toward resuscitated patients with inherited disease and normal LV function, such as Brugada syndrome, long-QT syndrome, idiopathic VF, and HCM.

The present study, 14 patients with reduced LVEF (≤35%) who underwent S-ICD implantation also met the indication for conventional TV-ICD implantation. The majority of these patients (n=9, 64%) did not have a history of sudden cardiac arrest due to VT/VF and underwent S-ICD implantation for primary prevention. Underlying heart disease was prior MI in 10 patients (71%), DCM in 3 patients, and drug-induced cardiomyopathy. Although optimal pharmacological therapy including β-blocker has been achieved in all patients, none of them met the indications of pacing for bradycardia at the time of S-ICD implantation.

Safety and Efficacy of S-ICD

One of the greatest advantages of the S-ICD system is avoidance of TV-ICD lead complications, such as lead failure and venous obstruction. With regard to S-ICD implantation, the most common complications were infection requiring device removal and skin erosion, which accounted for 4.1% in total, followed by other procedural complications, which accounted for 1.1%. In the present study, none of the 60 patients had implantation-related complications or suboptimal positioning of pulse generator and/or parasternal S-ICD lead requiring re-implantation. Although the present follow-up period was short, these results suggest the safety of S-ICD implantation with intermuscular pocket formation.

In the present study, only 1 patient (1.7%) had appropriate shock for VF during follow-up. The possible reasons for the low incidence of appropriate shock in the present study are as follows. First, the follow-up period was short. The median follow-up period of 275 days is shorter than that of recent S-ICD cohorts/trials. Another reason related to the primary heart disease. Approximately 60% of eligible patients in the present study had prior MI, and S-ICD was for secondary prevention of SCD. Because only 1 patient had appropriate shock during follow-up, the confirmation of defibrillation efficacy of the S-ICD system was successful defibrillation rate on defibrillation test. In the present study, VF was induced in 93% of patients during the procedure and successfully terminated by a single 65-J shock in all patients.

Furthermore, given that the S-ICD provides a higher current across the left atrium at the time of defibrillation compared with the TV-ICD, it may be more likely to terminate AF. On defibrillation test, however, 2 long-standing AF patients without intracardiac thrombi had failure to terminate AF in the present study. Further studies are needed to clarify the efficacy of S-ICD for termination of AF. Although defibrillation test was not performed in 2 AF patients with thrombus in the LAA, these patients may be at risk for thromboembolism or development of sick sinus syndrome after possible termination of AF by S-ICD shock therapy. Careful attention should be paid in such cases.

S-ICD Inappropriate Shock

The potential limitation of the S-ICD system is the need for pre-implantation screening to prevent double-counting of QRS complexes or T-wave oversensing. The inappropriate shock rate ranges from 5% to 13%. In the present study, 5 patients (8.3%) had inappropriate shock during follow-up. In 4 of these patients, inappropriate shock was caused by interference of myopotential during daily life movement or T-wave oversensing at rest. Olde Nordkamp et al reported the incidence of inappropriate shocks in the EFFORTLES S-ICD Registry. During a follow-up period of 21±13 months, 101 inappropriate shocks were detected in 48 of 581 patients (8.3%). The most common cause was cardiac signal oversensing (73%) such as T-wave oversensing, followed by SVT in 18% and non-cardiac oversensing such as myopotential oversensing in 9%. Although the incidence of inappropriate shock (5/60; 8.3%) in the present study is similar to that in the EFFORTLES S-ICD Registry, the incidence of inappropriate shock due to myopotential oversensing was unexpectedly higher (3/5; 60%). One reason is the small number of patients. Another possible reason seems to be the relative change of position of the S-ICD pulse generator to the thorax. All inappropriate shocks due to myopotential oversensing were caused by interference of myopotential during daily life movement. Two patients had shock therapy while raising the left upper extremity upward periodically, and the secondary sensing vector was chosen in both patients at the time of inappropriate shock. This suggests that such a movement causes shifting of the S-ICD generator to the former upper part of the thorax, which may be related to the interference of myopotential. In the remaining 1 patient, sequential decrease of QRS amplitude was found in both surface ECG and subcutaneous ECG in association with progression of the underlying heart disease. Such changes on subcutaneous ECG may make it impossible to differentiate tachycardia from myopotential, leading to inappropriate shock. Although inappropriate shock was able to be avoided in that patient by changing a sensing vector from the initial vector to another, the QRS amplitude in the selected vector was still low and the risk of recurrent inappropriate shock remained. The experience of this patient suggests that there may be a potential limitation of S-ICD indication in patients with progressive heart diseases such as ARVC.

Notably, the majority of inappropriate shocks occurred ≥1 year after S-ICD implantation. These patients also passed a usual pre-implantation screening that included treadmill exercise test. This suggests that the conventional exercise test such as treadmill exercise test may be insufficient
to ensure optimal selection of patients suitable for S-ICD. A novel algorithm (SMART Pass algorithm) designed to reduce oversensing in the S-ICD, has recently been developed. This algorithm uses a high-pass filter (9 Hz) to sense and estimate heart rate more precisely. Therefore, the algorithm is expected to reduce inappropriate shock due to T-wave oversensing. We added this algorithm to all S-ICD in the present study, except in 1 patient, for whom the SMART Pass algorithm was not added to the S-ICD due to the limitation of QRS morphology in the selected vector. This patient had inappropriate shock due to T-wave oversensing. Inappropriate shock due to interference of myopotential, however, was caused in 3 of 5 patients, and this new algorithm had been added for 2 of them. Although the number of patients was small, this suggests that there might be a limitation in preventing interference of myopotential by the SMART Pass algorithm. A new screening system that is capable of avoiding inappropriate shock, is warranted.

Study Limitations
There were several limitations in the present study. First, this was a retrospective observational study and therefore generalization of the results may be limited. We, however, studied consecutive patients admitted during the study period, which seems to have minimized the bias caused by the study design. Second, this was a multicenter study, but only 2 hospitals participated and the number of patients was relatively small. Finally, the follow-up period may not have been sufficiently long to provide evidence. A further large-scale prospective study across the whole of Japan is required to confirm the present results.

Conclusions
The S-ICD as a viable alternative to conventional TV-ICD. The long-term safety and efficacy of the S-ICD need further investigation.

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