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ORIGINAL ARTICLE

Primary results from the Japanese Heart Failure and Sudden Cardiac Death Prevention Trial (HINODE)

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Abstract

Aims The HINODE study aimed to analyse rates of mortality, appropriately treated ventricular arrhythmias (VA), and heart failure in Japanese patients and compared with those in Western patients.

Methods and results After treatment decisions following contemporary practice in Japan, patients were prospectively enrolled into four cohorts: (i) internal cardioverter-defibrillator (ICD), (ii) cardiac resynchronization therapy (CRT) defibrillator (CRT-D), (iii) standard medical therapy ('non-device': ND), or (iv) pacing (indicated for CRT; received pacemaker or CRT pacing). Cohorts 1–3 required a left ventricular ejection fraction ≤35%, a history of heart failure, and a need for primary prevention of sudden cardiac death based on two to five previously identified risk factors. Endpoint outcomes were adjudicated by the independent committees. ICD and CRT-D cohorts, considered as high-voltage (HV) cohorts, were pooled for Kaplan–Meier analysis and propensity-matched to Multicenter Automatic Defibrillator Implantation Trial-Reduce Inappropriate Therapy (MADIT-RIT) arm B and C patients. The study enrolled 354 patients followed for 19.6 ± 6.5 months, with a minimum of 12 months. Propensity-matched HV cohorts showed comparable VA (P = 0.61) and mortality rates (P = 0.29) for HINODE and MADIT-RIT. The ND cohort presented a high crossover rate to ICD therapy (6.1%, n = 7/115), and the CRT-D cohort showed elevated mortality rates. The pacing cohort revealed that patients implanted with pacemakers had higher mortality (26.0%) than those with CRT-Pacing (8.4%, P = 0.05).

Conclusions The mortality and VA event rates of landmark trials are applicable to patients with primary prevention in Japan. Patients who did not receive guideline-indicated CRT devices had poor outcomes.

Keywords Defibrillator therapy; Ventricular arrhythmia; Sudden cardiac death; Japan, primary prevention; Electrophysiologic studies

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Introduction

Despite increase in the incidence of chronic heart failure and sudden cardiac death (SCD),[1–4] the current use of implantable cardioverter-defibrillator (ICD) and cardiac resynchronization therapy (CRT) with defibrillator (CRT-D) in Japan is much lower than in Western countries.[3,5–7] The present Japanese guidelines,[8] especially for primary prevention, do not fully

implement findings from landmark trials on ICD and CRT-D.[9–13] The benefit of ICD therapy for patients from Japan is widely questioned as not very cost-effective in Japan.[5,8,14] For a class I ICD indication, primary prevention patients need a history of non-sustained ventricular tachycardia (NSVT) and/or an electrophysiologic study with an inducible sustained ventricular arrhythmia (VA).[15] If there is no history of NSVT or positive EPS testing, there is only a class IIa recommendation (II: Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given procedure or treatment; IIa Weight of evidence/opinion is in favour of usefulness/efficacy) by the Japanese Circulation Society (JCS). Only patients with an ICD indication can be considered for CRT-D per JCS guideline. CRT-D class I indication is limited to patients in sinus rhythm with LBBB: NYHA class III/IV and QRS $\geq$ 120 ms or NYHA class II and QRS $\geq$ 150 ms. Without any VA history (NSVT or EPS) there is no expected reimbursement for CRT-D therapy. Specifically, the actual rate of ventricular arrhythmias (VAs) in ICD and CRT patients, the diminished value of electrophysiologic testing for risk stratification, and the use of CRT therapy for mildly symptomatic patients in New York Heart Association class I and II have not been well-established in Japan. While CRT-D has been proven to be a highly effective treatment for some patients with heart failure,[16] it remains unknown whether study data from the USA and Europe are fully applicable in Japan considering genetic and cultural differences. Kawashiro and colleagues (2015) stated that CRT-D therapy is very limited in Japan suggesting that 'it will be necessary to formulate evidence unique to Japan on the extent to which cutting-edge non-pharmacological treatments for arrhythmias improve the prognosis of patients'.[8] Notably, the occurrence of HF related mortality in non-ischaemic patients might be underestimated and having an ICD indication prior to CRT-D therapy may lead to delayed treatment.[17]

The **H**eart Fa**i**lure I**n**dicati**o**n and Sud**de**n Cardiac Death Prevention Trial Japan (HINODE) study was designed to prospectively assess the rates of mortality, appropriately treated VA, and heart failure for comparison with references from historical landmark trials like MADIT-RIT in Japanese patients who meet the European Society of Cardiology (ESC) guidelines for the SCD primary prevention or CRT treatment of heart failure across four clinical therapy cohorts: ICD, CRT-D, pacing (PA), and non-device (ND).[18] In addition to reduced left ventricular ejection fraction (LVEF) and heart failure, subjects were required to have two to five previously identified risk factors for sudden death.[19,20] The HINODE study aimed to identify current treatment practices for ICD and CRT-D in Japan for comparison with reference data from Multicenter Automatic Defibrillator Implantation Trial Reducing Inappropriate Therapy (MADIT-RIT).[21] This novel comparison is critical to evaluating current assumptions that patient outcomes in Japan are distinct from those observed in western studies.

Methods

Study design

Details of the study design, including inclusion and exclusion criteria, device programming, and event adjudication, have been published previously.[18] The protocol was approved by the ethics committees of the participating centres, and written informed consent was obtained from each enrolled subject. The investigation conformed to the principles outlined in the Declaration of Helsinki.

The study followed patients in four treatment cohorts to determine the rates of life-threatening VAs, all-cause mortality and occurrence of serious heart failure events. Equivalence in event rates between Japanese and western patients is essential evidence for acceptance of ESC like guidelines following clinical trial results. After the treatment plan was decided, based on current JCS guidelines, patients indicated for primary prevention according to the ESC guidelines were prospectively enrolled into one of four treatment cohorts (ICD, CRT-D, PA, or ND). Stable OMT was required prior to any device implant by JCS guidelines. Information on drug groups was collected at enrolment and closeout as well in relation to adverse events, re-implants and new device implants. Enrolment was limited to subjects with two to five of the following previously identified risk factors for SCD: (i) LVEF $\leq$35%, (ii) New York Heart Association (NYHA) functional class III or IV, (iii) left bundle branch block (LBBB) with QRS $\geq$ 130 ms or any QRS morphology $\geq$150 ms; (iv) renal dysfunction, defined as chronic blood urea nitrogen (BUN) $>$ 26 mg/dL or $\geq$9.28 mmol/L; (v) diabetes mellitus type I and II; (vi) chronic atrial fibrillation; (vii) prior myocardial infarction (MI); (viii) age $>$70 years; or (ix) smoking currently or during the last 5 years. Notably, all patients had LVEF $\leq$35%. The criteria for cohort enrolment are as follows:

- ICD Device Therapy Cohort: NYHA Class II-III, ischaemic heart disease or dilated cardiomyopathy, optimal medical therapy (OMT), and LVEF $\leq$35%.
- CRT-D Device Therapy Cohort: NYHA class I-IV despite OMT, LVEF $\leq$35%, sinus rhythm + QRS $>$ 130 ms and LBBB, or QRS $>$ 150 ms and non-LBBB; alternatively, AF rhythm, NYHA class III, QRS $\geq$ 130 ms.
- Non-Device (ND) Therapy Cohort: fulfilment of either the ICD or CRT-D cohort criteria
- Pacing (PA) Cohort with standard right ventricular pacemaker (PM) or CRT-Pacing (CRT-P) Therapy: NYHA class I-IV despite OMT, LVEF $\leq$50%

ICD device programming required a high cut-off rate or delayed therapy and followed the principles of MADIT-RIT. Patients' medical therapy was at the investigator's discretion except for ICD indicated patients OMT was required. Patients were followed up for a minimum of 12 months. All patients

using a device were required to be connected to a home monitoring system.

The primary endpoint for the ICD and CRT-D cohorts was the first appropriately treated VA along with possible life-threatening symptoms, while the primary endpoint for the PA and ND cohorts was all-cause mortality. Events were adjudicated by independent committees following the MADIT-RIT and MADIT-CRT criteria for the classification of endpoint VA events.

Statistical considerations

The appropriate anti-tachycardia pacing or shock treatment for VA was 5% in ICD and 3% in CRT-D patients at 12 months based on the results from MADIT-RIT. This data was used for sample size calculation.[22] Meanwhile, the sample sizes for the PA and ND cohorts were calculated using a 10% estimated all-cause mortality at 12 months based on the CARE-HF and MADIT-II study results.[23] The Kaplan–Meier estimates for freedom from all-cause mortality and first VA were determined at the 12- and 24-month follow-up for all cohorts. Estimates were further compared by subgroups within each cohort, as well as to MADIT-RIT outcomes using log-rank tests (*Table 3*).

An exploratory propensity score (PS) match analysis was performed per protocol to compare event rates for the high-voltage (HV) cohorts, ICD and CRT-D, to those in MADIT-RIT. To parallel the MADIT-RIT exclusion criteria in the HV cohort, ICD patients with CRT-D indication (LVEF $>$35% and LBBB with QRS $>$ 130 ms or QRS $>$ 150 ms) were excluded, along with patients with chronic AF. The remaining patients were matched 1:1 to the MADIT-RIT arm B and C patients (novel ICD programming) on select baseline characteristics that match the primary prevention indication. A reduction in the standardized mean difference ($<$0.20), post-PS match, and model fit were desired (Supporting Information, *Table S2*). Baseline characteristics included those with high relevance to the endpoint that were present in both studies. QRS width was excluded due to its unavailability for the MADIT-RIT ICD cohort, while BMI was excluded due to the burden on model fit. Event rates were re-estimated in the matched HINODE and MADIT-RIT cohorts and were compared using a log-rank test stratified on the quintiles of the PS. Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, USA).

Results

Between June 2017 and June 2019, 354 patients from 34 hospitals were enrolled in the HINODE trial. Due to the extended enrolment period, the mean follow-up time both overall (19.6 ± 6.5 months) and in three cohorts (ICD: 20.5 ± 6.2 months, CRT-D: 19.7 ± 7.1 months, and ND: 17.8 ± 5.5 months) exceeded the anticipated period and compensated for the low enrolment rate. The follow-up time for the PA cohort was 20.9 ± 7.3 months for 68 patients (1422.6 patient-months), in contrast with the expected 137 patients (1644 patient-months, Supporting Information, *Table S1*). No patients were lost to follow-up.

The four cohorts differed in terms of patient characteristics and disease history. Notably, CRT-D included patients across the ICD, ND, and PA cohorts. ICD and CRT-D patients had a median of four out of nine risk factors, while ND and PA patients had a median of three risk factors (*Table 1*). More than 10% of patients who underwent ICD or CRT-D therapy had a history of inducible VA (*Table 1*). The ICD cohort enrolled 68.6% DDDR (Resonate™ ICD EL D433, Dynagen™ D152 and Perciva™ DF4 D413), 15.7% S-ICD (Emblem MRI™ A219) and 15.7% VR devices (Resonate™ ICD D432, Perciva™ DF4 D412), the CRT-D cohort contained 100% Resonate™ X4 G447, G437 devices and the Pacing cohort included 22 pacemakers (Accolade™ [77.3% MRI DR (L331, L311) 18.2% MRI VR L310, and 4.5% DR L301]) and 46 CRT-P (100% Valitude™ X4 MRI, U128, U125).

The Ventricular Event Adjudication Committee assessed a total of 104 events, including first and subsequent treatments, as well as untreated ventricular events. Of 104 events, 72 (69.2%) were classified as life-threatening and appropriately treated. Of 171 HV patients, 15 (8.8%) received appropriate antitachycardia pacing (ATP) or shock therapy within the trial. This resulted in 12- and 24-month estimated event rates of 7.9% and 13.3%, respectively, for the ICD cohort and 3.0% and 4.6%, respectively, for the CRT-D cohort. Unmatched and propensity-matched MADIT-RIT subjects with ICD and CRT-D from the arms B and C had similar event rates, with no significant difference based on the Kaplan–Meier analysis at 12 and 24 months (*Table 2*). Other episodes (n = 32/104) did not qualify for endpoint events due to the rate, duration, or absence of symptoms during the arrhythmia. There were four instances of inappropriate ICD therapy (ATP or shock), resulting in an inappropriate therapy rate of 1.8% at 1 year (CRT-D, n = 1; ICD, n = 3). For comparison, the inappropriate therapy rate for the MADIT-RIT arms B and C with ICD and CRT-D devices at 1 year was approximately 5%.[22]

High-voltage cohort

The risk of mortality tended to be higher in the ICD and CRT-D cohorts than in the MADIT-RIT unmatched cohort and was significantly different at 24 months for CRT-D (P = 0.002) and HV (P = 0.005, *Table 2*). PS matching resulted in more comparable cohorts, with 134 subjects for each study (*Table 2*), improving the balance in the proportion of subjects by device type, age, sex, ischaemic cardiomyopathy, hypertension, and prior MI (Supporting Information, *Table S2*).

Table 1 Patient characteristics in the four treatment cohorts

Characteristic	Measurement	ICD cohort (*N* = 102)	CRT-D cohort (*N* = 69)	Pacing cohort (*N* = 68)	Non-device cohort (*N* = 115)
Risk factors at enrolment					
1. LVEF ≤ 35%	*N* (%)	102 (100.0%)	69 (100.0%)	37 (54.4%)	114 (99.1%)
2. NYHA Class III or IV	*N* (%)	20 (19.6%)	38 (55.1%)	20 (29.4%)	21 (18.3%)
3. Left Bundle Branch Block (LBBB) with QRS > 130 ms or QRS > 150 ms	*N* (%)	10 (9.8%)	64 (92.8%)	47 (69.1%)	29 (25.2%)
4. Renal dysfunction	*N* (%)	25 (24.5%)	11 (15.9%)	17 (25.0%)	32 (27.8%)
5. Diabetes Type I and II	*N* (%)	44 (43.1%)	25 (36.2%)	19 (27.9%)	44 (38.3%)
6. Chronic atrial fibrillation	*N* (%)	22 (21.6%)	6 (8.7%)	9 (13.2%)	24 (20.9%)
7. Prior MI	*N* (%)	48 (47.1%)	11 (15.9%)	11 (16.2%)	39 (33.9%)
8. Age >70 years	*N* (%)	50 (49.0%)	32 (46.4%)	46 (67.6%)	63 (54.8%)
9. Smoking history (last 5 years)	*N* (%)	32 (31.4%)	14 (20.3%)	10 (14.7%)	31 (27.0%)
Risk factors per cohort	Median (Range)	4.0 (2.0–5.0)	4.0 (2.0–5.0)	3.0 (1.0–5.0)	3.0 (2.0–5.0)
Age at time of consent (years)	Mean ± SD	68.2 ± 10.4	66.4 ± 13.4	75.0 ± 10.9	68.8 ± 11.8
	Median (Range)	70.0 (35.0–85.0)	69.0 (23.0–88.0)	76.5 (41.0–95.0)	70.0 (33.0–92.0)
Gender/female	(%)	14.7%	31.9%	35.3%	21.7%
BMI (kg/m^2)	Mean ± SD	23.2 ± 3.8	22.2 ± 4.1	22.3 ± 3.3	23.7 ± 4.0
Systolic blood pressure (mmHg)	Mean ± SD	108.2 ± 14.7	104.8 ± 17.2	113.9 ± 17.4	112.6 ± 17.0
Diastolic blood pressure (mmHg)	Mean ± SD	63.7 ± 10.9	63.5 ± 14.1	64.8 ± 11.2	66.3 ± 12.0
NYHA class	I [*N* (%)]	0/102 (0.0%)	3/68 (4.4%)	10/65 (15.4%)	4/115 (3.5%)
	II [*N* (%)]	82/102 (80.4%)	28/68 (41.2%)	36/65 (55.4%)	92/115 (80.0%)
	III [*N* (%)]	20/102 (19.6%)	34/68 (50.0%)	18/65 (27.7%)	18/115 (15.7%)
	IV [*N* (%)]	0/102 (0.0%)	3/68 (4.4%)	1/65 (1.5%)	1/115 (0.9%)
LVEF (%)[a]	Mean ± SD	27.1 ± 6.0	24.3 ± 6.1	35.8 ± 9.6	26.0 ± 5.9
	Median (Range)	29.0 (4.0–35.0)	24.0 (3.0–35.0)	34.0 (12.0–51.0)	27.0 (10.0–35.0)
LVEF category[a] ≤25%	(%)	38.2%	60.9%	10.3%	44.4%
Resting heart rate (b.p.m.)	Mean ± SD	68.9 ± 14.6	71.3 ± 15.9	63.0 ± 16.4	74.0 ± 15.1
QRS width (ms)	Mean ± SD	120.2 ± 23.1	152.2 ± 25.0	153.8 ± 29.3	120.5 ± 21.8
	Median (Range)	110.0 (91.0–223.0)	150.0 (101.0–218.0)	155.0 (84.0–225.0)	116.0 (82.0–190.0)
QRS width ≥120 ms	(%)	38.2%	91.0%	86.8%	44.3%
QRS width ≥150 ms	(%)	13.7%	58.2%	58.8%)	13.9%
PR interval (ms)	Mean ± SD	193.2 ± 35.0	200.6 ± 46.7	194.0 ± 51.6	183.8 ± 28.1
QT interval (ms)	Mean ± SD	438.4 ± 47.6	457.1 ± 58.9	492.0 ± 74.3	426.7 ± 45.3
QRS morphology	Normal (%)	47.5%	9.0%	14.9%	53.0%
	RBBB (%)	13.9%	10.4%	11.9%	10.4%
	LBBB (%)	8.9%	62.7%	50.7%	18.3%
	Other (%)	29.7%	17.9%	22.4%	18.3%
Ischaemic cardiomyopathy	Yes (%)	52.9%	26.1%	29.4%	42.6%
Hypertension	Yes (%)	50.0%	39.1%	50.0%	52.2%
Rhythm (pre-implant per core lab)	Sinus rhythm (%)	75.2%	86.8%	47.1%	76.6%
Atrial fibrillation history	Yes (%)	34.3%	17.4%	25.0%	29.6%
Type of atrial fibrillation	Paroxysmal (%)	37.1%	66.7%	41.2%	26.5%
	Chronic (%)	40.0%	33.3%	35.3%	44.1%
	Persistent (%)	22.9%	0.0%	17.6%	29.4%
	Unknown (%)	0.0%	0.0%	5.9%	0.0%
Previous hospitalization for heart failure	Yes (%)	61.8%	71.0%	52.9%	58.3%
History of non-sustained spontaneous ventricular arrhythmias >20–30s	Yes (%)	16.7%	11.6%	2.9%	4.3%

(*Continues*)

Table 1 (continued)

Characteristic	Measurement	ICD cohort (*N* = 102)	CRT-D cohort (*N* = 69)	Pacing cohort (*N* = 68)	Non-device cohort (*N* = 115)
History of inducible ventricular arrhythmias during last 12 months	Yes (%)	10.8%	10.1%	2.9%	5.2%
Previous ablation	Yes (%)	15.7%	14.5%	14.7%	14.8%
Previously implanted medical devices	Yes [*N* (%)]	6 (5.9%)	6 (8.7%)	21 (30.9%)	15 (13.0%)
Type of previously implanted device	Pacemaker [*N* (%)]	0/6 (0.0%)	0/5 (0.0%)	19/21 (90.5%)	0/15 (0.0%)
	CRT-P [*N* (%)]	0/6 (0.0%)	0/5 (0.0%)	2/21 (9.5%)	0/15 (0.0%)
	Stent [*N* (%)]	5/6 (83.3%)	3/5 (60.0%)	0/21 (0.0%)	15/15 (100.0%)
	Other devices [*N* (%)]	1/6 (16.7%)	2/5 (40.0%)	0/21 (0.0%)	0/15 (0.0%)
Medication use					
Angiotensin converting enzyme	(%)	46.1%	47.8%	32.4%	47.8%
ARB	(%)	31.4%	20.3%	27.9%	31.3%
Antiarrhythmic	(%)	36.3%	33.3%	19.1%	21.7%
Anticoagulant	(%)	52.0%	37.7%	41.2%	47.0%
Antiplatelet	(%)	52.0%	34.8%	47.1%	43.5%
Aldosterone-antagonist	(%)	40.2%	55.1%	30.9%	38.3%
Beta-blocker	(%)	94.1%	79.7%	54.4%	89.6%
Digitalis	(%)	3.9%	10.1%	2.9%	10.4%
Diuretics	(%)	76.5%	75.4%	61.8%	81.7%
Statins	(%)	57.8%	39.1%	42.6%	56.5%
Calcium antagonists	(%)	14.7%	8.7%	25.0%	10.4%

[a]If echocardiography or equivalent method assessed within 12 months but not before 3 months, exact LVEF % not available.
ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; BMI, body mass index; CRT-P, cardiac resynchronization therapy pacemaker; CRT-D, cardiac resynchronization therapy defibrillator; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; LBBB, left bundle branch block; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; NYHA, New York Heart Association; PM, pacemaker; RBBB, right bundle branch block (RBBB); SD, standard deviation.

Table 2 Endpoint results for HINODE ICD and CRT-D treatment cohorts compared with matched and unmatched MADIT-RIT results

	ICD cohorts		CRT-D cohorts		ICD and CRT-D cohorts		ICD and CRT-D MADIT-RIT matched 1:1 to HINODE cohorts	
Cohort	HINODE	MADIT-RIT	HINODE	MADIT-RIT	HINODE	MADIT-RIT	HINODE	MADIT-RIT
Number of patients	102	484	69	501	171	985	134	134
Appropriately treated VA-free at 12 m	92.1%	94.3%	97.0%	96.1%	94.0%)	95.2%	94.7%*	96.8%*
at 24 m	86.3%	87.7%	95.4%	91.8%	90.0%	89.8%	92.8%*	94.5%*
Mortality-free at 12 m	97.1%	96.7%	92.8%	98.7%	95.3%	97.7%	96.3%*	96.9%*
at 24 m	83.5%	92.8%	89.6%***	95.3%***	85.8%**	94.1%**	88.6%*	92.5%*
Total study mortality, % (*N*)	13.7% (14)	4.8% (23)	13.0% (9)	2.8% (14)	13.5% (23)	3.8% (37)	11.9% (16)	4.5% (6)
Mortality: Non-cardiac or unknown %	42.9%	52.2%	22.2%	35.7%	34.8%	45.9%	37.6%	0.0%
Mortality: Cardiac %	57.4%	47.8%	77.8%	64.3%	65.2%	54.1%	62.5%	100.0%
Out of cardiac: Arrhythmic %	12.5%	27.3%	14.3%	33.3%	13.3%	30.0%	10.0%	50.0%
Out of cardiac: Pump failure %	75.0%	63.6%	85.7%	44.4%	80.0%	55.0%	90.0%	50.0%
Out of cardiac: unknown %	12.5%	9.1%	0.0%	22.2%	6.7%	15.0%	0.0%	0.0%

*All *P*-values for matched groups >0.05; *P*-value from stratified log-rank test.
**Kaplan–Meier, *P*-value, 0.002; *P*-value from log-rank test.
***Kaplan–Meier, *P*-value, 0.005; *P*-value from log-rank test.
CRT-D, cardiac resynchronization therapy defibrillator; ICD, implantable cardioverter-defibrillator; VA, ventricular arrhythmia.

Stratified log-rank comparisons of mortality and VA-free rates showed no difference in the PS-matched data (*Figure 1*).

The HV cohort was stratified using a cut-off age of 70 years and was limited to subjects treated according to guidelines to assess the impact of age. There was no significant association between age and VA-associated symptom-free rates from 0–24 months ($P = 0.179$). However, a significant relationship was found between survival rates. Subjects aged 70 years or less had an estimated 97.2% survival at 24 months, whereas subjects older than 70 years had an estimated 82.9% survival ($P = 0.019$, *Table 3*). A similar analysis by gender revealed no significant differences for VA-free rate ($P = 0.387$) and survival ($P = 0.623$). Although HINODE patients are older than those in MADIT-RIT, the age of 70 remains a discriminator for mortality risk.[24]

In additional analysis the predictive value of electrophysiology studies (EPS) was assessed for all HV patients by comparing patients with a positive test and an inducible VA to patients who did not undergo EPS or obtained a negative test. No predictive association between positive findings and mortality or VA was found at 12 or 24 months (*Table 4*), which is consistent with current ESC guidelines.

Internal cardioverter-defibrillator treatment cohort

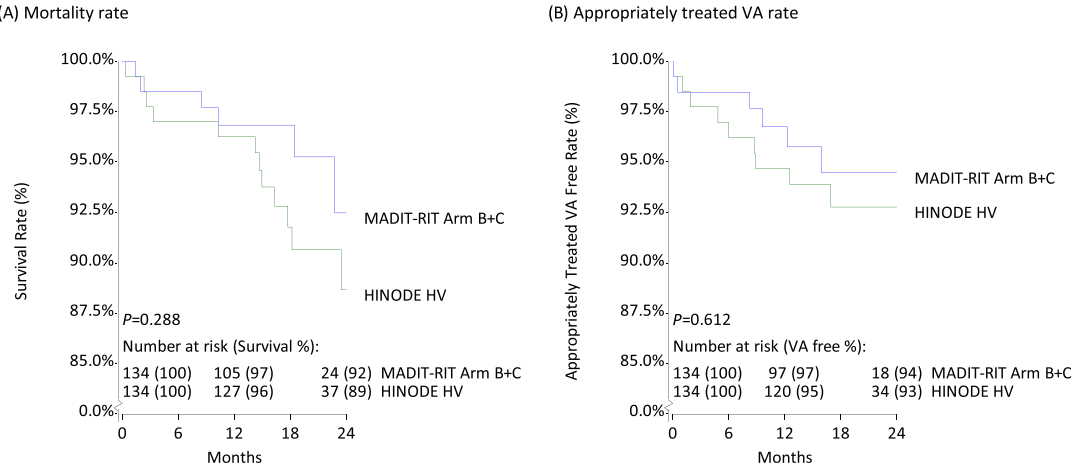
Exploratory subgroup analysis showed that the ICD cohort enrolled 9.8% ($n = 10/102$) of patients with CRT-D indication (risk factor: LBBB with QRS $>$ 130 ms or QRS $>$ 150 ms) and 28.4% ($n = 29/102$) with QRS $\geq$ 130 ms. Sub-group analysis on ESC guideline indicated CRT-D patients showed a significantly greater VA symptom probability ($P = 0.002$) and mortality ($P = 0.033$) at 24 months compared with the rest of the ICD cohort (*Table 3*). Further, patients with QRS $\geq$ 130 ms had a VA-free rate of 77.9% and a survival rate of 77.5% compared with a VA-free rate of 89.6% and a survival rate of 86.7% for patients with QRS $<$ 130 ms (VA-free $P = 0.283$, Survival $P = 0.644$, *Table 3*). For ICD sub-group patients without CRT-D indication, no significant differences in endpoints were found by the assumed risk factor cut-off age of 70 years. Though not significant, older patients ($>$ 70 years) tended to have lower VA rates($P = 0.213$), and higher mortality rates ($P = 0.086$, *Table 3*). Of the 102 patients in the ICD cohort, 16 received S-ICD and the S-ICD subgroup had one death.

Subgroup analysis

Cardiac resynchronization therapy defibrillator treatment cohort

The CRT-D cohort included 42 patients with LBBB and 25 patients with non-LBBB. Patients with LBBB tended to have

Figure 1 High-voltage (HV) cohort of HINODE matched 1:1 with MADIT-RIT cohort. Survival curves for mortality (A) and appropriately treated VA (B) comparing HV HINODE patients to 1:1 matched data from MADIT-RIT demonstrated similar rates. Stratified log-rank tests showed no difference in event occurrence between HINODE and MADIT-RIT patients. However, it is notable that event-free rates in HINODE are slightly lower than those in MADIT-RIT.



lower VA rates (P = 0.085) and lower mortality (P = 0.052, *Table 3*) than those without LBBB. CRT-D-treated patients with a QRS < 130 ms presented a similar 24-month VA rate (P = 0.645) but a significantly higher mortality rate compared to those with longer QRS width (30.8% vs. 5.9%; P = 0.004; *Table 3*). HINODE patients with LBBB (n = 42/67), compared with those with non-LBBB (n = 25/67), presented a wider QRS (159.4 ± 23.8 vs. 140.1 ± 22.6; P = 0.002) and tended to have less renal dysfunction (11.9% vs. 24.0%; P = 0.200).

Non-device cohort

The estimated mortality of the ND cohort was 4.4% at 12 months and 9.0% at 24 months. The ND cohort enrolled 25.2% (n = 29/115) patients with CRT-D indication (with LBBB, QRS > 130 ms or QRS > 150 ms, *Table 5*) and 74.8% with ICD indication (without LBBB, QRS > 130 ms or QRS > 150 ms). Further exploratory analyses suggested that patients with CRT-D had lower estimated survival at 24 months (87.9%) compared with patients with primary prevention ICD indication (91.4%), although the difference was not significant (P = 0.352). ND patients presented a high crossover rate (n = 9/115) to ICD (3) and CRT therapy (6).

Pacing cohort

The PA cohort enrolled 68 patients with ESC guideline indications for CRT (40 for CRT-P and 28 for CRT-D). Of these, 22 received standard PM therapy, and 46 received CRT-P therapy. A total of 54.4% (n = 37/68) of the patients had an LVEF ≤35%. Most patients receiving a PM did not meet JCS criteria for CRT due to having an LVEF ≥35% (21/22). This included patients with NYHA class I (n = 8), class II/III (n = 11), LBBB (n = 8), QRS ≥ 130 ms (n = 14), and AV-block (n = 15). The final PM subject had an unknown JCS criteria violation. The estimated survival rate in the pacing cohort was at 94.1% at 12 months and 86.2% at 24 months.

An additional comparison of patients who received PM and CRT-P revealed that patients who received a CRT-P device had a higher probability of 24-month survival (91.6% vs. 74.0%, P = 0.05).

Four deaths out of 46 CRT-P patients were observed: two among CRT-P subjects with ischaemic cardiomyopathy (N = 14) (plus LBBB) and two among those with non-ischaemic cardiomyopathy (N = 32) (no LBBB). All four subjects had LVEF ≥30%.

In the pacing cohort, 21 subjects (30.9%) had a previous device. Two CRT-P subjects had previously been implanted with CRT-P device and 14 had a previously implanted PM (n = 16/46). Also, five PM subjects had a previously implanted PM device (n = 5/22). There were three deaths among patients with a previous device (n = 21) and six deaths among those without (n = 47) leading to a probability of survival through 24 months of 81.8% and 87.8% respectively (P = 0.509).

Discussion

HINODE is a large single ethnicity population study of patients in four different therapy cohorts. One important implication of this study is that for ICD and sudden death, findings are neither geocentric nor ethnocentric.

ICD and CRT-D patients with a high risk of SCD have not previously been prospectively studied in Japan. The ASIAN HF study closed a large knowledge gap on Asian patients with heart failure by enrolling patients across many countries,

Table 3 Subgroups for patient outcomes of ventricular arrhythmia and mortality rate

Cohort	Subgroup	Subjects at risk	Ventricular arrhythmia associated symptoms free rate from 0–24 months[b]				All-cause mortality free rate from 0–24 months[b]			
			Number of failures	VA-free rate	*P*-value	Hazard ratio (95% CI)	Number of failures	Survival rate	*P*-value	Hazard ratio (95% CI)
Full ICD cohort	All	102	12	86.3%			11	83.5%		
	Without CRT-D indication[a]	92	8	90.7%	0.002	5.5 (1.6, 18.3)	8	88.0%	0.033	3.8 (1.0, 14.5)
	With CRT-D indication[a]	10	4	40.0%			3	45.7%		
	QRS ≥ 130 ms	29	5	77.9%	0.283	1.9 (0.6, 5.8)	4	77.5%	0.644	1.3 (0.4, 4.6)
	QRS < 130 ms	73	7	89.6%			7	86.7%		
ICD COHORT Without CRT-D indication[a]	Age ≤70 years	49	6	86.9%	0.213	0.4 (0.1, 1.9)	2	95.7%	0.086	3.7 (0.8 18.4)
	Age >70 years	43	2	95.3%			6	78.7%		
Full CRT-D cohort	All	69	4	94.0%			7	89.6%		
	QRS ≥ 130 ms	54	3	94.4%	0.645	0.6 (0.1, 5.7)	3	94.1%	0.004	0.1 (0.0, 0.7)
	QRS < 130 ms	13	1	92.3%			4	69.2%		
	With LBBB	42	1	97.6%	0.085	0.2 (0.0, 1.7)	2	95.1%	0.052	0.2 (0.0, 1.2)
	Others	25	3	87.4%			5	79.8%		
CRT-D cohort with QRS ≥ 130	Age ≤70 years	28	2	92.9%	0.601	0.5 (0.0, 5.9)	0	100.0%	0.071	NA[d]
	Age >70 years	26	1	96.0%			3	88.0%		
High-voltage ICD + CRT-D	All	171	16	89.4%			18	85.8%		
ICD therapy	QRS < 130 ms	73	7	89.6%	0.979	1.0 (0.1, 8.4)	7	86.7%	0.013	0.2 (0.1, 0.8)
CRT-D therapy	QRS < 130 ms	13	1	92.3%			4	69.2%		
High-voltage ICD + CRT-D	Female	37	5	85.1%	0.387	0.6 (0.2, 1.8)	5	82.5%	0.623	0.77 (0.3, 2.2)
	Male	134	11	90.7%			13	87.2%		
High-voltage ICD (ESC class I excluded) + CRT-D	Age ≤70	77	8	89.1%	0.179	0.4 (0.1, 1.6)	2	97.2%	0.019[c]	5.2 (1.1, 24.0)
	Age >70	69	3	95.4%			9	82.9%		

[a]CRT-D indication refers to subjects with the third risk factor: Left bundle branch block (LBBB) with QRS > 130 ms or QRS > 150 ms.
[b]Rates calculated using Kaplan–Meier estimation with *P*-values from log-rank test.
[c]Most significant split in age.
[d]Hazard ratio not available due to non-proportional hazards model violation.
CRT-D, cardiac resynchronization therapy defibrillator; ICD, internal cardioverter defibrillator; VA, ventricular arrhythmia.

Table 4 Patient endpoint outcomes and history of inducible VA within 12 months prior to enrolment

Endpoint	Cohort and time in months	Event-free rate[a] (*N* at risk)		Log-rank *P*-value
		No EPS or negative EPS	Patients with inducible VA during EPS	
All-cause mortality-free rate	Combined ICD/CRT-D 0–12	94.4% (*N* = 144)	100.0% (*N* = 18)	0.311
	0–24	83.4%	100.0%	0.140
	CRT-D only 0–12	91.5% (*N* = 59)	100.0% (*N* = 7)	0.433
	0–24	87.7%	100.0%	0.341
	ICD only 0–12	96.5% (*N* = 85)	100.0% (*N* = 11)	0.531
	0–24	80.3%	100.0%	0.231
Ventricular arrhythmia-associated symptom-free rate	Combined ICD/CRT-D 0–12	93.7% (*N* = 144)	94.4% (*N* = 18)	0.915
	0–24	88.8%	94.4%	0.576
	CRT-D only 0–12	94.8% (*N* = 59)	100.0% (*N* = 7)	0.542
	0–24	92.9%	100%	0.476
	ICD only 0–12	92.9% (*N* = 85)	90.9% (*N* = 11)	0.786
	0–24	86.0%	90.9%	0.842

[a]Kaplan–Meier calculation of event-free rate.
CRT-D, cardiac resynchronization therapy defibrillator; EPS, electrophysiology studies; ICD, internal cardioverter defibrillator; VA, ventricular arrhythmia.

including 540 in Japan.[25] That registry revealed a large pool of patients indicated for ICD or CRT-D primary prevention according to the ESC guidelines (with two to five risk factors) that did not receive the appropriate therapy. The study concluded that variation in phenotypes and ethnic differences might need to be considered when allocating public health resources for heart failure management.[25] Because the benefits of ICD and CRT-D therapy are not yet well-established in Japan, the validation of the applicability of VA, SCD, and heart failure rates was an important follow-up to ASIAN HF. HINODE demonstrates that results from previous landmark trials conducted outside of Japan (e.g. MADIT-RIT[21]) on VA and mortality in ICD and CRT-D are likely generalizable to Japanese primary prevention patients. Because heart failure prevalence is expected to increase in many industrialized countries, including Japan,[2] these findings have direct implications for clinical practice decisions. The present study fills a critical gap by providing data on the effectiveness of ICD and CRT-D in the primary prevention of heart failure and by comparing patients with HV devices (ICD and CRT-D) to those with similar indications that did not receive the appropriate treatment.

The MADIT-RIT trial was a randomized controlled trial examining algorithm effectiveness in reducing the rate of inappropriate ICD therapy in 1500 subjects with dual chamber ICDs implanted mainly from the USA and Europe.[26] MADIT-RIT reported rates of appropriate and inappropriate therapy, VAs, and mortality. The HINODE ICD cohort included 67.7% dual chamber, 15.7% single chamber, and 15.7% S-ICD devices. For S-ICDs no inappropriate treatments were found in HINODE, which followed the UNTOUCHED study programming[27] (required per protocol). A limitation to the VA rate of the HINODE ICD cohort might be the mix of device types. Though it is notable that UNTOUCHED had similar rates of both inappropriate and appropriate therapies, particularly for newer S-ICD models, thus it is unclear if there is any difference in VA detection and treatment between single and dual chamber ICD. The rate of inappropriate therapy in HINODE is very low. Thus, it is a valuable comparison between Japan and Western countries. Patients with ICD and CRT-D in HINODE followed MADIT-RIT programming arm B/C to allow direct comparison of event rates. Based on the comparison of patient characteristics, we assumed that the HINODE ICD and CRT-D treatment cohorts likely had more advanced disease at diagnosis and were treated at a later stage than patients in MADIT-RIT (Supporting Information, *Table S2*). Additionally, treatments did not always follow guidelines, which may have contributed to the increased risk of VA and mortality.

Post-hoc analysis of CRT-D patient sub-groups revealed trends toward lower VA rates ($P = 0.085$) and mortality rates ($P = 0.052$, *Table 3*) in LBBB patients. Similarly, MADIT-CRT reported that non-LBBB patients with a PR-interval >230 ms had increased VA and mortality rates.[28] MADIT-CRT also showed a higher risk of VA due to delayed remodelling and a low CRT response.[29] A similar relationship was hypothesized in MADIT-RIT, where a lower risk of VA was observed in patients receiving CRT compared with ICD therapy alone after the first 6 months of CRT therapy in which remodelling predominantly occurs. The present results of lower VA and mortality rates for LBBB patients align with earlier studies and support the importance of remodelling in CRT therapy for patients with LBBB and wide QRS complex.

The relative non-cardiac or unknown cause death rates were similar between the MADIT-RIT and HINODE HV cohorts (*Table 2*). The higher absolute mortality in HINODE (ICD: 13.7%, CRT-D: 13.0%) compared with the MADIT-RIT arm B and C (ICD: 4.8%, CRT-D: 2.8%) suggests that HINODE may have had a higher risk population. The rate of ICD penetration is still low in Japan, possibly due to socio-cultural and guideline and/or reimbursement factors. This is reflected by enrolment across cohorts in HINODE, where ND cohort had

Table 5 All-cause mortality in non-device and pacing cohorts with select subgroups

	Non-device cohort and subgroups							Pacing cohort and subgroup			
Mortality statistic	All	CRT-D indicated[a]	ICD indicated	QRS width ≥130 ms	QRS width <130 ms	No prior MI or ischaemic	Prior MI or ischaemic	All	CRT-P therapy		PM therapy
P-value[b] at 24 months		0.352			0.693		0.532			0.05	
Subjects at risk	115	29	86	38	77	66	49	68	46		22
Survival rate at:											
12 months[b]	95.6%	93.1%	96.5%	94.7%	96.1%	97.0%	93.7%	94.1%	95.6%		90.9%
24 months[b]	91.0%	87.9%	91.4%	88.8%	93.6%	89.5%	90.5%	86.2%	91.6%		74.0%
Total mortality % (*N*)	6.1% (7)	10.3% (3)	4.7% (4)					13.2% (9)	8.7% (4)		22.7% (5)
Non-cardiac/unknown (*N*)	4	0	4					6	2		4
Cardiac (*N*)	3	3	0					3	2		1

[a]CRT-D indication refers to subjects with the third risk factor: Left bundle branch block (LBBB) with QRS > 130 ms or QRS > 150 ms.
[b]Rates calculated using Kaplan Meier estimation with *P*-values from log-rank test on the event-free rates.
CRT-P, cardiac resynchronization therapy pacemaker; PM, pacemaker; CRT-D, cardiac resynchronization therapy defibrillator; ICD, internal cardioverter defibrillator; MI, myocardial infarction.

the largest enrolment. Additionally, in both studies, a large proportion of deaths were attributed to cardiac causes (over half of which were pump failure; *Table 2*). The ICD cohort included 29/102 patients with QRS ≥ 130 ms and LVEF ≤35%. The restrictive use of CRT-D therapy due to the necessity of ICD indication, which depends again on positive EPS or NSVT, may be negatively impacting effectiveness of ICD therapy. Patients with CRT-D or CRT-P indication who did not receive appropriate therapies drove mortality and device upgrade rates across cohorts, suggesting that they may have benefited from earlier CRT device implant.

Current ESC and US primary prevention guidelines do not recommend the use of EPS to induce arrhythmias during ICD or CRT-D implantation due to low sensitivity and specificity for predicting subsequent VA events. Results from the HINODE trial support this recommendation because electrophysiologic testing did not predict outcomes.

It is important to note that a subgroup of 29 ND patients with CRT indication did not receive ESC guideline-indicated CRT devices and subsequently had worse outcomes. This highlights the importance of guideline-directed CRT implantation in eligible patients despite NSVT and positive EPS. Beyond Japan, these findings may also be relevant to healthcare systems where limited access to CRT devices may force clinicians to triage implant in some patients.

Additionally, we analysed medication between five subgroups (ICD cohort: CRTD indicated class 1/not CRT-D indicated; QRS >/< 130 ms; Non-Device cohort: CRT-D indicated/ICD indicated; Pacing cohort: PM versus CRT-P). PM patients received less Beta blocker (18.2%) compared with CRT-P treated patients (71.7%, $P < .001$). There were no differences in the remaining groups.

According to the HINODE protocol, patients in this study had to have two to five risk factors associated with increased incidence of non-sustained ventricular tachycardia (NSVT) or life-threatening VA. Notably, patients in the ND cohort had fewer risk factors than those in the device-treated cohorts. While this suggests that they should have had a lower risk of VA than other patients, high rates of VA and mortality were still observed, which may have been prevented by the use of device implants.[19] This suggests that regardless of risk factors, all patients with indications for primary prevention with an ICD may benefit from timely and appropriate use of these devices.

The low rate of inappropriate therapy in the HV cohort (<2% at 1 year) supports the programming of high cut-off rates or delayed therapy, as shown in MADIT-RIT and UNTOUCHED.[27]

This study showed favourable outcomes in a small number of implanted S-ICD devices. S-ICD is a novel technology that does not require an intracardiac electrode, thus avoiding complications related to transvenous leads. Given its favourable risk profile, it is a reasonable option for patients

with primary prevention. Future studies may further examine S-ICD outcomes in primary prevention patients.

This study has some limitations. The sample size in this multi-cohort study was smaller than initially planned. However, no patients were lost to follow-up, and the study period was extended by 6 months. The increased mean follow-up time and total patient months in the trial allowed Kaplan–Meier analysis up to 24 months. Overall, the study design and low attrition rate facilitated a better estimate of event rates than a study with a larger sample size but shorter follow-up. The discrepancies between JCS and ESC guidelines and individual clinician judgement on therapy could have resulted in residual confounding despite propensity matching of the HV cohort. Due to a complex bias between CIDE and Non-device patients a direct comparison was not possible. OMT was required for all patients by the JCS guideline and although we tested for discrepancies between sub-groups, we cannot exclude the possibility that medication had an impact on differences between subgroups. Patient subgroups were identified for all four cohorts to better understand the cohort outcome, however not all were pre-defined. Additionally, this was an intention to treat study with therapy treatment conditions not directly manipulated or randomly assigned. Thus, the conclusions are not as robust as in a randomized controlled trial.

Future analysis of the data from HINODE will focus on patients in the ND cohort with an indication for ICD, as well as the risk of heart failure across all cohorts. Future studies should address the need for large-scale randomized studies to directly assess the effectiveness of new therapies in the Japanese population.

In conclusion, mortality and VA event rates in primary prevention patients in Japan are similar to those in matched MADIT-RIT patients, indicating that the results of landmark trials are applicable to Japan. This study found that regardless of cohort or indicated treatment patients that did not receive ESC guideline indicated care had worse outcomes than those reported in MADIT-RIT. The novel comparison facilitated by this study design allows direct comparison to western clinical data, and the present data suggest that Japanese patients may have better outcomes if they are treated in accordance with the western Guidelines.

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Conflict of interest

Ando K. received lecture fees from Japan Lifeline Co., Ltd., Terumo Co., Ltd., Bristol-Myers Squibb Co., Ltd., Medtronic Japan Co. Ltd., Biotronik Japan, and Bayer Co., Ltd., and consulting honoraria from Boston Scientific. Aonuma K. received speaker honoraria from Abbott Japan, Boehringer-Ingelheim, and Daiichi-Sankyo Co., Ltd., consulting honoraria from Boston Scientific, and belonged to the endowment department of Abbott Japan. Azlan H. received consulting fees from the ventricular event committee in Hinode. Chan Y. S. received consulting fees for the ventricular event committee in Hinode. Ikeda T. received scholarship funds or donations scholarship funds from Medtronic Japan Co., Ltd., Japan Lifeline Co., Ltd., Daiichi Sankyo Co., Ltd., honoraria for lectures from Bayer Co., Ltd., Ono Pharmaceutical Co., Ltd., and Bristol-Myers Squibb Co., Ltd., and consulting honoraria from Boston Scientific. Kutyifa V. received research grants from Boston Scientific, ZOLL, Biotronik, Spire Inc., and consultant fees from Biotronik, and ZOLL. Mitsuhashi T. received lecture fees from Medtronic Japan Co., Ltd. and Abbott Japan, and consulting honoraria from Boston Scientific. Murohara T. received consulting honoraria from Boston Scientific. Nishii N. belonged to the endowed department by Medtronic Japan Co., Ltd. and received lecture fees from Medtronic Japan Co., Ltd., Cook Japan, and Boston Scientific Japan, and consulting honoraria from Boston Scientific. Nogami A. received honoraria from Johnson & Johnson, Boehringer-Ingelheim, Daiichi-Sankyo Co., Ltd., and Abbott Japan, an endowment from Medtronic Japan Co., Ltd. and DVx Co., Ltd., and consulting honoraria from Boston Scientific. Sakata Y. received a scholarship fund and consulting honoraria from Boston Scientific Japan. Shimizu W. received scholarship funds from Abbott Japan Co., Ltd., Japan Lifeline Co., Ltd., Boehringer-Ingelheim, and Daiichi Sankyo Co., Ltd. and remuneration from Boehringer-Ingelheim, and Daiichi Sankyo Co., Ltd., Ono Pharmaceutical Co., Ltd., Bayer Co., Ltd., and Bristol-Myers Squibb Co., Ltd., and a consulting honoraria from Boston Scientific. Simon T., Beaudoint C., and Kayser T. were employees of Boston Scientific. Tachapong N. is a member of the advisory board of Boston Scientific and received consulting fees for the ventricular event committee in HINODE, lecture honoraria, and travel support from the company, in addition to lecture fees from Medtronic. Asai T., Inamura Y., Inoue K., and Kusano K.: none declared.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Study characteristics, follow-up availability, and endpoint data compliance.

Table S2. Baseline characteristics for HINODE high-voltage cohort compared to matched and unmatched MADIT-RIT cohorts.

Table S3. Ventricular arrhythmia classification in the HV cohort.

Table S4. Medication at enrolment in the pacing cohort by treatment device subgroup.

Table S5. JCS guideline overview on CRT indication for patient in sinus rhythm.

Table S6. JCS guideline overview on CRT indication for patient in AF and/or high frequency pacing needs.

Table S7. JCS guideline overview on conditions for ICD indication effecting ICD and CRT-D therapy.

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