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Intra-operative defibrillation testing and clinical shock efficacy in patients with implantable cardioverter-defibrillators: the NORDIC ICD randomized clinical trial

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Aims

This trial was designed to test the hypothesis that shock efficacy during follow-up is not impaired in patients implanted without defibrillation (DF) testing during first implantable cardioverter-defibrillator (ICD) implantation.

Methods and results

Between February 2011 and July 2013, 1077 patients were randomly assigned (1:1) to first time ICD implantation with ($n = 540$) or without ($n = 537$) DF testing. The intra-operative DF testing was standardized across all participating centres, and all ICD shocks were programmed to 40 J irrespective of DF test results. The primary end point was the average first shock efficacy (FSE) for all true ventricular tachycardia and fibrillation (VT/VF) episodes during follow-up. The secondary end points included procedural data, serious adverse events, and mortality. During a median follow-up of 22.8 months, the model-based FSE was found to be non-inferior in patients with an ICD implanted without a DF test, with a difference in FSE of 3.0% in favour of the no DF test [confidence interval (CI) –3.0 to 9.0%, $P_{\text{non-inferiority}} < 0.001$ for the pre-defined non-inferiority margin of –10%]. A total of 112 procedure-related serious adverse events occurred within 30 days in 94 patients (17.6%) tested compared with 89 events in 74 patients (13.9%) not tested ($P = 0.095$).

Conclusion

Defibrillation efficacy during follow-up is not inferior in patients with a 40 J ICD implanted without DF testing. Defibrillation testing during first time ICD implantation should no longer be recommended for routine left-sided ICD implantation.

Keywords

Defibrillation testing • Implantable cardioverter-defibrillator

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[†] Investigators who participated in the NORDIC ICD trial are listed in Supplementary material online, Appendix.

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Introduction

The goal of defibrillation (DF) testing is to verify the detection of ventricular tachyarrhythmias by implantable cardioverter-defibrillators (ICDs), and to ascertain DF efficacy. All clinical trials, which demonstrated the benefit of ICD therapy, have included some kind of DF testing. According to the Food and Drug Administration, the instructions for use of ICDs include the recommendation 'with DF testing' at the time of implantation.¹ The absence of DF testing may have medico-legal implications whether a device fails to terminate ventricular fibrillation (VF) during follow-up.¹ Nevertheless, DF testing has been deliberately omitted in the majority of patients enrolled in contemporary ICD studies.^{2–6}

Despite the stochastic nature of DF, ineffective shocks during VF induction result in system modifications in up to 5% of patients.^{7,8} System modifications, such as repositioning of the electrode, reversal of polarity, use of a high-energy device, use of a dual instead of a single-coil electrode, or the implantation of an additional subcutaneous electrode, may be unnecessary or even harmful since many patients have a successful retesting with the original system configuration.⁹ No single system modification in itself has ever been shown to improve outcome.¹⁰ With current devices and programming, an inadequate safety margin occurs infrequently,¹¹ and the incidence of ventricular tachyarrhythmias requiring shocks is low at 4–6% per year. While DF testing has never been shown to improve survival, it is associated with an increased, albeit small risk of major adverse events of ~0.4%.⁴ By omitting routine DF testing, the approach to ICD implantation will likely change considerably, as the procedures will be shorter and performed without technical support and anaesthesia.

Similar to the SIMPLE trial,¹² we hypothesized that, with current high-energy ICD devices, the omission of DF testing during implantation will not result in an inferior shock efficacy during follow-up when compared with standard DF testing. As opposed to the SIMPLE trial, which used the composite outcome of arrhythmic death or failed appropriate shock, the primary end point of our study was the shock efficacy of all true ventricular tachycardia (VT) and VF episodes occurring in any patient during follow-up.

Methods

Trial design and oversight

The NORDIC ICD trial (NCT01282918) was a prospective, randomized, parallel group, multi-centre non-inferiority trial conducted at 48 centres in five European countries, and designed to investigate the effect of DF testing at the time of ICD implantation on first shock efficacy (FSE) during follow-up. The study design and statistical considerations have been described in detail elsewhere.¹³ Briefly, patients with an indication for ICD implantation according to the current European Society of Cardiology guidelines were included. Patients with hypertrophic or arrhythmogenic right ventricular cardiomyopathy were excluded because of special considerations necessary during ICD implantation. Further inclusion and exclusion criteria are depicted in the design paper.¹³ One thousand and seventy-seven patients were randomized (1 : 1) to first time ICD implantation with or without DF testing during the procedure. Patients were followed for at least 12 months through regular on-site visits, and remotely via Home Monitoring[®] (HM; Biotronik SE & Co. KG, Berlin, Germany). All true ventricular tachyarrhythmias

treated with an ICD shock in any patient were included in the primary analysis.

The study was conducted in accordance with the Declaration of Helsinki, and country-specific regulatory requirements. The protocol was approved by the Institutional Review Board or Ethics Committee of each participating centre. All patients provided written informed consent prior to enrolment.

Intra-operative testing

A standard DF testing protocol was used by all participating centres, as described previously.¹³ Briefly, the initial shock for DF was programmed to 15 J. If successful, DF testing was terminated. If unsuccessful, a second shock programmed to 24 J was delivered, and had to be confirmed. If the shocks were successful twice, DF testing was terminated. If unsuccessful, a system revision was recommended, and the DF testing procedure was repeated.

End points

The primary end point was the FSE to terminate all true episodes of VT/VF during follow-up. A blinded two-member Clinical Event Committee reviewed the diagnostic information of the VT/VF treated with ICD shocks. Procedural end points included system reconfiguration, total fluoroscopy, and implantation time. Safety end points included procedural serious adverse events, VT/VF conversion rate, and all-cause, cardiac, or arrhythmic mortality during follow-up.

All adverse events were reviewed and adjudicated by a Data and Safety Monitoring Board (DSMB), consisting of three members. All patient deaths were adjudicated by the DSMB according to a classification originally described by Epstein *et al.*^{13,14}

Statistical analysis

The goal of the NORDIC ICD trial was to demonstrate the non-inferiority of no DF testing when compared with DF testing with respect to the primary endpoint of FSE. A non-inferiority margin of –10% was fixed before start of enrolment. This margin was chosen because the variation of FSE in published trials was in the range of 83–92%.^{2,11} After a pre-specified blinded re-assessment,¹³ the sample size was increased to 1080 patients recruited over a period of 28 months, with a follow-up of at least 12 months.

Three populations were pre-defined for analysis. The intention-to-treat (ITT) population which included all randomized patients, the evaluated-for-safety population which included randomized patients who received an ICD, and the per protocol (PPS) population which included randomized patients who received an ICD and did not have a major protocol violation. However, for time-dependent outcomes, these patients were included up to the date of the protocol violation. The primary analysis was performed in the per protocol episode data set (P-PPS), which included all sufficiently documented shocked episodes in PPS patients.

Baseline characteristics are presented group wise for the ITT population as mean (\pm SD) or frequency (%). To compensate for the dependence structure induced by recurrent episodes with similar outcome in some of the patients, a random effects logit model with patients as a random factor and group as a fixed factor was used for calculation of a two-sided 95% confidence interval (CI) of the difference $FSE_{noDFtest} - FSE_{DFtest}$. To state non-inferiority, this CI had to lie completely above the pre-specified non-inferiority margin of –10%. Without the use of a model that takes the correlation structure into account, the few patients with an extreme numbers of shocks would have dominated the results.

Table 1 Baseline demographic and clinical characteristics of subjects by treatment group (intention to treat)

Characteristic	Total (N = 1077)	Without DF test (N = 537)	With DF test (N = 540)
Age (year)	64.8 (± 10.9)	64.7 (± 11.2)	64.9 (± 10.6)
Male sex, n (%)	873 (81.1)	430 (80.1)	443 (82.0)
Ischaemic disease, n (%)	701 (65.1)	341 (63.5)	360 (66.7)
Hypertension, n/total n (%)	509/700 (72.7)	249/349 (71.3)	260/351 (74.1)
Diabetes mellitus, n (%)	368 (34.2)	183 (34.1)	185 (34.3)
Renal insufficiency, n (%)	303 (28.1)	144 (26.8)	159 (29.4)
NYHA class, n (%)			
I	59 (5.5)	31 (5.8)	28 (5.2)
II	464 (43.1)	226 (42.1)	238 (44.1)
III	487 (45.2)	254 (47.3)	233 (43.1)
IV	14 (1.3)	5 (0.9)	9 (1.7)
Unknown	53 (4.9)	21 (3.9)	32 (5.9)
NYHA class, n (%)			
≤ II	523 (48.6)	257 (47.9)	266 (49.3)
≥ III	501 (46.5)	259 (48.2)	242 (44.8)
Unknown	53 (4.9)	21 (3.9)	32 (5.9)
Estimated BMI (N = 1054)	28.2 (± 4.9)	28.1 (± 4.8)	28.2 (± 5.1)
LVEF, n (%)			
< 20%	101 (9.4)	53 (9.9)	48 (8.9)
20–30%	566 (52.6)	278 (51.8)	288 (53.3)
> 30%	404 (37.5)	204 (38.0)	200 (37.0)
Not done	6 (0.6)	2 (0.4)	4 (0.7)
AF at enrolment, n (%)	85 (7.9)	45 (8.4)	40 (7.4)
Indication for implantation, n/total n (%)			
Primary prevention	873/1067 (81.8)	434/531 (81.7)	439/536 (81.9)
Secondary prevention	194/1067 (18.2)	97/531 (18.3)	97/536 (18.1)
Hospital stay (days) (N = 1066)	4.0 (± 4.0)	4.0 (± 3.6)	4.0 (± 3.8)
Medication, n (%)			
ACE inhibitors/AT receptor blockers, n (%)	986 (91.6)	501 (93.3)	485 (89.8)
β-Blockers, n (%)	1007 (93.5)	500 (93.1)	507 (93.9)
Ca ²⁺ antagonists, n (%)	140 (13.0)	74 (13.8)	66 (12.2)
Spironolactones, n (%)	618 (57.4)	302 (56.2)	316 (58.5)
(Other) diuretics, n (%)	794 (73.7)	395 (73.6)	399 (73.9)
Nitrates, n (%)	75 (7.0)	38 (7.1)	37 (6.9)
Digitalis, n (%)	105 (9.7)	54 (10.1)	51 (9.4)
Lipid-lowering agents, n (%)	763 (70.8)	377 (70.2)	386 (71.5)
Amiodarone, n (%)	116 (10.8)	61 (11.4)	55 (10.2)
Dronedarone, n (%)	5 (0.5)	4 (0.7)	1 (0.2)
Sotalol, n (%)	9 (0.8)	5 (0.9)	4 (0.7)
(Other) anti-arrhythmics, n (%)	22 (2.0)	9 (1.7)	13 (2.4)
Platelet aggregation inhibitor, n (%)	753 (69.9)	370 (68.9)	383 (70.9)
Anti-coagulants, n (%)	350 (32.5)	183 (34.1)	167 (30.9)
Other cardiovascular medication, n (%)	255 (23.7)	121 (22.5)	134 (24.8)

Values are means ± SD. There were no significant differences at $P < 0.05$ between groups, except for ACE inhibitors $P = 0.039$. t -Test for metric variables, χ^2 -test for categorical, or Fisher's exact test (F) if χ^2 is not appropriate.

ACE inhibitors, angiotensin converting enzyme inhibitors; AF, atrial fibrillation; AT receptor blockers, angiotensin receptor blockers; BMI, body mass index; DF, defibrillation; NYHA, New York Heart Association; ITT, intention-to-treat; LVEF, left ventricular ejection fraction.

Procedural and safety outcomes were compared with a Student's t test, or χ^2 test or Fisher's exact test, whichever was appropriate. Mortality was analysed in the ITT population using the Kaplan–Meier approach and the log-rank test. Hazard rate reduction was

assessed using a Cox proportional hazards model. A two-tailed P -value < 0.05 was considered to be statistically significant.

Data were analysed using SAS (version 9.4) and Stata (version 13.1) by an independent statistical institute (Department of Medical Biometry

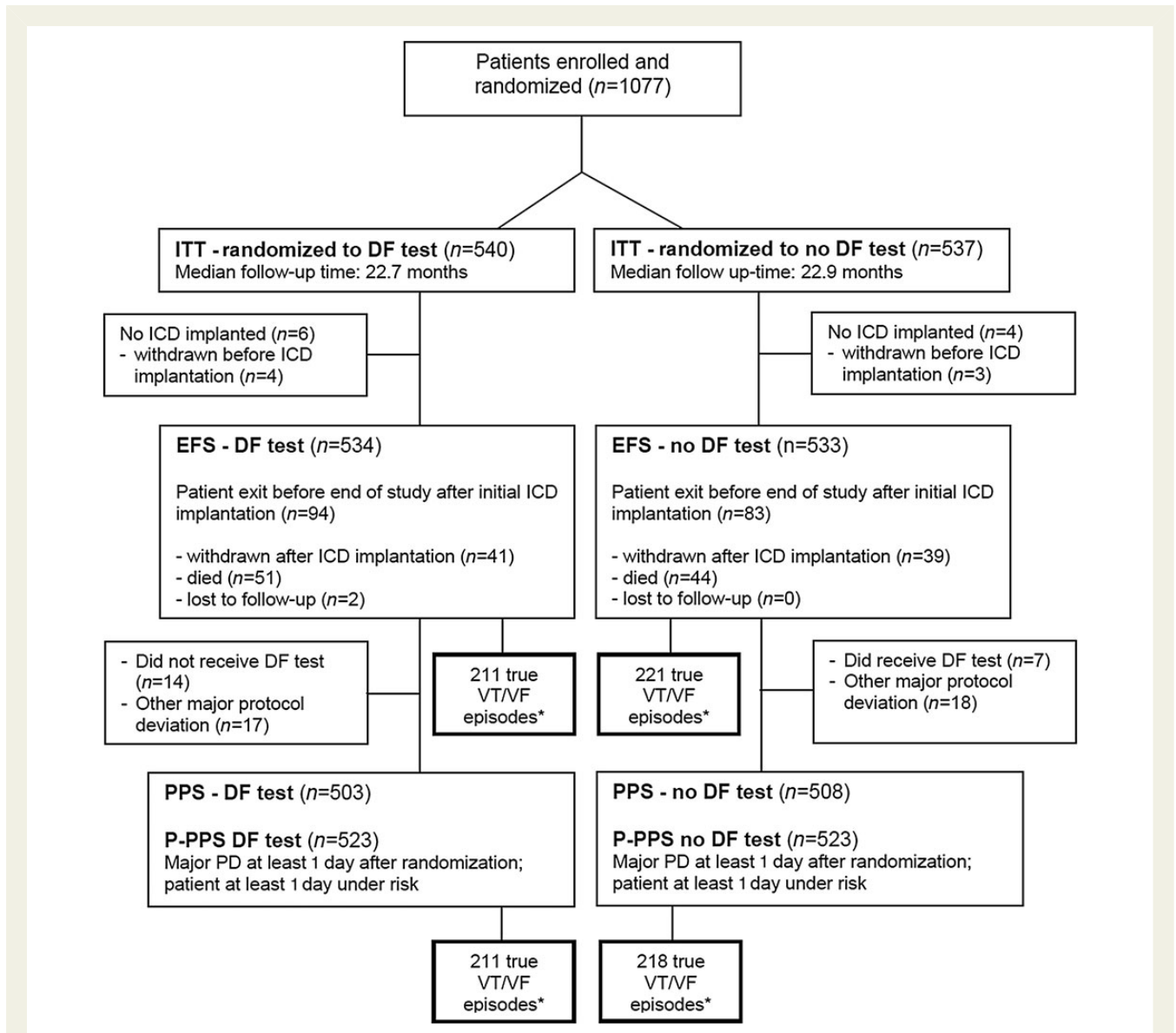


Figure 1 CONSORT flow diagram. *With at least one delivered appropriate ICD shock. ITT, full analysis set (all patients as randomized); EFS, evaluated for safety set (all patients randomized, who had a successful primary ICD implantation); PPS, per protocol set (all patients randomized, who are compliant with the study protocol); P-PPS, all randomized patients at least one day at risk before protocol deviation (includes all sufficiently documented shocked episodes until time point of protocol deviation).

and Epidemiology, University Medical Centre Hamburg Eppendorf, Germany) (A.S., K.W.). The first draft of the manuscript was written by the first author, and revised by all co-authors. The authors take full responsibility for the accuracy and completeness of the findings, as well as for the fidelity to the study protocol.

Results

Study population

The baseline clinical characteristics and cardiovascular medications of the 1077 patients comprising the intention-to-treat population (without DF = 537 and with DF = 540) are presented in Table 1.

Seven hundred and one patients (65.1%) had an ischaemic cardiomyopathy and 873 (81.8%) received the ICD for primary prevention of sudden cardiac death. Ten patients (six in the DF group and four in the without DF group) did not receive an ICD, leaving 1067 patients for the safety evaluation (Figure 1). Both groups were well matched for baseline demographics and clinical characteristics, as well as for the use of dual (51.6%) and a single coil (48.4%) electrode (Table 2).

Intra-operative testing

Of the 534 patients randomized to the DF arm with a successful first ICD implantation (Figure 1), testing was performed in 97.4%. In one

Table 2 Procedural characteristics according to treatment group (successful primary implantable cardioverter-defibrillator implantation; evaluated-for-safety)

Characteristic	Total (N = 1067)	Without DF test (N = 533)	With DF test (N = 534)	P-value
Implanted lead type, n (%)				
Single coil	516 (48.36)	262 (49.16)	254 (47.57)	0.603
Dual coil	551 (51.64)	271 (50.84)	280 (52.43)	
Type, n (%)				
Single chamber ICD	466 (43.67)	236 (44.28)	230 (43.07)	0.648
Dual chamber ICD	245 (22.96)	116 (21.76)	129 (24.16)	
CRT-D	356 (33.36)	181 (33.96)	175 (32.77)	
Left position, n (%)	1058 (99.16)	527 (98.87)	531 (99.44)	0.341 (F)
VEGM signal amplitude (mV) (N = 1057)	12.42 (± 5.30)	12.72 (± 5.37)	12.12 (± 5.21)	0.065
Pacing threshold (V) at pulse duration of 0.4 ms (N = 527)	0.51 (± 0.20)	0.49 (± 0.17)	0.53 (± 0.22)	0.040
Pacing threshold (V) at pulse duration of 0.5 ms (N = 533)	0.45 (± 0.23)	0.45 (± 0.27)	0.44 (± 0.17)	0.613
Patients received DF test, n (%) ^a	527 (49.39)	7 (1.31)	520 (97.38)	
Delivered ICD shocks per patient	0.71 (± 1.16)	0.01 (± 0.11)	1.41 (± 1.31)	<0.001
DF energy at final position (J) (N = 526)	16.74 (± 4.47)	–	16.67 (± 4.38)	
Patients with intra-procedural system revisions and ICD re-programming, n/total n (%)	25/527 (4.74)	–	25/520 (4.81)	
Patients with electrode repositionings, n/total n (%)	8/527 (1.52)	–	8/520 (1.54)	
Patients with changes of shock polarity, n/total n (%)	20/527 (3.80)	–	20/520 (3.85)	
Patients with modification of lead system (shock pathway), n/total n (%)	5/527 (0.95)	–	5/520 (0.96)	
Patients with other revisions/re-programming, n/total n (%)	7/527 (1.33)	–	7/520 (1.35)	
Procedure duration (min) (N = 1060)	64.54 (± 39.88)	63.11 (± 40.84)	65.97 (± 38.88)	0.243
Fluoroscopy exposure duration (min) (N = 1056)	8.02 (± 11.43)	8.00 (± 11.44)	8.05 (± 11.43)	0.943

CRT-D, cardiac-resynchronization therapy with defibrillator; DF, defibrillation; EFS, evaluated for safety; VEGM, ventricular electrogram; ICD, implantable cardioverter-defibrillator.

^aOne patient was not inducible.

patient, VT/VF was not inducible. Four hundred and ninety-four of 519 inducible patients (95.2%) passed the test without any system reconfiguration, and 440 patients (84.8%) had their VT/VF terminated with a 15 J shock. In 25 patients, the initial DF test was not successful, and system reconfigurations were performed once in 20 and more than once in 5 (Table 2). All patients subsequently passed the test successfully, but still with a higher energy level at the final position (22.2 ± 7.4 J vs. 16.4 ± 4.0 J, $P < 0.001$) and with significantly more shocks (5.7 ± 3.0 vs. 1.2 ± 0.7 , $P < 0.001$) than the 494 patients who passed the test immediately. In addition, the duration of the procedure (90.2 ± 56.2 min vs. 63.5 ± 36.1 min, $P < 0.001$) and fluoroscopy exposure (11.6 ± 14.2 min vs. 7.5 ± 10.7 min, $P = 0.064$) was increased.

Shock efficacy

During a median follow-up of 22.7 and 22.9 months, respectively, 211 true VT/VF episodes with at least one appropriate shock occurred in 8.6% of the per protocol patients with DF testing, while 218 true VT/VF episodes occurred in 8.8% of patients without DF testing (Table 3, Figure 1). All true VT/VF episodes were terminated with any appropriate ICD shock in the without DF test group, whereas 96.7% of all VT/VF were terminated in the group with DF test. Thus, the conversion efficacy was 100.0%

without DF testing and 96.7% with DF testing. The model-based shock efficacy was 97.1% without DF testing and 94.1% with DF testing. The difference in FSE was 3.0% (CI – 3.0%, 9.0%) in favour of the without DF test group, and remained above the pre-defined – 10% margin for the primary end point ($P_{\text{non-inferiority}} < 0.001$, Table 3, Figure 2).

Serious adverse events

A total of 201 serious adverse events related to the study procedure occurred in 168 patients (15.7%), of which 89 events occurred in 74 patients without DF testing and 112 events occurred in 94 patients with DF testing within 30 days of follow-up ($P = 0.095$). The only significant difference in single serious adverse events was intra-operative hypotension, which manifested more often in patient with DF testing (1.7%) than those without DF testing (0.0%) ($P = 0.004$). Lead-related complications occurred in 15 patients without DF testing (2.8%) compared with 24 events in 21 patients with DF testing (3.9%) ($P = 0.311$). One sudden death occurred in each study group within 30 days of follow-up, and the mean length of hospitalization was 4.0 days in both study groups (Table 1). The proportion of patients with inappropriate shocks during follow-up was low at 3.7%, and similar between groups.

Table 3 Primary analysis—shock efficacy (per protocol episode data set)

	Total	Without DF test	With DF test
All patients with at least one delivered appropriate shock for a true VT/VF episode, <i>n</i> /total <i>n</i> (%)	91/1046 (8.7)	46/523 (8.8)	45/523 (8.6)
All true VT/VF episodes with at least one delivered appropriate ICD shock (VT/VF), <i>n</i>	429	218	211
Delivered appropriate shocks per true VT/VF episode (mean (± SD))	1.18 (± 0.69)	1.09 (± 0.37)	1.28 (± 0.90)
True VT/VF episodes terminated with first appropriate ICD shock, <i>n</i> /total <i>n</i> (%)	384/429 (89.5)	204/218 (93.6)	180/211 (85.3)
True VT/VF episodes terminated with any appropriate ICD shock, <i>n</i> /total <i>n</i> (%)	422/429 (98.4)	218/218 (100.0)	204/211 (96.7)
True VT/VF episodes not terminated with any appropriate ICD shock, <i>n</i> /total <i>n</i> (%)	7/429 (1.6)	0/218 (0.0)	7/211 (3.3)
Conversion efficacy [proportion (95% CI)]	0.98 (0.97;0.99)	1.00 (0.98;1.00)	0.97 (0.93;0.99)
First shock efficacy model based [proportion (95% CI)]	0.96 (0.89;0.98)	0.97 (0.91;0.99)	0.94 (0.83;0.98)

Difference between the groups (without DF testing vs. with DF testing): 0.03 (−0.03;0.09).

DF, defibrillation; ICD, implantable cardioverter-defibrillator; P-PPS, per protocol episode data set; VT/VF, ventricular tachycardia/ventricular fibrillation.

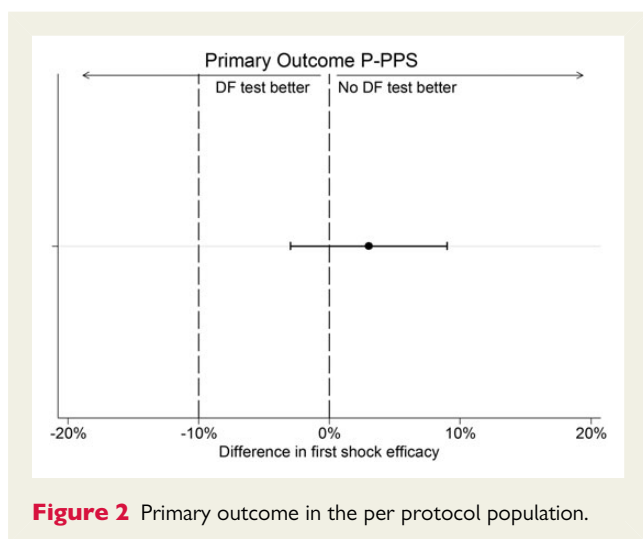


Figure 2 Primary outcome in the per protocol population.

Mortality

Forty-four and 52 patients without and with DF testing died, respectively ($P = 0.377$, Table 4). Differences with respect to non-cardiac and cardiac mortality were not statistically significant. Six deaths (5 with DF and 1 without DF testing) were adjudicated arrhythmic and due to repetitive ventricular tachyarrhythmias/VT clusters ($P = 0.100$, Table 4).

Discussion

Defibrillation testing during ICD implantation has been a matter of debate for the last two decades. To the best of our knowledge, the NORDIC ICD trial is the first prospective randomized trial, which investigated the effect of DF testing on the actual FSE during follow-up as the single primary end point. This is in contrast with the recently published SIMPLE trial, which used the composite outcome of arrhythmic death or failed appropriate shock to terminate a spontaneous episode of VT/VF to determine the non-inferiority of the no testing approach.¹² NORDIC ICD also provides detailed information about intra-operative DF testing outcome.

In 91–96% of ICD implants, the initial system and implant configuration can successfully detect and terminate VT and VF.^{2,15–18} System modifications were reported in 2.2–12.0% of patients.^{5,15,17,19–25} With the high-energy devices used in the NORDIC ICD study, only 4.8% of all inducible patients had an inadequate safety margin, which required one or two system reconfigurations in 3.8 and 1.0%, respectively. This is in agreement with the results of the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT), in which 97.8% of patients had a DF threshold ≤ 20 J.¹¹ Following the system revisions, all patients passed the test successfully, but with a significantly higher energy level than for those who did not require revision (22.2 J vs. 16.4 J, $P < 0.001$). This is in agreement with a Canadian survey in which an insufficient safety margin with the initial system configuration could be improved in only 56% of patients.⁵ While the device revisions provided no benefit to our patients during follow-up, they significantly increased the total procedure time by ~30 min and the fluoroscopy exposure by ~40%. The mean number of shocks needed to find an acceptable safety margin was also increased more than four-fold.

Our FSE was higher than the 83.0% reported in the SCD-HeFT trial.¹¹ It is noteworthy that only low-energy devices were used in that trial. However, in a trial with variable use of devices, the shock efficacy is similar to that observed in the NORDIC ICD trial.²

The observed lower rate of arrhythmic death for patients without DF testing (0.2 vs. 0.9%) corresponds to the sudden cardiac death rate reported in another trial (0.9 and 1.2% in patients without and with DF testing) during a similar follow-up period.⁶

Because the SIMPLE trial did not use a specific model for multiple shock events in the same patient, the shock efficacy can only be compared at the level of raw shock efficacy. In the NORDIC ICD and the SIMPLE trials, a higher raw shock efficacy was observed in the group without DF vs. with DF testing (NORDIC ICD: 93.6 vs. 85.3% and SIMPLE: 92.0 vs. 88.5%). On the other hand, the higher first shock energy we used (40 J vs. 31 J in SIMPLE) was not associated with a higher FSE irrespective of testing. The high level of FSE is consistent with the relatively low mean DF energy (16.7 J) during testing, with >95% of the inducible patients undergoing successful testing without any system reconfiguration.

A 15.7% serious adverse events rate (17.6% with testing and 13.9% without testing, $P = 0.095$) was found within 30 days

Table 4 Mortality (intention-to-treat)

Outcome	Events		Incidence ^a		Log rank		95% CI	
	Without DF test (N = 537)	With DF test (N = 540)	Without DF test	With DF test	P-value	HR	Lower	Upper
All-cause mortality	44 (8.2%)	52 (9.6%)	0.044	0.053	0.377	0.835	0.559	1.248
Non-cardiac mortality	24 (4.5%)	23 (4.3%)	0.024	0.023	0.907	1.035	0.584	1.833
Unknown (primary organ cause)	6 (1.1%)	10 (1.9%)	0.006	0.01	0.306	0.593	0.216	1.632
Cardiac mortality	14 (2.6%)	19 (3.5%)	0.014	0.019	0.350	0.721	0.361	1.438
Arrhythmic mortality	1 (0.2%)	5 (0.9%)	0.001	0.005	0.100	0.198	0.023	1.694
Non-arrhythmic mortality	13 (2.4%)	13 (2.4%)	0.013	0.013	0.948	0.975	0.452	2.103
Unknown cardiac mortality	0 (0.0%)	1 (0.2%)	0	0.001				

DF, defibrillation; HR, hazard ratio; ITT, intention to treat.

^aIncidence referring to person-years without DF test (1001.5) and with DF test (985.9).

following successful ICD implantation. This is much higher than what has been described in recent reports, in which the complication rates ranged between 2.3 and 2.7% in patients with and without an adequate safety margins during DF testing²⁵ or compared with the SIMPLE trial results regarding adverse events included in the pre-defined as the primary safety outcome (5.6% without DF testing vs. 6.5% with DF testing).¹² It is noteworthy that the NORDIC ICD trial not only collected data on protocol-specified complications but also on all procedure- and patient-related adverse events which might explain our higher event rate. The 30-day procedure-related mortality rate was 0.2%, and consisted of two sudden deaths which is in the range of recent reports.² The stroke rate was 0.8% for patients without and 0.2% for patients with DF testing ($P = 0.217$), which is in agreement with the 0.4% rate reported in the CREDIT registry.⁵ The two types of adverse events that were increased in patients with DF testing were intra-operative hypotension (1.7% vs. 0.0%, $P = 0.004$) and lead-related complications (3.9 vs. 2.8%, $P = 0.311$). A recent article summarized implant-related complications that were directly or indirectly related to the DF testing procedure. The rate of haemodynamic complications was 1%, and lead dislodgement was listed as the most frequent single complication with rates between 1 and 6%.¹ This latter observation suggests that testing may cause some degree of electrode instability. Both the NORDIC ICD and SIMPLE trials showed a trend towards lower procedural complication rates in patients without DF testing despite the different definitions and methods used for analysing these events (NORDIC ICD: 13.9 vs. 17.6%, $P = 0.095$, SIMPLE: 5.6 vs. 6.5%, $P = 0.33$). A meta-analysis would confirm if a significant difference does indeed exist.

The rates of all-cause, cardiac, and non-cardiac mortality were similar between patients with and without DF testing, which is in agreement with most non-randomized trials reported.⁶ In accordance with the SIMPLE trial, no statistical difference in all-cause mortality between patients with and without DF testing was observed. However, the annual mortality rates of NORDIC ICD were lower when compared with other large randomized ICD trials,^{26,27} and also lower than those of the SIMPLE trial.

Conclusion

The NORDIC ICD trial supports the hypothesis that if 40 J devices are used, DF testing does not improve DF efficacy during follow-up. It suggests that DF testing or the various measures to improve DF efficacy lengthen the procedure, and may even be harmful. The NORDIC ICD trial is one of two large prospective randomized trials, which do not support the routine use of DF testing during left-sided first time ICD implantation.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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References

1. Russo AM, Chung MK. Is defibrillation testing necessary? *Cardiol Clin* 2014;**32**: 211–224.

2. Pires LA, Johnson KM. Intraoperative testing of the implantable cardioverter-defibrillator: how much is enough? *J Cardiovasc Electrophysiol* 2006;**17**:140–145.
3. Christ G, Becker R, Voss F, Kelemen K, Senges-Becker J, Hauck M, Schoels W, Bald I, Katus H, Bauer A. Indications for predismittal testing with arrhythmia-induction in patients receiving an implantable cardioverter defibrillator. *Clin Res Cardiol* 2007;**96**:613–620.
4. Brignole M, Raciti G, Bongiorni MG, De Martino G, Favale S, Gasparini M, Luise R, Occhetta E, Proclemer A. Defibrillation testing at the time of implantation of cardioverter defibrillator in the clinical practice: a nation-wide survey. *Europace* 2007;**9**:540–543.
5. Healey JS, Dorian P, Mitchell LB, Talajic M, Philippon F, Simpson C, Yee R, Morillo CA, Lamy A, Basta M, Birnie DH, Wang X, Nair GM, Crystal E, Kerr CR, Connolly SJ, CREDIT Investigators. Canadian Registry of ICD Implant Testing procedures (CREDIT): current practice, risks, and costs of intraoperative defibrillation testing. *J Cardiovasc Electrophysiol* 2010;**21**:177–182.
6. Brignole M, Occhetta E, Bongiorni MG, Proclemer A, Favale S, Iacopino S, Cal? L, Vado A, Buja G, Mascioli G, Quartieri F, Tritto M, Parravicini U, Castro A, Tomasi C, Villani GQ, D'Acri MG, Klersy C, Gasparini M, SAFE-ICD Study Investigators. Clinical evaluation of defibrillation testing in an unselected population of 2,120 consecutive patients undergoing first implantable cardioverter-defibrillator implant. *J Am Coll Cardiol* 2012;**60**:981–987.
7. Swerdlow CD, Russo AM, Degroot PJ. The dilemma of ICD implant testing. *Pacing Clin Electrophysiol* 2007;**30**:675–700.
8. Bänsch D, Kottkamp H, Grönefeld G, Vogt J, Israel C, Böcker D, Hindricks G, Kuck KH, Quick-ICD Investigators. The quick-implantable-defibrillator trial. *Europace* 2007;**9**:1144–1150.
9. Smits K, Virag N, Swerdlow CD. Impact of defibrillation testing on predicted ICD shock efficacy: implications for clinical practice. *Heart Rhythm* 2013;**10**:709–717.
10. Shukla HH, Flaker GC, Jayam V, Roberts D. High defibrillation thresholds in transvenous biphasic implantable defibrillators: clinical predictors and prognostic implications. *Pacing Clin Electrophysiol* 2003;**26**:44–48.
11. Blatt JA, Poole JE, Johnson GW, Callans DJ, Raitt MH, Reddy RK, Marchlinski FE, Yee R, Guarnieri T, Talajic M, Wilber DJ, Anderson J, Chung K, Wong WS, Mark DB, Lee KL, Bardy GH, SCD-HeFT Investigators. No benefits from defibrillation threshold testing in the SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial). *J Am Coll Cardiol* 2008;**52**:551–556.
12. Healey JS, Hohnloser SH, Glikson M, Neuzner J, Mabo P, Vinolas X, Kautzner J, O'Hara G, VanErven L, Gadler F, Pogue J, Appl U, Gilkerson J, Pochet T, Stein KM, Merkely B, Chrolavicius S, Meeks B, Foldesi C, Thibault B, Connolly SJ, Shockless IMPLant Evaluation (SIMPLE) Investigators. Cardioverter defibrillator implantation without induction of ventricular fibrillation: a single-blind, non-inferiority, randomised controlled trial (SIMPLE). *Lancet* 2015;**385**:785–791.
13. Bänsch D, Bonnemeier H, Brandt J, Bode F, Svendsen JH, Felk A, Hauser T, Wegscheider K, NORDIC ICD Trial Investigators. The NO Regular Defibrillation testing In Cardioverter Defibrillator Implantation (NORDIC ICD) trial: concept and design of a randomized, controlled trial of intra-operative defibrillation testing during de novo defibrillator implantation. *Europace* 2015;**17**:142–147.
14. Epstein AE, Carlson MD, Fogoros RN, Higgins SL, Venditti FJ Jr. Classification of death in antiarrhythmia trials. *J Am Coll Cardiol* 1996;**27**:433–442.
15. Russo AM, Sauer W, Gerstenfeld EP, Hsia HH, Lin D, Cooper JM, Dixit S, Verdino RJ, Nayak HM, Callans DJ, Patel V, Marchlinski FE. Defibrillation threshold testing: is it really necessary at the time of implantable cardioverter-defibrillator insertion? *Heart Rhythm* 2005;**2**:456–461.
16. Osswald BR, De Simone R, Most S, Tochtermann U, Tanzeem A, Karck M. High defibrillation threshold in patients with implantable defibrillator: how effective is the subcutaneous finger lead? *Eur J Cardiothorac Surg* 2009;**35**:489–492.
17. Healey JS, Gula LJ, Birnie DH, Sterns L, Connolly SJ, Sapp J, Crystal E, Simpson C, Exner DV, Kus T, Philippon F, Wells G, Tang AS. A randomized-controlled pilot study comparing ICD implantation with and without intraoperative defibrillation testing in patients with heart failure and severe left ventricular dysfunction: a sub-study of the RAFT trial. *J Cardiovasc Electrophysiol* 2012;**23**:1313–1316.
18. Aoukar PS, Poole JE, Johnson GW, Anderson J, Hellkamp AS, Mark DB, Lee KL, Bardy GH. No benefit of a dual coil over a single coil ICD lead: evidence from the Sudden Cardiac Death in Heart Failure Trial. *Heart Rhythm* 2013;**10**:970–976.
19. Leong-Sit P, Gula LJ, Diamantouros P, Krahn AD, Skanes AC, Yee R, Klein GJ. Effect of defibrillation testing on management during implantable cardioverter-defibrillator implantation. *Am Heart J* 2008;**152**:1104–1108.
20. Mainigi SK, Cooper JM, Russo AM, Nayak HM, Lin D, Dixit S, Gerstenfeld EP, Hsia HH, Callans DJ, Marchlinski FE, Verdino RJ. Elevated defibrillation thresholds in patients undergoing biventricular defibrillator implantation: incidence and predictors. *Heart Rhythm* 2006;**3**:1010–1016.
21. Day JD, Olshansky B, Moore S, Brown S, Stolen KQ, Lerew DR, INTRINSIC RV Study Investigators. High defibrillation energy requirements are encountered rarely with modern dual-chamber implantable cardioverter-defibrillator systems. *Europace* 2008;**10**:347–350.
22. Sauer WH, Lowery CM, Bargas RL, Schuller JL, Stees CS, Aleong RG, Varosy PD. Utility of postoperative testing of implantable cardioverter-defibrillators. *Pacing Clin Electrophysiol* 2011;**34**:186–192.
23. Vischer AS, Sticherling C, Kühne MS, Osswald S, Schaer BA. Role of defibrillation threshold testing in the contemporary defibrillator patient population. *J Cardiovasc Electrophysiol* 2013;**24**:437–441.
24. Lin EF, Dalal D, Cheng A, Marine JE, Nazarian S, Sinha S, Spragg DD, Tandri H, Halperin H, Calkins H, Berger RD, Tomaselli GF, Henrikson CA. Predictors of high defibrillation threshold in the modern era. *Pacing Clin Electrophysiol* 2013;**36**:231–237.
25. Hsu JC, Marcus GM, Al-Khatib SM, Wang Y, Curtis JP, Sood N, Parker MW, Kluger J, Lampert R, Russo AM. Predictors of an inadequate defibrillation safety margin at ICD implantation: insights from the National Cardiovascular Data Registry. *J Am Coll Cardiol* 2014;**64**:256–264.
26. Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, Domanski M, Troutman C, Anderson J, Johnson G, McNulty SE, Clapp-Channing N, Davidson-Ray LD, Fraulo ES, Fishbein DP, Luceri RM, Ip JH; Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) Investigators. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med* 2005;**352**:225–237.
27. Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS, Daubert JP, Higgins SL, Brown MW, Andrews ML; Multicenter Automatic Defibrillation Trial II Investigators. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med* 2002;**346**:877–883.