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Clinical Evaluation of Defibrillation Testing in an Unselected Population of 2,120 Consecutive Patients Undergoing First Implantable Cardioverter-Defibrillator Implant

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Objectives The purpose of this study is to assess the effectiveness of defibrillation testing (DT) in patients undergoing implantable cardioverter-defibrillator (ICD) insertion.

Background Although DT is considered a standard procedure during ICD implantation, its usefulness has not been definitively proven.

Methods The SAFE-ICD (Safety of Two Strategies of ICD Management at Implantation) study is a prospective observational study designed to evaluate the outcome of 2 strategies: performing defibrillation testing (DT+) versus not performing defibrillation testing (DT−) during de novo ICD implants. No deviation from the centers' current practice was introduced. In all, 2,120 consecutive patients (836 DT+ and 1,284 DT−) age ≥18 years were enrolled at 41 Italian centers from April 2008 to May 2009 and followed up for 24 months until June 2011. The primary endpoint was a composite of severe complications at ICD implant and sudden cardiac death or resuscitation at 2 years.

Results The primary endpoint occurred in 34 patients: 12 intraoperative complications (8 in DT+ group; 4 in DT− group) and 22 during follow-up (10 in DT+ group; 12 in DT− group). Overall, the estimated yearly incidence (95% confidence interval) was DT+ 1.15% (0.73 to 1.83) and DT− 0.68% (0.42 to 1.12). The difference between the 2 groups was negligible: 0.47% per year (−0.15 to 1.10). Mortality from any cause was similar at 2 years (adjusted hazard ratio: 0.97 [0.76 to 1.23], p = 0.80).

Conclusions In this large cohort of new ICD implants, event rates were similar and extremely low in both groups. These data indicate a limited clinical relevance for DT testing, thus supporting a strategy of omitting DT during an ICD implant. (Safety of Two Strategies of ICD Management at Implantation [SAFE-ICD]; NCT00661037) (J Am Coll Cardiol 2012;60:981–7) © 2012 by the American College of Cardiology Foundation

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Abbreviations and Acronyms

CI = confidence interval
DT = defibrillation testing
ICD = implantable cardioverter-defibrillator
VF = ventricular fibrillation

The standardized requirements for implantable cardioverter-defibrillators (ICD) insertion include defibrillation testing (DT), consisting of induction and termination of ventricular fibrillation (VF). Historically, an effective DT has been considered part of standard procedures at insertion to ensure adequate sensing of VF, appropriate connection of high-voltage electrodes, and the ability of the device to terminate VF with a shock. Nevertheless, implant techniques and technology have evolved in recent years, and deviations from this clinical practice are frequent. Reasons may be that ICDs are much more efficient than in the past due to the improved safety margin of modern ICDs (1–3), and physicians are concerned more about the risk of severe complications related to DT (reported to occur in 0.2% to 0.4% of cases in large multicenter surveys) (4,5). In a national retrospective population survey involving 229 Italian centers (4), DT was not performed in 30% of the 7,857 de novo ICD implantations. In the Ontario ICD Registry (6) involving 10 centers, DT was not performed in 35% and 33% of new ICD implants for primary and secondary prevention, respectively, and in 76% of ICD replacements (N = 2,173). Although DT has never been reliably shown to improve clinical outcomes, the practice of not performing DT is arbitrary, and its safety is yet unproven given the lack of prospective follow-up studies.

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The aim of the SAFE-ICD (Safety of Two Strategies of ICD Management at Implantation) study was to evaluate the safety, over a follow-up of 2 years, of 2 strategies, adopted at ICD implant in current clinical practice: induction, including patients who underwent DT at implant (DT+ group), and noninduction, including patients who did not undergo DT at implant (DT− group).

Methods

The SAFE-ICD study was a multicenter, prospective, longitudinal, observational study designed to assess the safety of DT+ performed during the implantation procedure, and DT− strategies in consecutive patients undergoing de novo ICD insertion. No deviation from the centers' current practice was introduced by this study protocol. On the basis of data from the 2005 National Survey (4), 41 Italian centers were selected according to their common practice of performing or not performing DT at implantation, with the aim of obtaining balanced populations of DT+ and DT− patients.

Study population. Consecutive patients, 18 years of age or more, with a conventional indication for ICD, regardless of manufacturer, who were undergoing an initial ICD or cardiac resynchronization therapy device with defibrillation backup implantation were enrolled. The only exclusion criterion was a patient's refusal to provide consent.

Investigators were asked to perform DT or not perform DT according to their standard practice. Therefore, no deviation from the centers' current practice was introduced by this study protocol. To check for consecutiveness, a logbook of patients who refused to participate was kept by each center. Implantation tests were done according to the center's practice. Follow-up visits were performed every 6 months until the 24th (±1) month.

The primary endpoint consisted of a composite of: 1) severe implant-related complications at ICD insertion (cardiopulmonary arrest due to VF requiring 3 or more external shocks for termination or due to electromechanical dissociation, transient ischemic attack or stroke, cardiogenic shock, pulmonary edema, embolic events, anoxic coma, pericardial tamponade, or death); and 2) events at follow-up (sudden cardiac death, resuscitation after ineffective documented appropriate ICD shocks). Secondary endpoints were total mortality and survival after a full series of ineffective appropriate ICD shocks without resuscitation maneuvers.

Definitions. Sudden cardiac death was defined as witnessed unexpected death occurring <1 h from symptoms onset or unwitnessed during sleep (7,8). Instantaneous cardiac death was defined as witnessed unexpected death occurring within 5 min from symptom onset. Resuscitation after ineffective documented ICD shock was defined as any intervention of cardiopulmonary resuscitation including external defibrillation shock and after ineffective ICD therapy. Cardiac death was defined as any death caused by a primary cardiovascular problem, including sudden and nonsudden cardiac death. Noncardiac death was defined as any death not caused by a primary cardiovascular problem. Death from unknown causes was considered censored data. The timing for the occurrence of the event was the date of death. Survival after ineffective ventricular shock without resuscitation maneuvers was defined as an episode of sustained ventricular arrhythmias in which a full series of ICD shocks failed to restore normal sinus rhythm, without intervention of cardiopulmonary resuscitation including external defibrillation shock.

The clinical outcomes of the primary and secondary endpoints were adjudicated by a Clinical Events Committee, whose members were unaware of the patients' study group.

Sample size and statistical analysis. Limited data are available on sudden death related to shock failure to treat VF in ICD patients. Sudden death in patients already having an ICD are reported to be approximately 1.8% to 2.6% during a follow-up ranging from 1 to 3 years (9–11). We assumed a 0.5% incidence of primary endpoint events at ICD implant (4) and a further 2% at the 2-year follow-up in the DT population, for an overall incidence of events of 2.5% at 2 years. We aimed at an estimated incidence with a desired precision of 5%. Thus, on the basis of the expected

incidence of events at the end of the study of 2.5%, 784 patients allow a 2-sided 97.5% confidence interval to extend 1.3% from the observed incidence (i.e., confidence interval: 1.2% to 3.8%). Similarly, no intraoperative events were expected for the DT− population, whereas a 2.5% incidence of the primary endpoint was expected at the end of the follow-up, thus leading to the same sample of 784 patients as above, with a 2-sided 97.5% confidence interval extending 1.3% from the observed incidence (i.e., confidence interval: 1.2% to 3.8%). Therefore, enrollment continued until at least 784 DT+ and DT− patients had been enrolled.

Continuous data are shown as average ± SD. Absolute and relative frequency were used to show categorical data. Unpaired Student's *t* test or Fisher's exact test was used to compare continuous and categorical variables. Yearly incidences of the studied outcomes and 95% confidence intervals (95% CI) were calculated. Kaplan-Meier survival estimates for all-cause mortality were plotted, and a Cox model was fitted, while adjusting (through inverse probability weights) for the propensity score, to compare all-cause mortality among DT+ and DT− patients. The propensity score was computed from a logistic model with DT+/DT− as the dependent variable and robust standard error accounting for intracenter correlation, and included the baseline clinical variables listed in Table 1. The corresponding c statistic was 0.66. The Stata 12 software (StataCorp, College Station, Texas) was used for computation.

Results

Of 2,183 consecutive eligible patients in 41 Italian centers, a total of 2,120 (97%) patients were enrolled from April 2008 to May 2009 and followed up prospectively for 24 (±1) months; 95% of them either completed the follow-up or died before the 24-month visit. The study ended in June 2011. The frequency of DT varied considerably among different centers, ranging from 0% to 100% of all ICD implants per center (median 39%; interquartile range: 0% to 79%). Overall, 836 (39%) patients had DT performed during the ICD insertion procedure and 1,284 (61%) did not. Their characteristics are listed in Table 1. In particular, among DT+ patients, the mean effective shock energy tested during implant was 23 ± 5 J. Safety margin data were available for 695 patients in the DT+ group: a safety margin ≥10 J was present in 648 (93%) patients and <10 J in 47 (7%). One single induction was performed in 720 patients (86%), 2 inductions in 100 (12%), and ≥3 in 16 (2%). An external shock was needed in 30 (3.6%) patients because of ineffective ICD shock at its maximum energy; 4 of these latter had cardiopulmonary arrest requiring 3 or more external shocks for termination, and therefore were counted as primary endpoint (see following text). In 8 patients, the defibrillator was unable to convert VF at any attempt during insertion.

Primary endpoint. The primary combined endpoint occurred in 18 DT+ patients and in 16 DT− patients (Fig. 1, Tables 2 and 3). Overall, the estimated yearly incidence (95% CI) was DT+ 1.15% (0.73 to 1.83) and DT− 0.68% (0.42 to 1.12) (Fig. 2). The difference between the 2 groups was negligible: 0.47% per year (−0.15 to 1.10). The slightly higher event rate in DT+ patients was mainly due to their higher intraoperative complication rate (Table 2). After weighting for baseline clinical variables by the propensity score, the estimated difference between groups remained negligible

Table 1 Baseline Characteristics of Patients, According to Defibrillation Testing Groups

Characteristics	DT+ (n = 836)	DT− (n = 1,284)	p Value
Age, yrs	66 ± 12	67 ± 11	0.05
Male	684 (82%)	1,016 (79%)	0.13
Cardiac condition at procedure			
Ischemic cardiopathy	467 (56%)	726 (57%)	0.79
Dilated cardiomyopathy	247 (30%)	404 (31%)	0.65
Others	122 (15%)	154 (12%)	0.56
History of congestive heart failure	400 (48%)	752 (59%)	0.001
NYHA functional classification			
I	163 (19%)	157 (12%)	0.001
II	411 (49%)	530 (41%)	
III	248 (30%)	567 (44%)	
IV	12 (1%)	28 (2%)	
Echocardiographic ejection fraction, %	32.1 ± 11.6	31.0 ± 10.4	0.02
Heart rate at enrollment, beats/min	70 ± 12	71 ± 14	0.02
Systolic blood pressure at enrollment, mm Hg	124 ± 17	123 ± 17	0.28
Coexisting conditions			
Previous myocardial infarction	431 (52%)	676 (53%)	0.042
Previous CABG and/or PCI	376 (45%)	526 (41%)	0.07
History of atrial fibrillation	221 (27%)	417 (32%)	0.007
Diabetes mellitus	192 (23%)	360 (28%)	0.01
Hypertension	365 (44%)	744 (58%)	0.001
Previous TIA/stroke	44 (5%)	69 (5%)	1.00
Renal insufficiency	182 (22%)	314 (24%)	0.09
Pharmacological therapy			
ACE/ARB inhibitors	554 (66%)	913 (71%)	0.02
Beta-blockers	546 (65%)	901 (70%)	0.02
Diuretics	579 (69%)	1,002 (78%)	0.001
Nitrates	127 (15%)	177 (14%)	0.37
Calcium-channel blockers	40 (5%)	75 (6%)	0.33
Antialdosterone	199 (24%)	310 (24%)	0.88
Digitalis	81 (10%)	178 (14%)	0.004
Antiarrhythmics	220 (26%)	298 (23%)	0.11
Anticoagulants	194 (23%)	414 (32%)	0.001
Antiplatelet	378 (45%)	527 (41%)	0.06
Statins	303 (36%)	534 (42%)	0.01
Potassium supplements	51 (6%)	99 (8%)	0.17
ICD indications			
Primary prevention	575 (69%)	900 (70%)	0.08
Secondary prevention	254 (30%)	364 (28%)	0.08
Unknown	7 (1%)	20 (2%)	—
CRT devices	291 (35%)	595 (46%)	0.001
High-shock energy devices, >40 J*	166 (51%)	273 (51%)	0.98

Values are mean ± SD or n (%). *Data available for 325 DT+ patients (defibrillation testing performed) and 535 DT− patients (defibrillation testing not performed).

ACE = angiotensin-converting enzyme; ARB = angiotensin-receptor blocker; CABG = coronary artery bypass graft surgery; CRT = cardiac resynchronization therapy; ICD = implantable cardioverter-defibrillator; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; TIA = transient ischemic attack.

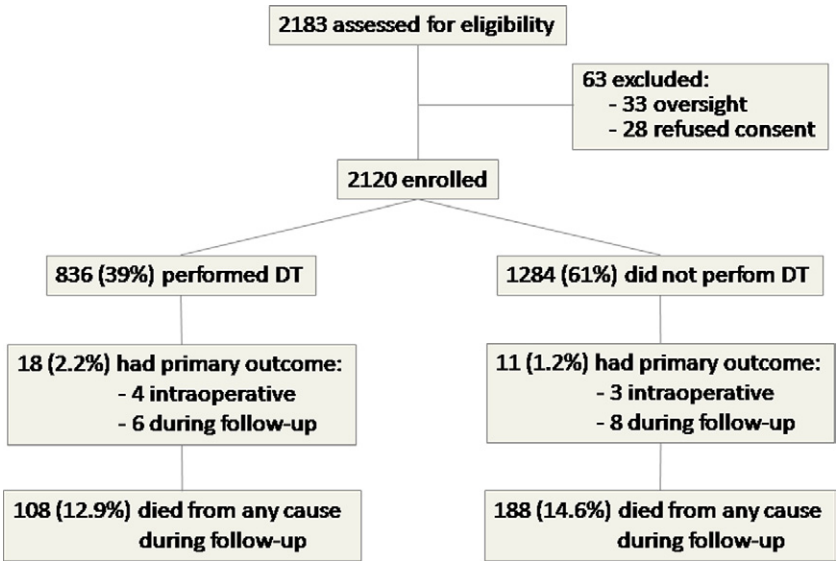

Figure 1 Patient Flow and Main Results

The observed rate at 2-year follow-up of the primary combined endpoint (severe implant-related complications at implantable cardioverter-defibrillator [ICD] insertion and sudden cardiac death at follow-up) and of death from any cause among patients who had undergone defibrillation testing (DT) and among patients who had not.

(0.60%), with a hazard ratio of 1.90 (95% CI: 0.96 to 3.95, p = 0.07) in DT+ compared with DT− patients.

No primary endpoint occurred during the follow-up among the patients with a safety margin <10 J. The primary endpoint occurred in 23 of 1,475 (1.6%) patients in primary prevention and 11 of 618 (1.8%) patients in secondary prevention.

Secondary endpoints. Although fairly balanced, DT+ patients had less severe underlying structural heart disease than DT− patients, as evidenced by lower rate of congestive heart failure, New York Heart Association functional class III or IV, atrial fibrillation, higher ejection fraction, and less usage of diuretics and digoxin (Table 1). Mortality from any cause at 2 years was slightly (not significantly) lower among the DT+ patients than among DT− patients (Table 2, Fig. 3), with a hazard ratio of 0.86 (95% CI: 0.68 to 1.09, p = 0.20). After weighting for baseline clinical variables by the propensity score, the hazard ratio was 0.97 (95% CI: 0.76 to 1.23, p = 0.80).

During the follow-up, appropriate effective shocks occurred in 223 patients, with a similar proportion in DT+ and DT− groups (Table 2); they occurred in 11.6% of patients with standard-energy devices and in 12.3% of patients with high-energy devices (p = 0.36). Appropriate ineffective shocks occurred in 13 patients, with a similar proportion in DT+ and DT− groups (Table 2); they occurred in 0.95% of patients with standard-energy devices and in 1.1% of patients with high-energy devices (p = 0.96). Among the patients with appropriate ineffective shocks, 1 DT+ patient and 2 DT− patients survived despite a full series of ineffective appropriate ICD shocks without resuscitation maneuvers (secondary study endpoint).

Discussion

In this very large cohort of patients who underwent insertion of a new ICD, both practices of performing or not performing DT at implant were safe, with a low, similar rate of potentially ICD-related events, including severe complications during implant and sudden cardiac death at follow-up. Therefore, the clinical relevance of DT testing is limited, thus supporting the practice of omitting DT at implant.

While the rate of acute implant-related complications was consistent with that expected, the observed sudden cardiac death rate in the trial (1.2% and 0.9% in DT+ and DT− patients, respectively) was lower than had been anticipated from prior studies (9–11). The reasons are not clear, but seem not to be related to a lower severity of the disease. Indeed, the overall incidence of appropriate shocks at 1 year was 7.7%, substantially comparable with that reported in recent multicenter registries and randomized controlled trials. For example, in the SCD-HeFT (Sudden Cardiac Death in Heart Failure) trial (12), the average annual rate of appropriate ICD shocks was 5.1%; and in the large ALTITUDE registry (13), which included both ICD and cardiac resynchronization therapy, the 1-year incidence of appropriate shocks was 8%. Alternative explanations may be that modern ICDs have a greater safety margin due to lower defibrillation threshold, higher shock energy, and better arrhythmia discrimination, making ICD therapy more reliable than in the past, and to the higher percentage of primary prevention indication, which was similar in this study to that observed in the United States (14), than in the past.

Table 2 Patient Outcomes, Intraoperatively and During Follow-Up, According to Defibrillation Testing Groups

Characteristics	DT+ (n = 836)	DT− (n = 1,284)	p Value
Primary combined outcome	18 (2.1%)	16 (1.2%)	0.11
Implant-related complications	8 (1.0%)	4 (0.3%)	0.10
Cardiopulmonary arrest due to VF induction requiring ≥3 external shocks	4	0	
TIA or stroke	0	1	
Cardiogenic shock	1	0	
Pulmonary edema	0	2	
Embolic event	1	0	
Anoxic coma	0	0	
Pericardial tamponade	0	0	
Death	2	3	
Events during follow-up	10 (1.2%)	12 (0.9%)	0.58
Sudden cardiac death	9	11	
Instantaneous, within 5 min	2	3	
Resuscitation after ineffective documented appropriate ICD shocks	1	1	
Total mortality	108 (12.9%)	188 (14.6%)	0.29
Cardiac	62	118	
Noncardiac	40	66	
Unknown	6	4	
Patients with appropriate ineffective ventricular shocks during follow-up	7 (0.8%)	6 (0.5%)	0.28
Patients with appropriate effective ventricular shocks during 2-year follow-up	85 (10.2%)	138 (10.7%)	0.66
With ICD	64/545 (11.7%)	84/689 (12.2%)	0.86
With CRT-D	21/291 (7.2%)	54/595 (9.1%)	0.37

Values are n (%), n, or n/N (%).

CRT-D = cardiac resynchronization therapy with defibrillation backup; VF = ventricular fibrillation; other abbreviations as in Table 1.

The SAFE-ICD study shows that, on the one hand, current ICD recipients are very well protected from sudden cardiac death irrespective of performing DT or not and, on the other, that the DT strategy is unlikely to further decrease sudden cardiac death rate to a value that is clinically relevant, lower than that of 1% observed in the present study in DT− patients.

Similarly, we did not observe any substantial difference in all-cause mortality between DT+ and DT− groups. The slight, nonsignificant lower mortality among DT+ patients might be due to these patients having less severe underlying structural heart disease than DT− patients, and it disappeared when the 2 groups were analyzed after adjustment of their baseline clinical characteristics.

The SAFE-ICD is the largest study to date that evaluated clinical hard endpoints and compared the safety of 2 different DT strategies. Until now, only a few small retrospective outcome studies (15–17) of selected populations and largely underpowered to show either superiority or noninferiority of DT+ compared to DT− have been published. In the SCD-HeFT trial (18), the first shock efficacy for ventricular tachyarrhythmias was high regardless of baseline defibrillation threshold testing results, and baseline defibrillation threshold testing did not predict long-term mortality or shock efficacy. Strengths of the SAFE-ICD study include a large population matching the general ICD population of Western countries, its prospective design, a follow-up of 2 years for all patients, the enrollment of consecutive patients, with a dropout rate of only 3%, the use of any commercially available ICD device, and no deviation from the centers' current practice introduced by the protocol. All these aspects allow the study to provide a reliable real-world picture of the practice of modern ICD utilization.

Study limitations. The present study population had a slightly lower than expected primary endpoint event rate because of the low incidence of SCD during follow-up, which could have been insufficient to show a difference in

Table 3 Cause of Death in the 25 Patients Who Reached the Primary Endpoint During Follow-Up

Patient #	Group	Time Course	Description
1	DT+	Acute	Cardiogenic shock
2	DT+	Acute	Cardiogenic shock
3	DT+	Follow-up	Instantaneous SCD with documented recurrent VF
4	DT+	Follow-up	Instantaneous SCD (<5 min from symptoms onset), cardiac rupture likely
5	DT+	Follow-up	SCD with documented VF, <5 min <60 from symptom onset
6	DT+	Follow-up	SCD, cardiac rupture likely
7	DT+	Follow-up	SCD, acute coronary syndrome likely
8	DT+	Follow-up	SCD, acute coronary syndrome likely
9	DT+	Follow-up	SCD, acute coronary syndrome likely
10	DT+	Follow-up	SCD during sleep
11	DT+	Follow-up	SCD during sleep
12	DT−	Acute	Cardiogenic shock
13	DT−	Acute	Prolonged hypotension, electromechanical dissociation 15 min after pocket closure, cardioembolic event likely
14	DT−	Acute	Cardiogenic shock
15	DT−	Follow-up	Instantaneous SCD with documented VF occurred in coronary care unit (ICD and external shocks ineffective)
16	DT−	Follow-up	Instantaneous SCD (<5 min after symptoms onset); no detail available
17	DT−	Follow-up	Instantaneous SCD (<5 min after symptoms onset); no detail available
18	DT−	Follow-up	SCD with documented VF, <5 min <60 from symptom onset
19	DT−	Follow-up	SCD with documented VF, <5 min <60 from symptom onset
20	DT−	Follow-up	SCD with documented electromechanical dissociation after incessant VT, <5 min <60 from symptom onset
21	DT−	Follow-up	SCD with documented electromechanical dissociation, <5 min <60 from symptom onset
22	DT−	Follow-up	SCD during sleep
23	DT−	Follow-up	SCD; cardiac pump failure likely
24	DT−	Follow-up	SCD; no detail available
25	DT−	Follow-up	SCD; no detail available

SCD = sudden cardiac death; VT = ventricular tachycardia; other abbreviations as in Tables 1 and 2.

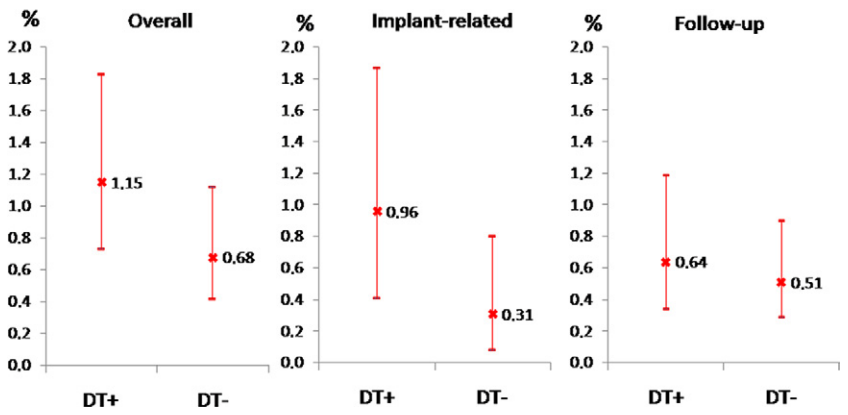

Figure 2 **Yearly Incidences of Primary Endpoint**

Yearly estimated incidences per 100 patients (with 95% confidence interval) of the primary outcome among patients who had undergone defibrillation testing (DT+) and among patients who had not (DT−).

the clinical effect of DT. Nevertheless, it is noteworthy that the shock rate was sufficiently high and consistent with literature data and that the consecutiveness of enrollment in a large mix of general hospitals represent the general practice of a Western country.

Admittedly, the absence of randomization and the modest differences in patient characteristics between the DT+ and DT− groups do not allow us to draw a definite conclusion. Nevertheless, our findings, with a similar incidence of events with narrow confidence intervals, lead us to hypothesize that even 2 perfectly matched arms would not change the results substantially. A randomized (noninferiority) design would have made the conclusions much stronger, according to the rules of evidence-based medicine. However, the ongoing large, prospective, multicenter, randomized, SIMPLE (Shockless Implant Evaluation) study (19) may confirm and reinforce the results of the SAFE-ICD study.

Finally, some of the DT performed was possibly inadequate to establish an accurate safety margin. However, this reflects the current clinical practice as well as that of recent trials. For example, in the SCD-HeFT trial (18), the adopted safety margin test was not so different from the strategy adopted in our study. Indeed, in that study, the first shock was delivered at 20 J; if unsuccessful, the second attempt was performed with 30 J, and no further VF

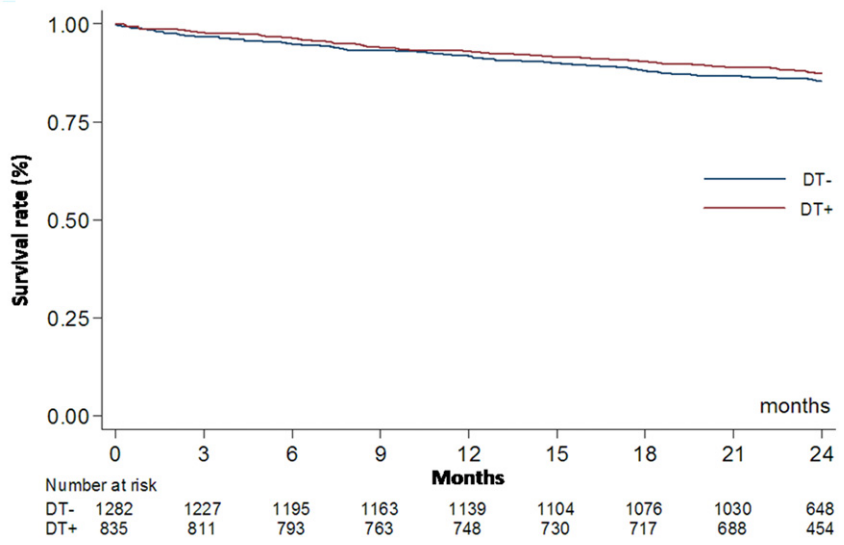

Figure 3 **All-Cause Mortality**

Kaplan-Meier survival estimates for all-cause mortality among patients who had undergone defibrillation testing (DT+ **[red line]**) and patients who had not (DT− **[blue line]**).

induction was recommended regardless of defibrillation success of this second induction.

Conclusions

There is ongoing debate as to the need to conduct intraoperative DT at the time of ICD insertion (2,9,20–27). Data coming from real-world experience suggest that despite the absence of scientific evidence, an increasing number of first implantation procedures are performed without any induction test. For example, in 2 large single-center populations, Russo et al. (2) did not perform any induction test in 4.7% of implants performed between 1997 and 2003; and Pires and Johnson (9) did not perform any induction test in 24% of implants performed between 1996 and 2003. These initial rates increased to 30% in 2005 (4), to 33% to 35% in 2007 and 2008 (6), and to 61% in 2008 and 2009 in the present study. The results of the SAFE-ICD trial support the increasing practice of omitting DT. We expect that the results of this study may contribute to standardize the "de novo" ICD implant procedure without DT for the majority of patients. However, it is possible that DT may continue to be utilized at implant or delayed after some months (27,28) in difficult cases such as selected cases of nonstandard lead position, right-sided ICD pocket, or pediatric implants.

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Key Words: defibrillation testing ■ implantable defibrillators ■ sudden death.

APPENDIX

For a list of the investigators in the SAFE-ICD study, please see the online version of this article.