Journal of the American Heart Association

ORIGINAL RESEARCH

Dutch Outcome in Implantable Cardioverter-Defibrillator Therapy: Implantable Cardioverter-Defibrillator–Related Complications in a Contemporary Primary Prevention Cohort

Marit van Barreveld, MS*; Tom E. Verstraelen, MD, MS*; Pascal F. H. M. van Dessel, MD, PhD; Lucas V. A. Boersma, MD, PhD; Peter Paul H. M. Delnoy, MD, PhD; Anton E. Tuinenburg, MD, PhD; Dominic A. M. J. Theuns, PhD; Pepijn H. van der Voort, MD; Geert-Jan Kimman, MD, PhD; Erik Buskens, MD, PhD; Aeilko H. Zwinderman, MD, PhD; Arthur A. M. Wilde, MD, PhD†; Marcel G. W. Dijkgraaf, MD, PhD†; on behalf of the DO-IT Registry Investigators‡

BACKGROUND: One third of primary prevention implantable cardioverter-defibrillator patients receive appropriate therapy, but all remain at risk of defibrillator complications. Information on these complications in contemporary cohorts is limited. This study assessed complications and their risk factors after defibrillator implantation in a Dutch nationwide prospective registry cohort and forecasts the potential reduction in complications under distinct scenarios of updated indication criteria.

METHODS AND RESULTS: Complications in a prospective multicenter registry cohort of 1442 primary implantable cardioverter-defibrillator implant patients were classified as major or minor. The potential for reducing complications was derived from a newly developed prediction model of appropriate therapy to identify patients with a low probability of benefitting from the implantable cardioverter-defibrillator. During a follow-up of 2.2 years (interquartile range, 2.0–2.6 years), 228 complications occurred in 195 patients (13.6%), with 113 patients (7.8%) experiencing at least one major complication. Most common ones were lead related (n=93) and infection (n=18). Minor complications occurred in 6.8% of patients, with lead-related (n=47) and pocket-related (n=40) complications as the most prevailing ones. A surgical reintervention or additional hospitalization was required in 53% or 61% of complications, respectively. Complications were strongly associated with device type. Application of stricter implant indication results in a comparable proportional reduction of (major) complications.

CONCLUSIONS: One in 13 patients experiences at least one major implantable cardioverter-defibrillator–related complication, and many patients undergo a surgical reintervention. Complications are related to defibrillator implantations, and these should be discussed with the patient. Stricter implant indication criteria and careful selection of device type implanted may have significant clinical and financial benefits.

Key Words: complications ■ implantable cardioverter-defibrillator ■ inappropriate shocks ■ indication

Correspondence to: Marit van Barreveld, MS, Meibergdreef 9, J1B-2017, 1105 AZ Amsterdam, the Netherlands. E-mail: m.vanbarreveld@amsterdamumc.nland Tom E. Verstraelen, MD, MS, Cartesiusweg 81, 3534BB Utrecht, the Netherlands. E-mail: t.e.verstraelen@amsterdamumc.nl

*M. van Barreveld and T.E. Verstraelen contributed equally.

†A.A.M. Wilde and M.G.W. Dijkgraaf are co–senior authors.

‡A complete list of DO-IT Registry investigators can be found in the Supplemental Material.

Supplementary Material for this article is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.120.018063

For Sources of Funding and Disclosures, see page 11.

© 2021 The Authors. Published on behalf of the American Heart Association, Inc., by Wiley. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- In a contemporary large primary prevention cohort, 13.5% of patients received at least one implantable cardioverter-defibrillator (ICD)–related complication, with over half of these complications being major.
- The occurrence of device-related complications and inappropriate shocks differed significantly per device type implanted.
- The occurrence of device-related complications was associated with substantial clinical consequences, need for surgical revisions, and increase in hospitalizations and hospital treatment days
- Stricter ICD indication criteria based on the probability of ICD benefit will likely result in a comparable reduction of (major) ICD-related complications.

What Are the Clinical Implications?

- This study provides reliable information on the adverse outcomes in ICD recipients with different types of defibrillators, which is useful for decision making on primary prevention ICD implantation.
- Careful consideration of selecting the right device for the right patient at the right time may reduce device-related complications and subsequent treatment, and thus facilitates allocating scarce resources more efficiently.

Nonstandard Abbreviations and Acronyms

DO-IT	Dutch Outcome in Implantable Cardioverter-Defibrillator Implantation
S-ICD	subcutaneous implantable cardioverter-defibrillator
TV-ICD	transvenous implantable cardioverter-defibrillator

Implantable cardioverters-defibrillators (ICDs) have become the standard of care for patients with structural heart disease and a reduced left ventricular function and for patients with prior sustained, hemodynamically significant, ventricular arrhythmias.[1–4] However, ICD implantations have the potential for adverse consequences, inappropriate shocks, and device-related complications. Because the number of ICD implantations increased in recent years due to the aging population and widening indication criteria, the number of ICD complications increased as well. Specifically, the number of cardiac resynchronization therapy defibrillator implantations has markedly increased in Europe,[5] and it has repeatedly been demonstrated that these devices are associated with more ICD-related complications than a single- or dual-chamber ICD.[6–9]

Many primary prevention ICD patients never receive appropriate therapies but remain at risk for device-related complications and inappropriate shocks. An estimation of ICD-related complications is important in this population because the decision for implantation requires knowledge of beneficial effects and adverse consequences. Several studies focused on improving risk stratification and predicting ICD benefit in primary prevention patients.[10–13] However, information on the rates and predictors of complications in these patients in current clinical practice is limited,[14,15] and most studies only selectively report on (early) complications.[8,16,17] Furthermore, complications do not only impact patient outcome but are also associated with an increase in healthcare costs.[18] When ICDs in primary prevention patients with low expected benefit are avoided, these costs and complications can also be prevented.

Accordingly, the aim of this article is to provide information on complications after primary prevention ICD implantation and establish risk factors associated with their occurrences. By applying several more strict ICD implant indication scenarios based on the DO-IT (Dutch Outcome in ICD Implantation) Registry,[19] we also quantify how many complications in patients can be prevented and if this reduction is proportional with size of the subpopulation in which ICD implantation can be deferred.

METHODS

Availability of Data and Materials

The DO-IT Registry data used in this article will be made available through a public repository (University of Amsterdam Figshare) within 3 months of publication in agreement with active privacy regulations. A written request for use of data, including purpose and analysis plan, should be directed to the corresponding author (m.vanbarreveld@amsterdamumc.nl) or one of the senior authors (a.a.wilde@msterdamumc.nl; m.g.dijkgraaf@amsterdamumc.nl). Each request will be discussed with DO-IT Registry steering committee representatives for appropriateness.

Patient Population

We examined patients included in the nationwide DO-IT Registry database who received their first ICD for primary prevention of sudden cardiac death between September 2014 and June 2016. The rationale, design,

and methods have been published previously.[19] In brief, this nationwide registry prospectively enrolled a primary prevention ICD cohort in all 28 ICD implanting centers in the Netherlands and was approved by all the institutional review boards. This ICD cohort was set up to identify patients who do not derive benefit from ICD therapy within 2 years after implantation by developing prediction models for ICD therapy and all-cause mortality.

After obtaining written informed consent, baseline data were collected on demographics, medical history, diagnostics, left ventricular ejection fraction, and implant-related data. During follow-up, clinical and device-related event data were collected on the basis of regular protocol-based follow-up routine and extracted from medical records, including in-clinic and remote follow-up on devices. All event data were extensively monitored. The primary end points of the DO-IT Registry study were mortality and appropriate ICD therapy (shock or antitachycardia pacing for ventricular tachycardia or ventricular fibrillation). The focus of the present study is complications of ICD implantation.

Definitions

Complications were defined as any undesirable clinical occurrence related to the ICD implantation and function. The occurrence of inappropriate shocks is not considered an ICD-related complication but is classified as a separate adverse outcome, defined as an ICD shock for anything else but ventricular fibrillation or sustained ventricular tachycardia. In this study, the complications were categorized as major or minor. A complication was considered major if (1) it had the potential of being life threatening, (2) it required ≥1 surgical intervention, (3) it required intravenous treatment with vasoactive drugs, antibiotics for device-related infection, or any transfusion for device-related bleeding, or (4) it led to a fatal outcome. Minor complications were distinguished from major if they did not fit the criteria for major complication but did meet at least one of the following criteria: (1) requiring nonsurgical, medical intervention by a healthcare professional, (2) leading to hospitalization or increased level of care, or (3) prompting evaluation or unscheduled performance of diagnostic tests.

Potential Risk Factors

The risk factors considered in the analysis consisted of baseline variables, as listed in Table 1, on demographics, medical history, comorbidity, medication use, diagnostics, and ICD characteristics.

Statistical Analysis

Descriptive statistics on demographics, medical history information, and ICD characteristics collected at baseline are presented as mean and SD for continuous variables or as number and percentage for categorical items. Comparisons of these items between subjects without any complication, only minor complication(s), or at least one major complication during the study were made using χ^2 tests for categorical items or a 1-way ANOVA test for continuous variables.

To establish risk factors for ICD-related complications, multivariate models were developed for the outcomes any complication versus no complication and any major complication versus no major complication. Missing values for baseline characteristics were imputed 20 times using chained equations. In each imputation set (n=20), we performed Cox regression on time until the first complication with lasso penalty selection of covariates. For the selection of the lasso penalty, cross validation was used. Each covariate that remained in at least 50% of the resulting 20 imputation models was selected in the final model (Figure S1). Multivariable Cox regression was used for the final model over the complete data sets, and the results were averaged with the Rubin rule to produce overall estimates and CIs. The association between complications and mortality was assessed by Cox regression analysis on time until death, with complications as a time-varying covariate. An exploratory ad hoc analysis of an association between yearly hospital ICD implantation volume and complication rate was performed on request of the National Health Care Institute in the Netherlands after study completion and in response to one of the reviewers (Data S1). A 2-sided $P<0.05$ was considered statistically significant. Statistical analyses were performed with SPSS version 24.0 or R version 3.5.1, as appropriate.

Several distinct scenarios for more strict ICD implantation guidelines based on the developed prediction model for the 2-year risk of appropriate ICD therapy were analyzed. Under these scenarios, ICD implantation is postponed for at least 2 years in patients when their predicted risk remains below a certain threshold. The selected 5 cutoff values to (temporarily) refrain from ICD implantation based on patients' predicted probabilities of receiving appropriate ICD therapy were: <2%, <3%, 4%, <5%, and <7.5%. For these scenarios, the percentage (relative to the total study cohort) of patients without an ICD implantation and with preventable ICD-related complication(s) and/or preventable inappropriate shock(s) was quantified.

RESULTS

A total of 1443 patients were included in the DO-IT Registry database. Their characteristics are listed in

Table 1. Baseline Characteristics

Baseline Variables*	All Patients	No Complication	Minor Complication	≥1 Major Complication	*P* Value
Total	1443 (100)	1248 (86.5)	82 (5.7)	113 (7.8)	
Sex (men)	1044 (72)	913 (73)	57 (70)	74 (65)	0.20
Age, y	65.9 (10.2)	65.8 (10.1)	66.7 (11.0)	66.3 (10.4)	0.63
Academic implanting hospital	487 (34)	416 (33)	41 (50)	30 (27)	0.40
BMI (N=1422), kg/m^2	27.3 (4.7)	27.3 (4.7)	27.2 (4.6)	27.2 (5.0)	0.94
NYHA functional class (N=1435)					0.90
I	207 (14)	182 (15)	11 (13)	14 (13)	
II	905 (63)	778 (62)	53 (65)	74 (67)	
III/IV	323 (23)	282 (23)	18 (22)	23 (21)	
Ischemic	882 (61)	772 (62)	48 (59)	62 (55)	0.30
LVEF (%) (N=1436)	26.1 (6.2)	26.1 (6.2)	25.5 (6.4)	26.5 (5.6)	0.58
RV function (normal) (N=1221)	867 (71)	754 (71)	46 (66)	67 (75)	0.40
HF hospitalization <1 y (N=1430)	303 (21)	265 (21)	16 (20)	22 (20)	0.90
Prior cardiac surgery	371 (26)	326 (26)	20 (24)	25 (22)	0.60
NS-VT (N=1395)	170 (12)	143 (12)	13 (16)	14 (13)	0.50
MR severity (N=1336)					0.50
None	880 (66)	762 (66)	43 (59)	75 (71)	
Moderate	290 (22)	248 (21)	20 (27)	22 (21)	
Severe	166 (12)	147 (13)	10 (14)	9 (8)	
CVA/TIA (N=1414)	185 (13)	160 (13)	10 (13)	15 (13)	0.99
Vascular disease (N=1321)	291 (22)	256 (22)	13 (17)	22 (21)	0.60
Atrial fibrillation (N=1415)	438 (31)	373 (30)	29 (36)	36 (33)	0.50
COPD (N=1422)	211 (15)	186 (15)	16 (20)	9 (8)	0.05
Hypertension (N=1409)	618 (44)	527 (43)	44 (54)	47 (42)	0.10
Diabetes mellitus (N=1434)	386 (27)	334 (27)	26 (32)	26 (23)	0.40
Hypercholesterolemia (N=1372)	594 (43)	519 (44)	38 (48)	37 (33)	0.06
Familial SCD (N=1152)	176 (12)	142 (14)	17 (25)	17 (17)	0.05
Smoking (N=1237)†	846 (68)	723 (68)	54 (73)	69 (70)	0.60
β blocker	1232 (85)	1063 (85)	(72) (88)	79 (86)	0.80
Diuretic (N=1442)	1032 (72)	900 (72)	58 (71)	74 (65)	0.30
Aldosterone antagonist	667 (46)	578 (46)	39 (48)	50 (44)	0.90
ACE or ARB (N=1442)	1288 (89)	1122 (90)	67 (82)	99 (88)	0.05
Oral anticoagulant	684 (47)	588 (47)	43 (53)	53 (47)	0.60
Digoxin	143 (10)	125 (10)	8 (10)	2 (10)	0.90
Statin	976 (68)	846 (68)	58 (71)	72 (64)	0.60
Heart rate (N=1424)	71.5 (14.5)	71.7 (14.7)	71.5 (14.2)	69.9 (12.52)	0.46
PR interval (N=1413)					0.60
Normal	832 (59)	728 (59)	43 (56)	61 (55)	
PR prolongation	304 (21)	265 (22)	16 (21)	23 (21)	
Not applicable	277 (20)	232 (19)	18 (23)	27 (24)	

(*Continued*)

Table 1. Continued

Baseline Variables*	All Patients	No Complication	Minor Complication	≥1 Major Complication	*P* Value
QRS axis (N=1332)					0.90
Normal	849 (64)	740 (64)	45 (62)	64 (64)	
Left	407 (31)	356 (31)	23 (32)	28 (28)	
Right	56 (4)	48 (4)	2 (3)	6 (6)	
Extreme	20 (1)	16 (1)	2 (3)	2 (2)	
QRS duration (N=1359), ms					0.00
<120	614 (45)	558 (47)	25 (34)	31 (31)	
120–150	333 (25)	290 (25)	15 (20)	28 (28)	
>150	412 (30)	336 (28)	34 (46)	42 (41)	
QTc Bazett (N=1421)	465.1 (47.9)	463.6 (47.8)	472.4 (46.1)	476.3 (48.4)	0.01
QRS morphological features (N=1355)					0.01
Normal	582 (43)	526 (45)	25 (34)	31 (31)	
LBBB	496 (36)	413 (35)	37 (50)	46 (46)	
RBBB	77 (6)	64 (5)	3 (4)	10 (10)	
Aspecific	200 (15)	178 (15)	9 (12)	13 (13)	
eGFR (mL/min) (N=1405)	61.3 (18.9)	61.1 (18.7)	60.2 (18.3)	64.3 (20.5)	0.23
Sodium (mmol/L) (N=1402)	139.4 (3.0)	139.4 (3.0)	139.0 (3.3)	139.5 (2.5)	0.43
Potassium (mmol/L) (N=1401)	4.4 (0.4)	4.4 (0.4)	4.4 (0.4)	4.4 (0.4)	0.85
Hemoglobin (mmol/L) (N=1357)	8.6 (1.0)	8.6 (1.0)	8.7 (1.1)	8.6 (1.0)	0.95
NT-proBNP (pmol/L) (N=588)	338.9 (570.0)	344.2 (588.1)	253.1 (429.5)	341.2 (435.5)	0.66
Previous pacemaker	76 (5)	58 (5)	7 (9)	11 (10)	0.03
Device type					0.00
Single chamber	480 (33)	441 (35)	18 (22)	21 (19)	
Dual chamber	231 (16)	198 (16)	9 (11)	24 (21)	
CRT-D	623 (43)	520 (42)	46 (56)	57 (50)	
S-ICD	109 (8)	89 (7)	9 (11)	11 (10)	
Vascular access (N=1438)					0.30
Subclavia	707 (49)	606 (49)	42 (52)	59 (52)	
Other	622 (43)	549 (44)	30 (37)	43 (38)	
None	109 (8)	89 (7)	9 (11)	11 (10)	

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CRT-D, cardiac resynchronization therapy defibrillator; CVA, cerebrovascular accident; eGFR, estimated glomerular filtration rate; HF, heart failure; LBBB, left bundle-branch block; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; NS-VT, nonsustained ventricular tachycardia; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; QTc, heart rate–corrected QT; RBBB, right bundle-branch block; RV, right ventricular; SCD, sudden cardiac death; S-ICD, subcutaneous implantable cardioverter-defibrillator; and TIA, transient ischemic attack.

*Number (percentage) or mean (SD).

†Smoking, current or former smoker.

Table 1 (column for all patients). Mean age was 66 years, and 72% were men. A total of 882 patients (61%) had ischemic cardiomyopathy and mean left ventricular ejection fraction was 26%. Most patients were in New York Heart Association class II (63%), and a single-chamber ICD was implanted in 33%, dual-chamber ICD was implanted in 16%, biventricular ICD was implanted in 43%, and a subcutaneous ICD (S-ICD) was implanted in 8%. One patient was excluded from further analysis because of unavailable follow-up data (N=1442 remaining).

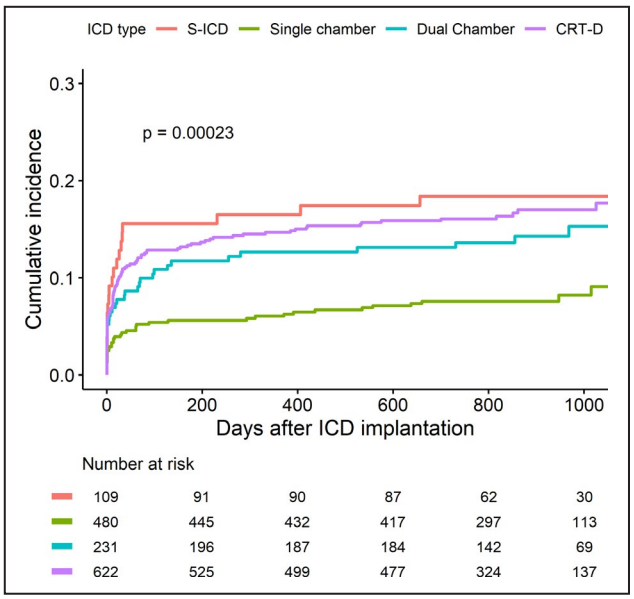


Figure 1. Cumulative incidence of implantable cardioverter-defibrillator (ICD)–related complications per device type.
In pairwise comparisons (uncorrected for multiple testing), differences were observed between single-chamber ICD and all other ICD types. CRT-D indicates cardiac resynchronization therapy defibrillator; and S-ICD, subcutaneous ICD.

Complications and Inappropriate Shocks

During a median follow up of 28.7 months (interquartile range, 25.2–33.7 months), 230 complications occurred in 195 patients (13.5%), with a rate of 6.7 per 100 person-years. Patients experienced their first complication at a median of 14 days (interquartile range, 1–96 days) after ICD implantation. In 113 patients (7.8%), 128 major complications were observed. In 98 (6.8%) patients, 102 minor complications occurred. The Kaplan-Meier curves for any complication by ICD type are displayed in Figure 1 (*P*=0.00023). The Kaplan-Meier curves for major and minor complication by ICD type are provided in Figures S2 and S3.

In 66 patients (4.6%), 90 inappropriate shock episodes occurred, with 222 inappropriate shocks in total. Of these patients, 11 (0.8%) also experienced a major complication (minor N=14 [1%]). The first inappropriate shock occurred at a median 264 (interquartile range, 52–525) days after implantation. The rates of inappropriate shocks per device type were 8.3%, 5.8%, 3.5%, and 3.4% for S-ICD, single chamber, dual chamber, and cardiac resynchronization therapy defibrillator devices, respectively. Their Kaplan-Meier curves are displayed in Figure S4.

Types of Complications

A more detailed overview of the types of complications is provided in Table 2. Most frequent major

Table 2. Type of Complications After ICD Implantation

Type of Complication	No. of Complications (N=1442)
Any complication, including inappropriate shocks	320 (N=247)
Any complication, excluding inappropriate shocks	230 (N=195)
Major complications	128 (N=113)
Lead related	93
Lead dislodgement	44
Lead dysfunction	13
No placement of LV lead, requiring reintervention*	14
Pneumothorax, requiring drainage	7
Perforation, requiring intervention†	7
Diaphragmatic stimulation, requiring lead intervention	4
Twiddler syndrome	2
Inappropriate sensing	2
Infection	18
Pocket infection	6
Systemic infection	12
Pocket related	9
Pocket revision because of pain	5
Hematoma or bleeding, requiring intervention	4
Other	8
Early battery depletion	1
Other‡	7
Minor complications	102 (N=98)
Lead related	47
Lead dislodgement without reintervention	4
Lead dysfunction without reintervention	6
No placement of LV lead without reintervention*	3
Pneumothorax conservatively treated	6
Diaphragmatic stimulation	12
Venous thrombosis	6
Inappropriate sensing	10
Infection	7
Pocket infection treated with antibiotics	7
Pocket related	40
Pocket hematoma or bleeding	25
Pocket problem	15
Other	8
Other§	8

ICD indicates implantable cardioverter-defibrillator; and LV, left ventricular.
*Placement of LV lead not possible in patients with cardiac resynchronization therapy defibrillator indication.
†Lead revision, pericardiocentesis, or both.
‡Malfunction during testing (n=3), pericarditis (n=2), hemothorax (n=1), and sustained ventricular tachycardia during implantation attributable to right ventricular lead manipulation, requiring external cardioversion (n=1).
§Pericarditis (n=3), adverse effects of antibiotics (n=1), fever and increased infection parameters attributable to phlebitis (n=1), shock impedance out of range (n=1), erroneous injection of chlorhexidine (n=1), and guidewire fracture leading to abandoning of distal part in venous branch (n=1).

complications were lead related and systemic infections. Among the minor complications, pocket hematoma, other pocket problems, and diaphragmatic stimulation (n=12) were the most prevailing ones. In Figure 2, the occurrence of major and minor complications after ICD implantation is presented. See Figure S5 for the timing of any complication for every patient after ICD implantation. Most complications were observed within 30 days or during the first year of follow-up, with 55% or 83% and 55% or 85% for major and minor complications, respectively. For an overview of the type of complications by ICD type, see Table S1.

Impact on Patient Outcome

In 121 (53%) of the 230 complications, a surgical procedure was required. A total of 140 surgical interventions were performed in 107 patients (7.4%), with 81 patients undergoing 1, 20 patients undergoing 2, 5 patients undergoing 3, and 1 patient undergoing 4 surgical interventions. In 64% of complications, a new or extended hospitalization was required, with an average of 6.9 and 0.57 (extra) days for major and minor complications, respectively. A complication required a mean of 0.6 reoperations, 0.7 rehospitalizations, and 4.1 additional hospital inpatient days, which resulted in a total of 943 additional hospital inpatient days. The impact of different types of major complications on patient outcome is shown in Table 3. Systemic infections and lead-related complications generated most additional hospitalization days and number of surgical interventions. During the observation period, 193 (13.4%) patients died. The mortality rates between patients with no complications (13%), only minor complications (16%), and major complications (16%) were similar. Patients who experienced a complication had a nonsignificant increased risk for mortality, with a hazard ratio of 1.43 (95% CI, 0.97–2.1; *P*=0.07) for any complication and 1.44 (95% CI, 0.88–2.33; *P*=0.135) for major complication. For inappropriate shock, in 27 episodes, a hospitalization was required, with an average of 4.2 days and a total of 114 hospitalization days.

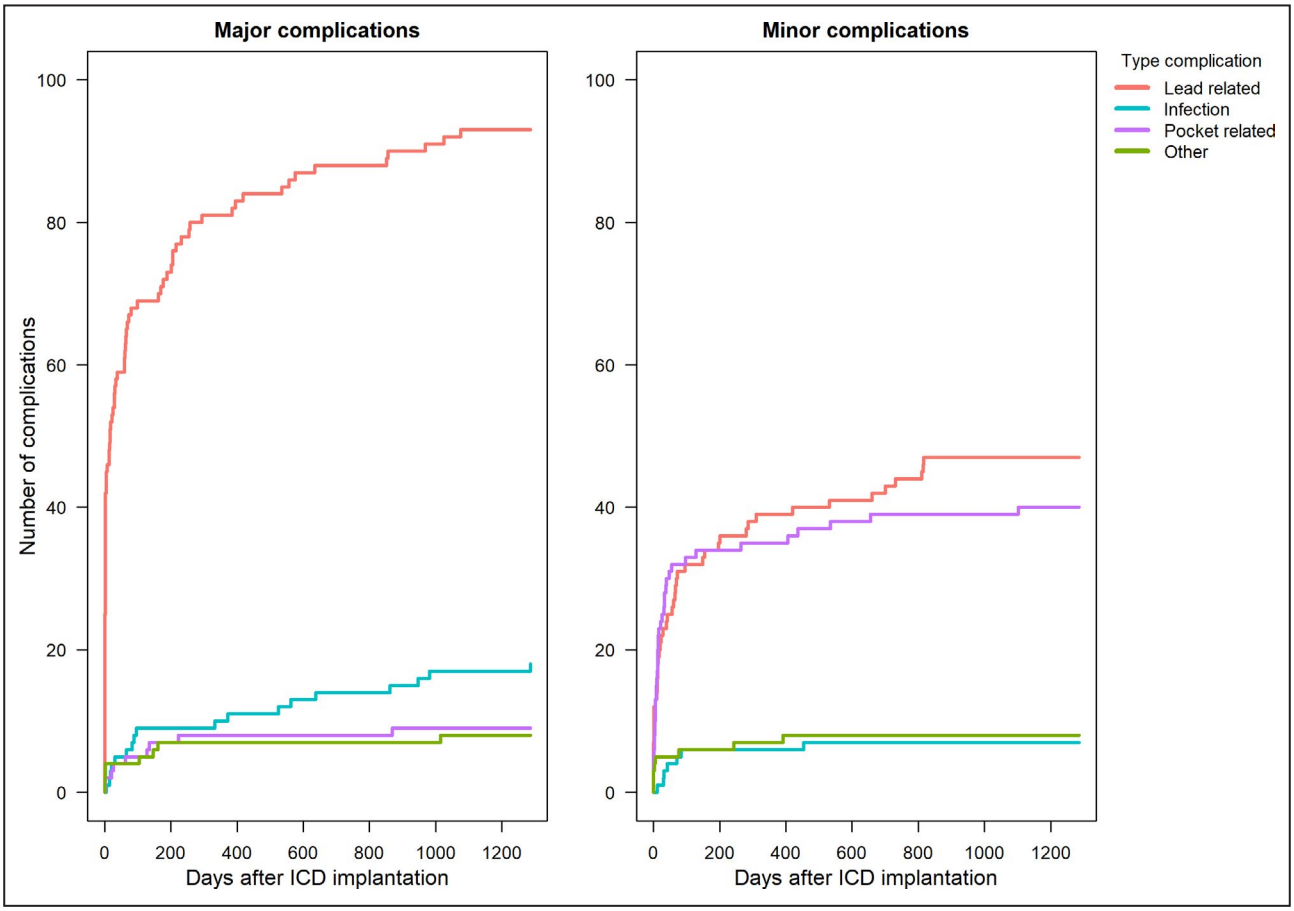


Figure 2. Major and minor complications after implantable cardioverter-defibrillator (ICD) implantation, according to complication type.

Table 3. Impact of Major Device-Related Complications on Patient Outcome

Type of Major Complication	No. of Complications	No. of Patients	Surgical Interventions		Rehospitalizations		Hospitalization Treatment Time, Total, Median (Range), d	Dead, N
			Total, Median (Range)	Patients With Multiple Surgical Interventions	Total, Median (Range)	Patients With Multiple Rehospitalizations		
Lead related	93	85	99, 1 (1–3)	13	100, 1 (1–3)	14	343, 3 (0–24)	1
Lead dislodgement	44	43	45, 1 (1–2)	2	46, 1 (1–2)	3	129, 2 (1–9)	0
Lead dysfunction	13	12	15, 1 (1–3)	2	15, 1 (1–3)	2	51, 4 (2–6)	0
No placement of LV lead*	14	14	15, 1 (1–2)	1	15, 1 (1–2)	1	74, 4 (2–24)	1
Pneumothorax	7	7	7, 1 (1–1)	0	6, 1 (1–1)	0	30, 4 (0–8)	0
Perforation	7	7	9, 1 (1–2)	2	9, 1 (1–2)	2	31, 5 (2–7)	0
Diaphragmatic stimulation	4	4	5, 1 (1–2)	1	5, 1 (1–2)	1	16, 4 (2–7)	0
Twiddler syndrome	2	2	2, 1 (1–1)	0	2, 1 (1–1)	0	8, 4 (2–6)	0
Inappropriate sensing	2	2	1, 1 (0–1)	0	2, 2 (2–2)	0	4, 2 (1–3)	0
Infection	18	18	25, 2 (0–2)	10	26, 1 (1–2)	8	478, 18 (6–88)	4
Pocket infection	6	6	10, 2 (0–2)	5	10, 2 (1–2)	4	91, 11 (6–43)	0
Systemic infection	12	12	15, 1 (0–2)	5	16, 1 (1–2)	4	387, 25 (10–88)	4
Pocket related	9	9	8, 1 (0–2)	1	11, 1 (1–2)	2	30, 4 (1–7)	0
Pocket pain	5	5	6, 1 (1–2)	1	6, 1 (1–2)	1	12, 2 (1–4)	0
Hematoma or bleeding	4	4	2, 1 (0–1)	0	5, 1 (1–2)	1	18, 5 (1–7)	0
Other	8	7	8, 1 (0–2)	1	10, 1 (0–2)	2	34, 5 (0–8)	0
Early battery depletion	1	1	1	0	1	0	2	0
Other†	7	6	7, 1 (0–2)	1	9, 1 (0–2)	2	32, 6 (0–8)	0
Total	128	113	140, 1 (0–3)	26	147, 1 (0–3)	29	885, 4 (0-88)	5

LV indicates left ventricular.

*Placement of LV lead not possible in patients with cardiac resynchronization therapy defibrillator indication.

†Malfunction during testing (n=3), pericarditis (n=2), hemothorax (n=1), and sustained ventricular tachycardia during implantation attributable to right ventricular lead manipulation, requiring external cardioversion (n=1).

Table 4. Multivariable Predictors of Any and Major Complications

Variables	Any Complication			Major Complication		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Sex (men)	0.76	0.56–1.04	0.08	0.70	0.47–1.04	0.08
Familial SCD	1.55	1.05–2.27	0.03			
ACE or ARB	0.68	0.45–1.03	0.07			
QRS duration 120–150 ms*	1.10	0.49–2.45	0.82			
QRS duration >150 ms*	1.49	0.62–3.58	0.37			
QTc Bazett per 100 ms	1.08	0.75–1.54	0.69	1.38	0.89–2.15	0.15
QRS morphological feature LBBB†	1.59	0.66–3.84	0.30	1.84	0.89–3.83	0.10
QRS morphological feature RBBB†	1.39	0.53–3.57	0.51	2.48	1.10–5.60	0.03
QRS morphological feature aspecific†	1.29	0.53–3.15	0.58	1.84	0.86–3.95	0.12
NT-proBNP (1000 pmol/L)	0.76	0.42–1.35	0.34			
Previous pacemaker	1.77	0.90–3.50	0.10			
S-ICD‡	2.31	1.33–4.00	0.00	2.17	1.05–4.52	0.04
CRT-D‡	1.08	0.61–1.92	0.80	1.16	0.57–2.37	0.68
Dual chamber‡	1.55	0.95–2.51	0.08	1.96	1.07–3.59	0.03
Implanting hospital academic				0.72	0.47–1.10	0.13
COPD				0.54	0.27–1.07	0.08
Hypercholesterolemia				0.66	0.44–0.99	0.05
Diuretic				0.71	0.48–1.05	0.09

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease; CRT-D, cardiac resynchronization therapy defibrillator; HR, hazard ratio; LBBB, left bundle-branch block; NT-proBNP, N-terminal pro-B-type natriuretic peptide; QTc, heart rate–corrected QT; RBBB, right bundle-branch block; SCD, sudden cardiac death; and S-ICD, subcutaneous implantable cardioverter-defibrillator.

*QRS duration <120 ms as reference category.

†Normal QRS morphological feature as reference category.

‡Single-chamber implantable cardioverter-defibrillator as reference category.

Risk Factors of Complications

In Table 1, significant baseline differences between no, minor, or major complications were observed for chronic obstructive pulmonary disease, hypercholesterolemia, familial sudden cardiac death, use of angiotensin-converting enzyme inhibitors, ECG parameters, and device characteristics. Risk factors of any and major complications are summarized in Table 4. Women were more likely to develop (major) complications than men. Subcutaneous and dual-chamber defibrillator patients had an increased risk of (major) complications compared with those who received a single-chamber device. A decreased risk of major complications was seen in patients with normal QRS morphological features, and the risk of any complication is increased in patients with sudden cardiac death in the family. Use of angiotensin-converting enzyme inhibitors decreased the risk of any complications, and major complications were decreased in patients with chronic obstructive pulmonary disease, hypercholesterolemia, and diuretic use.

Stricter ICD Implantation Scenarios

Our recently developed model for the prediction of appropriate ICD therapy has demonstrated the plausibility of several distinct indication thresholds, based on increasing minimal probabilities of ICD benefit (ie, experiencing appropriate ICD therapy).[10] Table 5 shows the number of patients under the various scenarios who would have scored below the minimal probability of ICD benefit and the number of complications they experienced. The percentage of patients with potentially preventable ICD implantation ranged from 6.2% to 45.1%. The experience of an ICD-related complication would be preventable in 10% to 15.3% of patients in whom ICD implantation would be postponed for at least 2 years.

Table 6 shows that the occurrence of *major* ICD-related complications would be preventable in 6.7% to 9.7% of patients who would temporarily no longer receive an ICD under restricted indications. In 4 of 5 stricter ICD implantation scenarios, disproportionally more (major) complications would be prevented in patients not receiving an ICD compared with the population averages of experiencing (major) complications when all presenting patients would receive an ICD. Only in the least stringent adjustment of indication criteria (<2%), the percentages of patients experiencing any complication, 10%, or a major complication, 6.7%, would be lower than the 13.5% any complication and the 13.5% major complication of the contemporary

Table 5. ICD-Related Complications in Patients Not Fulfilling Stricter Indications for ICD Implantation

Predicted Probability of Appropriate ICD Therapy, %	Patients With Predicted Insufficient ICD Benefit	% of Presenting Patients	Observed Complications	% of All Complications (N=230)	Observed Patients With Complications	% of Patients With Complications Among Patients With Predicted Insufficient ICD Benefit
<2	90	6.2	10	4.4	9	10
<3	242	16.8	43	18.7	37	15.3
<4	309	21.4	55	23.9	47	15.2
<5	374	25.9	67	29.1	57	15.2
<7.5	651	45.1	111	48.3	92	14.1

ICD indicates implantable cardioverter-defibrillator.

ICD population. Inappropriate shocks would become preventable in 1.1% to 2.3% of patients in whom ICD implantation would be postponed for at least 2 years under the various scenarios, against 4.6% in the contemporary ICD population.

DISCUSSION

In this multicenter cohort of the current clinical practice, 13.5% of patients experienced an ICD-related complication after de novo defibrillator implantation for a primary prevention indication, with 1 in 13 patients experiencing at least one major ICD-related complication. In addition, nearly 5% of patients received at least one inappropriate shock. Combined, 17% of patients experienced adverse consequences after ICD implantation. The most frequent minor complications were pocket or lead related. Among the major complications, lead complications and systemic infections were most prevailing and had the greatest negative impact on patient outcome. If stricter primary prevention ICD indication criteria were to be applied on the basis of the probability of ICD benefit by receiving appropriate ICD therapy, we found in most scenarios an at least comparable proportional reduction of (major) complications; fewer ICD implantations do not reduce inappropriate therapies to a similar extent.

Several studies have reported on ICD-related complications beyond the index hospitalization for device implantation in a primary prevention population, with rates varying between 4.3% and 15.9%.[8,14–17,20] Comparisons are impeded by varying follow-up periods, variations in study design, and different definitions of complications. Overall, our complication rate is in line with prior similar studies, such as the DAI-PP (Defibrillateur Automatique Implantable-Prevention Primaire)[14] and MADIT-CRT (Multicenter Automatic Defibrillator Implantation With Cardiac Resynchronization Therapy).[16] However, the complication rate of the MADIT-CRT trial only reported on complications that occurred within 30 days after ICD implantation (8% rate in the DO-IT Registry); more complications are expected if longer-term term complications were accounted for.

Our analysis showed that ICD-related complications were more frequent in more complex devices than in single lead devices, which is consistent with previous studies.[7,21–23] However, the relatively increased incidence of (major) complications in patients with an S-ICD implanted compared with those receiving transvenous ICD (TV-ICD) is unanticipated, but in previous studies, a similar complication rate with a range from 11.1% to 14% has been reported.[24–26] In addition, inappropriate shocks occurred more frequently in S-ICD devices, and the rate was 2 times higher than among dual chamber of cardiac resynchronization therapy defibrillator devices. Caution is needed for interpretation of our results; although the DO-IT Registry is a large nationwide study, only 8% of patients received an S-ICD (ie, only 109 patients in 15 centers). A similar trend of more inappropriate shocks was seen in the PRAETORIAN (Prospective Randomized

Table 6. ICD-Related Major Complications in Patients Not Fulfilling Stricter Indications for ICD Implantation

Predicted Probability of Appropriate ICD Therapy, %	Patients With Predicted Insufficient ICD Benefit	% of Presenting Patients	Observed Major Complications	% of All Major Complications (N=128)	Observed Patients With Major Complications	% of Patients With Major Complications Among Patients With Predicted Insufficient ICD Benefit
<2	90	6.2	7	5.5	6	6.7
<3	242	16.8	28	21.9	23	9.5
<4	309	21.4	37	28.9	30	9.7
<5	374	25.9	42	32.8	35	9.4
<7.5	651	45.1	64	50	53	8.1

ICD indicates implantable cardioverter-defibrillator.

Comparison of Subcutaneous and Transvenous Implantable Cardioverter Defibrillator Therapy) trial. However, in this first randomized study, comparing the TV-ICD against the S-ICD in mostly primary prevention patients (±80%) and a medium follow-up of 49.1 months, noninferiority for the S-ICD compared with the TV-ICD was demonstrated, in terms of both device-related complications and inappropriate shocks.[27] Furthermore, improved sensing algorithms in more recent S-ICD devices have shown a significant decrease in the inappropriate shock rate.[28] In addition, fewer lead-related complications are postulated by some authors for S-ICDs compared with TV-ICDs on the long run. The field is awaiting the results of the ATLAS (Avoid Transvenous Leads in Approproate Subjectects) trial, which primarily evaluates early and midterm vascular and lead-related complications among S-ICD versus TV-ICD recipients.[29] In this perspective, an improvement of S-ICD safety is expected by reducing inappropriate shocks and device-related complications. This claim should be closely monitored in further research.

As mentioned, the primary risk factor associated with both any and major complications was the type of device implanted, with an increased risk in patients receiving a dual-chamber ICD and a 2-fold increased risk if a subcutaneous ICD was implanted. We observed a nonsignificant effect for cardiac resynchronization therapy defibrillator devices, but further analysis confirmed a significant increased risk for complications if QRS duration and QRS morphological features were excluded from the analysis (data not shown). This is in concordance with the results reported by others.[6,8,14,30]

Our results show that device-related complications are associated with clinical consequences, such as surgical revisions and additional hospitalizations, substantially increasing healthcare costs. However, these events were not associated with a worse clinical outcome, confirming findings from a previous study[7] but conflicting with recent data from the DAI-PP registry.[14]

This study adds to the current knowledge of adverse consequences after ICD implantation in primary prevention patients by comprehensively evaluating early and long-term complications in a large multicenter cohort of primary prevention ICD patients in real-world clinical practice. Furthermore, all Dutch ICD implanting hospitals participated, and data were collected prospectively, limiting possible inclusion bias. Finally, identifying risk factors through systematically evaluating a wide range of baseline variables, which are associated with an increased risk of complications, is also an important contribution of our study. This study highlights the importance of preventing ICD-related complications because most major complications affect patient's outcome by resulting in an additional surgical procedure and hospitalization. Minor complications remain clinically important because these may result in discomfort and may decrease quality of life.

Several limitations should be considered in the interpretation of the results. First, there is a possibility of underreporting by the participating sites. However, patient data were extensively monitored, and the relatively high complication rate suggests that underreporting, if any, would have been minimal. Second, patients were only followed up for a median of 2.4 years (interquartile range, 2.1–2.8 years). Almost half of the complications in this study occurred after 30 days and are likely to continue to occur after our observation period. Furthermore, device replacements for (early) battery depletion and their subsequent complications are largely not captured, because on average device replacements for battery depletion occur after at least 3 to 4 years.[7,14,23,31,32] Last, several risk factors were identified, but a causal relationship between these factors and complications cannot be established.

In summary, in this nationwide registry, a high rate of complications was observed among patients with an ICD implanted for primary prevention, with 1 in 13 patients experiencing a major complication and 7.4% undergoing a surgical reintervention. If stricter ICD indication criteria are applied on the basis of the probability of ICD benefit, ICD-related complications will reduce proportionally. This confirms the fact that observed (major) complications are ICD related and that anyone with an ICD implanted can experience a complication at some individual risk. A better understanding of the adverse consequences of ICD implantations is useful for decision making on ICD implantation for a primary prevention patient, and the risk of complications and surgical revisions should be discussed with the patient. Careful consideration of selecting the right device for the right patient at the right time might lead to better outcomes, and more efficient allocation of scarce resources.

ARTICLE INFORMATION

Received December 23, 2020; accepted February 24, 2021.

Affiliations

From the Department of Cardiology, Heart Center (M.v.B., T.E.V., L.V.B., A.A.W.) and Department of Epidemiology and Data Science (M.v.B., A.H.Z., M.G.D.), Amsterdam UMC, University of Amsterdam, the Netherlands; Department of Cardiology, Thorax Center Twente, Medisch Spectrum Twente, Enschede, the Netherlands (P.F.v.D.); Cardiology Department, St. Antonius Ziekenhuis Nieuwegein, Nieuwegein, the Netherlands (L.V.B.); Department of Cardiology, Isala Klinieken, Zwolle, the Netherlands (P.P.D.); Division of Heart and Lungs, Department of Cardiology, University Medical Centre, Utrecht, the Netherlands (A.E.T.); Department of Cardiology, Erasmus MC, Rotterdam, the Netherlands (D.A.T.); Department of Cardiology, Catharina Ziekenhuis Eindhoven, Eindhoven, the Netherlands (P.H.v.d.V.); Department of Cardiology, Noordwest Ziekenhuisgroep, Alkmaar, the Netherlands (G.K.); and Department of Epidemiology, University Medical Centre Groningen, Groningen, the Netherlands (E.B.).

Acknowledgments

The authors acknowledge all the investigators of the DO-IT (Dutch Outcome in Implantable Cardioverter-Defibrillator Implantation) Registry.

Sources of Funding

This research was supported by grant 837004009 from Dutch Organization for Health Research and Development and National Health Care Institute, the Netherlands. The funding bodies had no role in the design and conduct of the study; in the collection, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript.

Disclosures

Dr Boersma reports other from Boston Scientific and other from Medtronic, outside the submitted work; Dr Delnoy reports grants from Medtronic, grants from Boston Scientific, grants from Microport, grants from Abbott, and grants from Biotronik, outside the submitted work. All remaining authors have no disclosures to report.

Supplementary Material

Appendix S1
Data S1
Table S1
Figures S1–S5

REFERENCES

1. Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS, Daubert JP, Higgins SL, Brown MW, Andrews ML. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med*. 2002;346:877–883. DOI: 10.1056/NEJMoa013474.
2. Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, Domanski M, Troutman C, Anderson J, Johnson G, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med*. 2005;352:225–237. DOI: 10.1056/NEJMoa043399.
3. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. *N Engl J Med*. 1997;337:1576–1583. DOI: 10.1056/NEJM199711273372202.
4. Connolly SJ, Gent M, Roberts RS, Dorian P, Roy D, Sheldon RS, Mitchell LB, Green MS, Klein GJ, O'Brien B. Canadian Implantable Defibrillator Study (CIDS): a randomized trial of the implantable cardioverter defibrillator against amiodarone. *Circulation*. 2000;101:1297–1302. DOI: 10.1161/01.CIR.101.11.1297.
5. van Veldhuisen DJ, Maass AH, Priori SG, Stolt P, van Gelder IC, Dickstein K, Swedberg K. Implementation of device therapy (cardiac resynchronization therapy and implantable cardioverter defibrillator) for patients with heart failure in Europe: changes from 2004 to 2008. *Eur J Heart Fail*. 2009;11:1143–1151. DOI: 10.1093/eurjhf/hfp149.
6. Duray GZ, Schmitt J, Cicek-Hartvig S, Hohnloser SH, Israel CW. Complications leading to surgical revision in implantable cardioverter defibrillator patients: comparison of patients with single-chamber, dual-chamber, and biventricular devices. *Europace*. 2009;11:297–302. DOI: 10.1093/europace/eun322.
7. Landolina M, Gasparini M, Lunati M, Iacopino S, Boriani G, Bonanno C, Vado A, Proclemer A, Capucci A, Zucchiatti C, et al. Long-term complications related to biventricular defibrillator implantation: rate of surgical revisions and impact on survival: insights from the Italian Clinical Service Database. *Circulation*. 2011;123:2526–2535. DOI: 10.1161/CIRCULATIONAHA.110.015024.
8. Lee DS, Krahn AD, Healey JS, Birnie D, Crystal E, Dorian P, Simpson CS, Khaykin Y, Cameron D, Janmohamed A, et al. Evaluation of early complications related to de novo cardioverter defibrillator implantation insights from the Ontario ICD database. *J Am Coll Cardiol*. 2010;55:774–782. DOI: 10.1016/j.jacc.2009.11.029.
9. Palmisano P, Accogli M, Zaccaria M, Luzzi G, Nacci F, Anaclerio M, Favale S. Rate, causes, and impact on patient outcome of implantable device complications requiring surgical revision: large population survey from two centres in Italy. *Europace*. 2013;15:531–540. DOI: 10.1093/europace/eus337.
10. Verstraelen TE, van Barreveld M, van Dessel PHFM, Boersma LVA, Delnoy P-P, Tuinenburg AE, Theuns DAMJ, van der Voort PH, Kimman GP, Buskens E, et al. Development and external validation of prediction models to predict implantable cardioverter-defibrillator efficacy in primary prevention of sudden cardiac death. *Europace*. 2021:euab012. Feb 14 [epub ahead of print].;10.1093/europace/euab012.
11. Zabel M, Sticherling C, Willems R, Lubinski A, Bauer A, Bergau L, Braunschweig F, Brugada J, Brusich S, Conen D, et al. Rationale and design of the EU-CERT-ICD prospective study: comparative effectiveness of prophylactic ICD implantation. *ESC Heart Fail*. 2019;6:182–193. DOI: 10.1002/ehf2.12367.
12. Goldenberg I, Vyas AK, Hall WJ, Moss AJ, Wang H, He H, Zareba W, McNitt S, Andrews ML. Risk stratification for primary implantation of a cardioverter-defibrillator in patients with ischemic left ventricular dysfunction. *J Am Coll Cardiol*. 2008;51:288–296. DOI: 10.1016/j.jacc.2007.08.058.
13. Køber L, Thune JJ, Nielsen JC, Haarbo J, Videbæk L, Korup E, Jensen G, Hildebrandt P, Steffensen FH, Bruun NE, et al. Defibrillator implantation in patients with nonischemic systolic heart failure. *N Engl J Med*. 2016;375:1221–1230. DOI: 10.1056/NEJMoa1608029.
14. Ascoeta MS, Marijon E, Defaye P, Klug D, Beganton F, Perier M-C, Gras D, Algalarrondo V, Deharo J-C, Leclercq C, et al. Impact of early complications on outcomes in patients with implantable cardioverter-defibrillator for primary prevention. *Heart Rhythm*. 2016;13:1045–1051. DOI: 10.1016/j.hrthm.2015.12.046.
15. Expósito V, Rodríguez-Mañero M, González-Enríquez S, Arias MA, Sánchez-Gómez JM, Andrés La Huerta A, Bertomeu-González V, Arce-León Á, Barrio-López MT, Arguedas-Jiménez H, et al. Primary prevention implantable cardioverter-defibrillator and cardiac resynchronization therapy-defibrillator in elderly patients: results of a Spanish multicentre study. *Europace*. 2016;18:1203–1210. DOI: 10.1093/europace/euv337.
16. Jamerson D, McNitt S, Polonsky S, Zareba W, Moss A, Tompkins C. Early procedure-related adverse events by gender in MADIT-CRT. *J Cardiovasc Electrophysiol*. 2014;25:985–989. DOI: 10.1111/jce.12438.
17. Peterson PN, Varosy PD, Heidenreich PA, Wang Y, Dewland TA, Curtis JP, Go AS, Greenlee RT, Magid DJ, Normand S-L, et al. Association of single- vs dual-chamber ICDs with mortality, readmissions, and complications among patients receiving an ICD for primary prevention. *JAMA*. 2013;309:2025–2034. DOI: 10.1001/jama.2013.4982.
18. Reynolds MR, Cohen DJ, Kugelmass AD, Brown PP, Becker ER, Culler SD, Simon AW. The frequency and incremental cost of major complications among Medicare beneficiaries receiving implantable cardioverter-defibrillators. *J Am Coll Cardiol*. 2006;47:2493–2497. DOI: 10.1016/j.jacc.2006.02.049.
19. van Barreveld M, Dijkgraaf MGW, Hulleman M, Boersma LVA, Delnoy P, Meine M, Tuinenburg AE, Theuns D, van der Voort PH, Kimman GP, et al. Dutch outcome in implantable cardioverter-defibrillator therapy (DO-IT): registry design and baseline characteristics of a prospective observational cohort study to predict appropriate indication for implantable cardioverter-defibrillator. *Neth Heart J*. 2017;25:574–580. DOI: 10.1007/s12471-017-1016-x.
20. Arnous S, Murphy NF, Pyne-Daly P, Nawoor Z, Keane D, Ledwidge M, McDonald K. Clinical and psychological impact of prophylactic implantable cardioverter-defibrillators in a community heart failure population. *Ir J Med Sci*. 2011;180:369–374. DOI: 10.1007/s11845-010-0659-z.
21. Hawkins NM, Grubisic M, Andrade JG, Huang F, Ding L, Gao M, Bashir J. Long-term complications, reoperations and survival following cardioverter-defibrillator implant. *Heart*. 2018;104:237–243. DOI: 10.1136/heartjnl-2017-311638.
22. Defaye P, Boveda S, Klug D, Beganton F, Piot O, Narayanan K, Perier MC, Gras D, Fauchier L, Bordachar P, et al. Dual- vs. single-chamber defibrillators for primary prevention of sudden cardiac death: long-term follow-up of the Defibrillateur Automatique Implantable-Prevention Primaire registry. *Europace*. 2017;19:1478–1484. DOI: 10.1093/europace/euw230.
23. Kirkfeldt RE, Johansen JB, Nohr EA, Jorgensen OD, Nielsen JC. Complications after cardiac implantable electronic device implantations: an analysis of a complete, nationwide cohort in Denmark. *Eur Heart J*. 2014;35:1186–1194. DOI: 10.1093/eurheartj/eht511.
24. Olde Nordkamp LR, Dabiri Abkenari L, Boersma LV, Maass AH, de Groot JR, van Oostrom AJ, Theuns DA, Jordaens LJ, Wilde AA, Knops RE. The entirely subcutaneous implantable cardioverter-defibrillator: initial clinical experience in a large Dutch cohort. *J Am Coll Cardiol*. 2012;60:1933–1939. DOI: 10.1016/j.jacc.2012.06.053.
25. Burke MC, Gold MR, Knight BP, Barr CS, Theuns DAMJ, Boersma LVA, Knops RE, Weiss R, Leon AR, Herre JM, et al. Safety and efficacy of the totally subcutaneous implantable defibrillator: 2-year results from a pooled analysis of the IDE study and EFFORTLESS registry. *J Am Coll Cardiol*. 2015;65:1605–1615. DOI: 10.1016/j.jacc.2015.02.047.

26. Brouwer TF, Yilmaz D, Lindeboom R, Buiten MS, Olde Nordkamp LR, Schalij MJ, Wilde AA, van Erven L, Knops RE. Long-term clinical outcomes of subcutaneous versus transvenous implantable defibrillator therapy. *J Am Coll Cardiol*. 2016;68:2047–2055. DOI: 10.1016/j.jacc.2016.08.044.
27. Knops RE, Olde Nordkamp LRA, Delnoy P-P, Boersma LVA, Kuschyk J, El-Chami MF, Bonnemeier H, Behr ER, Brouwer TF, Kääb S, et al. Subcutaneous or transvenous defibrillator therapy. *N Engl J Med*. 2020;383:526–536. DOI: 10.1056/NEJMoa1915932.
28. Gold MR, Lambiase PD, El-Chami MF, Knops RE, Aasbo JD, Bongiorni MG, Russo AM, Deharo J-C, Burke MC, Dinerman J, et al. Primary results from the understanding outcomes with the S-ICD in primary prevention patients with low ejection fraction (UNTOUCHED) trial. *Circulation*. 2021;143:7–17. DOI: 10.1161/CIRCULATIONAHA.120.048728.
29. Mondésert B, Bashir J, Philippon F, Dubuc M, Amit G, Exner D, Joza J, Birnie DH, Lane C, Tsang B, et al. Rationale and design of the randomized prospective ATLAS study: Avoid Transvenous Leads in Appropriate Subjects. *Am Heart J*. 2019;207:1–9. DOI: 10.1016/j.ahj.2018.09.008.
30. Al-Khatib SM, Greiner MA, Peterson ED, Hernandez AF, Schulman KA, Curtis LH. Patient and implanting physician factors associated with mortality and complications after implantable cardioverter-defibrillator implantation, 2002–2005. *Circ Arrhythm Electrophysiol*. 2008;1:240–249. DOI: 10.1161/CIRCEP.108.777888.
31. Poole JE, Gleva MJ, Mela T, Chung MK, Uslan DZ, Borge R, Gottipaty V, Shinn T, Dan D, Feldman LA, et al. Complication rates associated with pacemaker or implantable cardioverter-defibrillator generator replacements and upgrade procedures: results from the REPLACE registry. *Circulation*. 2010;122:1553–1561. DOI: 10.1161/CIRCULATIONAHA.110.976076.
32. Biffi M, Ammendola E, Menardi E, Parisi Q, Narducci ML, De Filippo P, Manzo M, Stabile G, Potenza DR, Zanon F, et al. Real-life outcome of implantable cardioverter-defibrillator and cardiac resynchronization defibrillator replacement/upgrade in a contemporary population: observations from the multicentre DECODE registry. *Europace*. 2019;21:1527–1536. DOI: 10.1093/europace/euz166.

SUPPLEMENTAL MATERIAL

Appendix

List of DO-IT investigators

Albert Schweitzer Hospital (M.W.F. van Gent); Amphia Hospital (S. Strikwerda); Amsterdam UMC, location Academic Medical Centre (A.A.M Wilde); Amsterdam UMC, location VU University Medical Centre (C.P. Allaart); Canisius Wilhelmina Hospital (J. Elders); Catharina Ziekenhuis (P.H. van der Voort); Elisabeth Tweesteden Hospital Tilbug (J.W.M.G. Widdershoven); Erasmus Medical Centre (D.A.M.J. Theuns); Flevo Hospital (N.R. Bijsterveld); Haaglanden Medical Centre (R.W. Grauss); Haga Hospital (R. Abels); Isala Klinieken (P.P.H.M. Delnoy); Leiden University Medical Centre (L. van Erven); Maasstad Hospital (M. Firouzi); Maastricht University Medical Centre (K. Vernooy); Martini Hospital (G.L. Bartels); Medical Centre Leeuwarden (A.E. Borger van der Burg); Medisch Spectrum Twente (M.F. Scholten); Noordwest Ziekenhuisgroep (G.P. Kimman); Onze Lieve Vrouwe Gasthuis (M. Khan); Radboud University Medical Centre (M.A. Brouwer); Rijnstate Hospital (R. Derksen); Scheper Hospital (M.W. Vet); Sint Franciscus Vlietland Group (H.A.M. Spierenburg); Spaarne Gasthuis (R. Tukkie); St. Antonius Ziekenhuis (L.V.A. Boersma); University Medical Centre Groningen (A.H. Maass); University Medical Centre Utrecht (M. Meine).

Data S1.

Supplemental Methods and Results

Hospital ICD volume and complication rate

Upon request of the Dutch National Health Care Institute (ZINL) and suggested by the reviewer we ad hoc studied the associations between hospital ICD volume and complication rate. The Dutch National Health Care Institute provided us with data on the yearly volume of ICD implantations by hospital cluster. Seven clusters of implanting hospitals with increasing yearly volume of ICD implantations were made. Applied to our data, the results showed that hospital cluster is not associated with the proportion of patients with complication(s) (Chi-2 1.97, df=6, p=0.92) or proportion of patients with a major complication(s) (Chi-2 1.86, df=6, p=0.93). In addition, we repeated the statistical analysis as reported in the manuscript (Statistical analysis, page 6, line 139-144) including hospital cluster code. In both prediction models hospital cluster code was not once selected in the 20 imputation sets. We therefore conclude that we found no correlation between volumes of ICD implantations and complication rate in this study.

Table S1. Type of complication by ICD type.

		S-ICD	Single chamber	Dual chamber	CRT-D
Patients with implanted device	**1442**	**109**	**480**	**231**	**622**
Major complications	**128**	**11**	**22**	**29**	**66**
Patients with major complication	**113**	**11 (10,1%)**	**21 (4,4%)**	**24 (10,4%)**	**57 (9,2%)**
Lead related	*93 (73%)*	*4 (36%)*	*16 (72%)*	*19 (66%)*	*54 (82%)*
Lead dislodgement	44	2	10	7	25
Lead failure	13	1	2	5	5
No placement LV lead*	14	0	0	0	14
Pneumothorax	7	0	2	0	5
Perforation	7	0	1	3	3
Diaphragmatic stimulation	4	0	0	0	4
Twiddler's syndrome	2	0	0	0	2
Inappropriate sensing	2	1	1	0	0
Infection	*18 (14%)*	*3 (27%)*	*4 (18%)*	*3 (10%)*	*8 (12%)*
Pocket infection	6	2	1	1	2
Systemic infection	12	1	3	2	6
Pocket related	*9 (7%)*	*1 (9%)*	*1 (5%)*	*3 (10%)*	*4 (6%)*
Pocket pain	5	1	1	2	1
Hematoma or bleeding	4	0	0	1	3
Other	*8 (6%)*	*3 (27%)*	*1 (5%)*	*4 (14%)*	*0 (0%)*
Early battery depletion	1	0	1	0	0
Other†	7	3	0	4	0

Minor complications	**102**	**10**	**20**	**15**	**57**
Patients with minor complication	**98**	**9 (8,2%)**	**18 (3,8%)**	**9 (3,9%)**	**46 (7,4%)**
Lead related	*47 (46%)*	*2 (20%)*	*6 (30%)*	*7 (47%)*	*32 (56%)*
Lead dislodgement	4	0	0	2	2
Lead failure	6	1	0	2	3
No placement LV lead*	3	0	0	0	3
Pneumothorax	6	0	2	1	3
Diaphragmatic stimulation	12	0	0	1	11
Inappropriate sensing	10	1	2	0	7
Venous thrombosis	6	0	2	1	3
Infection	*7 (7%)*	*0 (0%)*	*2 (10%)*	*2 (13%)*	*3 (5%)*
Pocket infection	7	0	2	2	3
Pocket related	*40 (39%)*	*8 (80%)*	*11 (55%)*	*3 (20%)*	*18 (32%)*
Pocket hematoma or bleeding	25	4	8	2	11
Pocket problem	15	4	3	1	7
Other	*8 (8%)*	*0 (0%)*	*1 (5%)*	*3 (20%)*	*4 (7%)*
Other‡	8	0	1	3	4

*Placement of left ventricular lead not possible in patients with CRT-D indication.

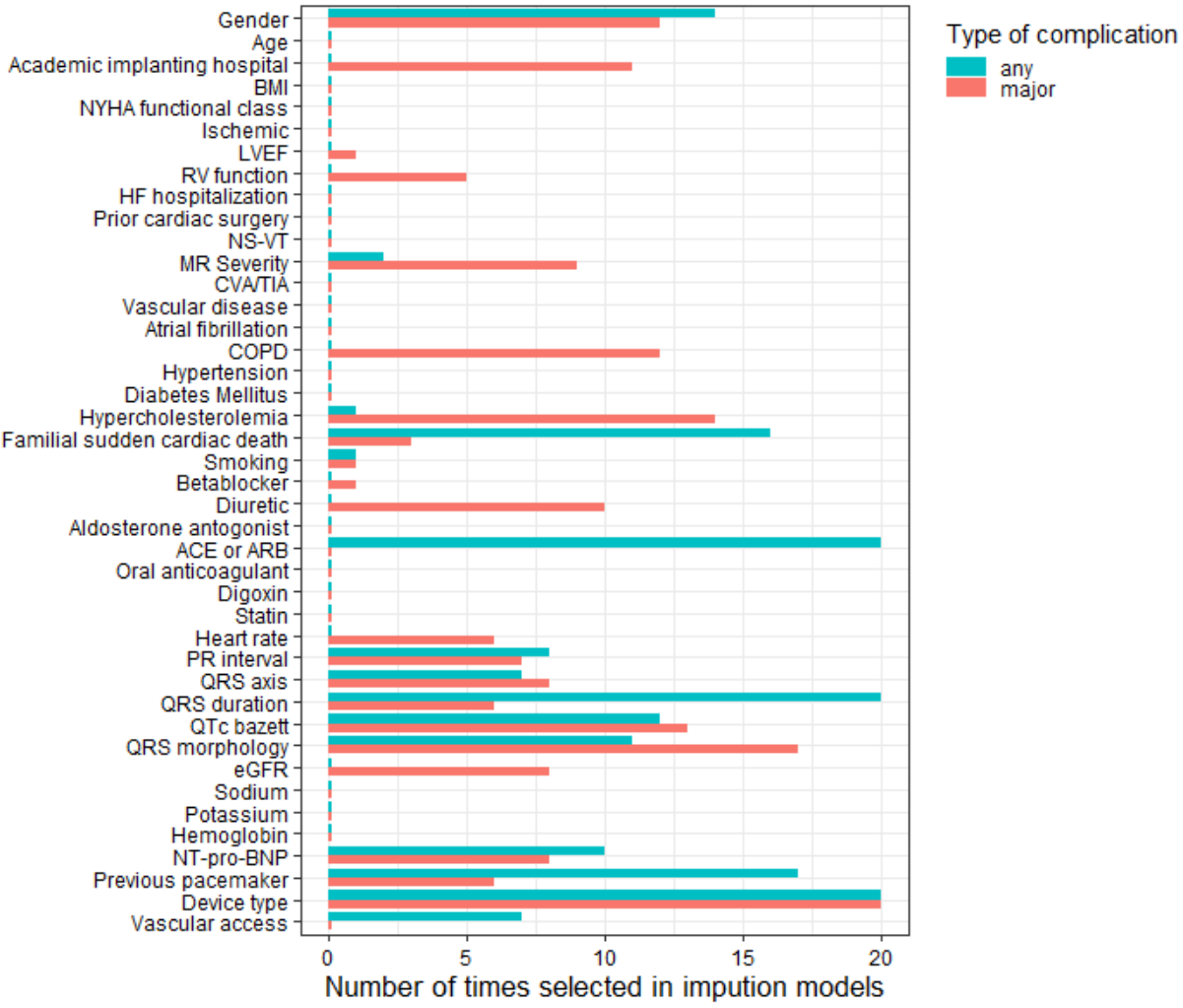
†Malfunction during testing (n=3), pericarditis (n=2), hemothorax (n=1), sustained ventricular tachycardia during implantation due right ventricular lead manipulation requiring external cardioversion (n=1).

‡Pericarditis (n=3), side effects of antibiotics (n=1), fever and increased infection parameters due to phlebitis (n=1), shock impedance out of range (n=1), erroneously injection of

chlorhexidine (n=1), guidewire fracture leading to abandoning of distal part in venous branch (n=1).

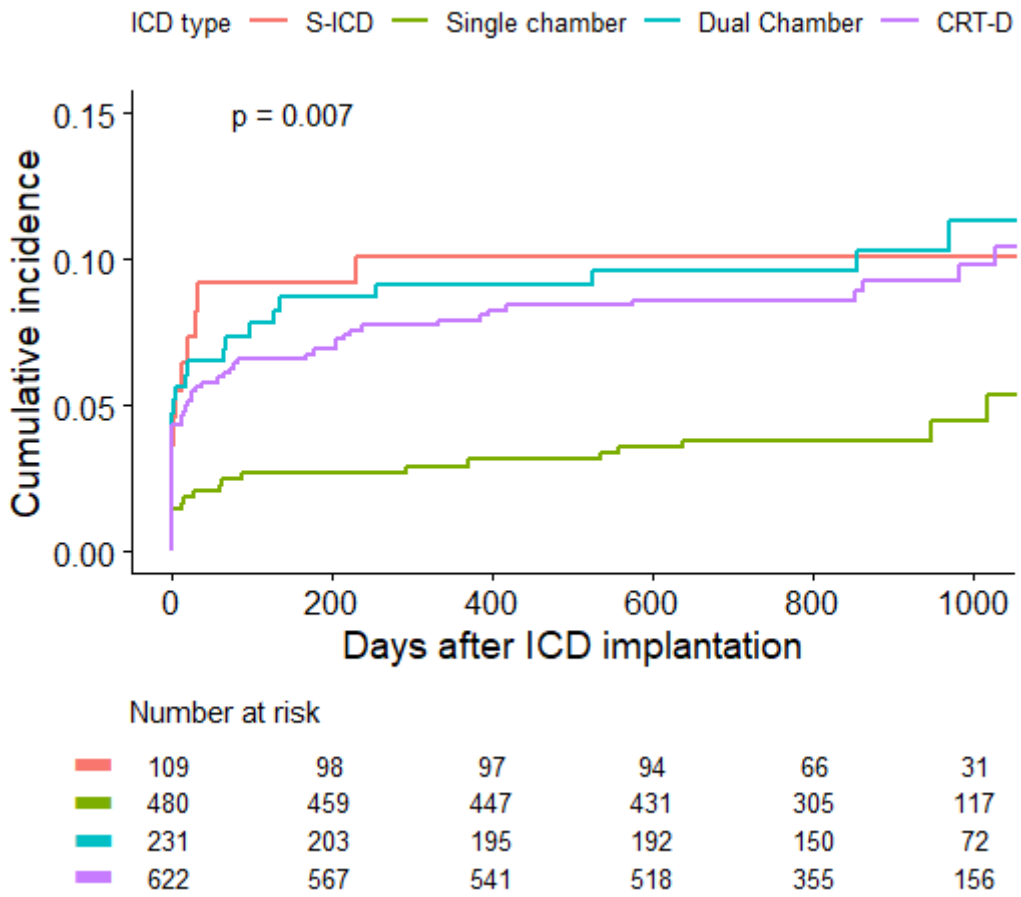
S-ICD indicates subcutaneous implantable cardioverter defibrillator; and CRT-D, cardiac resynchronization therapy defibrillator.

Figure S1. Number of times baseline characteristics were selected in Cox regression on time until first complication over 20 complete datasets.



BMI indicates body mass index; NYHA, new york heart association; LVEF, left ventricular ejection fraction; RV, right ventricular; HF, heart failure; NS-VT, non-sustained ventricular tachycardia; MR, mitral regurgitation; CVA, cerebrovascular accident; TIA, transient ischemic attack; COPD, chronic obstructive pulmonary disease; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blockers; QTc, heart rate-corrected QT; eGFR, estimated glomerular filtration rate; and NT-pro-BNP, N-terminal pro b-type natriuretic peptide.

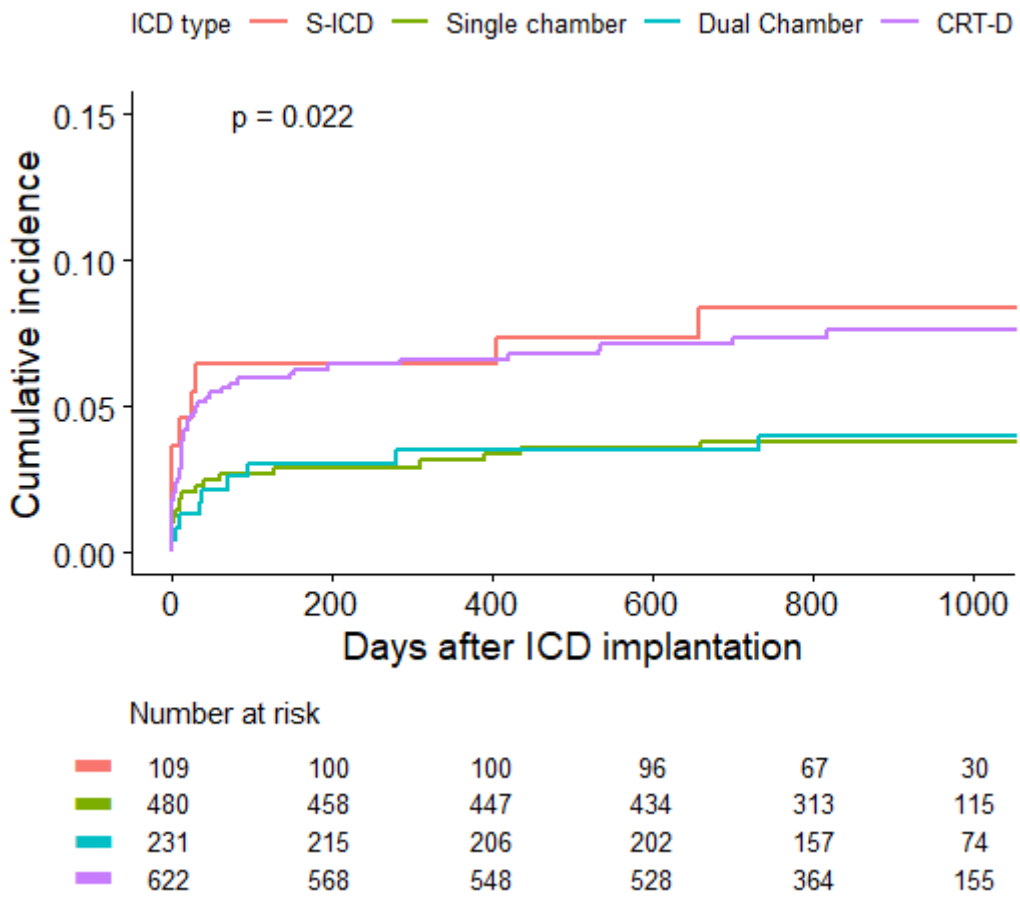
Figure S2. Cumulative incidence of major ICD-related complications per device type.



*In pairwise comparisons (uncorrected for multiple testing) differences were observed between single chamber ICD and all other ICD types

ICD indicates implantable cardioverter defibrillator; S-ICD, subcutaneous implantable cardioverter defibrillator; and CRT-D, cardiac resynchronization therapy defibrillator.

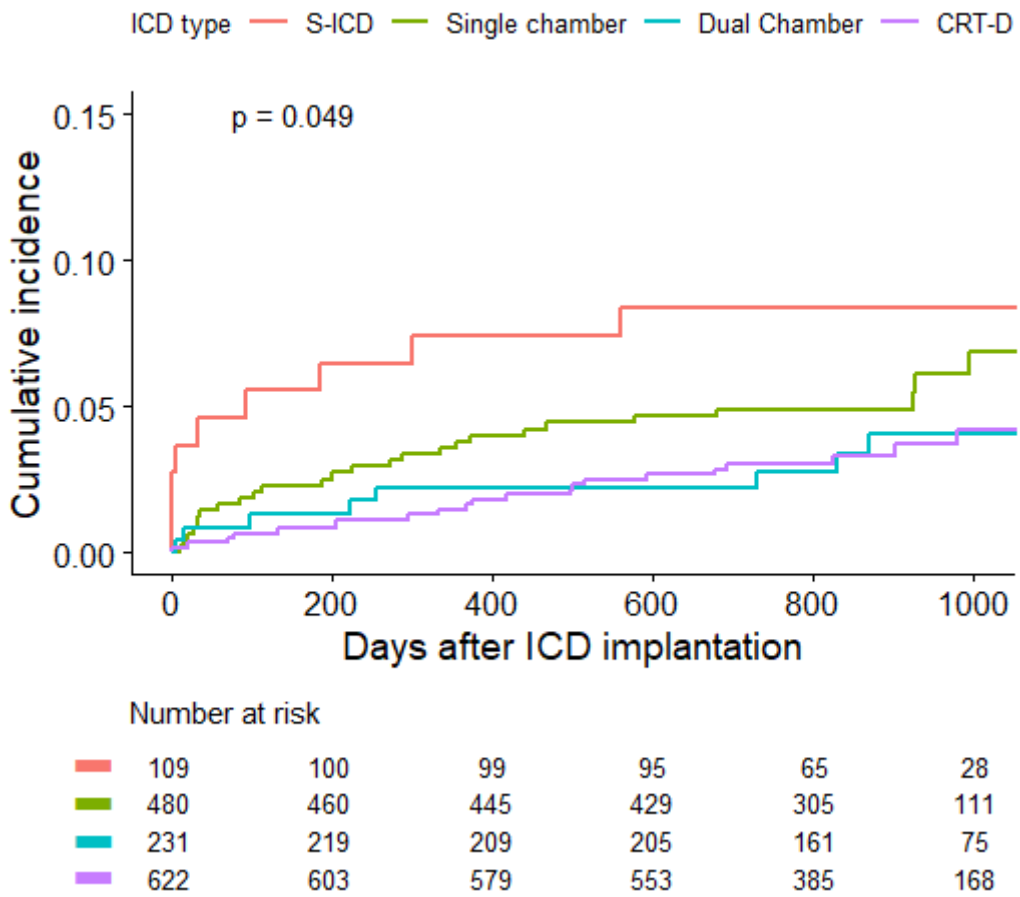
Figure S3. Cumulative incidence of minor ICD-related complications per device type.



*In pairwise comparisons (uncorrected for multiple testing) differences were observed between single chamber ICD and S-ICD and single chamber ICD and CRT-D

ICD indicates implantable cardioverter defibrillator; S-ICD, subcutaneous implantable cardioverter defibrillator; and CRT-D, cardiac resynchronization therapy defibrillator.

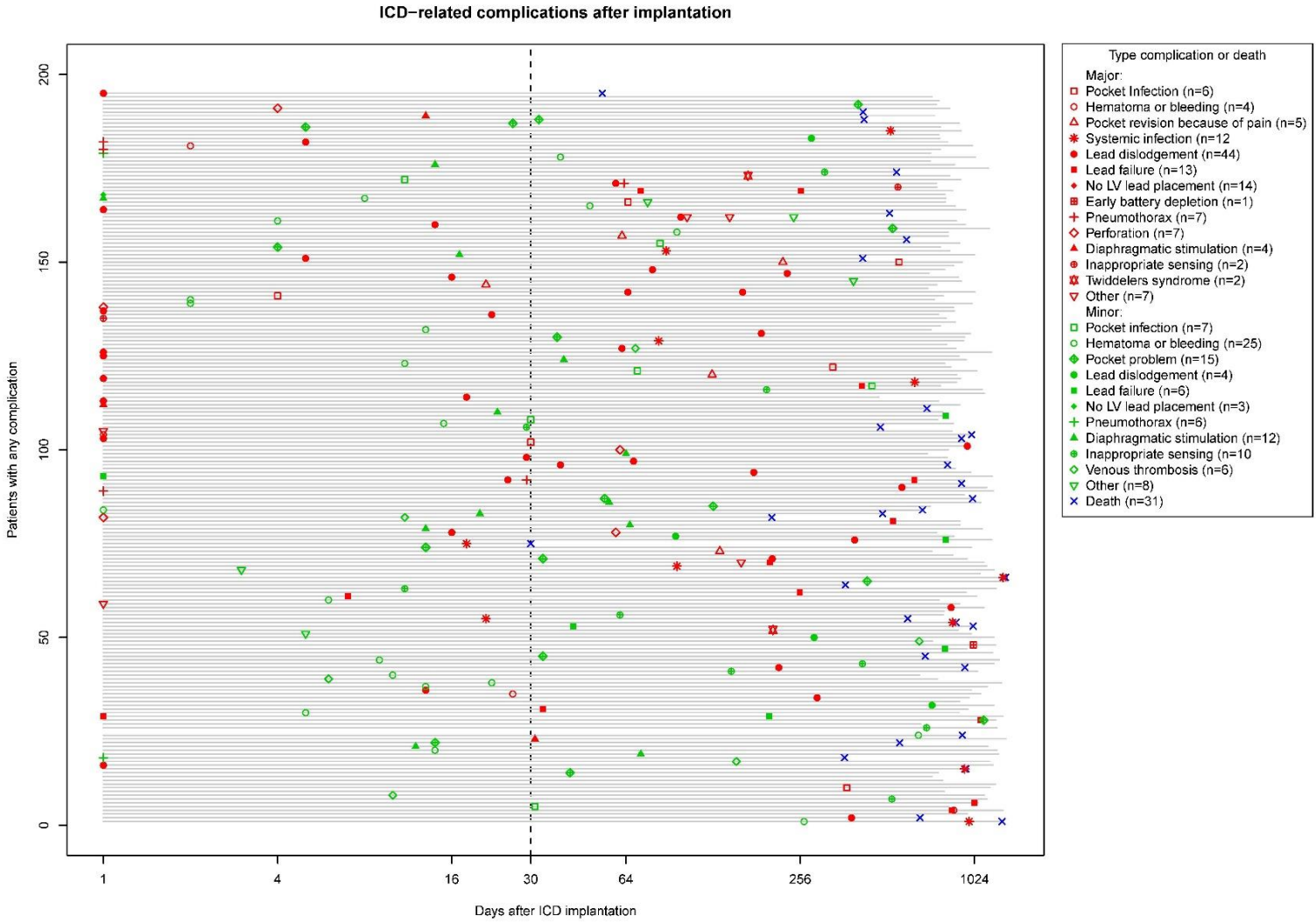
Figure S4. Cumulative incidence of inappropriate shocks per device type.



*In pairwise comparisons (uncorrected for multiple testing) differences were observed between CRT-D and S-ICD and CRT-D and single chamber ICD

ICD indicates implantable cardioverter defibrillator; S-ICD, subcutaneous implantable cardioverter defibrillator; and CRT-D, cardiac resynchronization therapy defibrillator.

Figure S5. ICD-related complications in days (log scale) after implantation for every patient with a complication.



ICD indicates implantable cardioverter defibrillator; and LV, left ventricular.