SUPPLEMENTAL MATERIAL

Appropriate therapy in PRAETORIAN

Contents

Supplementary methods section

The follow-up duration for the time-to-event variables was calculated from the date of ICD implantation to the date of first occurrence of the end point, or to December 1st 2019, or to or the last known event-free time point in patients with full withdrawal of informed consent or in patients who were lost to follow-up.

Hypothesis testing for all end points was performed following the modified intention-to-treat (M-ITT) principle: patients were analyzed in accordance to the treatment group to which they were originally assigned, regardless of withdrawals, losses to follow-up or crossovers. Patients who did not receive a device and patients who proved ineligible for one of the treatments due to incomplete or inadequate screening were excluded from this analysis.

Descriptive statistics are reported as mean ± SD or median with interquartile range (IQR) for continuous variables and numbers and percentages for categorical variables. Baseline variables were compared using the fisher exact test, $\chi 2$ test, Student's t-test or Mann–Whitney U-test when appropriate. For time to event variables, Kaplan-Meier curves displaying the pattern of events are constructed and 4-year Kaplan-Meier estimates of the event rate are reported for both study groups and compared using log-rank tests. Hazard ratios and 95% confidence intervals were calculated using Cox' proportional hazards model. The proportional Hazard assumption was assessed by scaled Schoenfeld residuals and visually comparing the plot of the log of cumulative hazard between treatments. In Kaplan-Meier and Cox regression analyses, missing data were presumed to be missing at random. Univariable and multivariable Cox' proportional hazard models were performed to find predictors of appropriate therapy. Predictors were included in the multivariate analysis when a p-value < 0.2 was observed in the univariate analysis. Relative risks and 95% confidence intervals were estimated using the wald method. In order to adjust for multiple episodes per patient, shock and ATP

efficacy estimations were adjusted using the generalized estimating equation (GEE) method with logit-link function and exchangeable correlation matrix. The factor patient was used as cluster, with a minimum of one and a maximum of 31 episodes per patient. A negative binomial regression analysis was performed to assess the rate ratio of appropriate shocks between the groups. As our data showed more zero counts than expected in a Poisson distribution, an additional zero-inflated Poisson regression model was performed.

A sensitivity analysis was performed in the as-treated and per protocol population. In the as-treated analysis, patients were analyzed in the group of the specific ICD type which they received at initial implantation regardless of randomization result. In the per protocol analysis, patients were censored if they receive a different ICD, not according to the randomization result, at any moment in the study.

A P-value < 0.05 was considered statistically significant. All statistical analyses were performed using R software version 4.0.3 (RStudio PBC, Boston, Massachussets).

Table S1. Baseline characteristics of the population included in the primary analysis of the PRAETORIAN trial.

	S-ICD	TV-ICD
	(N=426)	**(N=423)**
Median age (IQR) — yr	63 (54–69)	64 (56–70)
Female sex — no. (%)	89 (20.9)	78 (18.4)
Diagnosis — no. (%)		
Ischemic cardiomyopathy	289 (67.8)	298 (70.4)
Nonischemic cardiomyopathy	99 (23.2)	98 (23.2)
Genetic arrhythmia syndrome	20 (4.7)	18 (4.3)
Hypertrophic cardiomyopathy	15 (3.5)	7 (1.7)
Idiopathic VF	11 (2.6)	5 (1.2)
Congenital heart disease	3 (0.7)	3 (0.7)
Other†	4 (0.9)	1 (0.2)
Secondary prevention — no. (%)	80 (18.8)	84 (19.9)
Median ejection fraction (IQR) — %	30 (25–35)	30 (25–35)
Mean QRS duration ± SD — ms	105 ± 19	105 ± 20
NYHA class — no./total no. (%)		
I	144/423 (34.0)	134/421 (31.8)
II	205/423 (48.5)	223/421 (53.0)
III/IV	74/423 (17.5)	64/421 (15.2)
Median body-mass index (IQR)‡	27.0 (24.5–30.5)	27.9 (25.2–31.7)
Hypertension or antihypertensive drugs - no./total no. (%)	227/424 (53.5)	240/419 (57.3)
Hypercholesterolemia or lipid-lowering drugs - no./total no. (%)	161/419 (38.4)	175/418 (41.9)

Current or recent smoker - no./total no. (%)	119/406 (29.3)	139/401 (34.7)
Diabetes mellitus - no./total no. (%)	112/426 (26.3)	126/421 (30.0)
Previous CABG - no./total no. (%)	86/425 (20.2)	85/421 (20.2)
History of atrial fibrillation - no./total no. (%)	115/426 (27.0)	93/420 (22.1)
History of nonsustained VT - no./total no. (%)	46/423 (10.9)	44/417 (10.6)
History of syncope - no./total no. (%)	23/420 (5.5)	33/418 (7.9)
Site location - no. (%)		
Europe	394 (92.5)	395 (93.4)
United States	32 (7.5)	28 (6.6)
Median time from randomization to device implantation (IQR) - days	7.5 (1.0-29.0)	6.0 (1.0-26.5)

* CABG denotes coronary artery bypass grafting, IQR interquartile range, NYHA New York Heart Association, SD standard deviation, VF ventricular fibrillation, and VT ventricular tachycardia.

† The patients in this category had ventricular fibrillation due to coronary spasm (n=2), coronary dissection (n=1), ischemic stroke (n=1) and myocarditis (n=1).

‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

Table S2. List of crossovers

Patient	Randomized to	Crossover to	Time to crossover (days)	Appropriate therapy before crossover	Appropriate therapy after crossover
1	S-ICD	TV-ICD	7	0	3 (only ATP)
2	TV-ICD	CRT-D	908	15	5
3	S-ICD	CRT-D	2506	1	0
4	TV-ICD	S-ICD	0	0	1
5	S-ICD	CRT-D	1198	11	2 (only ATP)
6	S-ICD	CRT-D	457	0	8 (only ATP)
7	TV-ICD	CRT-D	1075	2	0
8	TV-ICD	S-ICD	0	0	2
9	TV-ICD	CRT-D	2255	1	0
10	TV-ICD	CRT-D	700	1	0
11	TV-ICD	S-ICD	0	0	1
12	S-ICD	CRT-D	1088	0	1
13	S-ICD	CRT-D	1437	2	0

14	S-ICD	CRT-D	816	2	1
15	S-ICD	CRT-D	967	1	0
16	TV-ICD	CRT-D	0	0	5
17	S-ICD	TV-ICD	1122	1	4 (only ATP)
18	S-ICD	CRT-D	236	14	0
19	S-ICD	TV-ICD	128	2	0
20	S-ICD	TV-ICD	1537	1	0
21	S-ICD	TV-ICD	12	0	1 (only ATP)

Table S3A. Predictors of appropriate therapy in the univariable analysis.

	Hazard ratio	95% confidence interval	P-value
S-ICD	1.12	0.82-1.53	0.45
Age, per 1 year increase	1.00	0.99-1.02	0.89
Female	0.82	0.54-1.23	0.33
LVEF, per 1% increase	0.99	0.97-1.00	0.08*
NYHA class 3	0.84	0.52-1.37	0.49
Secondary prevention	1.72	1.22-2.42	0.002*
BMI, per 1 kg/m^2 increase	0.98	0.95-1.02	0.32
Sustained ventricular tachycardia	1.53	1.08-2.15	0.02*
Betablocker	0.88	0.59-1.31	0.51
Amiodaron	1.50	0.79-2.84	0.22

***** These variables were used in the multivariable prediction model.

Table S3B. Predictors of appropriate therapy in the multivariable analysis.

	Hazard ratio	95% confidence interval	P-value
LVEF, per 1% increase	0.97	0.96-0.99	0.001*
Secondary prevention	3.49	1.67-7.29	0.001*
Sustained ventricular tachycardia	0.71	0.32-1.55	0.39

Table S4. Rate ratio of appropriate shocks in the PRAETORIAN trial

	S-ICD	TV-ICD	Rate ratio (95%CI)	P-value
Negative binominal model. S-ICD versus TV-ICD	0.60	0.54	1.11 (0.68 - 1.80)	0.68
Zero inflated negative binominal model. S-ICD versus TV-ICD			0.68 (0.36 - 1.25)	0.21

Table S5A. Unadjusted and GEE adjusted shock efficacy

A	Unadjusted		GEE adjusted*	
	S-ICD	**TV-ICD**	**S-ICD**	**TV-ICD**
First shock efficacy (95%CI)	93.8% (90.0% - 96.2%)	91.6% (86.8% - 94.8%)	92.6% (80.9% - 99.6%)	93.2% (84.0% - 97.3%)
Second shock efficacy (95%CI) **	90.0% (59.6% - 98.2%)	46.7% (24.8% - 69.9%)	-	-
Third shock efficacy (95%CI)**	-	57.1% (20.2% - 88.2%)	-	-
Fourth shock efficacy (95%CI)**	-	33.3% (6.1% - 79.2%)	-	-
Final shock efficacy (95%CI)	97.9% (95.3% - 99.1%)	98.4% (95.5% - 99.5%)	97.5% (81.5% - 99.8%)	98.1% (87.5% - 99.7%)

* The adjusted shock efficacy estimation takes into account multiple episodes per patient, using the generalized estimating equation (GEE) method, with an exchangeable correlation matrix.

** Calculations are based on limited number of episodes, due to a high first shock efficacy. The second shock efficacy was calculated on 10 episodes in the S-ICD group and 15 episodes in the TV-ICD group. The third shock efficacy was calculated on 7 episodes and the fourth shock efficacy was calculated on 3 episodes in the TV-ICD group. As only one episode with a third shock was available in the S-ICD group, the third and fourth shock efficacy were not calculated.

Table S5B. Unadjusted and GEE adjusted ATP efficacy

B	Unadjusted	GEE adjusted*
First ATP efficacy (95%CI)	46.2% (39.9% - 52.6%)	49.9% (39.7% - 60.5%)
Overall ATP conversion efficacy (95%CI)	52.0% (45.8% - 58.5%)	46.9% (36.4% - 57.7%)
Second ATP efficacy (95%CI)	36.1% (21.3% - 53.8%)	-
Third ATP efficacy (95%CI)	11.1% (0.6% - 49.3%)	-

* The adjusted shock efficacy estimation takes into account multiple episodes per patient, using the generalized estimating equation (GEE) method, with an exchangeable correlation matrix.

Table S6. Number of shocks across the different arrhythmia rates.

	S-ICD	TV-ICD
Patients with shock therapy	**N = 83**	**N = 57**
Total number of shocks	254	228
<200 beats per minute	65 (36.9%)	23 (19.3%)
200-249 beats per minute	66 (37.5%)	57 (47.9%)
≥ 250 beats per minute	45 (25.6%)	39 (32.8%)
Unknown	78	109

Table S7. Efficacy of ATP on monomorphic VTs across different arrhythmia rates.

	<200 beats per minute	**200-249 beats per minute**	**≥250 beats per minute**	**Unknown rate**
First ATP	**N = 56**	**N = 92**	**N = 22**	**N = 64**
Conversion to sinus rhythm or atrial fibrillation	27 (48.2%)	51 (55.4%)	10 (45.4%)	20 (31.2%)
No conversion	22 (39.3%)	32 (34.8%)	8 (36.4%)	42 (65.6%)
Acceleration of ventricular tachycardia*	7 (12.5%)	9 (9.8%)	4 (18.2%)	2 (3.2%)

* In the total cohort, 20/234 (8.5%) first ATP attempts resulted in an accelerated VT and 2/234 (0.9%) first ATP attempts resulted in a conversion to VF.

Table S8A. Relative risk of electrical storms in the modified intention-to-treat population.

	S-ICD	TV-ICD	Relative risk (95% confidence interval)	P-value *
	N = 86	**N = 78**		
Patients with an electrical storm	10 (11.6%)	18 (23.1%)	1.98 (0.98 – 4.04)	0.05

* P-values were calculated using the Pearson's Chi-squared test

Table S8B. Relative risk of electrical storms in the as-treated population.

	S-ICD	TV-ICD	Relative risk (95% confidence interval)	P-value *
	N = 85	**N = 74**		
Patients with an electrical storm	10 (11.8%)	18 (24.3%)	1.99 (1.02 – 4.04)	0.04

* P-values were calculated using the Pearson's Chi-squared test

Table S8C. Relative risk of electrical storms in the per protocol population.

	S-ICD	TV-ICD	Relative risk (95% confidence interval)	P-value *
	N = 82	**N = 74**		
Patients with an electrical storm	10 (12.2%)	18 (24.3%)	1.99 (0.98 – 4.04)	0.05

* P-values were calculated using the Pearson's Chi-squared test

Table S9. Baseline characteristics of patients with and without an electrical storm

Patients with appropriate therapy (n= 164)							
	Patients with electrical storm			**Patients without electrical storm**			P-value (with storm/without storm)
	Total (n= 28)	S-ICD (n= 10)	TV-ICD (n= 18)	Total (n= 136)	S-ICD (n= 76)	TV-ICD (n= 60)	
Median age (IQR)	64.5 (54.5-68.3)	67.5 (61.3-68.8)	64.0 (50.8-68.0)	63.0 (55.0-68.0)	63.0 (54.8-68.0)	63.0 (56.5-68.3)	0.87
Female — no. (%)	6 (21.4)	3 (30.0)	3 (16.7)	22 (16.2)	8 (10.5)	14 (23.3)	0.50
Diagnosis — no. (%)							
- Ischemic CMP	16 (57.1)	6 (60.0)	10 (55.5)	96 (70.6)	52 (68.4)	44 (73.3)	
- Nonischemic CMP	10 (35.7)	4 (40.0)	6 (33.3)	29 (21.3)	17 (22.4)	12 (20.0)	
- Genetic arrhythmia syndrome	1 (3.6)	0 (0.0)	1 (5.6)	7 (5.1)	4 (5.3)	3 (5.0)	
- Idiopathic VF	1 (3.6)	0 (0.0)	1 (5.6)	2 (1.5)	1 (1.3)	1 (1.7)	
- Congenital heart disease	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (1.3)	0 (0.0)	

- Other	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (1.3)	0 (0.0)	
Secondary prevention — no. (%)	7 (25.0)	2 (20.0)	5 (27.8)	39 (28.7)	20 (26.3)	19 (31.7)	0.69
Median ejection fraction (IQR)	28.0 (24.0-30.0)	27.0 (25.0-29.0)	29.5 (23.5-33.8)	28.0 (20.0-35.0)	28.5 (20.0-35.0)	27.5 (21.8-35.0)	0.95
NYHA class — no. (%)							0.35
- I	8/28 (28.6)	2/10 (20.0)	6/18 (33.3)	58/135 (43.0)	30/76 (39.5)	28/59 (47.5)	
- II	16/28 (57.1)	6 (60.0)	10/18 (55.6)	59/135 (43.7)	32/76 (47.8)	27/59 (45.8)	
- III/IV	4/28 (14.3)	2 (20.0)	2 (11.1)	18/135 (13.3)	14/76 (18.4)	4/59 (6.8)	
Median BMI (IQR)	27.4 (24.1-30.8)	26.2 (23.5-29.2)	27.4 (24.4-34.2)	27.2 (25.0-30.5)	27.2 (24.6-30.4)	27.4 (25.0-30.4)	0.90
Medication — no. (%)							
- B-blokker	22 (78.6)	8 (80.0)	14 (77.8)	113 (83.1)	60 (78.9)	53 (88.3)	0.59
- Amiodaron	4 (14.3)	1 (10.0)	3 (16.7)	6 (4.4)	5 (6.6)	1 (1.7)	0.07

Figure S1. Shock efficacy

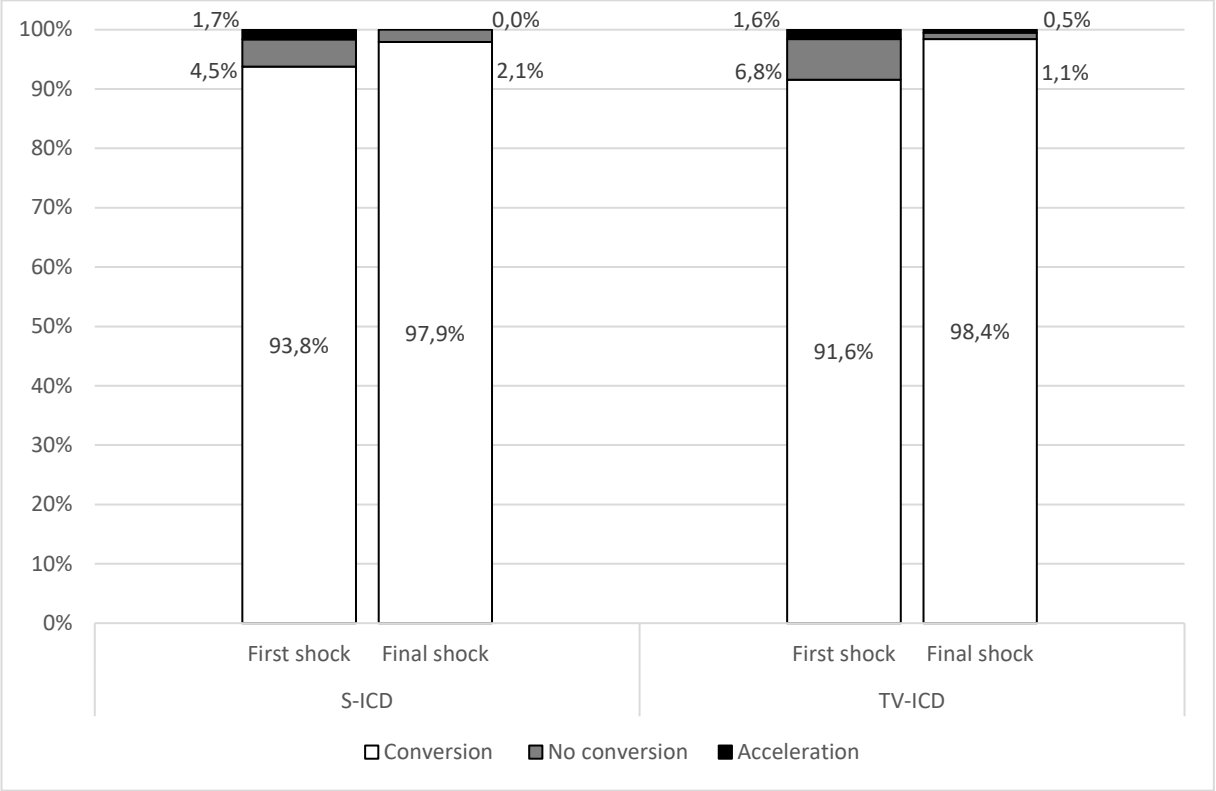

Figure S2. **Missing electrograms of the storm episodes in the TV-ICD group**

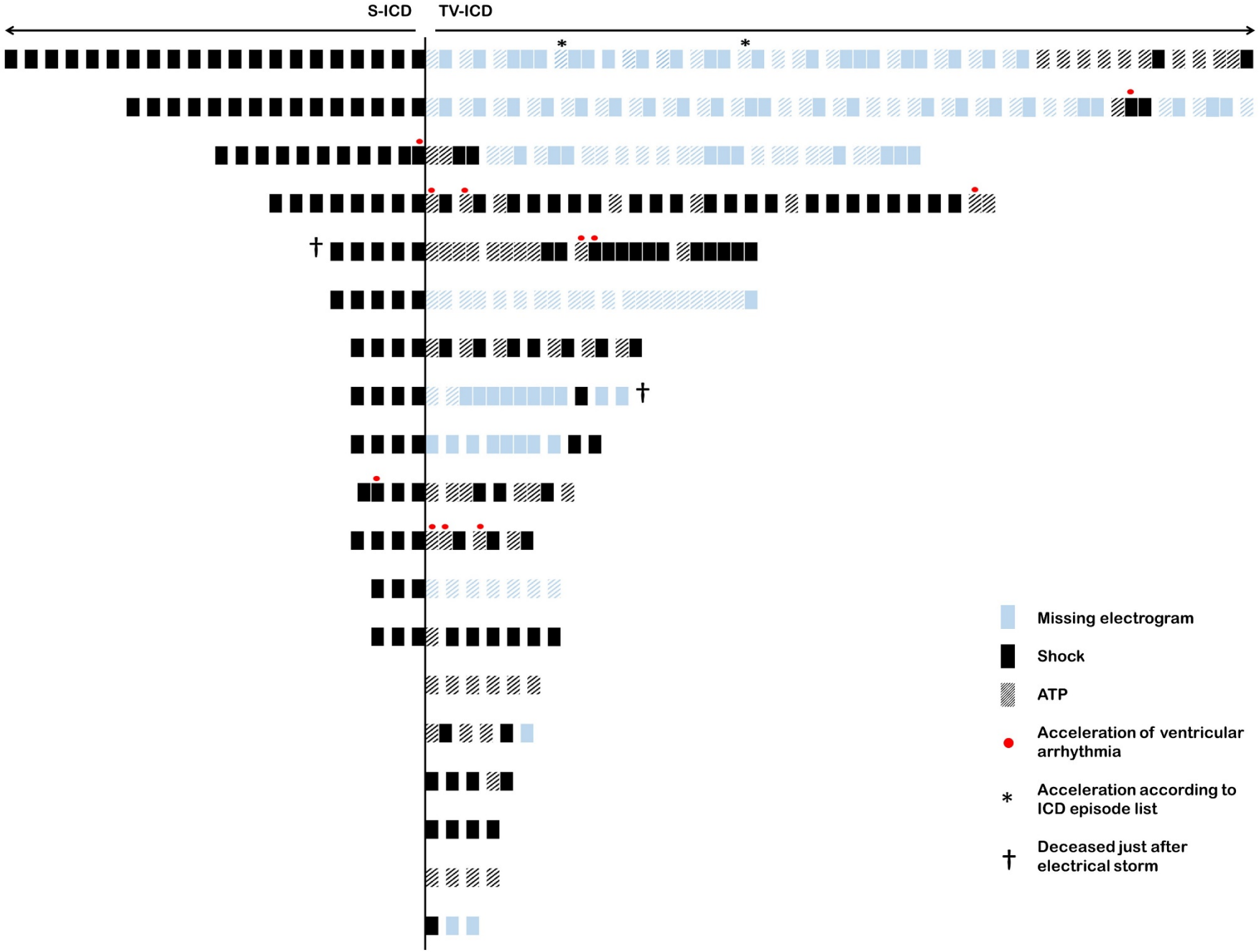

Figure S3. Example of the episode list stored by the ICD.

VT/VF Episodes

Date / Time	Type	Rate (min-1)	Duration (M:S)	Therapy Delivered	Alerts
21 Oct 2015 21:04	Non-sustained		00:12		
21 Oct 2015 20:56	SVT	173	00:19		x1
21 Oct 2015 20:53	Non-sustained		00:12		
21 Oct 2015 20:53	Non-sustained		00:12		
21 Oct 2015 20:52	Non-sustained		00:32		
21 Oct 2015 20:52	Non-sustained		00:28		
21 Oct 2015 20:51	VT-1	176	00:43	(Monitor Only)	x1
21 Oct 2015 20:50	VF	461	00:14	36J	x1
21 Oct 2015 20:50	Non-sustained		00:04		
21 Oct 2015 20:50	VF	315	00:15		x2
21 Oct 2015 20:49	VT-1	173	01:01	(Monitor Only)	x2
21 Oct 2015 20:48	VF	352	00:24	36J	x1
21 Oct 2015 20:48	Non-sustained		00:26		
21 Oct 2015 20:47	VF	387	00:29		x2
21 Oct 2015 20:47	VT-1	184	01:17	(Monitor Only)	x2
21 Oct 2015 20:46	VF	266	00:59	ATP	x1
21 Oct 2015 20:44	VF	292	00:39	ATP, 36J	x1
21 Oct 2015 20:44	Non-sustained		00:10		
21 Oct 2015 20:44	VF	250	00:18	ATP	x1
21 Oct 2015 20:43	SVT	169	00:54		
19 Oct 2015 21:56	Non-sustained		00:04		
16 Oct 2015 18:46	Non-sustained		00:06		
16 Oct 2015 0:47	Non-sustained		00:12		
16 Oct 2015 0:44	SVT	171	00:21		
16 Oct 2015 0:31	VT-1	179	00:31	(Monitor Only)	x1
16 Oct 2015 0:30	VT-1	173	00:32	(Monitor Only)	x1
16 Oct 2015 0:27	VT-1	181	03:12	(Monitor Only)	x2
16 Oct 2015 0:22	VT-1	173	00:58	(Monitor Only)	x1
16 Oct 2015 0:21	VF	400	03:43		x2
16 Oct 2015 0:07	VT-1	187	10:31	(Monitor Only)	x2
15 Oct 2015 15:21	Non-sustained		00:04		
14 Oct 2015 22:03	Non-sustained		00:08		
14 Oct 2015 22:03	Non-sustained		00:14		
14 Oct 2015 21:31	Non-sustained		00:06		
4 Oct 2015 1:06	Non-sustained		00:06		
3 Oct 2015 19:59	Non-sustained		00:06		
1 Oct 2015 17:56	Non-sustained		00:06		
30 Sep 2015 17:29	Non-sustained		00:10		
30 Sep 2015 13:15	Non-sustained		00:06		
28 Sep 2015 16:13	Non-sustained		00:08		
27 Sep 2015 1:07	Non-sustained		00:08		
25 Sep 2015 1:00	Non-sustained		00:04		