Appendices

Appendix A. Statistical Methods

A.1. Models

We utilized Bayesian hierarchical models to combine data from all trials while accounting for the variation of survival times, or rehospitalization indications, within and between studies. One important feature of the Bayesian hierarchical models is that, because they allow for borrowing of information across studies/subgroups, they allow us to make inferences about subgroups that may be under-represented in a subset of the trials. Moreover, missing values are treated as additional variates whose values can be naturally imputed as part of the estimation procedure with Markov Chain Monte Carlo methods.[1, 2]

The Bayesian paradigm requires specification of both the likelihood for the observations as well as priors for the model parameters. Preliminary analysis of the survival data from all trials indicated that the Weibull parametric survival model adequately fit the survival data, in particular, with results similar to those obtained under the Cox-Proportional Hazards Model. We thus utilized the Weibull parametric survival model to time to death from all causes. Under this model, we formulate the hazard function for an individual observed in study as:

(1)

where is the baseline hazard function in study . We assumed that , that is, the hazard function from a Weibull distribution with shape parameter and scale parameter . Furthermore, refers to treatment, refers to age, and the vector with the remaining covariates for subject . We are interested in investigating whether the efficacy of ICD relative to usual care is modified by age and thus we also include an interaction between treatment and age. The above formulation allows for trial-specific baseline hazard functions, as well as trial-specific

main effects of treatment. This formulation allows us to account for the possible heterogeneity in treatment effect or in the underlying risk of death from all causes between patients in the different trials. Furthermore, allowing for random effects addresses the correlated nature of the data in its multi-level resolution with patients clustered within trials. To allow for borrowing of information, we assumed that:

(2)

We completed the model formulation with the following priors:

(3)

that is, we assumed non-informative priors for the population (mean) parameters. Moreover, we assumed that for the variance components,

In our applications, we utilized These values were chosen to be minimally informative and such that, the preliminary analysis of simpler Bayesian hierarchical models (e.g. only random effects for treatment effect or only trial-specific baseline hazard functions), resulted in similar inference to those from the frequentist Cox-proportional hazards model.

We formulated a model for the indicator of at least one rehospitalization by analogy. Let denote the probability that individual had at least one rehospitalization. Then, we assumed

(4)

with a hierarchical formulation similar to that described by equations (2)-(3).

Variations of the above models were formulated to address specific sensitivity analysis. All models were estimated using Markov Chain Monte Carlo (MCMC) methods with Winbugs.

A.2. Missing Data

Let denote a particular covariate with missing value (for example, that QRS > 120) for an individual in trial . To allow for imputation of missing values, we assume that each covariate follows a Bernoulli model. Specifically, let denote the probability of the event defined by the covariate in trial . We assume that and that, a priori,

The above model implies that each missing covariate value is imputed via simulation prediction within each iteration of the MCMC procedure. Thus the procedure incorporates the uncertainty on the missing value.

A3. Posterior Inference

Under the Weibull proportional hazards and logistic regression models (1)-(4) there are natural measures of treatment effectiveness as given by the hazard ratio and odds ratio, respectively. To assess the "significance" of the interaction parameter , in analogy to p-values that are attained under frequentist analyses, we computed the two-sided posterior tail probability of no interaction which is . When the two-sided posterior tailed probability of no interaction was less than 0.05 we concluded that there was enough evidence for an interaction between treatment and age.

To graphically represent the overall treatment effect as dependent on age (that is, to interpret the interaction), we evaluated the hazard ratio comparing "typical" individuals in the same trial, with the same covariate values for X and W, but differing with respect to treatment, that is, receiving ICD versus usual care. In this calculation we replaced the study-specific treatment effect with the overall treatment effect so that the heterogeneity in treatment effects across trials is accounted for. Thus, we obtained the following expression:

(3)

The above expression is a function of W, that is, age only. Thus, to obtain Figure 4, we use posterior samples of and evaluate expression (3) above – thus, obtaining posterior samples of the hazard ratio evaluated at any given age W. We do the same for a range of values of W. The posterior samples are then summarized. We use the posterior median value of the hazard ratio at each given age as the point estimate and the 95% posterior credible intervals are obtained by computing the 2.5 and 97.5 quantiles of the posterior samples.

Appendix B. Supplementary Tables

Supplementary Table 1. Baseline Characteristics Stratified by Trial

		Age at Enrollment										
		<55					55-64					
Characteristic	**Total (n=1010)**	**DEFINITE (n=181)**	**MADIT I (n=33)**	**MADIT-II (n=192)**	**MUSTT (n=24)**	**SCD-HeFT (n=580)**	**Total (n=1055)**	**DEFINITE (n=120)**	**MADIT I (n=58)**	**MADIT-II (n=321)**	**MUSTT (n=57)**	**SCD-HeFT (n=499)**
Randomized to ICD, %	52.2	54.1	57.6	58.9	33.3	49.8	50.1	41.7	44.8	60.4	40.4	47.1
Age, median (IQR)	48 (43-52)	46 (41-50)	51 (49-53)	50 (45-52)	50.5 (44.8-53)	47 (42-52)	60 (57-62)	59 (57-62)	60 (59-62)	60 (58-62)	60 (57-62)	60 (57-62.5)
Male, %	78.1	75.1	93.9	85.9	95.8	74.8	81.5	73.3	96.6	85.1	89.5	78.6
Race												
White	73.1	65.8	90.9	87.0	87.5	69.1	81	69.2	93.1	87.2	86.0	78.0
Black	20.8	28.7	9.1	7.8	4.2	24.0	14.4	26.7	5.2	8.7	8.8	16.8
Other	6.1	5.5	0.0	5.2	8.3	6.9	4.6	4.2	1.7	4.1	5.3	5.2
Left ventricular ejection fraction, median (IQR)	23 (18-28)	20 (15-25)	24 (20-30)	25 (20-27)	28 (19.3-35)	23.3 (19-30)	25 (20-30)	22 (18-26)	25 (20-30)	25 (20-28)	25 (20-30)	25 (20-30)
New York Heart Association Class												
I	13.6	22.1	39.4	38.0	45.8	0	19.1	22.5	37.9	41.4	33.3	0
II	60.5	55.3	45.5	33.3	45.8	72.6	55.8	64.2	41.4	38.3	35.1	69.1
III	25.9	22.7	15.2	28.7	8.3	27.4	25.1	13.3	20.7	20.3	31.6	30.9
Medical history, %												
Atrial fibrillation	6.6	16.0	0	0	0	3.6	8.1	24.2	0	0	0	4.2
Coronary artery bypass grafting	26.9	0	42.4	45.3	75.0	17.9	41.1	0	43.1	59.2	61.4	26.9
Diabetes	23.3	18.3	3.0	23.4	0	25.9	34.2	23.3	3.5	40.0	0	36.7
Hypercholesterolemia	65.5	0	65.5	0.0	0	0.0	46.9	0	46.9	0	0	0
Hypertension	47.0	0	36.4	42.4	0	49.1	53.8	0	37.9	52.8	0	56.3
Ischemic heart disease	45.6	0	100	100	100	36.6	64.6	0	100	100	96.5	49.7
Myocardial infarction	44.1	0	100	100	91.7	34.1	62.1	0	100	100	87.7	45.3
Peripheral vascular disease	2.8	1.7	9.1	0	0	0.0	6.2	0.8	17.2	0	0	0
Percutaneous coronary intervention	25.2	0	18.18	53.4	29.17	16.2	30.3	0	22.4	44.2	19.3	23.7
Pulmonary disease	12.8	16.0	0	0	0	3.6	19.4	24.2	0	0	0	4.2
Smoking	81.1	95.6	83.9	89.6	0	73.6	83.6	94.2	77.6	86.6	0	79.8
Medication, %												
Angiotensin converting enzyme inhibitor	91.2	87.9	66.7	79.2	87.5	97.8	86.5	83.3	53.5	80.7	64.9	97.2
β-blocker	74.5	86.2	30.3	76.6	37.5	74.1	66.3	85.8	25.9	66.4	42.1	68.9
Diuretic	79.6	82.9	45.5	65.1	75.0	85.5	79.1	86.7	44.8	70.7	61.4	88.6
Antiarrhythmic	1.8	2.8	21.2	3.1	0	0	4	6.7	32.8	2.2	14.0	0
Laboratory data												
Serum creatinine, median (IQR)	1.0 (0.9-1.2)	NA	1.2 (1-1.4)	1 (0.9-1.2)	NA	1.1 (0.9-1.2)	1.1 (1.0, 1.3)	NA	1.1 (1-1.3)	1.1 (0.9-1.3)	NA	1.1 (1-1.4)
Left bundle branch block, %	16.4	0	9.1	8.1	9.1	19.8	18	0	8.6	14.8	12.5	21.6
QRS duration, median (IQR)	104 (94-120)	102 (92-116)	102 (100-130)	100 (90-120)	107 (98-118)	108 (96-128)	110 (100-140)	108 (96-133)	120 (100-140)	110 (100-140)	116 (107-136)	112 (100-141)
Included patients, n												
MADIT-I	33	0	33	0	0	0	58	0	58	0	0	0

MUSTT	24	0	0	0	24	0	57	0	0	0	57	0
MADIT-II	192	0	0	192	0	0	321	0	0	321	0	0
DEFINITE	181	181	0	0	0	0	120	120	0	0	0	0
SCD-HeFT	580	0	0	0	0	580	499	0	0	0	0	499

ICD indicates implantable cardioverter-defibrillator and IQR interquartile range.
*Data are presented as % unless otherwise indicated and are based on patients with available data.

Supplementary Table 1 (continued).

	Age at Enrollment												
		65-74						≥75					P
	Total (n=1075)	DEFINITE (n=114)	MADIT I (n=74)	MADIT-II (n=402)	MUSTT (n=76)	SCD-HeFT (n=409)	Total (n=390)	DEFINITE (n=43)	MADIT I (n=14)	MADIT-II (n=174)	MUSTT (n=25)	SCD-HeFT (n=134)	
	51.6	44.7	48.7	60.0	35.5	48.9	58	69.8	35.7	63.8	28.0	54.5	0.065
Age, median (IQR)	69 (67-72)	69 (67-71.8)	69 (67-71)	69 (67-72)	70 (67-72)	69 (67-72)	78 (76-80)	77 (76-78)	76 (75.3-77)	78 (76-80)	77 (76-79)	78 (76-80)	
Male, %	80.7	66.7	89.2	85.6	90.8	76.5	81	60.5	78.6	84.5	84.0	82.8	0.233
Race													<0.001
White	81.4	66.7	87.8	86.3	86.8	78.5	91	72.1	100	92.5	88.0	94.8	
Black	13.3	24.6	10.8	9.2	13.2	14.7	5.4	14.0	0	4.0	12.0	3.7	
Other	5.3	8.8	1.4	4.5	0	6.9	4	14.0	0	3.5	0	1.5	
Left ventricular ejection fraction, median (IQR)	25 (20-30)	23 (18-25)	25.5 (20-30)	25 (20-28)	25 (20-30.3)	25 (19-30)	25 (20-29)	20 (17.5-25)	28.5 (22.3-33.8)	25 (20-27)	25 (20-30)	25 (20-30)	<0.001
New York Heart Association Class													<0.001
I	20.2	16.7	31.1	36.8	35.5	0	24.4	30.2	28.6	40.2	32.0	0	
II	52.5	58.8	50.0	38.1	38.2	68.0	43.9	44.2	57.1	31.0	32.0	61.2	
III	27.4	24.6	18.9	25.1	26.3	32.0	31.8	25.6	14.3	28.7	36.0	38.8	
Medical history, %													
Atrial fibrillation	14.7	32.5	0	0	0	9.8	20.9	39.5	0	0	0	14.9	<0.001
Coronary artery bypass grafting	48.5	0	50.0	61.9	51.3	34.5	54.8	0	57.1	63.8	60.0	41.8	<0.001
Diabetes	33.4	29.0	9.5	38.1	0	34.5	23.8	25.6	7.1	27.0	0	20.9	<0.001
Hypercholesterolemia	42.9	0	42.9	0	0	0	9.1	0	9.1	0	0	0	0.013
Hypertension	58	0	44.6	58.8	0	59.7	55	0	57.1	48.3	0	63.4	<0.001
Ischemic heart disease	72.9	0	100	100	94.7	57.7	76.4	0	100	100	96.0	64.2	<0.001
Myocardial infarction	69.8	0	100	100	85.5	51.1	73.1	0	100	100	84.0	56.7	<0.001
Peripheral vascular disease	9	3.5	17.6	0	0	0	7	4.7	14.3	0	0	0	0.068
Percutaneous coronary intervention	32.5	0	24.3	44.9	25.0	23.2	31.6	0	14.3	41.3	16.0	23.9	0.007
Pulmonary disease	23.7	32.5	0	0	0	9.8	20.3	39.5	0	0	0	14.9	<0.001
Smoking	75.9	90.4	71.2	76.1	0	72.4	74.5	90.7	83.3	70.9	0	73.1	<0.001
Medication, %													
Angiotensin converting enzyme inhibitor	81.6	83.3	50.0	75.1	68.4	95.6	76.4	74.4	85.7	73.6	36.0	87.3	<0.001
β-blocker	59	86.8	13.5	60.7	42.1	60.9	55.4	81.4	7.1	50.0	28.0	64.2	<0.001
Diuretic	79.2	86.8	48.7	77.6	69.7	85.8	78.2	93.0	71.4	77.0	52.0	80.6	0.952
Antiarrhythmic	4.3	7.0	28.4	3.5	4.0	0	3.1	4.7	35.7	2.3	4.0	0	0.008
Laboratory data													
Serum creatinine, median (IQR)	1.2 (1.1-1.4)	NA	1.3 (1.1-1.6)	1.2 (1-1.4)	NA	1.2 (1-1.4)	1.3 (1.1-1.6)	NA	1.6 (1.1-2)	1.3 (1-1.6)	NA	1.3 (1.1-1.6)	<0.001
Left bundle branch block, %	22	0	8.6	22.5	10.9	25.7	24.1	0	0	27.2	4.8	26.1	0.003
QRS duration, median (IQR)	120 (100-146)	112 (98-144)	110 (100-130)	120 (100-160)	116 (103-143)	118 (98-144)	120 (100-160)	110 (97-135)	125 (100-160)	130 (100-160)	105 (100-118)	120 (100-151)	<0.001
Included patients, n													
MADIT-I	74	0	74	0	0	0	14	0	14	0	0	0	
MUSTT	76	0	0	0	76	0	25	0	0	0	25	0	
MADIT-II	402	0	0	402	0	0	174	0	0	174	0	0	

DEFINITE	114	114	0	0	0	0	43	43	0	0	0	0	
SCD-HeFT	409	0	0	0	0	409	134	0	0	0	0	134	

ICD indicates implantable cardioverter-defibrillator and IQR interquartile range.
*Data are presented as % unless otherwise indicated and are based on patients with available data.

Supplementary Table 2. Baseline Characteristics Stratified by Sex

	Age at Enrollment												
		<55			55-64			65-74			≥75		P
Characteristic	**Total (n=1010)**	**Men (n=789)**	**Women (n=221)**	**Total (n=1055)**	**Men (n=860)**	**Women (n=195)**	**Total (n=1075)**	**Men (n=868)**	**Women (n=207)**	**Total (n=390)**	**Men (n=316)**	**Women (n=74)**	
Randomized to ICD, %	52.2	52.6	50.7	50.1	49.7	51.8	51.6	51.5	52.2	58	57.6	59.5	0.065
Age, median (IQR)	48 (43-52)	48 (43-52)	46 (39-51)	60 (57-62)	60 (57-62)	59 (57-62)	69 (67-72)	69 (67-72)	69 (67-71)	78 (76-80)	78 (76-80)	78 (76-79)	
Male, %	78.1	100	0	81.5	100	0	80.7	100	0	81	100	0	0.233
Race													<0.001
White	73.1	77.3	57.9	81	83.0	72.3	81.4	84.3	69.1	91	91.8	87.8	
Black	20.8	16.5	36.2	14.4	12.3	23.6	13.3	10.5	25.1	5.4	4.8	8.1	
Other	6.1	6.2	5.9	4.6	4.7	4.1	5.3	5.2	5.8	4	3.5	4.1	
Left ventricular ejection fraction, median (IQR)	23 (18-28)	22 (18-28)	25 (20-29)	25 (20-30)	25 (20-29)	25 (20-30)	25 (20-30)	25 (20-30)	23 (20-30)	25 (20-29)	25 (20-29)	24.5 (20-29.8)	<0.001
New York Heart Association Class													<0.001
I	13.6	14.3	10.9	19.1	20.7	11.8	20.2	21.8	13.5	24.4	25.6	18.9	
II	60.5	61.2	57.9	55.8	55.2	58.5	52.5	52.3	53.1	43.9	44.0	43.2	
III	25.9	24.5	31.2	25.1	24.1	29.7	27.4	25.9	33.3	31.8	30.4	37.8	
Medical history, %													
Atrial fibrillation	6.6	8.1	2.1	8.1	9.2	4.3	14.7	15.2	13.4	20.9	22.6	15.0	<0.001
Coronary artery bypass grafting	26.9	30.9	11.9	41.1	45.1	22.1	48.5	51.6	33.7	54.8	56.9	43.9	<0.001
Diabetes	23.3	21.8	28.3	34.2	34.9	31.2	33.4	33.0	35.0	23.8	23.7	24.3	<0.001
Hypercholesterolemia	65.5	66.7	50.0	46.9	46.8	50.0	42.9	42.0	50.0	9.1	12.5	0.0	0.013
Hypertension	47	47.7	44.6	53.8	54.2	52.2	58	56.5	64.8	55	52.0	69.8	<0.001
Ischemic heart disease	45.6	51.1	26.2	64.6	69.2	44.6	72.9	77.8	52.7	76.4	79.8	62.2	<0.001
Myocardial infarction	44.1	49.3	25.3	62.1	66.3	43.6	69.8	74.5	49.8	73.1	75.6	62.2	<0.001
Peripheral vascular disease	2.8	3.6	0.0	6.2	6.9	2.9	9	9.9	6.5	7	5.4	10.0	0.068
Percutaneous coronary intervention	25.2	27.5	17.1	30.3	31.1	26.4	32.5	32.8	31.0	31.6	34.0	19.3	0.007
Pulmonary disease	12.8	13.5	25.4	19.4	19.2	23.6	23.7	24.8	19.7	20.3	18.2	25.6	<0.001
Smoking	81.1	83.4	73.2	83.6	84.7	78.8	75.9	79.1	62.8	74.5	78.7	57.1	<0.001
Medication, %													
Angiotensin converting enzyme inhibitor	91.2	91.1	91.4	86.5	87.0	84.1	81.6	81.5	82.1	76.4	75.6	79.7	<0.001
β-blocker	74.5	75.3	71.5	66.3	65.4	70.3	59	57.6	64.7	55.4	54.8	58.1	<0.001
Diuretic	79.6	77.1	88.7	79.1	76.9	88.7	79.2	78.1	83.6	78.2	74.7	93.2	0.952
Antiarrhythmic	1.8	2.3	0.0	4	4.5	1.5	4.3	4.4	3.9	3.1	3.2	2.7	0.008
Laboratory data													

Serum creatinine, median (IQR)	1.0 (0.9-1.2)	1.1 (0.9-1.3)	0.9 (0.7-1.1)	1.1 (1.0-1.3)	1.1 (1.0-1.4)	1.0 (0.8-1.1)	1.2 (1.1-1.4)	1.2 (1.0-1.5)	1.0 (0.9-1.3)	1.3 (1.1-1.6)	1.3 (1.1-1.6)	1.1 (0.8-1.5)	<0.001
Left bundle branch block, %	16.4	14.4	24.0	18	15.5	30.2	22	19.4	34.2	24.1	22.6	30.9	0.003
QRS duration, median (IQR)	104 (94-120)	100 (90-123)	107 (96-120)	110 (100-140)	110 (95-150)	112 (100-140)	120 (100-146)	110 (92-150)	120 (100-146)	120 (100-160)	120 (95-152)	120 (100-160)	<0.001
Included patients, n													
MADIT-I	33	31	2	58	56	2	74	66	8	14	11	3	
MUSTT	24	23	1	57	51	6	76	69	7	25	21	4	
MADIT-II	192	165	27	321	273	48	402	344	58	174	147	27	
DEFINITE	181	136	45	120	88	32	114	76	38	43	26	17	
SCD-HeFT	580	434	146	499	392	107	409	313	96	134	111	23	

ICD indicates implantable cardioverter-defibrillator and IQR interquartile range.
*Data are presented as % unless otherwise indicated and are based on patients with available data.

References

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