Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods. Supplementary Methods

Baseline LVEF, NYHA Functional Class, and Covariate Ascertainment

Baseline data on demographics, clinical characteristics, past medical history, lifestyle habits, cardiac test results, and medications were collected. The baseline LVEF was chosen to be the most recent assessment on which current medical treatment was based at the time of entry into the study. Modalities utilized to assess LVEF included echocardiograms (N=3092 [54%]), invasive catheterization (N= 1166 [20%]), nuclear imaging (N= 1122 [19%], or cardiac magnetic resonance imaging (N= 380 [7%]). NYHA functional class was assessed using consensus guideline criteria.[6]

Ascertainment and Classification of Incident Cardiovascular Events and Death

Questionnaires inquiring about intervening cardiac arrest, ICD implantation, and other pertinent cardiovascular endpoints were mailed to participants every six months. If the questionnaire was not returned, telephone contact with the participant was initiated to complete the interval health assessment and assess vital status, followed by telephone calls to patient contacts, next-of-kin, and clinical site study staff. Vital status was further assessed using contact with postal authorities, obituary searches, and serial searches of the National Death Index for names of non-respondents.

Ascertainment and Classification of Incident Cardiovascular Events and Death

Cardiac deaths included those that were classified as SAD or were documented to be due to myocardial infarction, pump failure with progressive symptomatic deterioration, stroke, cardiovascular procedural deaths, or other vascular causes. Deaths known to have occurred after a chronic terminal illness (e.g. malignancy not in remission) and/or occurring in hospice without information regarding the circumstances surrounding the fatal event were classified as

non-SAD deaths even if no specific information was available regarding the terminal event. Finally, the presence of an ICD was not considered in the application of death adjudication criteria.

Competing Risk Analysis

For competing-risk analyses with the primary SAD endpoint as the outcome, non-SAD deaths (non-sudden, non-arrhythmic cardiovascular, non-cardiovascular, unclassified) were treated as competing risk. Similarly, when non-SAD deaths were considered as the outcome, participants experiencing the primary endpoint (including those experiencing out of hospital VF arrest) were treated as competing risk.

eTable 1. Circumstances and Clinical History Prior to Sudden and/or Arrhythmic Death

	Sudden Arrhythmic Death (N=125)
Location of death or cardiac arrest, n (%)	
Home	89 (71)
Public	25 (20)
In-Hospital	8 (7)
Unknown	3 (2)
Witnessed, n (%)	
Yes	66 (53)
No	55 (44)
Unknown	4 (3)
Rhythm Monitor at Time of Death, n (%)	
Yes	57 (46)
No	68 (54)
Initial Rhythm in Monitored Deaths, n (% of monitored)	
Ventricular fibrillation or tachycardia	34 (60)
Asystole	16 (28)
Pulseless electrical activity	6 (10)
Bradycardia	1 (2)
Clinical History (% of those with history ascertainment)	
Unstable angina within 1 month	18 of 94 (19)
History of worsening heart failure within 3 months	5 of 87 (6)
Newly documented LVEF < 35% prior to death	21 of 93 (23)
ICD implantation prior to SAD death	6 of 125 (5)
Most vigorous activity in the one hour prior to death, n (%)	
Sleeping	30 (24)
At rest	52 (42)
Light exertion	18 (14)
Moderate exertion	7 (6)
Vigorous exertion	4 (3)
Unknown	14 (11)
Symptoms reported prior to death, n (%)	
Yes	45 (36)
No	72 (58)
Unknown	8 (6)
Cardiac symptoms, n (% of those with symptom ascertainment)	14 (12)
Chest pain	18 (15)
Dyspnea	8 (7)
Syncope/Presyncope	6 (5)
Diaphoresis/Nausea/Indigestion	

SAD, sudden and/or arrhythmic death

eTable 2. Cause-specific Hazard for the Association of Clinical Risk Factors with Sudden and/or Arrhythmic versus Competing Modes of Death

Clinical Subgroup	**Hazard Ratio SAD**	**Hazard Ratio Non-SAD**
Age		
≤ 59	Reference	Reference
60-69	0.77 (0.47-1.24)	2.60 (1.80-3.75)
>69	1.45 (0.95-2.21)	7.55 (5.40-10.55)
Male Sex	1.10 (0.71-1.70)	0.86 (0.70-1.07)
White Race	1.04 (0.59-1.85)	0.76 (0.54-1.08)
History of Smoking	1.48 (0.98-2.23)	1.36 (1.10-1.69)
Hypertension	1.73 (1.06-2.83)	1.70 (1.31-2.19)
History of Revascularization	1.03 (0.52-2.03)	0.73 (0.53-0.99)
Family History Sudden Death	1.23 (0.86-1.89)	1.05 (0.84-1.30)
Diabetes Mellitus	2.16 (1.51-3.09)	1.99 (1.65-2.41)
Atrial Fibrillation	2.23 (1.47-3.37)	2.52 (2.04-3.12)
Left Ventricular Ejection Fraction		
≥ 60%	Reference	Reference
50-59%	1.81 (0.96-3.39)	1.32 (0.99-1.75)
40-49%	3.78 (2.10-6.78)	2.01 (1.54-2.64)
30-39%	5.46 (2.71-10.99)	3.07 (2.18-4.32)
NYHA Class		
I	Reference	Reference
II	1.02 (0.61-1.69)	2.09 (1.68-2.60)
III/IV	2.84 (1.52-5.31)	3.41 (2.45-4.75)

SAD, sudden and/or arrhythmic death. NYHA, New York Heart Association.

eTable 3. Sudden and/or Arrhythmic Proportion of Total Mortality in Clinical Subgroups

Clinical Subgroup	Subgroup N	No. SAD / No. Non-SAD	% Total Deaths, SAD	P, for difference % SAD
Age				
≤ 59	1882	37/39	49%	<0.001
60-69	1990	30/106	22%	
>69	1889	52/281	16%	
Sex				
Male	4391	93/314	23%	0.32
Female	1370	26/112	19%	
Race/Ethnicity				
White	5128	106/391	21%	0.36
Other	633	13/35	27%	
Smoking				
Never	1945	31/118	21%	0.72
Ever	3814	88/308	22%	
Hypertension				
Yes	4371	100/356	22%	0.90
No	1390	19/70	21%	
History of Revascularization				
Yes	5328	110/381	22%	0.33
No	433	9/45	17%	
Family History Sudden Death				
Yes	1432	35/108	24%	0.37
No	4329	84/318	21%	
Diabetes Mellitus				
Yes	1860	58/198	23%	0.66
No	3901	61/228	21%	
Atrial Fibrillation				
Yes	791	30/118	20%	0.59
No	4969	89/308	22%	
Left Ventricular Ejection Fraction	1591	14/77	15%	0.25
≥ 60%	1997	31/124	20%	
50-59%	1756	56/167	25%	
40-49%	417	18/58	24%	
30-39%				
NYHA Class				
I	4597	90/273	25%	0.03
II	925	18/113	14%	
III/IV	223	11/40	22%	

SAD, sudden and/or arrhythmic death.

eTable 4. Differential Association of Clinical Risk Factors with SAD and Non-SAD: Sensitivity Analysis Excluding 36 Participants with Unclassified Mode of Death

Clinical Subgroup	**Subdistribution Hazard Ratio SAD**	**Subdistribution Hazard Ratio Non-SAD**	**P, for Δ association**
Age ≤ 59 60-69 >69	 Reference 0.76 (0.47-1.22) 1.37 (0.90-2.08)	 Reference 2.62 (1.78-3.86) 7.81 (5.49-11.10)	<0.001
Male Sex	1.10 (0.71-1.70)	0.90 (0.72-1.13)	0.42
Non-White Race	1.05 (0.59-1.86)	0.71 (0.49-1.02)	0.28
History of Smoking	1.47 (0.98-2.22)	1.34 (1.07-1.67)	0.67
Hypertension	1.70 (1.04-2.78)	1.70 (1.30-2.22)	0.96
History of Revascularization	1.04 (0.53-2.06)	0.71 (0.51-0.98)	0.32
Family History Sudden Death	1.27 (0.86-1.89)	1.05 (0.84-1.31)	0.41
Diabetes Mellitus	2.10 (1.47-3.01)	1.94 (1.59-2.37)	0.65
Atrial Fibrillation	2.12 (1.40-3.20)	2.55 (2.04-3.18)	0.55
Left Ventricular Ejection Fraction ≥ 60% 50-59% 40-49% 30-39%	 Reference 1.80 (0.96-3.38) 3.70 (2.06-6.64) 5.27 (2.62-10.61)	 Reference 1.22 (0.91-1.64) 1.93 (1.46-2.54) 2.86 (2.00-4.09)	- 0.27 0.04 0.11
NYHA Class I II III/IV	 Reference 1.00 (0.60-1.65) 2.65 (1.41-4.96)	 Reference 2.03 (1.61-2.55) 3.36 (2.37-4.74)	- 0.01 0.62

SAD, sudden and/or arrhythmic death

eTable 5. Differential Association of Clinical Risk Factors with SAD versus non-SAD: Sensitivity Analysis Excluding 30 Participants with Probable Sudden Cardiac Death

Clinical Subgroup	**Subdistribution Hazard Ratio SAD**	**Subdistribution Hazard Ratio Non-SAD**	**P, for Δ association**
Age ≤ 59 60-69 >69	 Reference 0.73 (0.42-1.28) 1.34 (0.83-2.17)	 Reference 2.27 (1.62-3.18) 6.38 (4.70-8.66)	<0.001
Male Sex	1.14 (0.69-1.89)	0.87 (0.71-1.08)	0.34
Non-White Race	1.21 (0.64-2.27)	0.75 (0.54-1.05)	0.21
History of Smoking	1.57 (0.97-2.54)	1.35 (1.10-1.66)	0.54
Hypertension	1.89 (1.05-3.40)	1.66 (1.30-2.12)	0.65
History of Revascularization	0.87 (0.42-1.80)	0.76 (0.56-1.04)	0.77
Family History Sudden Death	1.19 (0.75-1.90)	1.07 (0.87-1.32)	0.67
Diabetes Mellitus	2.15 (1.42-3.25)	1.97 (1.64-2.36)	0.62
Atrial Fibrillation	2.04 (1.26-3.31)	2.49 (2.03-3.06)	0.57
Left Ventricular Ejection Fraction ≥ 60% 50-59% 40-49% 30-39%	 Reference 2.32 (1.04-5.19) 5.15 (2.43-10.91) 6.46 (2.68-15.59)	 Reference 1.29 (0.98-1.70) 1.97 (1.52-2.55) 3.05 (2.19-4.24)	- 0.16 0.01 0.14
NYHA Class I II III/IV	 Reference 1.14 (0.65-2.00) 2.96 (1.47-5.95)	 Reference 1.97 (1.59-2.43) 3.21 (2.33-4.43)	- 0.08 0.96

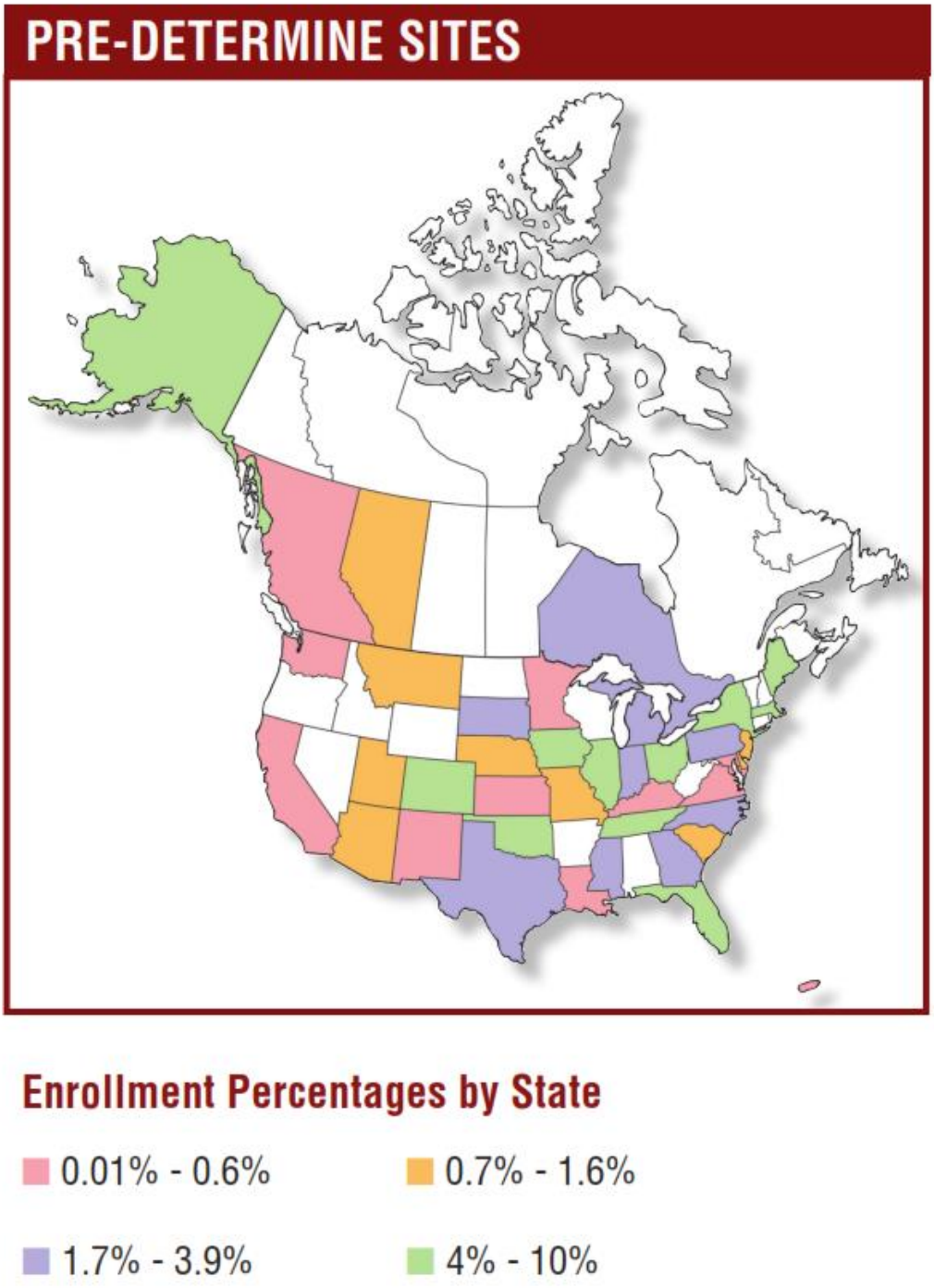
SAD, sudden and/or arrhythmic death.

eTable 6. Differential Association of Clinical Risk Factors with SAD versus Non-SAD: Sensitivity Analysis Excluding 13 Participants with Out of Hospital Cardiac Arrest

Clinical Subgroup	**Subdistribution Hazard Ratio SAD**	**Subdistribution Hazard Ratio Non-SAD**	**P, for Δ association**
Age ≤ 59 60-69 >69	 Reference 0.74 (0.45-1.22) 1.27 (0.82-1.99)	 Reference 2.60 (1.80-3.75) 7.51 (5.38-10.50)	 <0.001
Male Sex	1.06 (0.67-1.67)	0.87 (0.70-1.07)	0.44
Non-White Race	1.19 (0.67-2.12)	0.76 (0.54-1.08)	0.21
History of Smoking	1.31 (0.86-1.99)	1.36 (1.10-1.68)	0.90
Hypertension	1.82 (1.07-3.09)	1.69 (1.31-2.18)	0.77
History of Revascularization	0.92 (0.46-1.82)	0.73 (0.53-0.99)	0.56
Family History Sudden Death	1.21 (0.79-1.84)	1.04 (0.84-1.30)	0.56
Diabetes Mellitus	2.28 (1.56-3.33)	1.96 (1.62-2.37)	0.44
Atrial Fibrillation	2.25 (1.46-3.46)	2.49 (2.01-3.08)	0.80
Left Ventricular Ejection Fraction ≥ 60% 50-59% 40-49% 30-39%	 Reference 1.80 (0.94-3.46) 3.47 (1.88-6.39) 4.68 (2.23-9.81)	 Reference 1.31 (0.99-1.74) 1.98 (1.51-2.60) 3.01 (2.13-4.24)	- 0.37 0.08 0.26
NYHA Class I II III/IV	 Reference 1.06 (0.63-1.79) 2.70 (1.40-5.24)	 Reference 2.09 (1.68-2.61) 3.33 (2.39-4.63)	- 0.02 0.69

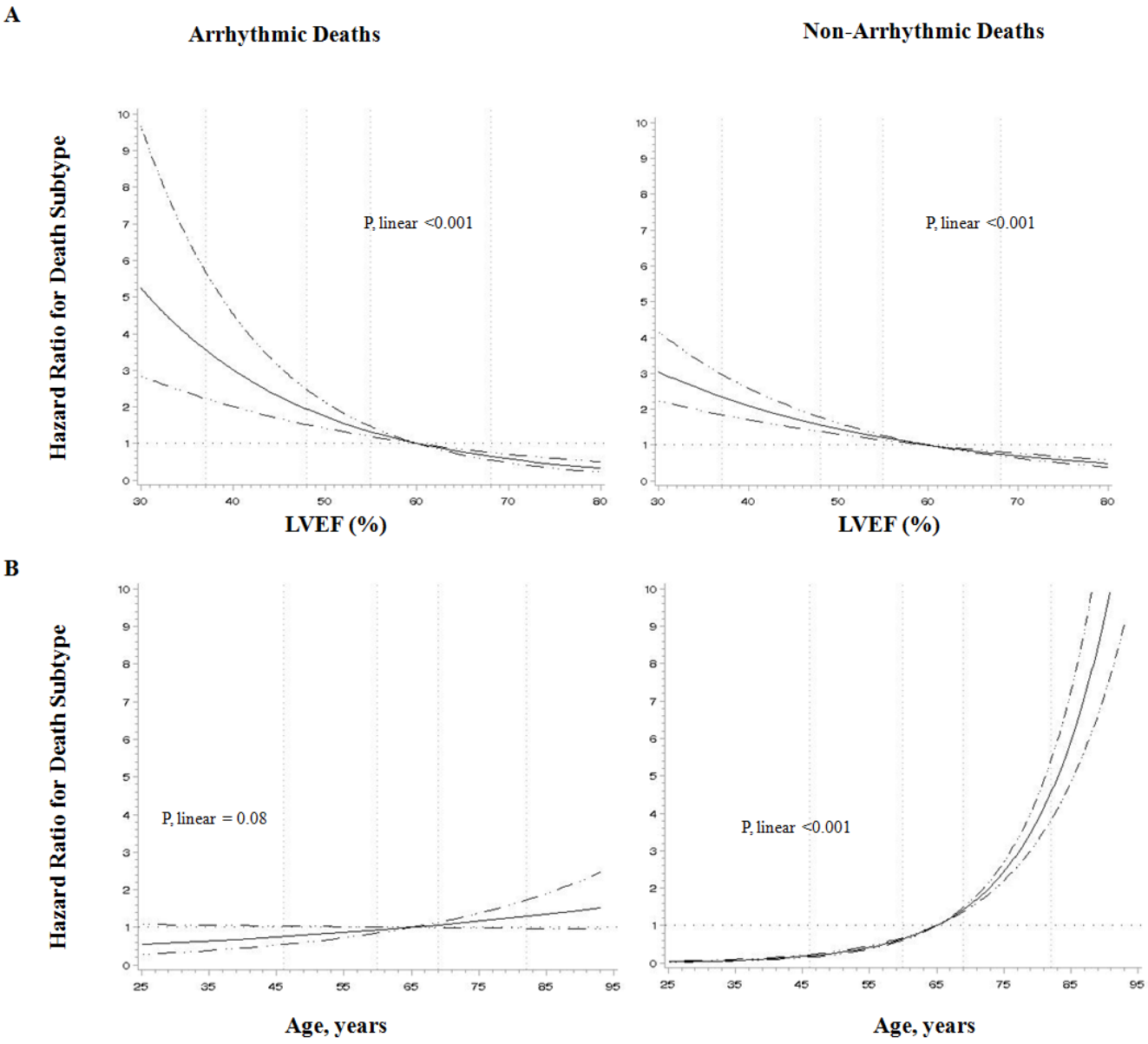
SAD, sudden and/or arrhythmic death

eFigure 1. Geographic Distribution of Enrollment Sites in PRE-DETERMINE.



Shown is the geographic distribution of enrollment sites in the PRE-DETERMINE study in the United States and Canada.

eFigure 2. Continuous Association between LV Ejection Fraction and Age with Cause-Specific Death



Cubic restricted spline models were used to examine the continuous association between left ventricular ejection fraction (Panel A) and age (Panel B) with cause-specific modes of death (SAD, non-SAD). There was no statistical evidence of non-linearity; continuous, linear associations are shown. SAD, sudden and/or arrhythmic death.