

Supplementary Online Content

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

eAppendix. Cox Proportional Hazards Modelling and Missing Data

Univariable and multivariable Cox regression models were fitted for the main study endpoint and tested for non-linearity of continuous predictors by inclusion of quadratic terms. The correct functional forms of continuous predictor variables were also assessed by visual analysis of cumulative plots of Martingale residuals. Candidate predictor variables were selected based previous description of an association with the study endpoint or pathophysiological plausibility. Sample size guidelines for Cox regression suggest that at least 10 events per candidate variable are required to obtain unbiased parameter estimates (coefficients and HRs) with correct standard errors ¹. The proportional hazards assumption was verified using Schoenfeld residuals ². To determine the degree of bias due to missing data, the characteristics of patients with missing information were compared with those with complete information. Logistic regression was used to identify the predictors of missingness. Data were assumed to be missing at random, and values for the missing predictors were imputed using multiple imputation techniques based on chained equations ³. All predictors of missingness were included in the multiple imputation model, together with the outcome, potential predictors and the estimate of the cumulative hazard function ⁴. The number of imputations was based on the percentage of missingness and the estimates were combined using Rubin's rules ⁵.

Missing data

Missing data was observed for the following variables: left atrium diameter 3.9%, maximum wall thickness 1.1%, LV end-diastolic diameter 4.4%, LV ejection fraction 9.5%, LV outflow tract gradient 13.4%, unexplained syncope 1.0%, non-sustained ventricular tachycardia on Holter 14.1%, family history of SCD 2.9%, NYHA class 4.2%, history of hypertension 2.2%. Complete data was present in 3500 patients (71.5%). Missingness was associated with history of sustained ventricular tachycardia/fibrillation, country, centre, ICD, presentation period, main composite endpoint, HF death/transplantation, non-CV death, follow up duration.

eReferences

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eTable 1. Characteristics of the Study Population According to Era of First Evaluation

	Prior to 1990 (n=204)	1990-1999 (n=1022)	2000-2004 (n=1839)	2005-2013 (n=1828)	P- value
Age at presentation (yrs)	44.2 ± 15.5	44.2 ± 15.6	49.4 ± 16.1	52.3 ± 16.4	<0.001
Male sex	133 (65.2%)	621 (60.8%)	1224 (66.6%)	1148 (62.8%)	0.01
Follow up duration (yrs)	15.7 ± 8.7	10.8 ± 5.6	7.5 ± 3.3	3.4 ± 2.1	<0.001
Family history of SCD	50/183 (27.3%)	291/935 (31.1%)	440/1824 (24.1%)	346/1810 (19.1%)	<0.001
Previous VF/ sustained VT	3 (1.5%)	39 (3.8%)	39 (2.1%)	53 (2.9%)	0.04
NYHA class	I II III/IV	461 (48.0%) 396 (41.2%) 104 (10.8%)	948 (53.4%) 620 (34.9%) 207 (11.7%)	1055 (59.7%) 537 (30.4%) 175 (9.9%)	<0.001
NSVT on Holter	49/167 (29.3%)	220/915 (24.0%)	353/1621 (21.8%)	302/1501 (20.1%)	0.01
Hypertension	35/200 (17.5%)	173/984 (17.6%)	542/1792 (30.3%)	696/1807 (38.5%)	<0.001
Max LV wall thickness (mm)	21.9 ± 6.1	20.0 ± 5.4	19.4 ± 5.2	18.9 ± 4.7	<0.001
EF ≤50%	22/190 (11.6%)	80/988 (8.1%)	138/1696 (8.1%)	156/1554 (10.0%)	0.11
LVOT gradient >50 mmHg	16/188 (8.5%)	116/785 (14.8%)	440/1580 (27.8%)	515/1685 (30.6%)	<0.001
LA diameter (mm)	45.1 ± 9.5	43.8 ± 8.1	44.7 ± 7.7	43.6 ± 7.5	<0.001
ICD ^a	24 (11.8%)	182 (17.8%)	336 (18.3%)	274 (15%)	0.009
Septal myectomy	4 (2.0%)	51 (5.0%)	145 (7.9%)	97 (5.3%)	<0.001
Alcohol septal ablation	3 (1.5%)	27 (2.6%)	56 (3%)	22 (1.2%)	0.001

^a at baseline or during follow up ICD: implantable cardioverter defibrillator; EF: ejection fraction; LA: left atrium; LV: left ventricle; LVOT: left ventricular outflow tract obstruction; NSVT: non-sustained ventricular tachycardia; SCD: sudden cardiac death; VF: ventricular fibrillation; VT: ventricular tachycardia.

eTable 2. Characteristics, Treatment and Outcome of the Study Population by Country

	Greece (n=566)	Spain (n=1497)	Italy (n=733)	UK (n=2097)	P- value
Age at presentation (y)	46.7 ± 16.2	55.1 ± 16.3	49.9 ± 15.9	45.4 ± 15.5	<0.001
Male sex	396 (70.0%)	927 (61.9%)	458 (62.5%)	1345 (64.1%)	0.007
Follow up duration (y)	8.2 ± 4.1	5.5 ± 4.2	5.7 ± 6.4	8.2 ± 5.2	<0.001
Family history of SCD	184/566 (32.5%)	238/1484 (16.0%)	145/729 (19.9%)	560/1973 (28.4%)	<0.001
Previous VF/sustained VT	14 (2.5%)	57 (3.8%)	32 (4.4%)	31 (1.5%)	<0.001
NYHA class	I 329 (58.1%) II 186 (32.9%) III/IV 51 (9.0%)	816 (55.3%) 439 (29.7%) 221 (15.0%)	398 (59.4%) 209 (31.2%) 63 (9.4%)	1017 (51.5%) 779 (39.4%) 179 (9.1%)	<0.001
NSVT on Holter	121/566 (21.4%)	283/1330 (21.3%)	138/596 (23.2%)	382/1712 (22.3%)	0.78
Hypertension	151/566 (26.7%)	666/1493 (44.6%)	219/733 (29.9%)	410/1991 (20.6%)	<0.001
Max LV wall thickness (mm)	18.1 ± 4.0	19.7 ± 5.1	20.2 ± 4.9	19.3 ± 5.5	<0.001
EF ≤50%	26/566 (4.6%)	167/1338 (12.5%)	58/523 (11.1%)	145/2001 (7.2%)	<0.001
LVOT gradient >50 mmHg	161/566 (28.4%)	391/1195 (32.7%)	170/718 (23.7%)	365/1759 (20.8%)	<0.001
LA diameter (mm)	43.8 ± 6.4	44.1 ± 7.8	45.6 ± 8.5	43.7 ± 7.9	<0.001
ICD ^a	67 (11.8%)	209 (14%)	129 (17.6%)	411 (19.6%)	<0.001
Septal myectomy	5 (0.9%)	56 (3.7%)	39 (5.3%)	197 (9.4%)	<0.001
Alcohol septal ablation	3 (0.5%)	24 (1.6%)	5 (0.7%)	76 (3.6%)	<0.001
Heart transplant	3 (0.5%)	34 (2.3%)	22 (3%)	26 (1.2%)	0.001
Main study endpoint rate ^b	1.57%/yr	3.17%/yr	2.74%/yr	1.59%/yr	
SCD/aborted SCD rate	0.43%/yr	0.40%/yr	0.81%/yr	0.47%/yr	
HF death/transplantation	0.49%/yr	1.01%/yr	1.00%/yr	0.38%/yr	
Other CV death rate	0.13%/yr	0.58%/yr	0.36%/yr	0.22%/yr	
Non-CV death rate	0.47%/yr	0.99%/yr	0.52%/yr	0.50%/yr	

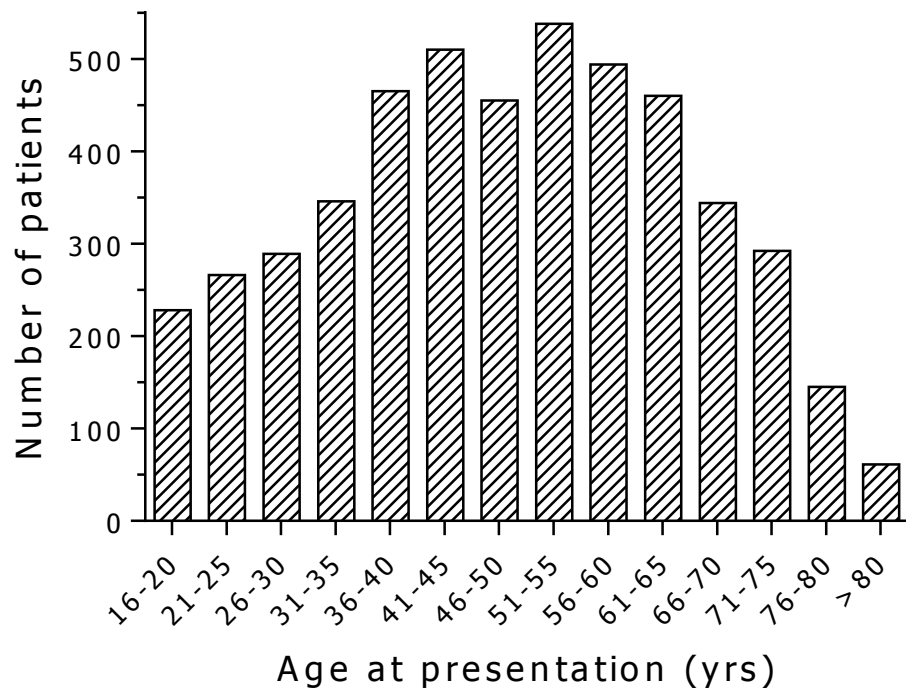
^a at baseline or during follow up; ^b composite endpoint consisting of all-cause mortality, aborted SCD and heart transplantation. CV: cardiovascular; EF: ejection fraction; HF: heart failure; ICD: implantable cardioverter defibrillator; LA: left atrium; LV: left ventricle; LVOT: left ventricular outflow tract obstruction; NSVT: non-sustained ventricular tachycardia; SCD: sudden cardiac death; VF: ventricular fibrillation; VT: ventricular tachycardia

eTable 3. Multivariable Cox Analysis for the Main Survival Analysis (Composite of All-Cause Mortality, Transplantation and Aborted Sudden Cardiac Death)

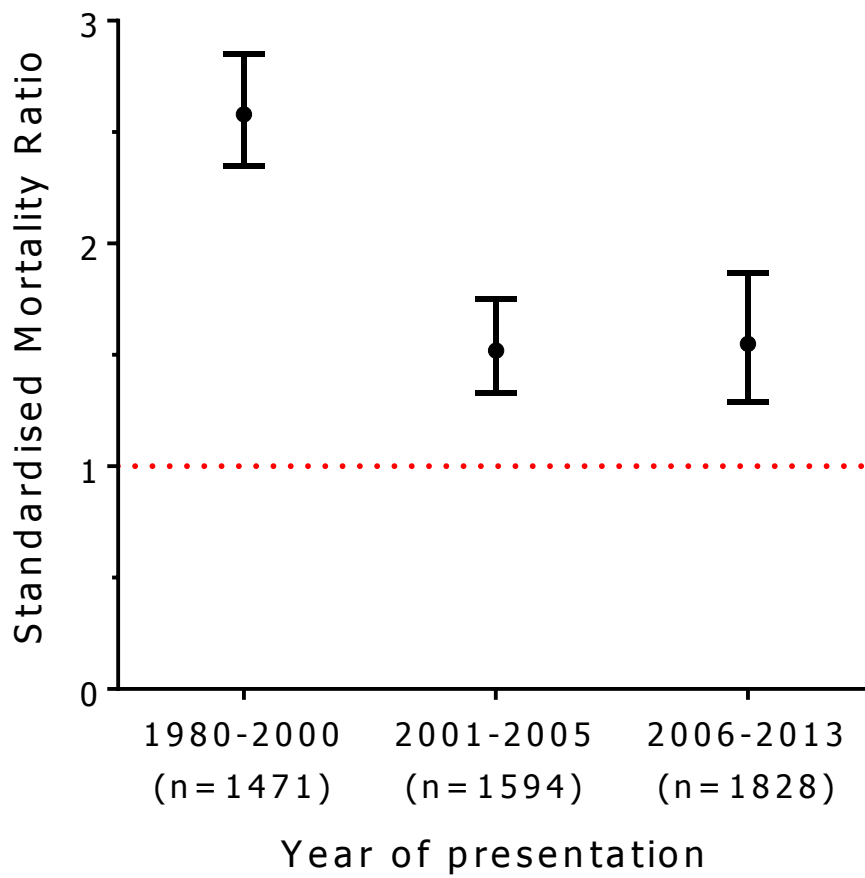
Predictor	Univariable analysis			Multivariable analysis			
	HR	95% CI	P-value	HR	95% CI	P-value	
Age at presentation (10 y)	1.49	1.41-1.57	<0.001	1.40	1.32-1.48	<0.001	
Female sex	1.48	1.28-1.71	<0.001	1.28	1.09-1.49	0.003	
Previous VF/VT	2.17	1.58-2.97	<0.001	2.12	1.53-2.92	<0.001	
NYHA	II III/IV	1.52 4.06	1.28-1.81 3.36-4.92	<0.001	1.18 2.36	0.99-1.41 1.91-2.94	<0.001
Syncope	1.20	0.99-1.45	0.07			0.86	
EF ≤50%	3.48	2.88-4.21	<0.001	2.31	1.89-2.83	<0.001	
MWT (5mm)	2.17	1.42-3.31	<0.001	1.44	0.93-2.23	0.01	
[MWT (5mm)] ²	0.92	0.88-0.97	0.001	0.97	0.92-1.02	0.23	
LA diameter (5mm)	1.34	1.28-1.39	<0.001	1.21	1.15-1.27	<0.001	
LVOT max (25mmHg increase)	1.07	1.02-1.12	0.01			0.72	
Atrial fibrillation ^a	1.54	1.33-1.78	<0.001	1.37	1.16-1.63	<0.001	
NSVT on Holter	1.58	1.33-1.88	<0.001	1.17	0.97-1.42	0.11	
Family history of SCD	1.01	0.85-1.20	0.89				
Stroke	1.64	1.31-2.06	<0.001	1.19	0.95-1.51	0.14	
Hypertension	1.33	1.13-1.56	0.001	1.36	1.15-1.62	<0.001	
Septal myectomy	0.62	0.43-0.90	0.01	0.56	0.39-0.83	0.003	
Alcohol septal ablation	0.82	0.49-1.36	0.43				

^a at baseline or during follow up; EF: ejection fraction; LA: left atrium; LVOT: left ventricular outflow tract gradient; MWT: maximum wall thickness; NSVT: non-sustained ventricular tachycardia; SCD: sudden cardiac death; VF: ventricular fibrillation; VT: ventricular tachycardia.

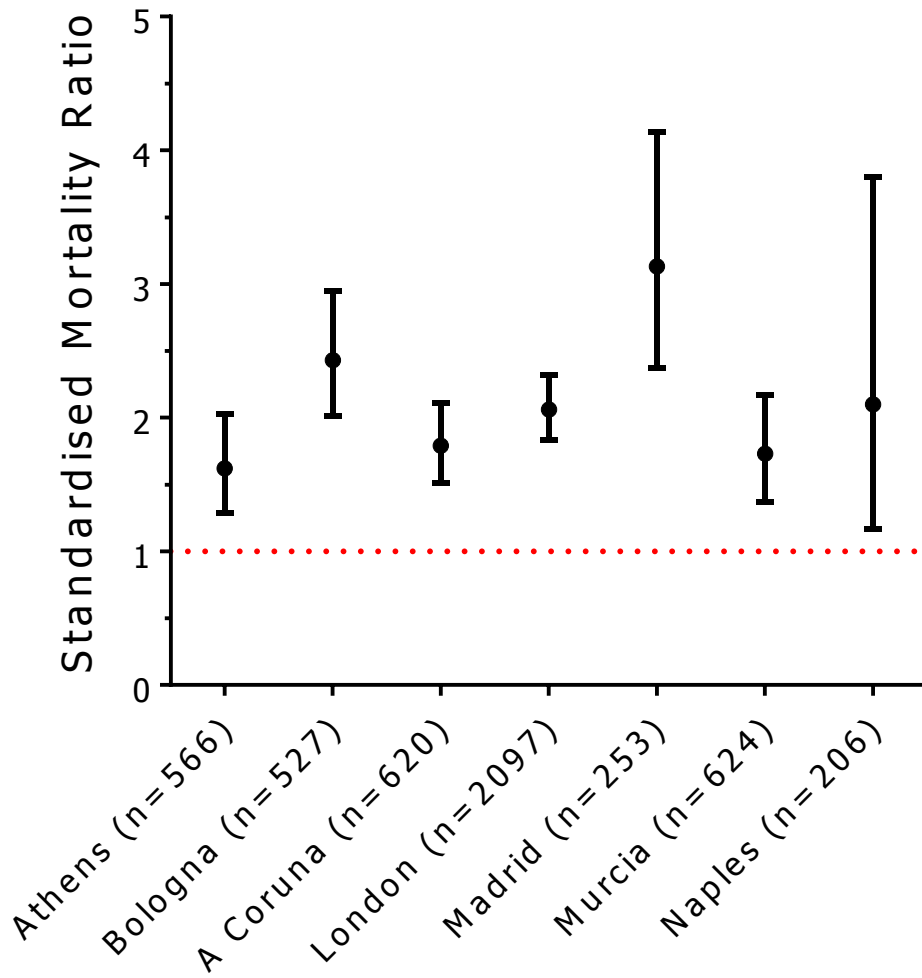
eFigure 1. Distribution of Study Cohort by Age at Presentation



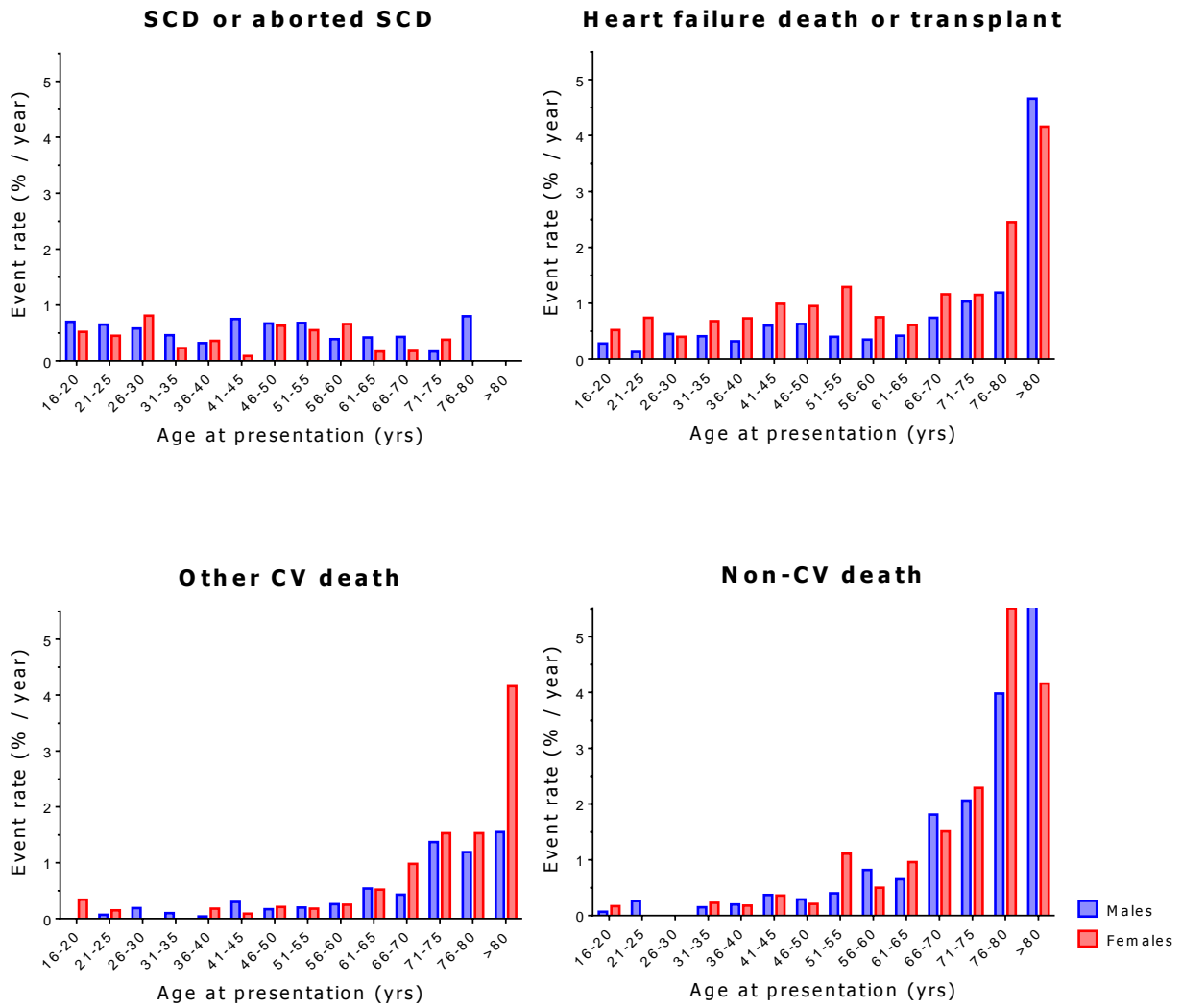
eFigure 2. Standardized Mortality Ratios According Era of First Evaluation



eFigure 3. Standardized Mortality Ratios According to Centre



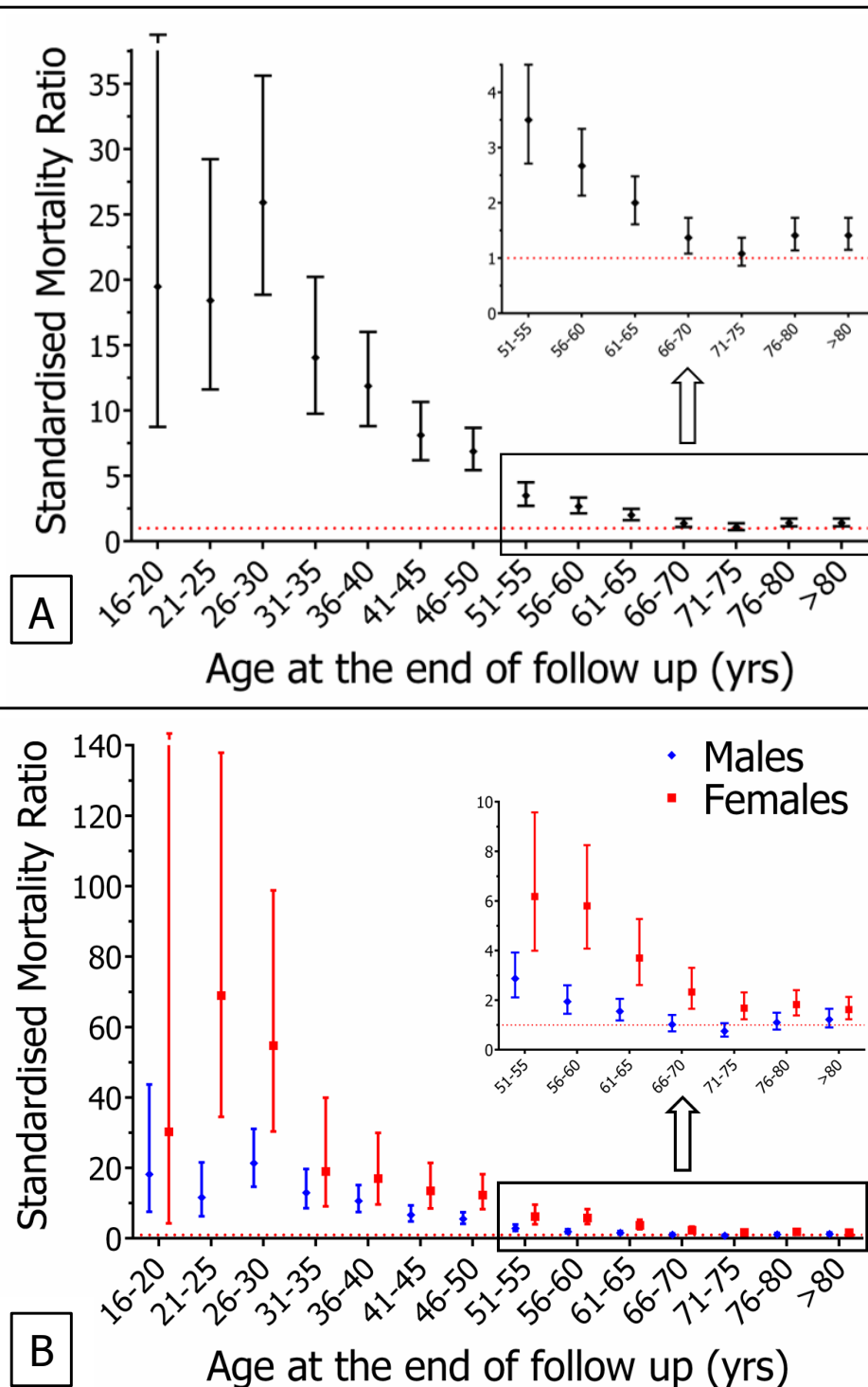
eFigure 4. Event rates in the Study Population by Sex, According to Age at Presentation



CV: cardiovascular. Non-CV death in males age >80: 9.33%

eFigure 5. Secondary Analysis Including ICD Shocks: Standardized Mortality Ratios by Age and Age and Sex in the Study Population

Analysis including ICD shocks



Panel A: Standardized mortality ratios in the study population by age; for the age group 16 to 20 the upper 95% CI limit is 43.36. Panel B: Standardized mortality ratios in the study population by age and sex. For females aged 16 to 20 the upper 95% CI limit is 215.12. Error bars indicate 95% CIs.