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Age and Outcomes of Primary Prevention Implantable Cardioverter Defibrillators in Patients with Non-Ischemic Systolic Heart Failure

Running Title: *Elming et al.; Age and effect of ICD in the DANISH trial*

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Abstract

Background—The Danish Study to Assess the Efficacy of Implantable Cardioverter Defibrillators (ICD) in Patients with Non-ischemic Systolic Heart Failure on Mortality (DANISH) did not demonstrate an overall effect on all-cause mortality with ICD implantation. However, the pre-specified subgroup analysis suggested a possible age-dependent association between the ICD and mortality with survival benefit seen only in the youngest patients. The nature of this relationship between age and outcome of a primary prevention ICD in patients with non-ischemic systolic heart failure warrants further investigation.

Methods—All 1116 patients from the DANISH study were included in this pre-specified subgroup analysis. We assessed the relationship between the ICD and mortality by age, and an optimal age cut-off was estimated non-parametrically using selection impact curves. Modes of death were divided into sudden cardiac death (SCD) and non-sudden death and compared between patients younger and older than this age cut-off, respectively, with the use of Chi2-analysis.

Results—Median age of the study population was 63 years (range 21 – 84 years). There was a linearly decreasing relationship between the ICD and mortality with age, HR 1.03 (95% CI 1.003 – 1.06), p=0.03. An optimal age cut-off for ICD implantation was present at ≤70 years. There was an association between reduced all-cause mortality and the ICD in patients ≤70 years, HR 0.70 (0.51 – 0.96), p=0.03, but not in patients >70 years, HR 1.05 (0.68 – 1.62), p=0.84. For patients ≤70 years, SCD rate was 1.8 (1.3 – 2.5) and non-sudden death rate was 2.7 (2.1 – 3.5) events/100 patient years, whereas for patients older than 70 years SCD rate was 1.6 (0.8 – 3.2) and non-sudden death rate was 5.4 (3.7 – 7.8) events/100 patient years. This difference in modes of death between the two age groups was statistically significant (p=0.01).

Conclusions—In patients with systolic heart failure not caused by ischemic heart disease, the association between the ICD and survival decreased linearly with increasing age. In this study population, an age cut-off for ICD implantation at ≤70 years yielded the highest survival for the population as a whole.

Key Words: implanted cardioverter defibrillator; aging; heart failure

Clinical Perspective

What is new?

- In the present study we explored further the association between the ICD and all-cause mortality by age in the DANISH study.
- We found a mortality reduction in association with an ICD in the younger part of the population only, and data from this study suggest an age cut-off of 70 years.
- Modes of death differ according to age, and younger patients more often die of sudden cardiac death which is why an ICD was found to be associated with improved survival rates.

What are the clinical implications?

- The ICD was associated with reduced all-cause mortality only in the younger part of the population of patients with non-ischemic systolic heart failure.
- Younger patients seem to benefit more from an ICD than older patients, primarily caused by the fact, that sudden cardiac death accounts for a higher proportion of death in the younger patients.

Patients with systolic heart failure are at increased risk of sudden cardiac death (SCD)[1]. An implantable cardioverter-defibrillator (ICD) significantly reduces this risk in patients with systolic heart failure caused by ischemic heart disease[2]. However, no single study based on exclusively patients with systolic heart failure not caused by coronary artery disease has demonstrated a mortality reduction with ICD implantation. The recent Danish Study to Assess the Efficacy of ICDs in Patients with Non-ischemic Systolic Heart Failure on Mortality (DANISH) found no reduction in all-cause mortality when patients with non-ischemic systolic heart failure were treated with an ICD[3]. However, the association of ICD implantation with survival was significantly different depending on age, with lower all-cause mortality in the two youngest tertiles combined, but not in the older tertile. Although a possible age-dependent relationship of the ICD with survival is a relevant clinical question, few data exist on this. The majority of deaths in patients with chronic systolic heart failure are due to cardiovascular causes, mainly fatal arrhythmias or worsening of heart failure, but a substantial number of patients also die from non-cardiovascular causes[4]. An ICD can only prevent sudden cardiac death caused by ventricular tachy-arrhythmia, severe bradycardia, or complete heart block; and cannot provide protection against other causes of death[5]. The causes of death in patients with heart failure change with age[6]. Younger patients may be more prone to ventricular tachy-arrhythmia, whereas older patients may be more likely to die from pump failure or non-cardiovascular reasons[4].

The purpose of the present analysis is to provide further insight into the relationship between the ICD and all-cause mortality and sudden cardiac death by age.

Methods

The DANISH study

The detailed design of the DANISH trial was reported previously[7]. In brief, DANISH was a randomized controlled trial addressing ICD implantation to patients with non-ischemic systolic heart failure[3]. In total, 1116 patients with documented non-ischemic systolic heart failure with left ventricular ejection fraction (LVEF) ≤35% and increased levels (>200 pg/ml) of N-terminal pro-brain natriuretic peptide (NT-proBNP) were randomized to ICD or control. Exclusion of ischemic heart disease as the cause of heart failure was done either by coronary angiography (96% of patients), computed tomography (CT) angiography, or nuclear myocardial perfusion imaging. Patients were primarily in New York Heart Association (NYHA) functional class II or III, NYHA class IV was accepted in candidates for cardiac resynchronization therapy (CRT). Patients with pre-existing conventional pacemaker (PM) or CRT-PM could be included. Patients with permanent atrial fibrillation and a resting heart rate >100 beats per minute, and patients with end-stage renal failure (dialysis) were excluded.

Ethics

The study was performed according to the principles of the Helsinki declaration. Patients have been enrolled only after providing informed consent. The study is approved by the regional scientific ethical committee for the capital region, ID-no. H-D-2007-0101, and the Danish Data Protection Agency. In addition, the trial is registered at clinicaltrials.gov with the identifier NCT00542945.

Age-groups and causes of death

Age was the only pre-specified subgroup with a significant treatment-by-subgroup interaction in the DANISH trial (p=0.009 for interaction with age divided into tertiles). Age-tertiles based on

age at randomization were used for initial demographic analysis: ´Age-group 1´ <59 years, ´Age-group 2´ 59 – <68 years, and ´Age-group 3´ ≥68 years according to the pre-specified analysis plan.

The primary end-point, death from any cause, and the secondary end-points cardiovascular death, sudden cardiac death, and non-cardiac death were adjudicated according to previously reported criteria by a clinical end-point committee[7]. Cardiovascular deaths were sub-classified as sudden or non-sudden. Sudden cardiac death was defined as death occurring unexpectedly in a previously stable patient, death occurring within an hour of onset or worsening of symptoms, or unwitnessed death, when patients were last seen alive <72 hours before death with no sign of life-threatening disease or symptoms, and when circumstances suggested sudden death such as when the patient was found in bed. Non-cardiovascular deaths were defined as all deaths, not adjudicated as cardiovascular death. Cardiovascular deaths classified as non-sudden and all non-cardiovascular death were categorized together as non-sudden death.

Statistical analysis

Baseline characteristics of the age-groups were compared using Chi-square test for categorical variables and Kruskal-Wallis test for continuous variables. Outcomes were analysed with the use of time-to-event methods. All analyses were performed in the intention-to-treat population. The relationship between the ICD and survival by age was assessed using linear and spline-based models for effects on the log hazard of death, with separate effects of age estimated in each treatment group. The model with the lowest Akaike information criterion was selected as having the best balance between fit and parsimony[8,9].

In addition, a selection impact analysis was performed, describing the expected survival in the full population under different age-based thresholds for ICD treatment assignment[10,11]. The

selection impact estimate is non-parametric, as each time point represents a weighed combination of Kaplan-Meier (K-M) estimates from the relevant treatment groups. Thus, the overall survival for the population, including both the patients who receive an ICD and those who do not, is estimated. For example, the estimated effect of assigning patients 50 years or younger to ICD is the weighted average of the K-M estimates for survival in the ICD arm for patients aged ≤50 years and in the control arm for patients aged >50 years, with the average weighed by the proportions of patients in the corresponding age-groups. Ninety-five percent confidence intervals (CI) were estimated using the bootstrap. Cumulative incidence curves were calculated for all-cause mortality, and for cardiovascular death, sudden cardiac death, and non-sudden death taking competing risks into account. Formal assessment of proportional hazard did not find significant non-proportionality (p=0.23). Differences in the distribution of mode of death between age-groups were assessed using frequency tables and Chi-square test. Incidences rates were estimated by Poisson regression and are expressed as events per 100 patient years. In a multivariable cox regression model, we tested the interaction between age and treatment strategy controlling for known risk factors. Two-sided p-values <0.05 were considered statistically significant. All analyses were performed with SAS software version 9.4 (SAS Institute), and R software version 3.3.1 (R Project for Statistical Computing).

Results

Baseline characteristics for the age-tertiles are presented in table 1. Median age of the study population was 63 years (range 21 – 84 years), figure 1. The oldest age-group had a significantly higher prevalence of comorbidities, longer duration of heart failure, adverse biomarker profile (NT-proBNP and lower renal function (estimated glomerular filtration rate (eGFR)), and slightly

fewer received target doses of guideline therapy. The median follow-up time for the entire population was 67.6 months, no difference between groups. Baseline characteristics for patients according to age-tertiles and randomization, ≤68 and >68 years, and ≤70 and >70 years is presented in the supplement, table 1, 2 and 3.

Figure 2 shows the relation between age and risk of all-cause mortality comparing ICD-treatment and control. Increasing the model complexity beyond a linear relationship with age did not sufficiently improve model fit to justify the additional model complexity. Each year of younger age was associated with a 3.0% (0.03 – 6.0%, p=0.03) further reduction in the Hazard Ratio (HR) for the benefit of an ICD, and the point estimate crossed 1.0 at age just after 70 years. The selection impact curve is presented in figure 3. Each point on the curve shows the estimated total 7-year survival for the population in case this specific age was chosen as the cut-off for ICD treatment. The 7-year survival rate in the overall population is estimated to 70% if no one received an ICD and 72% if everyone received an ICD. The maximum survival rate of the entire population was estimated with a cut-off of ≤70 years for ICD implantation, with 75% surviving. A cut-off at ≤70 years is therefore used for further analysis of modes of death. A selection impact analysis with 1-year age intervals, depicting age ≤70 as the highest age-cutoff with significant survival benefit for the entire population, is shown in the supplement, figure 1.

In figure 4 the time to event curves for all-cause mortality are stratified by the ≤70 years cut-off. Patients ≤70 years had significantly better survival when treated with an ICD, HR 0.70 (95% CI 0.51 – 0.96), p=0.03. After 7 years of follow-up, patients with an ICD had 8% lower absolute mortality (1.1% per year). For patients older than 70 years ICD implantation was not associated with improved all-cause mortality, HR 1.05 (95% CI 0.68 – 1.62), p=0.84. In a multivariable model adjusted for sex, CRT, BMI, NT-proBNP, eGFR, NYHA class, duration of

heart failure, hypertension, diabetes, atrial fibrillation, and the use of beta-blocker, ace inhibitor or ARB, and MRA, the ICD was significantly associated with improved survival (p=0.02) for patients younger than 70 years.

Figure 5 shows the cumulative rates of sudden cardiac death and non-sudden death in the control group only. Among patients ≤70 years randomized to the control group, the incidence rate of sudden cardiac death was 1.8 (1.3 – 2.5) and for non-sudden death 2.7 (2.1 – 3.5) events per 100 patient years. In contrast, for patients older than 70 years the incidence rate for sudden cardiac death was 1.6 (0.8 – 3.2) and for non-sudden death 5.4 (3.7 – 7.8) events per 100 patient years. This difference in distribution of mode of death was statistically significant, p=0.01. The corresponding cumulative rates of sudden cardiac death and non-sudden death for patients randomized to ICD treatment are presented in figure 6. Figure 2 and figure 3 in the supplement shows the risk of sudden cardiac death and non-sudden death respectively according treatment with ICD or control, for patients ≤70 years and >70 years.

A successful ICD shock was experienced by 46 patients younger than 70 years and 10 patients older than 70 years. The cumulative incidence of first successful ICD shock after 7 years of follow-up was 0.72% (0.66 – 0.78) for patients younger than 70 years compared to 0.48% (0.39 – 0.61) for patients older than 70 years. All results reported with age ≤70 as a cut-off were similar if using age ≤68 years instead with no changes in statistical significance.

Discussion

In this study in patients with non-ischemic systolic heart failure, the association between the ICD and all-cause mortality decreased with advancing age in a linear relation and no association between the ICD and survival was observed in older patients. Modes of death vary with age and

while sudden death rates were roughly similar between younger and older patients, the rate of non-sudden death was twice as high in the older population as in the younger.

Limited data exist on the relation between the ICD and all-cause mortality by age. A previous meta-analysis found a survival benefit of ICD implantation for all patients, but with benefit decreasing with increasing age[12]. In the current international guidelines implantation of an ICD is recommended to patients with systolic heart failure irrespectively of etiology and age[13,14]. Meta-analyses of all trials of patients with non-ischemic systolic heart failure including the results of the DANISH study found a significant reduction in all-cause mortality for the entire population[15,16]. However, the result from our study suggests that ICD implantation in patients with non-ischemic systolic heart failure only significantly decreases all-cause mortality in the younger patients. This is in accordance with a meta-analysis of the Multicenter Automatic Defibrillator Implantation II (MADIT II) trial, Sudden Cardiac Death in Heart Failure (SCD-HeFT) trial and Defibrillators in Non-ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) trial, which showed that age may be associated with the benefit of an ICD with a smaller reduction in all-cause mortality in older patients compared to younger[17].

For an ICD to prevent death the underlying cause must be arrhythmic, the potential benefit of ICD implantation, therefore, depends on a patient's risk of sudden cardiac death relative to the risk of non-sudden death. Correspondingly, we found no association between the ICD and non-sudden death regardless of age. The potential benefit of ICD implantation therefore depends on a patient's risk of sudden cardiac death relative to the risk of non-sudden death. In the present study, we investigated the modes of death in patients not treated with an ICD. Older patients were twice as likely as younger patients to die from other causes than sudden cardiac death and, consequently, sudden cardiac death accounted for a higher proportion of deaths

among the younger patients than in the older patients. This pattern was also seen in an analysis of more than 6000 patients with structural heart disease, primarily heart failure caused by coronary artery disease, where death by any cause increased with age whereas the incidence of sudden cardiac death decreased[6]. All this may explain why ICD implantation has less impact in older patients. A dichotomous age cut-off point for effect of an ICD will be arbitrary, but our analyses suggest an optimal cut-off at ≤70 years of age in the population randomized in the DANISH study. However, since other factors may also be of importance when ICD implantation is considered, a rigid age cut-off should not be stated. Overall the mortality rates in DANISH were lower than in previous studies addressing ICD implantation[18,19].

Many factors are important when considering ICD implantation. First, patients' preferences should be taken into account. Studies have shown that patients with heart failure express different preferences concerning treatment strategy according to age. Younger patients often emphasize longer life expectancy and prefer increased survival time, whereas older patients consider quality of life of greater importance[20]. Secondly, the balance between the potential benefits and risks of ICD implantation is important. ICD implantation is an invasive procedure with risk of perioperative complications such as pneumothorax, bleeding, and cardiac perforation, and also late complications associated with ICD treatment such as inappropriate shocks, device-related infection, the fear of appropriate shocks, and quality of life are to be considered[21]. Consequently, risk stratification techniques are needed in order to adequately optimize the risk/benefit balance of ICD implantation in individual patients[22]. In this study, the patients in the oldest age-group presented worse on almost all clinical parameters. A worse risk-factor profile might be associated with modes of death and outcomes of an ICD, and should be taken into account before ICD implantation.

Limitations

In the present analysis, the bulk of patients were between 40 and 80 years old with very few patients outside this range. Consequently, conclusions outside this age-span are based on extrapolations. We found the highest survival for the entire population with ICD implantation in patients ≤70 years, but confidence limits of the estimate were wide and we cannot conclude that ≤70 is significantly superior to any other age cut-off. As in any clinical trial, patient selection may be an issue and selection bias might be more pronounced with age. Consequently 68% of patients older than 70 who were included in DANISH were scheduled for CRT and this might have impacted our results. Also, this is a sub-group analysis, and randomization to ICD or control was not stratified by age. Randomization was not blinded due to the surgical procedure, and this may have influenced the clinical treatment strategy afterwards. CRT was implanted in 58% of the patients (and in 68% of patients older than 70) and this may have influenced our findings. The inclusion criteria of pro-BNP did not change according to age, which might have influenced the risk and severity of heart disease in the older population, and thereby also modes of death. All this must be borne in mind when interpreting our results and before applying them in clinical practice.

Conclusions

In this post-hoc analysis of the DANISH study, the ICD was associated with reduced all-cause mortality in patients 70 years or younger. The benefit of ICD implantation decreased with older age and was not apparent in patients older than 70 years. Older patients were more likely to die from other causes than sudden cardiac death compared to younger patients, which might be a reason for the diminishing association between the ICD and all-cause mortality with advancing age.

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Table 1. Baseline characteristics in the age-tertiles

	Age group 1 N =348 <59 yr.	Age group 2 N =375 59 – <68 yr.	Age group 3 N =393 ≥68 yr.	p-value
Median age (IQR) – yr.	53 (47 – 56)	63 (61 – 65)	73 (70 – 76)	-
Randomized to ICD – (%)	167 (48)	173 (46)	216 (55)	0.04
Men – (%)	260 (75)	273 (73)	276 (70)	0.39
Median blood pressure (IQR) – mmHg				
Systolic	120 (109 – 136)	123 (110 – 137)	126 (113 – 140)	0.02
Diastolic	74 (68 – 83)	74 (65 – 81)	73 (65 – 80)	0.02
Median BMI* (IQR)	27 (24 – 31)	27 (24 – 30)	26 (24 – 29)	0.004
Median NT-pro BNP (IQR) – pg/ml	817 (446 – 1692)	1245 (658 – 2307)	1466 (724 – 2682)	<0.0001
Median QRS duration (IQR) – msec	132 (102 – 162)	145 (112 – 166)	150 (120 – 166)	<0.0001
Median LVEF (IQR) – %	24 (19 – 30)	25 (20 – 30)	25 (20 – 30)	0.03
Median eGFR (IQR) – ml/min/1.73 m^2	87 (71 – 101)	73 (59 – 90)	63 (50 – 78)	<0.0001
NYHA class – (%)				<0.0003
II	216 (62)	201 (54)	180 (46)	
III	130 (37)	170 (45)	205 (52)	
IV	2 (1)	4 (1)	8 (2)	
Median duration of heart failure (IQR) – mo.	12 (7 – 40)	18 (8 – 72)	25 (11 – 75)	<0.0001
Coexisting conditions – (%)				
Hypertension	74 (21)	127 (34)	147 (37)	<0.0001
Permanent atrial fibrillation	45 (13)	86 (23)	117 (30)	<0.0001
Diabetes	54 (16)	83 (22)	76 (19)	0.08
Cause of heart failure – (%)				0.004
Idiopathic	274 (79)	286 (76)	289 (74)	
Valvular	12 (3)	10 (3)	19 (5)	
Hypertension	19 (5)	48 (13)	50 (13)	
Others	43 (12)	31 (8)	35 (9)	
Medication – (%)				
Beta-blocker	324 (93)	345 (92)	357 (91)	0.53
ACE inhibitor or ARB	343 (99)	361 (96)	373 (95)	0.03
MRA	228 (66)	217 (58)	201 (51)	0.0004
Amiodarone	15 (4)	27 (7)	24 (6)	0.25
CRT – (%)	181 (52)	210 (56)	254 (65)	0.002
Pre-existing pacemaker or CRT pacemaker – (%)	20 (6)	30 (8)	52 (13)	0.001

IQR denotes interquartile range, yr. years, no. numbers, ICD implantable cardioverter–defibrillator, BMI body mass index, NT-proBNP N-terminal pro–brain natriuretic peptide, LVEF left ventricular ejection fraction, eGFR estimated glomerular filtration rate, NYHA New York Heart Association, mo. month, ACE angiotensin-converting enzyme, ARB angiotensin-receptor blocker, MRA mineralocorticoid-receptor antagonist, and CRT cardiac resynchronization therapy.* The body-mass index is the weight in kilograms divided by the square of the height in meters.

Figure Legends

Figure 1. The age distribution for the study population from the DANISH trial. The different colours illustrate the age-tertiles.

Figure 2. The relation between age and risk of all-cause mortality regarding ICD-treatment or control. The figure shows the linear relationship between age and survival of patients by ICD implantation. On the x-axis age in years and on the y-axis the Hazard Ratio (HR). The dashed blue line indicates Hazard Ratio =1, which corresponds to an equal mortality in patients treated with ICD and control. The black line illustrates the risk for all-cause mortality according to age, and the dashed red lines are the 95% confidence interval. ICD denotes implantable cardioverter-defibrillator.

Figure 3. A selection impact curve to describe the expected survival in the full population under different age-based thresholds for ICD treatment assignment. Each point (black circle) on the figure shows the total 7-year survival in the population, if this age is chosen as cut-off for ICD treatment. The grey vertical lines are the 95% confidence interval. The estimate is non-parametric, as each point on the curve is a weighted combination of Kaplan-Meier estimates from the relevant treatment groups. The survival in the entire population is 75% when restricting ICD implementation to patients ≤70 years.

The figure does not show survival rates for patients with the specified ages along the horizontal axis, but rather the survival rate in the entire population when ICD use is assigned based on the different age thresholds.

Figure 4. All-cause mortality for the entire population in a) patients ≤70 years old and b) >70 years old. The blue lines represent the patients in the control group, and the red line represents patients randomized to ICD treatment. ICD denotes implantable cardioverter-defibrillator.

Figure 5. Cumulated event rates of causes of death in the control group for a) patients ≤70 years and b) >70 years. For both graphs the red lines are death caused by non-sudden death, and the blue lines are death caused by sudden cardiac death.

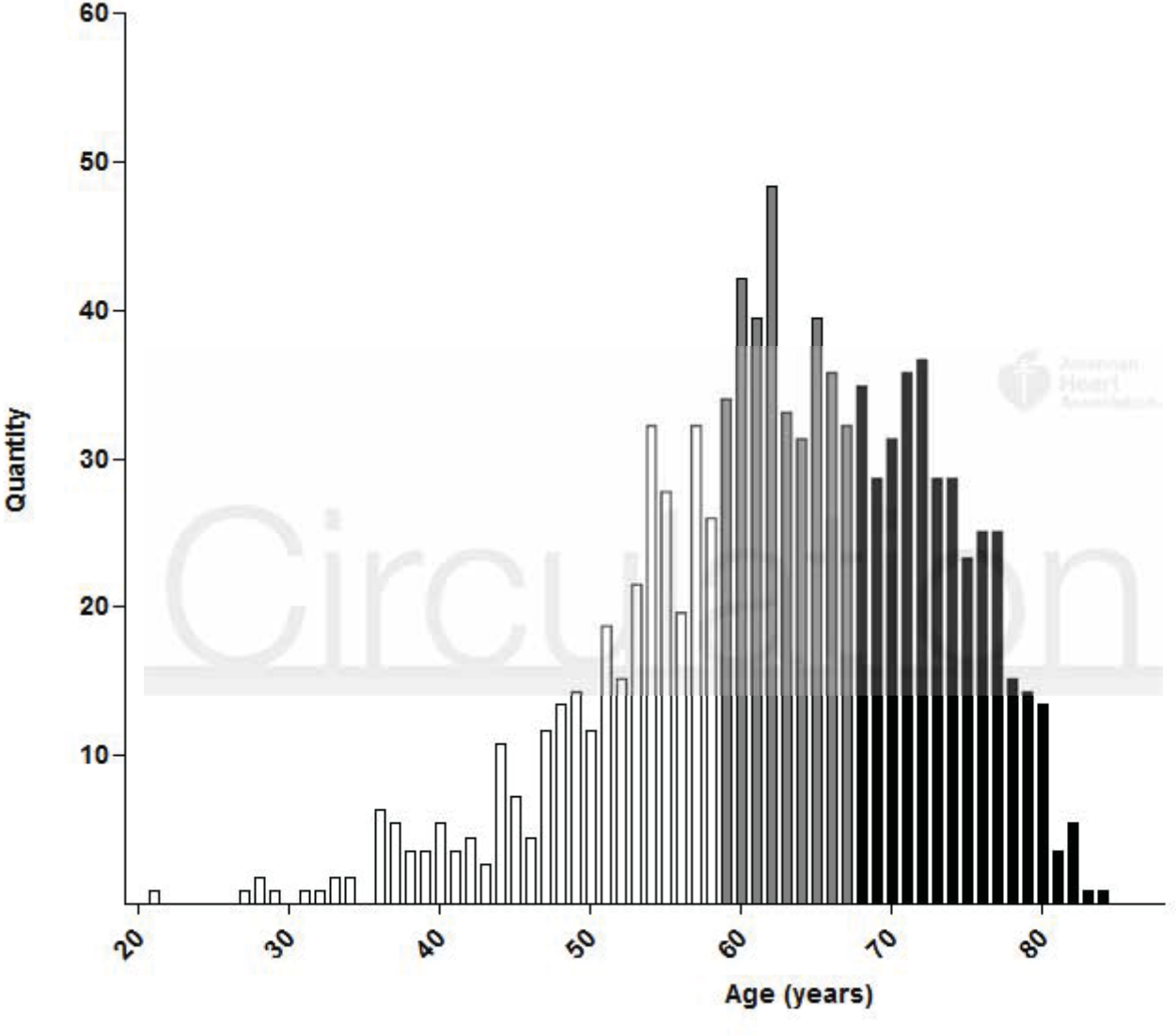
For patients younger than 70 years 96 patients died, 38 of sudden cardiac death and 58 of non-sudden death. For patients older than 70 years 35 patients died, 8 of sudden cardiac death and 27 of non-sudden death.

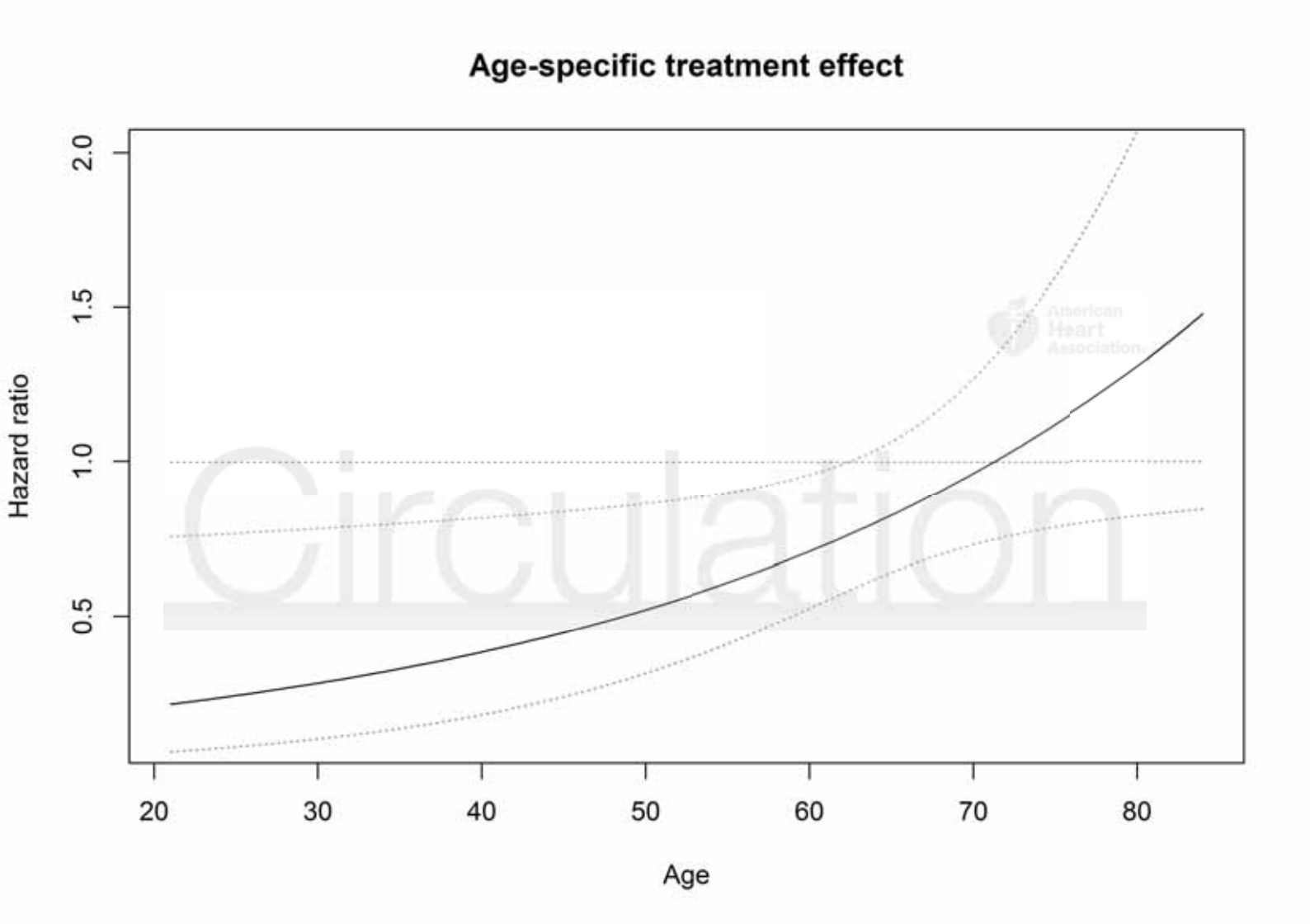
SCD denotes sudden cardiac death.

Figure 6. Cumulated event rates of causes of death in the ICD treated group for a) patients ≤70 years and b) >70 years. For both graphs the red lines are death caused by non-sudden death, and the blue lines are death caused by sudden cardiac death.

For patients younger than 70 years 65 patients died, 13 of sudden cardiac death and 52 of non-sudden death. For patients older than 70 years 55 patients died, 11 of sudden cardiac death and 44 of non-sudden death.

ICD denotes implantable cardioverter-defibrillator, SCD sudden cardiac death.


60
50
40
30
20
10
Quantity
20
30
40
50
60
70
80
Age (years)


Age-specific treatment effect
Hazard ratio
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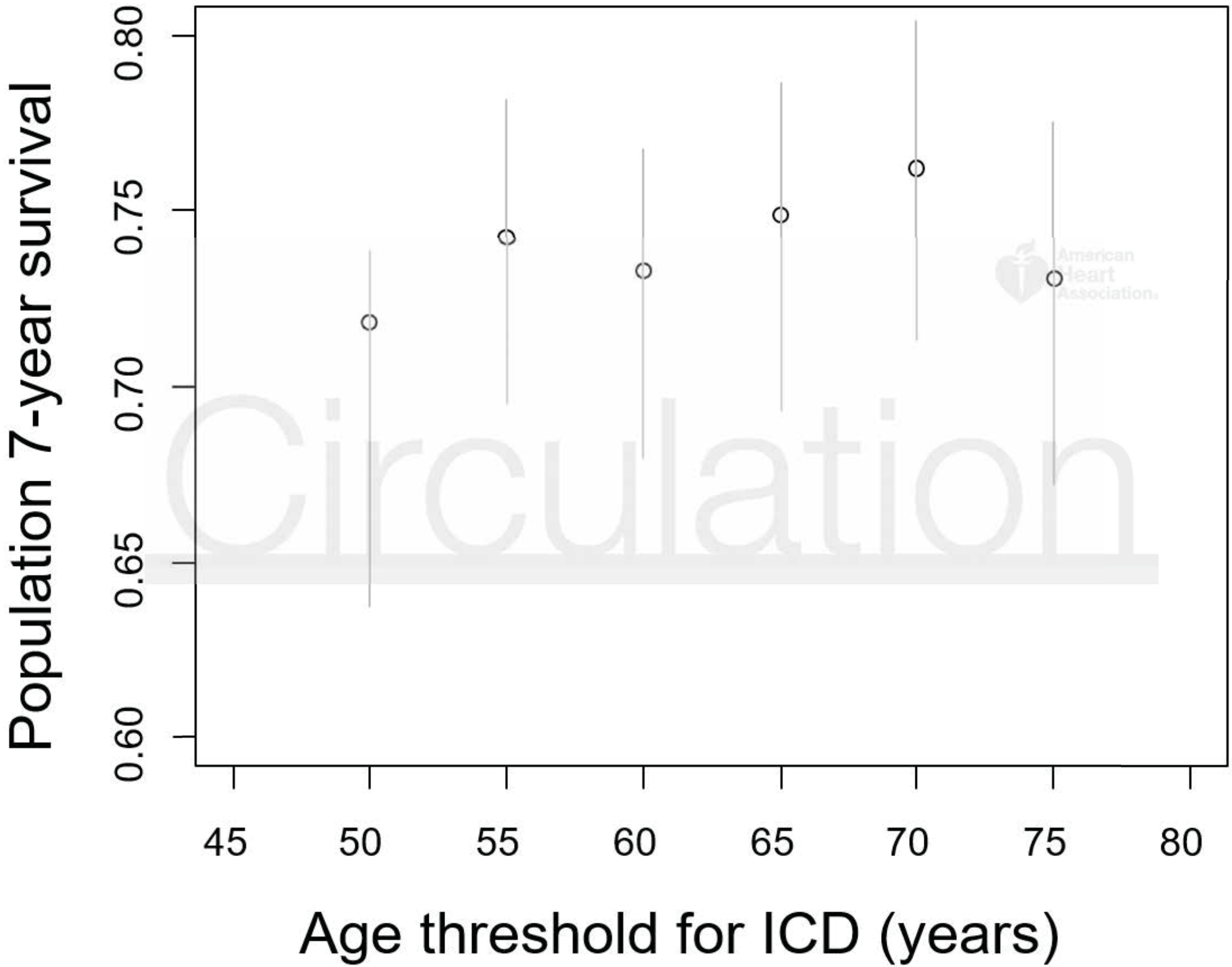
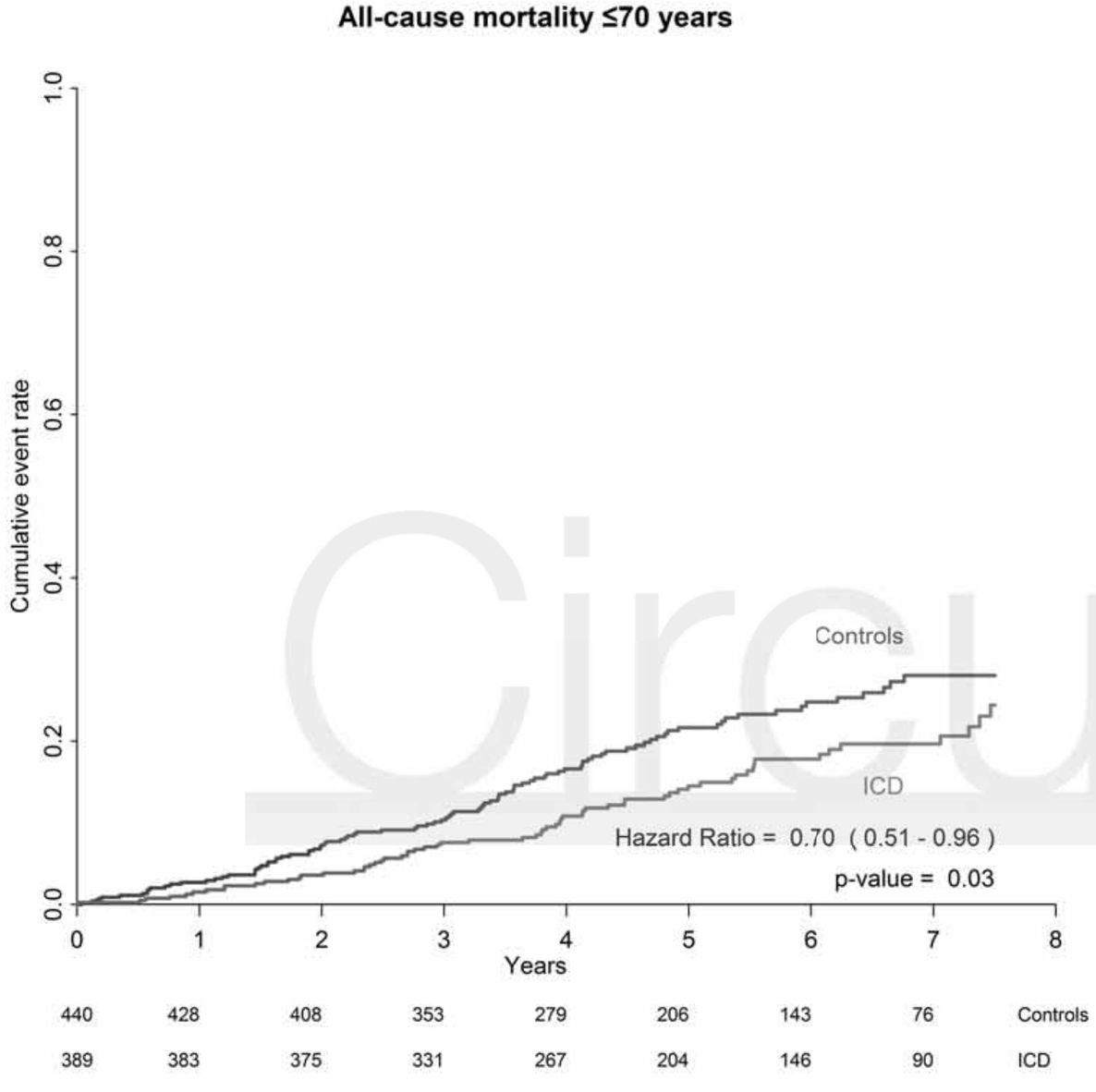
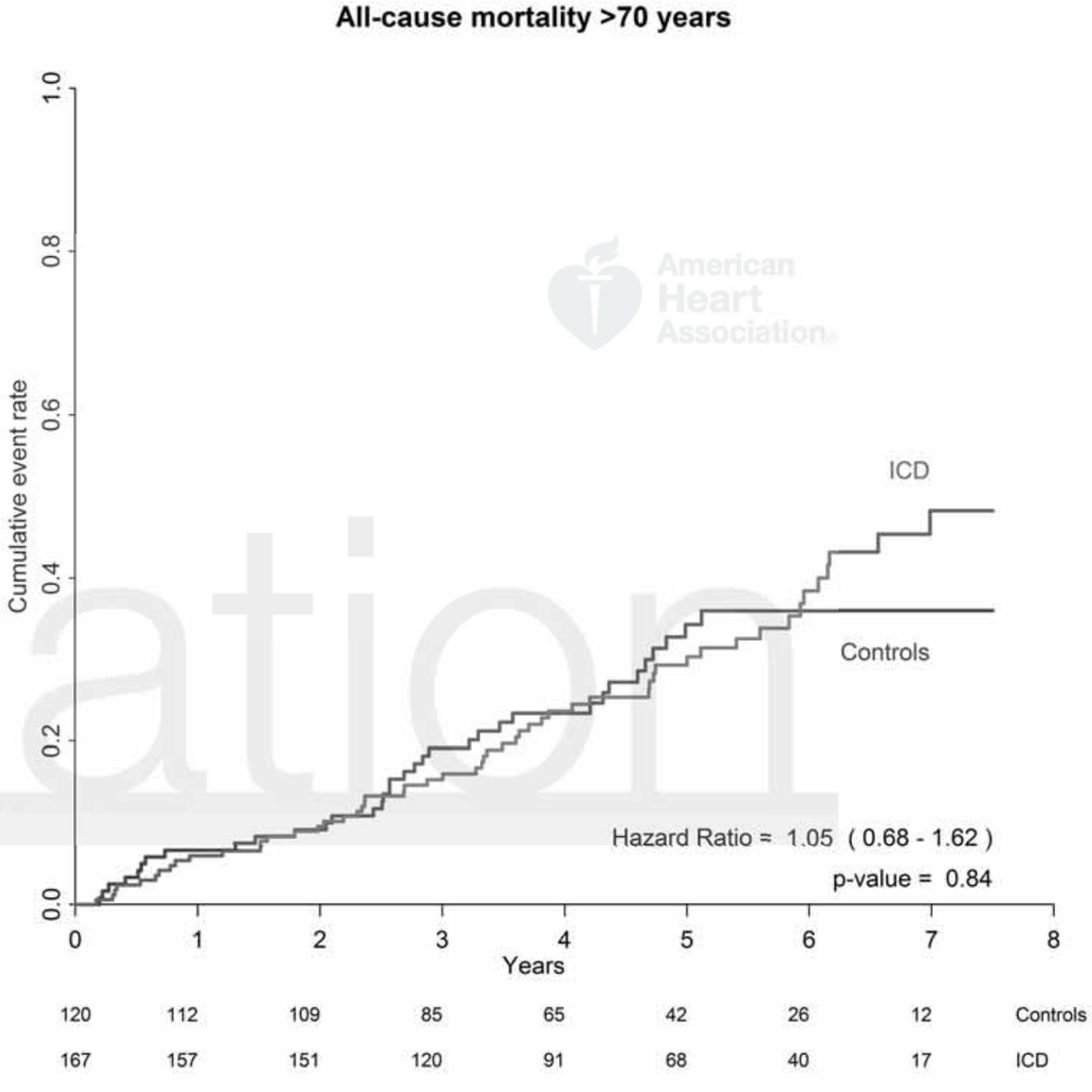
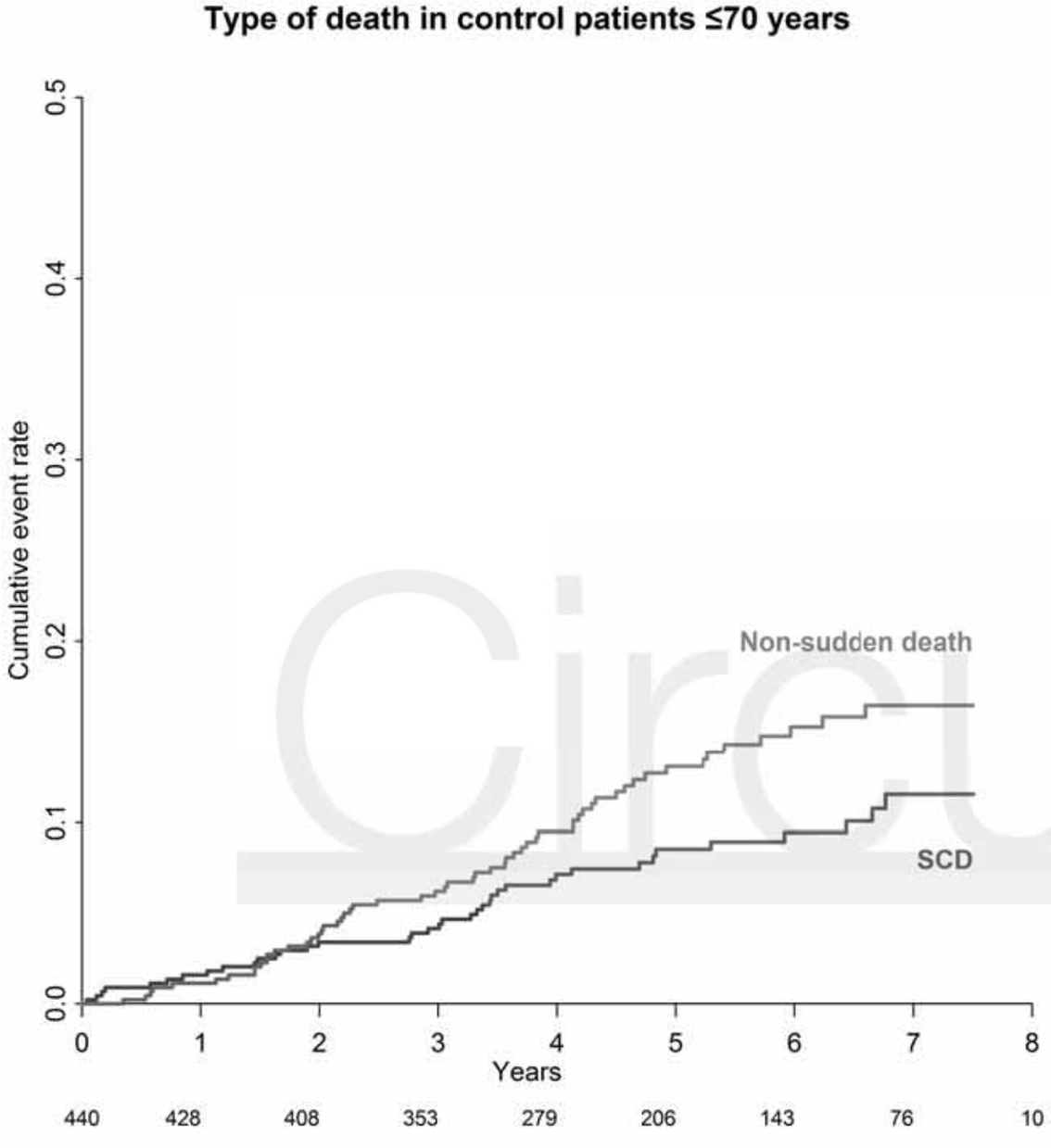
1.0
1.5
2.0
20
30
40
50
60
70
80
Age

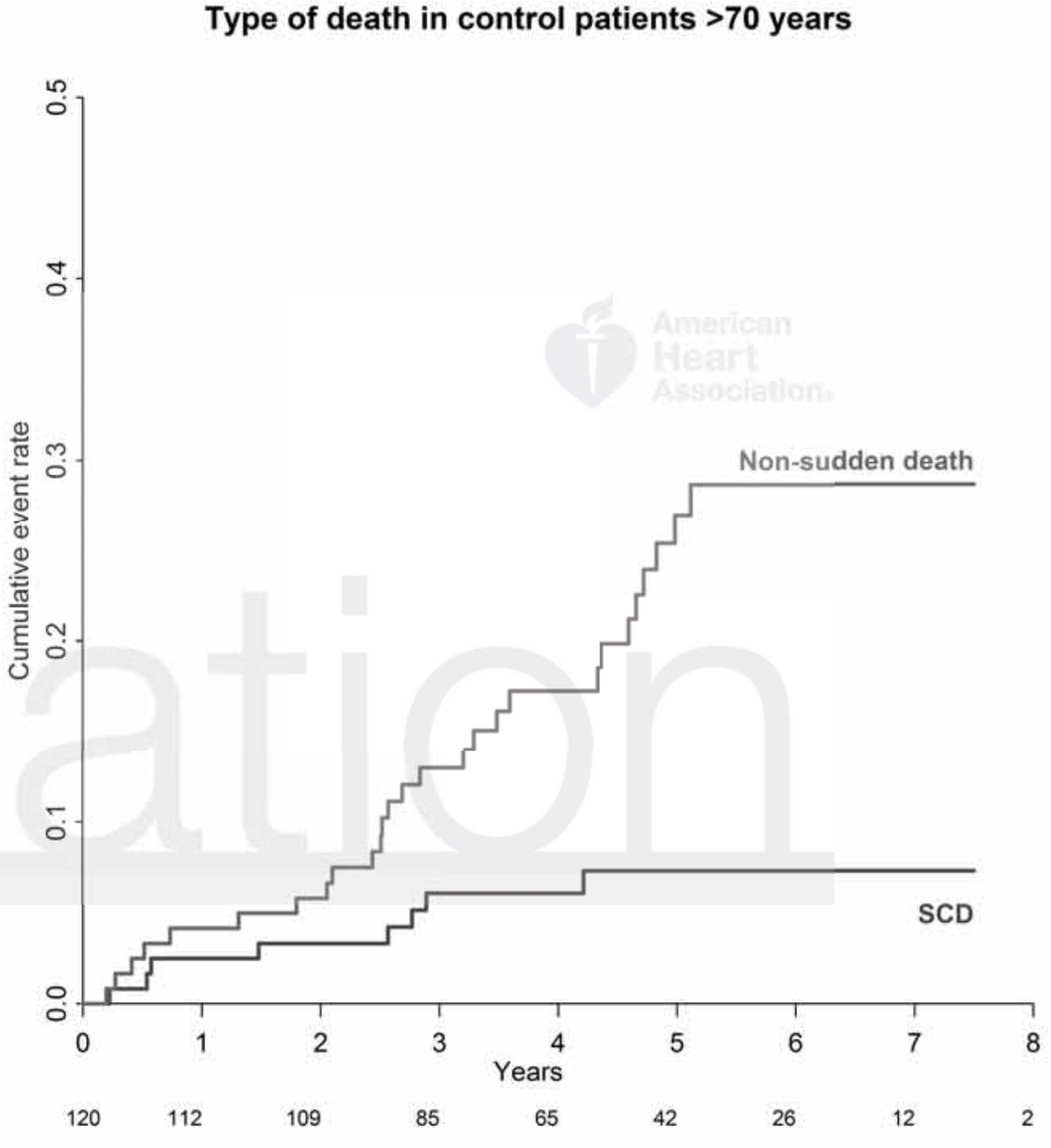
Treat if age <= x

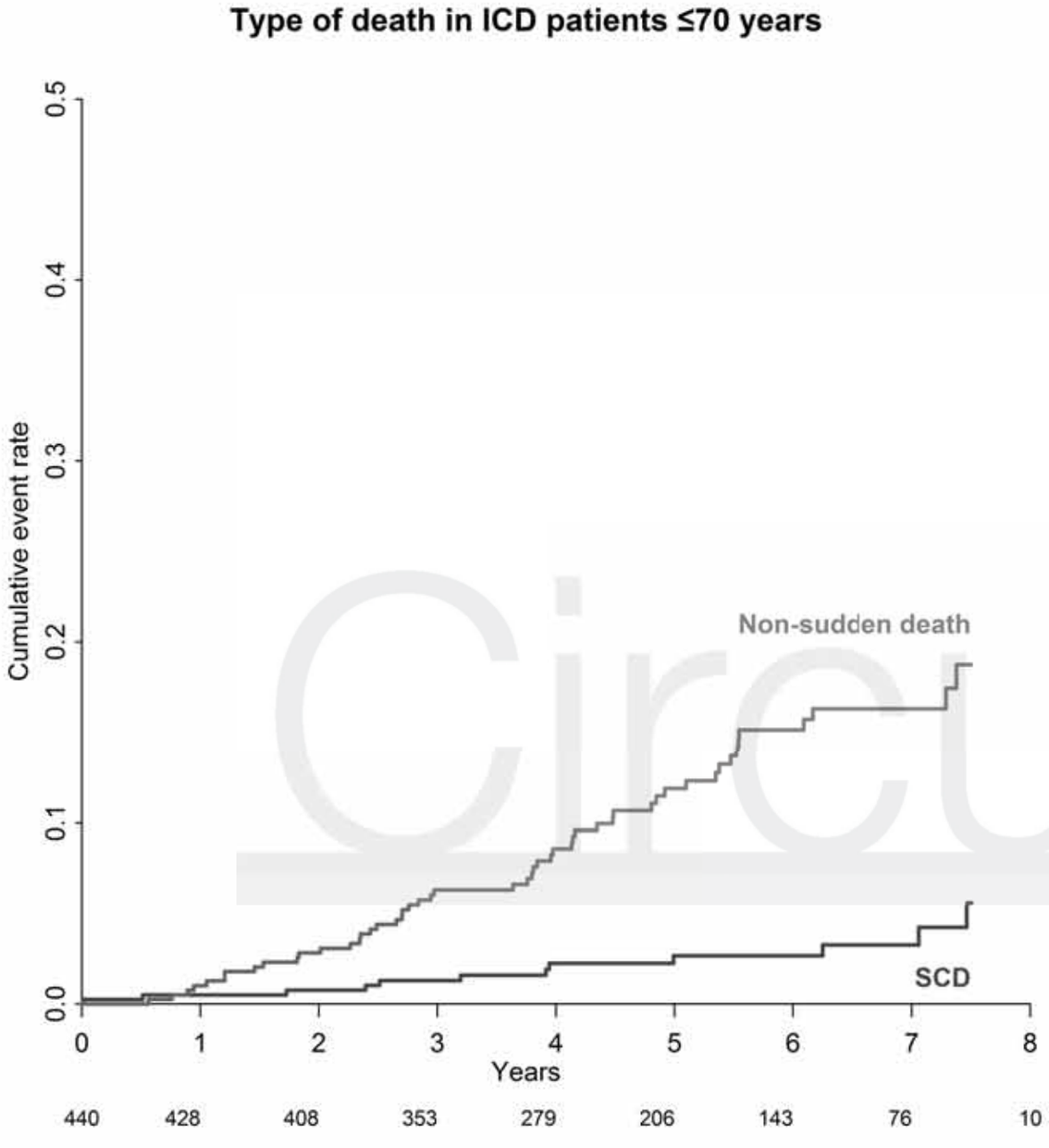


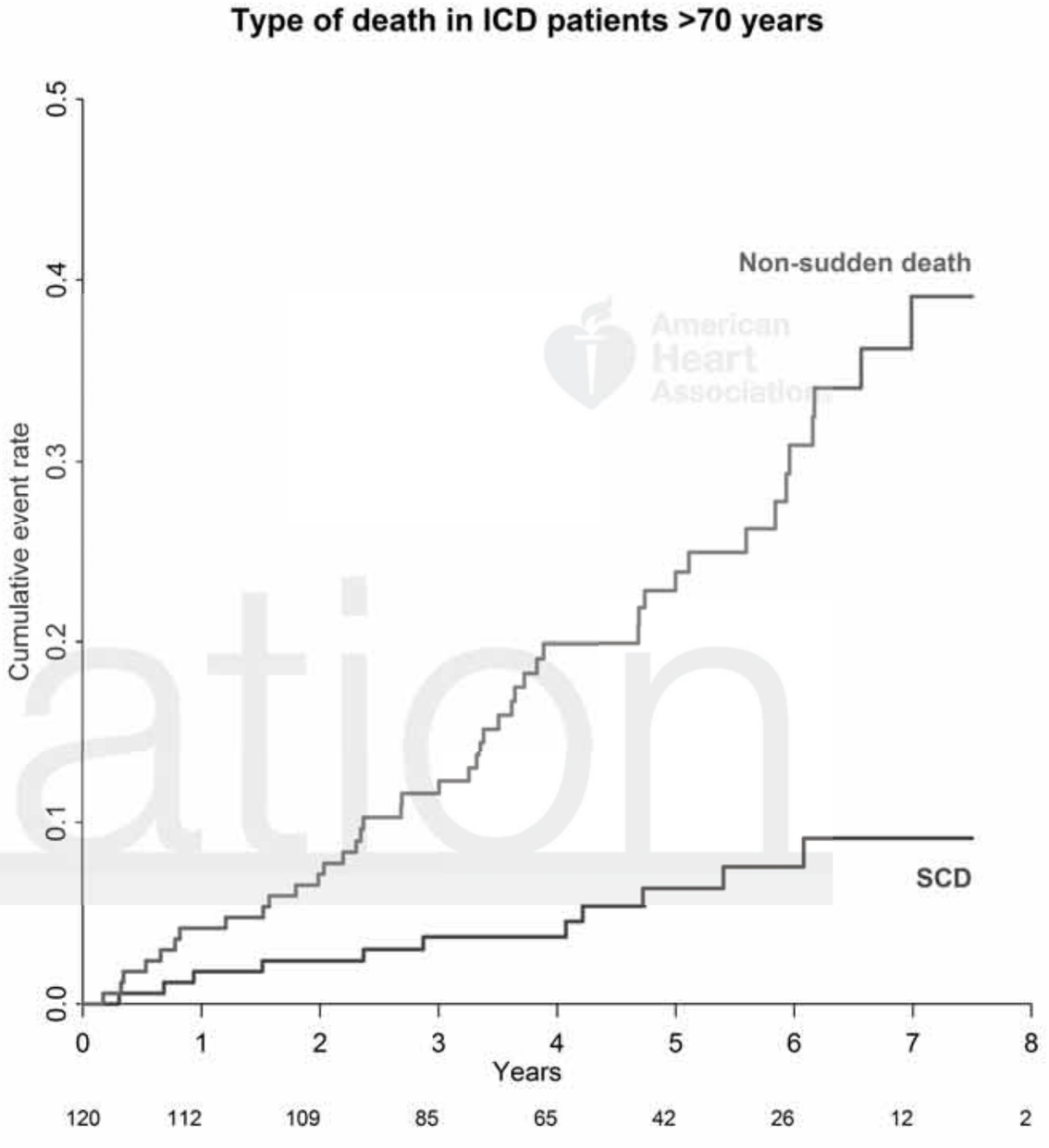












Supplement material

Supplement Table 1

	Age group 1 <59 yr. N =348		P-value	Age group 2 59 – <68 yr. N =375		P-value	Age group 3 ≥68 yr. N =393		P-value
	ICD N=167	Control N=181		ICD N=173	Control N=202		ICD N=216	Control N=177	
Median age (IQR) – yr.	52 (47 – 55)	53 (48 – 56)	0.13	63 (61 – 65)	63 (61 – 65)	0.75	73 (71 – 76)	73 (70 – 76)	0.42
Men – (%)	125 (75)	135 (75)	0.95	130 (75)	143 (71)	0.35	150 (69)	126 (71)	0.71
Median blood pressure (IQR) – mmHg									
Systolic	120 (109 – 136)	120 (108–138)	0.87	123 (110 – 139)	123 (110 – 136)	0.71	124 (110 – 141)	128 (115 – 139)	0.24
Diastolic	74 (68 – 83)	74 (69 – 84)	0.70	74 (65 – 81)	74 (65 – 80)	0.81	73 (65 – 80)	73 (65 – 81)	0.43
Median BMI* (IQR)	28 (24 – 32)	27 (24 – 30)	0.30	27 (24 – 31)	27 (24 – 30)	0.53	26 (24 – 29)	26 (23 – 29)	0.91
Median NT-pro BNP (IQR) – pg/ml	934 (479 – 1795)	712 (412 – 1572)	0.15	1364 (687 – 2307)	1211 (626 – 2279)	0.49	1379 (724 – 2699)	1484 (719 – 2573)	0.78
Median QRS duration (IQR) – msec	140 (104 – 165)	130 (100 – 162)	0.42	144 (116 – 165)	145 (110 – 166)	0.87	150 (120 – 168)	152 (119 – 165)	0.71
Median LVEF (IQR) – %	24 (19 – 30)	24 (18 – 29)	0.69	25 (20 – 30)	25 (20 – 30)	0.73	25 (20 – 30)	25 (20 – 30)	0.80
Median eGFR (IQR) – ml/min/1.73 m^2	87 (72 – 101)	85 (69 – 101)	0.43	71 (58 – 86)	75 (59 – 92)	0.20	63 (47 – 80)	63 (53 – 76)	0.97
NYHA class – (%)			0.11			0.16			0.08
II	97 (58)	119 (66)		96 (55)	105 (52)		104 (48)	76 (43)	
III	79 (42)	60 (33)		77 (45)	93 (46)		105 (49)	100 (57)	
IV	0 (0)	2 (1)		0(0)	4 (2)		7 (3)	1 (1)	
Median duration of heart failure (IQR) – mo.	12 (7 – 48)	12 (7 – 50)	0.78	21 (9 – 84)	18 (7 – 60)	0.28	30 (11 – 78)	24 (11 – 62)	0.40
Coexisting conditions – (%)									
Hypertension	35 (21)	39 (22)	0.89	54 (31)	73 (36)	0.30	92 (43)	55 (31)	0.02
Permanent AFLI	26 (16)	19 (11)	0.16	44 (35)	42 (21)	0.29	65 (30)	52 (29)	0.88
Diabetes	24 (14)	29 (16)	0.67	38 (22)	45 (22)	0.94	37 (17)	38 (21)	0.28
Cause of heart failure – (%)			0.62			0.59			0.32
Idiopathic	135 (81)	139 (77)		137 (79)	149 (74)		152 (70)	137 (77)	
Valvular	5 (3)	7 (4)		5 (3)	5 (2)		10 (5)	9 (5)	
Hypertension	10 (6)	9 (5)		19 (11)	29 (14)		33 (15)	17 (10)	

Others	17 (10)	26 (14)		12 (7)	19 (9)		21 (10)	14 (8)	
Medication – (%)									
Beta-blocker	155 (93)	169 (93)	0.84	156 (90)	189 (94)	0.23	198 (92)	159 (90)	0.53
ACE inhibitor or ARB	165 (99)	178 (98)	1	165 (95)	196 (97)	0.40	203 (94)	170 (96)	0.35
MRA	110 (66)	118 (65)	0.89	102 (59)	115 (57)	0.69	114 (53)	87 (49)	0.47
Amiodarone	8 (5)	7 (4)	0.67	15 (9)	12 (6)	0.31	11 (5)	13 (7)	0.35
CRT – (%)	88 (53)	93 (51)	0.81	95 (55)	115 (57)	0.69	139 (64)	115 (65)	0.90
Pre-existing PM or CRT-P – (%)	11 (7)	9 (5)	0.52	13 (8)	17 (8)	0.75	32 (15)	20 (11)	0.31

Baseline characteristics according to age tertiles and divided by randomisation to ICD or control.

ICD denotes implantable cardioverter–defibrillator, IQR interquartile range, yr. years, no. numbers, BMI body mass index, NT-proBNP N-terminal pro–brain natriuretic peptide, LVEF left ventricular ejection fraction, eGFR estimated glomerular filtration rate, NYHA New York Heart Association, mo. month, AFLI atrial fibrillation, ACE angiotensin-converting enzyme, ARB angiotensin-receptor blocker, MRA mineralocorticoid-receptor antagonist, CRT cardiac resynchronization therapy, PM pacemaker, and CRT-P cardiac resynchronization therapy pacemaker.

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

Supplement Table 2

	Age < 68 years N= 723		Age ≥ 68 years N= 393		P-value
	ICD N= 340	Control N= 383	ICD N= 216	Control N= 177	
Median age (IQR) – yr.	59 (52 – 63)	59 (54 – 63)	73 (71 – 76)	73 (70 – 76)	–
Men – (%)	255 (75)	278 (73)	150 (69)	126 (71)	0.21
Median blood pressure (IQR) – mmHg					
Systolic	121 (110 – 136)	122 (110 – 137)	124 (110 – 142)	128 (115 – 139)	0.006
Diastolic	74 (66 – 82)	74 (67 – 82)	73 (65 – 80)	73 (65 – 81)	0.03
Median BMI* (IQR)	27 (24 – 31)	27 (24 – 30)	26 (24 – 29)	26 (23 – 29)	0.001
Median NT-pro BNP (IQR) – pg/ml	1120 (528 – 2142)	975 (498 – 1956)	1379 (724 – 2699)	1484 (719 – 2573)	<0.0001
Median QRS duration (IQR) – msec	141 (108 – 165)	140 (106 – 164)	150 (120 – 168)	152 (119 – 165)	0.0006
Median LVEF (IQR) – %	25 (20 – 30)	25 (20 – 30)	25 (20 – 30)	25 (20 – 30)	0.07
Median eGFR (IQR) – ml/min/1.73 m^2	79 (63 – 95)	79 (63 – 96)	63 (47 – 80)	63 (53 – 76)	<0.0001
NYHA class – (%)					0.0003
II	193 (57)	224 (58)	104 (48)	76 (43)	
III	147 (43)	153 (40)	105 (49)	100 (57)	
IV	0 (0)	6 (2)	7 (3)	1 (1)	
Median duration of heart failure (IQR) – mo.	14 (8 – 61)	14 (7 – 54)	30 (11 – 78)	24 (11 – 62)	<0.0001
Coexisting conditions – (%)					
Hypertension	89 (26)	112 (29)	92 (43)	55 (31)	0.001
Permanent AFLI	70 (21)	61 (16)	65 (30)	52 (29)	<0.0001
Diabetes	62 (18)	74 (19)	37 (17)	38 (21)	0.91
Cause of heart failure – (%)					0.11
Idiopathic	272 (80)	288 (75)	152 (70)	137(77)	
Valvular	10 (3)	12 (3)	10 (5)	9 (5)	
Hypertension	29 (9)	38 (10)	33 (15)	17 (10)	
Others	29 (9)	45 (12)	21 (10)	14 (8)	
Medication – (%)					
Beta-blocker	311 (91)	358 (93)	198 (92)	159 (90)	0.32
ACE inhibitor or ARB	220 (97)	374 (98)	203 (94)	170 (96)	0.03
MRA	212 (62)	233 (61)	114 (53)	87 (49)	0.0008
Amiodarone	23 (7)	19 (5)	11 (5)	13 (7)	0.84
CRT – (%)	183 (54)	208 (54)	139 (64)	115 (65)	0.0007
Pre-existing pacemaker or CRT pacemaker – (%)	24 (7)	26 (7)	32 (15)	20 (11)	0.0005

Baseline characteristics according to age younger or older than 68 years and divided by randomisation to ICD or control. ICD denotes implantable cardioverter–defibrillator, IQR interquartile range, yr. years, no. numbers, BMI body mass index, NT-proBNP N-terminal pro–brain natriuretic peptide, LVEF left ventricular ejection fraction, eGFR estimated glomerular filtration rate, NYHA New York Heart Association, mo. month, AFLI atrial fibrillation, ACE angiotensin-converting enzyme, ARB angiotensin-receptor blocker, MRA mineralocorticoid-receptor antagonist, and CRT cardiac resynchronization therapy.

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

Supplement Table 3

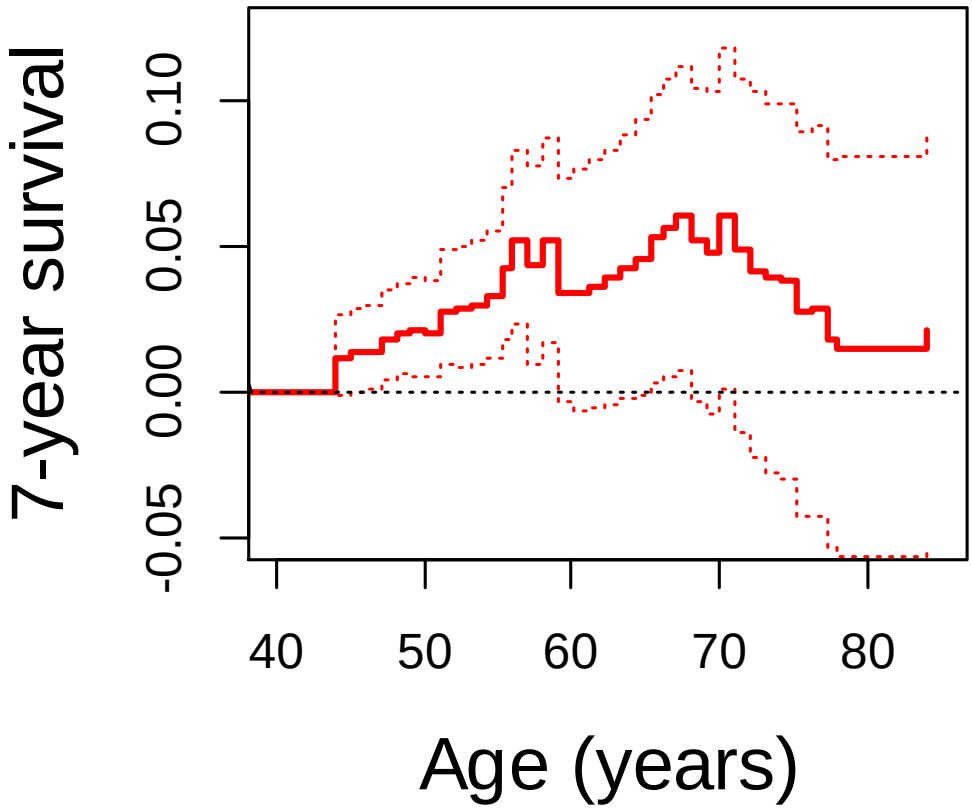
	Age ≤ 70 years N=829		Age > 70 years N=287		P-value
	ICD N=389	Control N=440	ICD N=167	Control N=120	
Median age (IQR) – yr.	60 (53 – 65)	60 (54 – 65)	74 (72 – 77)	75 (73 – 77)	–
Men – (%)	290 (75)	316 (72)	115 (69)	88 (73)	0.44
Median blood pressure (IQR) – mmHg					
Systolic	121 (110 – 136)	123 (110 – 137)	127 (110 – 143)	130 (114 – 140)	0.009
Diastolic	74 (66 – 81)	74 (67 – 82)	73 (64 – 80)	74 (64 – 80)	0.05
Median BMI* (IQR)	27 (24 – 31)	27 (24 – 30)	26 (23 – 29)	26 (24 – 29)	0.0001
Median NT-pro BNP (IQR) – pg/ml	1120 (528 – 2135)	999 (510 – 1964)	1744 (776 – 2859)	1663 (716 – 2816)	<0.0001
Median QRS duration (IQR) – msec	141 (110 – 165)	143 (108 – 164)	152 (124 – 170)	151 (117 – 166)	0.0003
Median LVEF (IQR) – %	25 (20 – 30)	25 (20 – 30)	25 (20 – 30)	25 (20 – 30)	0.47
Median eGFR (IQR) – ml/min/1.73 m^2	77 (62 – 94)	77 (61 – 95)	61 (46 – 78)	60 (49 – 74)	<0.0001
NYHA class – (%)					0.0008
II	219 (56)	251 (57)	78 (47)	49 (41)	
III	169 (43)	182 (41)	83 (50)	71 (59)	
IV	1 (0)	7 (2)	6 (4)	0 (0)	
Median duration of heart failure (IQR) – mo.	18 (8 – 63)	16 (8 – 57)	30 (12 – 78)	20 (10 – 61)	0.002
Coexisting conditions – (%)					
Hypertension	110 (28)	127 (29)	71 (43)	40 (33)	0.002
Permanent AFLI	81 (21)	75 (17)	54 (32)	38 (32)	<0.0001
Diabetes	74 (19)	85 (19)	25 (15)	27 (23)	0.69
Cause of heart failure – (%)					0.02
Idiopathic	313 (80)	335 (76)	111 (67)	90 (75)	
Valvular	10 (3)	15 (3)	10 (6)	6 (5)	
Hypertension	35 (9)	43 (10)	27 (16)	12 (10)	
Others	31 (8)	47 (11)	19 (11)	12 (10)	
Medication – (%)					
Beta-blocker	356 (92)	411 (93)	153 (92)	106 (88)	0.22
ACE inhibitor or ARB	378 (97)	430 (98)	155 (93)	114 (95)	0.003
MRA	246 (63)	265 (60)	80 (48)	55 (46)	<0.0001
Amiodarone	27 (7)	22 (5)	7 (4)	10 (8)	0.99
CRT – (%)	209 (54)	241 (55)	113 (68)	82 (68)	<0.0001
Pre-existing pacemaker or CRT pacemaker – (%)	27 (7)	30 (7)	29 (17)	16 (33)	<0.0001

Baseline characteristics according to age younger or older than 70 years and divided by randomisation to ICD or control.

ICD denotes implantable cardioverter–defibrillator, IQR interquartile range, yr. years, no. numbers, BMI body mass index, NT-proBNP N-terminal pro–brain natriuretic peptide, LVEF left ventricular ejection fraction, eGFR estimated glomerular filtration rate, NYHA New York Heart Association, mo. month, AFLI atrial fibrillation, ACE angiotensin-converting enzyme, ARB angiotensin-receptor blocker, MRA mineralocorticoid-receptor antagonist, and CRT cardiac resynchronization therapy.

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

Supplement Figure 1

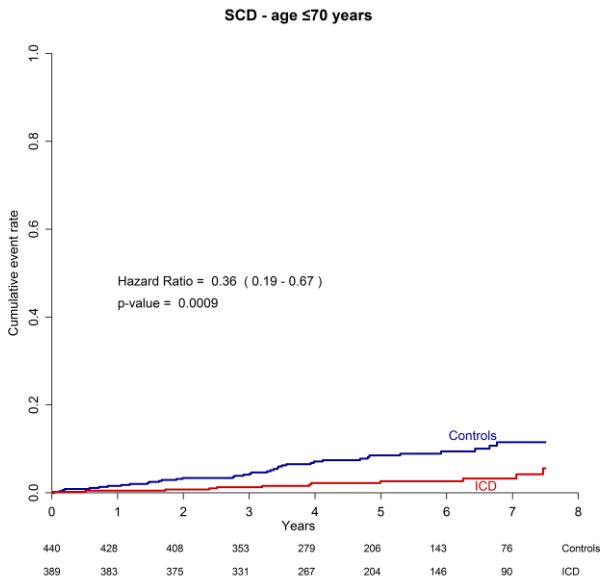


A selection impact curve to describe the expected survival in the full population under different age-based thresholds for ICD treatment assignment. Each point (black circle) on the figure shows the total 7-year survival in the population, if this age is chosen as cut-off for ICD treatment. The grey vertical lines are the 95% confidence interval. The estimate is non-parametric, as each point on the curve is a weighted combination of Kaplan-Meier estimates from the relevant treatment groups. The survival in the entire population is 75% when restricting ICD implementation to patients ≤70 years.

The figure does not show survival rates for patients with the specified ages along the horizontal axis, but rather the survival rate in the entire population when ICD use is assigned based on the different age thresholds.

Supplement Figure 2

a)



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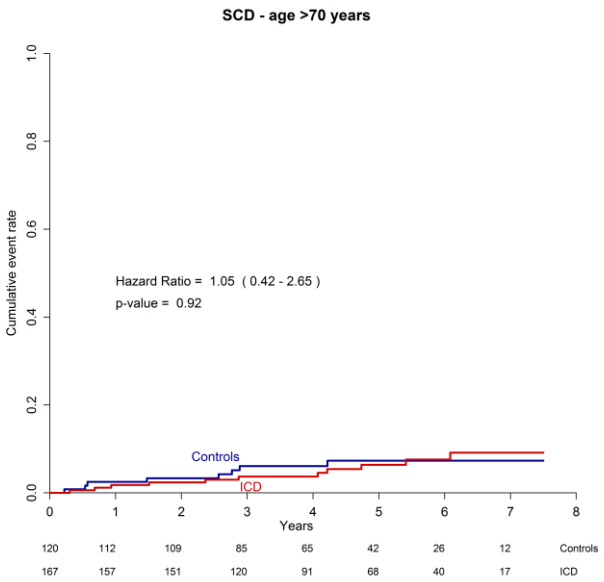
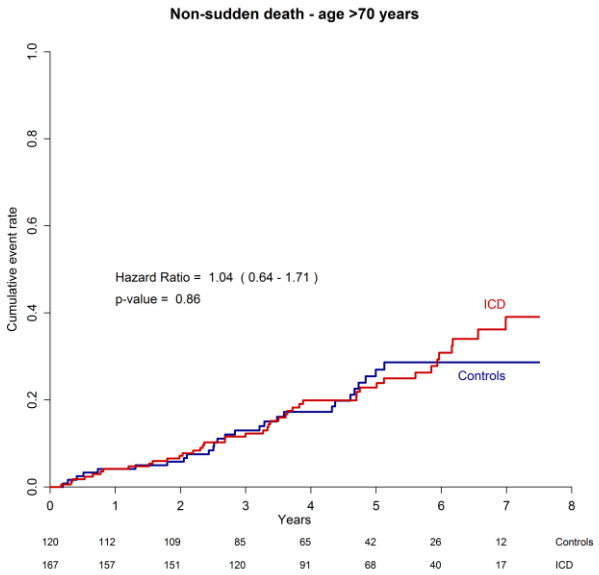


Cumulated event rates of sudden cardiac death according to randomisation for patients a) ≤70 years, and b) >70 years. For both graphs the red lines are patients randomised to ICD, and the blue lines are patients in the control group.
For patients younger than 70 years 51 died from SCD, 13 in the ICD group and 38 in the control group. For patients older than 70 years 19 died from SCD, 11 in the ICD group and 8 in the control group.
SCD denotes sudden cardiac death, ICD implantable cardioverter-defibrillator.

Supplement Figure 3

a)

b)



Cumulated event rates of non-sudden death according to randomisation for patients a) ≤70 years, and b) >70 years. For both graphs the red lines are patients randomised to ICD, and the blue lines are patients in the control group.
For patients younger than 70 years 110 died from non-sudden death, 52 in the ICD group and 58 in the control group. For patients older than 70 years 71 died from non-sudden death, 44 in the ICD group and 27 in the control group.
ICD denotes implantable cardioverter-defibrillator.