Mortality after cardioverter-defibrillator replacement: results of the DECODE SUrvival SCore Index (DECODE-SUSCI)

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Short Title: Mortality after cardioverter-defibrillator replacement

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Abstract

Background: Device replacement is the ideal time to reassess health care goals regarding continuing ICD therapy. Only few data are available on the decision making at this time.

Objective: To identify factors associated with poor prognosis at the time of ICD replacement and to develop a prognostic index able to stratify those patients at risk of dying early.

Methods: Detect long-term complications after ICD replacement (DECODE) was a prospective, single-arm, multicenter cohort study aimed at estimating long-term complications in a large population of patients who underwent ICD/CRT-D replacement. Potential predictors of death were investigated, and all these factors were gathered into a survival score index (SUSCI).

Results: We included 983 consecutive patients (median age 71 years, 76% male, 55% ischemic, 47% CRT-D). During a median follow-up time of 761[628-904] days, 114 (12%) patients died. At multivariate Cox regression analysis NYHA class III/IV, Ischemic cardiomyopathy, BMI<26, insulin administration, age≥75 years, history of AF and a hospitalization within 30 days before ICD replacement remained associated with death. The SUSCI score showed a good discriminatory power with an HR=2.6 (95%CI:2.2-3.1, p<0.0001). The risk of death increased according to the severity of the risk profile ranging from 0% - low-risk - to 47% - high-risk -.

Conclusions: A simple score that includes a limited set of variables appears to be predictive for total mortality in an unselected, real-world population undergoing ICD replacement. Evaluation of the patient's profile may assist in predicting vulnerability and should prompt individualized options, especially for high-risk patients.

Keywords: Replacement, Implantable cardioverter defibrillator, Prognostic index, Outcome, ICD indications

Introduction

Implantable cardioverter-defibrillation (ICD) therapy has proved to increase the survival of patients at risk of sudden cardiac death (SD) due to ventricular tachyarrhythmias[1]. After implantation, in order to ensure continuing therapy, ICD devices may require replacement because of battery depletion, device malfunction or the need for upgrade to a more advanced system. In addition, the progression of comorbidities and neurological deterioration with aging can severely affect patients' clinical conditions and quality of life within battery service-life[2]. Conversely, during the same period, some of these patients can be no longer deemed at risk of sudden death, while others may have a very limited prognosis that negates the potential benefit of ICD therapy. Moreover, the risk of surgical complications of ICD/CRTD replacement can significantly worsen the outcome of the frailest[3, 4]. Thus, device end-of-life is the ideal time to reassess healthcare goals regarding the continuation of ICD therapy. While a large body of information supports the decision to implant an ICD *de novo*[1], far fewer data are available to guide decision-making at the time of device replacement. Only a few studies have estimated the survival rate and the main risk factors associated with death after ICD replacement or upgrade[5-9].

The present study aims to assess the clinical characteristics and the main risk factors associated with mortality after ICD replacement or upgrade in the DECODE Registry, and to devise a prognostic score index able to identify those at the highest and earliest risk of death.

Methods

Patient Population and Study Design

The DECODE Registry was a prospective, single-arm, multicenter, cohort study aimed at providing an estimate of medium- to long-term adverse events (AEs) in a large population of ICD patients undergoing replacement/upgrade of an ICD or cardiac resynchronization therapy defibrillator (CRT-D), and at detecting the factors possibly associated with AEs. From March 2013 to May 2015, 983 consecutive patients aged≥18 years undergoing replacement or upgrade of a previously

implanted transvenous ICD/CRTD at 36 participating Italian centers were enrolled in the DECODE Registry[9]. Replacements/upgrades were performed on the basis of common guideline recommendations[1] and according to the investigators' clinical assessment. ICD programming at the time of replacement was performed as already reported in our previous publication[10]. Totally subcutaneous ICDs were not considered in the DECODE registry. No patients underwent downgrade to CRT-P or pacemaker device. The design of the study has been published previously[9, 11]. The study protocol complied with the Declaration of Helsinki and was approved by the local ethics committee at each participating center. All patients provided written informed consent for data storage and analysis.

The primary endpoint of the study was 24-month all-cause mortality. Secondary endpoints were: rates of appropriate ICD therapy delivery after replacement in the total population and in the patient subgroups constructed according to the survival score index (SUSCI), and the association between appropriate ICD therapy delivery and death. Deaths were classified as: 1) *cardiovascular* (CV) (sudden cardiac death, due to acute myocardial infarction, heart failure, stroke, pulmonary embolism, endocarditis, surgical cardiovascular procedures), 2) *non-cardiovascular* (non-CV) (cancer, kidney disease, pulmonary disease, liver disease, infection, other), 3) *undetermined.* An independent blinded committee analyzed the causes of death on the basis of the hospital charts for in-hospital deaths, or by direct contact with the patient's general practitioner or relatives, or from autopsy findings, when available.

According to the variables found to be predictive of mortality on multivariable Cox regression analysis, the DECODE Survival Score Index (SUSCI) was devised. Hazard ratios reflected the relative contribution of each variable to the risk of death, and were combined into a final aggregate score according to the equation:

SUSCI Score=((1.9359^ICM)+(2.2583^AGE≥75)+(2.0295^INS)
+(2.2369^NYHA)+(2.293^HOSP)+(1.7199^AF)+(2.1744^BMI)).

The 7 variables identified as predictive of survival/death were: 1) ICM (Ischemic cardiomyopathy [0=No; 1=Yes]); 2) AGE (Age at the time of device replacement/upgrade≥75 years [0=No; 1=Yes]); 3) INS (Insulin-dependent diabetes [0=No; 1=Yes]); 4) NYHA (NYHA Class [0=≤2; 1=≥3]); 5) HOSP (hospitalization in the 30 days prior to the procedure [0=No; 1=Yes]); 6) AF (history of atrial fibrillation [0=No; 1=Yes]), and 7) BMI (BMI<26 [0=No; 1=Yes]). For the purpose of analysis, five groups of increasing risk were constructed according to the SUSCI (<1, 1-4, 4-7, 7-10 and >10) in such a way as to form groups of adequate sample size.

Statistical analysis

Continuous data are expressed as mean ± standard deviation or median values with interquartile range, as appropriate, for all variables. Continuous variables were compared by means of Student's t-test, analysis of variance, or non-parametric test (median test or Mann–Whitney U test), as appropriate. Categorical data were compared by means of the χ^2 test (Pearson, Yates or Fisher's exact test, as appropriate).

The Kaplan–Meier method was used to analyze estimates of time to death during follow-up; differences between groups were analyzed by means of the log-rank test. Hazard ratios (HRs) and their 95% confidence intervals (CIs) were computed by means of Cox regression models, in which baseline parameters were considered as fixed covariates and combined endpoint events were considered as time-dependent covariates. After checking for collinearity, we included in the multivariate Cox models any variable with a *p*-value<0.05 on univariate analysis. A *p*-value<0.05 was considered significant for all tests. All statistical analyses were performed by means of STATISTICA software, version 7.1 (StatSoft, Inc., Tulsa, OK, USA).

Results

Study population

The DECODE registry enrolled 983 patients at 36 Italian centers; 804 (82%) underwent ICD generator replacement only, whereas 179 (18%) underwent upgrade to a device capable of

additional functionality as a result of the addition of transvenous lead(s). Of them, 96 (54%) patients underwent upgrade for clinical reasons (83 to a CRT-D device due to HF symptoms prior to replacement and 13 to a DC device due to addition of an atrial lead alone) and 83 (46%) patients underwent upgrade due to lead failure (3 RA-only, 60 RV-only, 18 LV-only and 2 RV plus LV leads added). Demographics and baseline characteristics of the study population are summarized in Table 1.

Mortality after ICD replacement/upgrade

During a median follow-up period of 761[628-904] days, 114 (11.6%) patients died (none because of refractory ventricular tachyarrhythmias) and 5 (0.5%) underwent heart transplantation: these latter 5 were excluded from the survival analysis at the time of heart transplantation and considered as dropped-outs. No deaths occurred during the replacement procedure. Sixty-five (57%) patients died of CV causes, with a marked prevalence of heart failure deaths. Details of the causes of death are shown in Table 2.

Prediction of death

On multivariate Cox regression analysis, adjusted for baseline confounders, only age≥75 years (HR=2.26; 95%CI: 1.54 to 3.32, p<0.0001), BMI<26 (HR=2.17, 95%CI: 1.48 to 3.2, p<0.0001), ischemic cardiomyopathy (HR=1.94, 95%CI: 1.25 to 3.0, p<0.0001), NYHA Class≥III (HR=2.24, 95%CI: 1.52 to 3.29, p<0.0001), history of AF (HR=1.74, 95%CI: 1.19 to 2.52, p=0.0041), hospitalization within 30 days prior to ICD replacement (HR=2.29, 95%CI: 1.38 to 3.81, p=0.0014) and insulin therapy (HR=2.03, 95%CI: 1.28 to 3.22, p=0.0028) remained associated with death (Table 3). The same findings were confirmed when considering replacement population only, as reported in Supplementary Table S1. The Kaplan–Meier estimates of time to death from any cause, according to independent risk factors, and the survival curve of the whole population are depicted in Figure 1, panels A-H.

Risk stratification according to SUSCI prediction score

Patients were stratified into five subgroups according to the SUSCI risk score level: 84 (8.5%) with a score lower than 1 point were classified at "low-risk", 347 (35.3%) with a score between 1 and 4 points at "low-to-intermediate-risk", 410 (41.7%) with a score between 4 and 7 points at "intermediate-risk", 106 (10.8%) with a score between 7 and 10 points at "intermediate-to-high-risk" and 36 (3.7%) with a score more than 10 points at "high-risk". The median SUSCI score was 4.15[2.18-6.21]. The SUSCI score (for each level of risk) showed a good discriminatory power, with an HR of 2.61 (95%CI: 2.17 to 3.15, p<0.0001). On plotting mean survival according to the SUSCI score, the overall mortality risk over 24 months of follow-up increased according to the severity of the risk profile (Figure 2). The time to death was significantly shorter among patients with a score >4.2 points – median value – (log-rank test, p<0.0001; HR=9.9 (95%CI: 5.36 to 18.46, p<0.0001); a mortality rate of 20.5% was recorded in patients with scores >4.2, and of 2.3% in those with scores <4.2). The high-risk group showed a 31% and 44% mortality at 12 and 18 months respectively.

ICD therapy during follow-up

During the 24-month follow-up period, 190 patients (19.3%) received at least one ICD appropriate therapy, and 28 (2.9%) at least one inappropriate ICD therapy. The rate of appropriate ICD therapy did not differ among the 5 SUSCI risk score subgroups (p=0.4038). Neither appropriate ICD therapy nor inappropriate ICD therapy after ICD replacement/upgrade was significantly associated with the primary endpoint of death (HR=0.81, 95%CI: 0.5 to 1.33, p=0.4132 for appropriate ICD therapy; HR=0.89, 95%CI: 0.29 to 2.79, p=0.8454 for inappropriate ICD therapy). However, in patients who died, appropriate ICD therapy rate decreased as the "risk score" level decreased (Figure 3). In the Kaplan-Meier curves, performed to compare total mortality and appropriate ICD therapy delivery rates over time, it appears that in the "high-risk" group, contrarily to the others, total mortality is much higher than that observed in the remaining groups notwithstanding similar rates of ICD therapy delivery (Supplementary Figure S1).

Discussion

This sub-analysis of the DECODE Registry focuses on the intriguing topic of mortality following ICD/CRTD replacement/upgrade. Owing to careful data collection, the cause of death can be reliably interpreted, unlike in larger registries, which are mainly based on administrative data[6, 7, 11]; this enables subgroups to be classified according to a risk score that pinpoints the most severe clinical profile. Indeed, the DECODE SUSCI Risk Score can identify subgroups with a 31% and 44% mortality risk at 12 and 18 months, respectively. This finding should be carefully evaluated before undertaking ICD replacement.

Our study population was contemporary and had a clinical profile comparable to patients in the large NCDR registry[6] (average EF about 35%, 47% of patients having a CRTD). Two-year mortality rate was around 12%, which is comparable to the NCDR rate (9.8% and 27% at 1 and 3 years, respectively), the Ontario ICD Data Base (8.7% at 6 months)[7], and the smaller German INSURE Study[12] of healthier patients (9.8% at 22 months, average EF=40%). This means that the DECODE study population can be reliably considered as representative of real-life ICD/CRTD replacement patients in western countries.

In the DECODE population, more than a half of deaths were cardiovascular (none sudden), heart failure playing the leading role (47% of overall deaths). The remaining deaths (40%) were non-cardiovascular (mainly due to cancer, infections and pulmonary diseases); in only a minority of patients (3%) the cause of death remained unknown. Unfortunately, the majority of studies on ICD replacement do not report the cause of death, which remains an unsolved issue with regard to the need for continued ICD therapy[5-7]. Only the INSURE Study provided a few unspecific data on this subject: cardiovascular and non-cardiovascular mortality accounted for one third of deaths each, while it was unavailable in the remaining third[12].

The 19% rate of appropriate ICD therapy after ICD generator replacement observed in our study population is in line with the average 23% (range 10.9%-31.4%) during a 32-month median follow-up reported in a large review by McCarthy et al.[13]. In this regard, our data show two further

interesting findings: 1) the rates of delivered ICD therapy observed in each of the 5 risk subgroups were not significantly different (p=0.4); 2) appropriate therapy delivery was not associated with overall mortality (p=0.4), though it was markedly higher in "high-risk" patients (11%) than in the other subgroups (ranging from 0% in the "low-risk" to 4.7% in the "intermediate-to-high-risk" groups). Similarly, Barra et al.[14] observed that patients assessed just before ICD replacement and included in the two quintiles with the poorest clinical conditions were those who had the highest and earliest mortality rate together with a 50% frequency of appropriate ICD therapy delivery at follow-up. This suggests that, in the sickest patients candidate to ICD replacement, the subsequent risk of dying is scantly modifiable, if at all, by the ability of the ICD to interrupt life-threatening ventricular arrhythmias (VA). A reasonable explanation for this clinical behavior lies in the progression of the underlying cardiac disease and of other co-morbidities, which may significantly worsen after the first ICD/CRTD implantation, and even more so after device replacement. Indeed, the resulting anatomical and functional changes may increase the propensity to develop VA but not change the prognostic weight of other co-morbidities that are not amenable to ICD treatment[2, 10, 15, 16]. Thus, the relative contribution of VA-driven mortality vs other competitive causes is of paramount importance in assisting the decision to replace the ICD.

In this sub-analysis, 7 variables proved to be significantly and independently related to all-cause mortality: BMI<26, age≥75 years, hospitalization for any cause within 30 days prior to replacement, NYHA class≥III, ischemic heart disease, insulin therapy and history of AF. Most of these 7 risk markers have also been observed in other investigations, such as the REPLACE study and the NCDR analysis[4-6]. Age, NYHA class≥III, AF history, complications of diabetes/peripheral vascular disease and HF hospitalizations in the previous year were included in both the NCDR and REPLACE-DARE Risk Scores. In our study, insulin therapy emerged as a powerful predictor, being an indicator of diabetes severity. By contrast, ischemic heart disease and BMI were the only two risk markers present exclusively in the DECODE Risk Score. Indeed, angina was also found as

a marker of short-term adverse outcome in the Ontario registry[7], being a marker of coronary instability and unpredictable new clinical events.

Unexpectedly, BMI proved to be one of the strongest predictors of death in our study (HR=2.17). A possible explanation for this finding lies in the so-called "BMI paradox", whereby overweight patients (BMI>25 Kg/m^2) have a survival advantage over those of normal weight. Since variable degrees of overweight are frequent in patients with coronary artery disease, stroke, atrial fibrillation, diabetes, pulmonary disease, cancer, and chronic kidney disease[17-21], who were substantially well represented in our study population, it can be hypothesized that a normal-to-low BMI holds such a high predictive value simply because it gathers together all the other risk markers previously reported[4-8] at an advanced stage of disease, when body weight, and hence physical adaptation to stressors, declines. As this factor is a potential marker of a declining global health, patients with a low BMI should undergo a multidisciplinary comprehensive evaluation, focusing on advanced HF or degenerative/oncologic co-morbidities that may hinder the benefit of continued ICD/CRT-D therapy. This might help counseling a minority of patients against a replacement/upgrade procedure with an unfavorable risk/benefit ratio[22].

Of interest, the results of our analysis seemed not to be affected by the underlying conditions of those patients upgraded to CRT-D for clinical reasons who represent about 10% of our study population, a factor that theoretically could have biased our findings.

The mortality risk score that we devised yields valuable prognostic information, suggesting that mortality rates are 31% and 44% at 12 and 18 months, respectively, in patients deemed at "high-risk", who accounted for almost 4% of our population. Even though the methodology was not comparable to that of other registries[5, 6], these findings are similar to those of the REPLACE-DARE Study, in which patients with the highest Death Risk Score had a mortality rate of approximately 50% at 6 months. In addition, our findings show that although the rate of appropriate ICD therapies among all risk patient subgroups was similar, early death was markedly higher in those with the highest SUSCI risk score. This suggests that in this patient subgroup the probability

of dying is poorly affected by ICD therapy. In agreement with guideline recommendations, this fraction of candidates for device replacement should be carefully assessed, since replacement may be unprofitable or even dangerous although the high rate of life-threatening VA as shown in other investigations[14]. In our opinion, the optimal management strategy for these patients should include the mandatory provision of complete information on prognosis and on the potential lack of benefit of the procedure. Indeed, if adequately informed, a significant proportion of patients are likely to forgo the option of replacement[22, 23].

Study limitations

A matching population of patients not undergoing ICD/CRTD replacement was lacking, and the Risk Score was not validated in other populations: this attenuates the strength of the results. Although the overall number of patients in the analysis was high, some subgroups were underrepresented to draw definitive conclusions regarding ICD replacement policy; for example, the difference in outcome between females and males has not been assessed, notwithstanding a trend in favor of the female gender, due to a small presence of women (24%) in the whole population. Furthermore, data on the prevalence of LBBB at the time of replacement were lacking, thus making the assessment of this variable precluded with regard to clinical outcome. Finally, appropriate ICD interventions are only a surrogate endpoint of mortality and cannot unequivocally regarded as instances of prevented sudden cardiac death. However, this endpoint has previously been adopted in literature.

Conclusions

Mortality after ICD replacement or upgrade is approximately 12% over 2-year follow-up. Age, history of ischemic heart disease and several non-cardiac comorbidities significantly influence early and late outcomes. A small subgroup of patients with a very poor prognosis can be identified already at ICD end-of-life; in these patients, appropriate counseling may avoid unnecessary device

replacement, and comprehensive clinical evaluation may enable action to be taken on major co-morbidities, which heavily impact on patient care.

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Table 1. Demographics and baseline characteristics of the study population

Parameter	All pts (n=983)	Survived (n=869)	Dead (n=114)	*p* value Survived vs Dead
Age (year)	71 (63-78)	71 (62-77)	76 (70-81)	<0.0001
LVEF (%)	35 (30-45)	35 (30-45)	30 (25-35)	<0.0001
Males (%)	750 (76.3)	654 (75.3)	96 (84.2)	0.0351
NYHA I/II (%)	743 (75.6)	680 (78.3)	63 (55.3)	<0.0001
History of AF (%)	372 (37.8)	309 (35.6)	63 (55.3)	<0.0001
BMI	26.3 (24.2-29.1)	26.3 (24.5-29.3)	25.7 (22.5-27.3)	0.0002
AV node ablation (%)	41 (4.2)	32 (3.7)	9 (7.9)	0.0446
Ischemic Cardiomyopathy, n (%)	537 (54.6)	454 (52.2)	83 (72.8)	<0.0001
PTCA/CABG within 6 months prior to the procedure (%)	95 (9.7)	81 (9.3)	14 (12.3)	0.3114
Diabetes (%)	282 (28.7)	239 (27.5)	43 (37.7)	0.0275
Hypertension (%)	608 (61.9)	539 (62)	69 (60.5)	0.7593
Chronic Kidney Disease (%)	249 (25.3)	196 (22.6)	53 (46.5)	<0.0001
Stroke/TIA/TE (%)	84 (8.5)	70 (8.1)	14 (12.3)	0.1516
History of Cancer (%)	60 (6.1)	47 (5.4)	13 (11.4)	0.0199
COPD (%)	189 (19.2)	156 (18)	33 (28.9)	0.0076
Current Smoker (%)	62 (6.3)	56 (6.4)	6 (5.3)	0.8372
Hospitalization within 30 days prior to the procedure (%)	73 (7.4)	54 (6.2)	19 (16.7)	0.0004
ACE Inibitors (%)	555 (56.5)	493 (56.7)	62 (54.4)	0.688
Ivabradine (%)	59 (5)	45 (5.2)	4 (3.5)	0.5059
ARBs (%)	186 (18.9)	168 (19.3)	18 (15.8)	0.4453
β-Blockers (%)	839 (85.4)	743 (85.5)	96 (84.2)	0.6746
Statins (%)	515 (52.4)	460 (52.9)	55 (48.2)	0.3701
Loop Diuretics (%)	701 (71.3)	604 (69.5)	97 (85.1)	0.0004
K+ Diuretics (%)	448 (45.6)	379 (43.6)	69 (60.5)	0.0009
Amiodarone (%)	218 (22.2)	175 (20.1)	43 (37.7)	<0.0001
Oral Antidiabetics (%)	164 (16.7)	141 (16.2)	23 (20.2)	0.2865
Insulin (%)	99 (10.1)	74 (8.5)	25 (21.9)	<0.0001
Anticoagulation therapy (%)	408 (41.5)	342 (39.4)	66 (57.9)	0.0002
Replaced Device: ICD-SC (%)	257 (26.1)	24 (21.1)		
Replaced Device: ICD-DC (%)	261 (26.6)	29 (25.4)		
Replaced Device: CRT-D (%)	460 (46.8)	399 (45.9)	61 (53.5)	0.1349
Replacement procedure (%)	804 (81.8)	717 (82.5)	87 (76.3)	0.1209
System upgrade (%)	179 (18.2)	152 (17.5)	27 (23.7)	0.1209
Clinical upgrade to CRT (%)	83 (8.4)	67 (7.7)	16 (14)	0.0304
Appropriate Shock therapy (%)	348 (35.4)	298 (34.3)	50 (43.9)	0.0481

Table 2. Overall Mortality

Cardiovascular Total 65 (57%)		Non-Cardiovascular Total 46 (40.4%)		Undetermined Total 3 (2.6%)
Pump failure (81.5%)	53	Cancer (10.5%)	12	
Pulmonary Embolism	1 (0.9%)	End-stage renal failure	5 (4.4%)	
Stroke (3.5%)	4	Pulmonary disease	8 (7%)	
Other (6.1%)	7	Liver disease (3.5%)	4	
		Infection (6.1%)	7	
		Other (8.8%)	10	

Table 3. Results of Univariate and Multivariate analyses

	Univariate			Multivariate		
Variable	**p**	**HR**	**95% CI**	**p**	**HR**	**95% CI**
Center volume ≥300 procedures/year	0.488	0.8641	0.5732 to 1.3028			
Ischemic Cardiomyopathy	<0.0001	2.3817	1.5798 to 3.5906	0.0032	1.9359	1.2501 to 2.9978
Age≥75 years	<0.0001	2.8178	1.9418 to 4.0892	<0.0001	2.2583	1.5345 to 3.3237
Current smoker	0.7324	0.8663	0.3822 to 1.9637			
History of Stroke/TIA/TE	0.1061	1.5873	0.9089 to 2.7721			
Insulin Therapy	<0.0001	2.8439	1.8283 to 4.4236	0.0028	2.0295	1.2789 to 3.2207
Hypertension	0.8084	0.9542	0.6543 to 1.3915			
LVEF≤35%**	0.0011	2.0784	1.3417 to 3.2196			
NYHA class ≥III vs <III	<0.0001	2.7245	1.8867 to 3.9342	<0.0001	2.2369	1.5216 to 3.2882
Hospitalization within 30 days prior to the procedure	<0.0001	2.8161	1.7247 to 4.5980	0.0014	2.293	1.3815 to 3.8059
COPD	0.006	1.7772	1.1818 to 2.6725	0.2543	1.2774	0.8403 to 1.9419
Male Gender	0.0373	1.7075	1.0347 to 2.8176	0.0861	1.5923	0.9386 to 2.7014
History of AF	0.0001	2.1177	1.4666 to 3.0577	0.0041	1.7353	1.1933 to 2.5235
History of cancer	0.0091	2.1593	1.2146 to 3.8386	0.0752	1.7199	0.9493 to 3.1161
Anticoagulation therapy*	0.0002	2.0271	1.4002 to 2.9345			
BMI<26	0.0001	2.0636	1.4221 to 2.9944	0.0001	2.1744	1.4758 to 3.2028
System Upgrade	0.1197	1.4089	0.9169 to 2.1650			
Clinical Upgrade to CRT***	0.0211	1.8627	1.1010 to 3.1516			
Appropriate ICD therapy before replacement****	0.0365	1.4842	1.0271 to 2.1446			

Abbreviations: BMI=Body Mass Index; LVEF=Left Ventricular Ejection Fraction; NYHA=New York Heart Association Class; COPD=Chronic Obstructive Pulmonary Disease; CRT=Cardiac Resynchronization Therapy; ICD=Implantable Cardioverter Defibrillator.

*Anticoagulation therapy was not entered into the multivariate model, owing to its correlation with history of atrial fibrillation. **LVEF≤35% and ***Clinical Upgrade to CRT were not entered into the multivariate model, owing to their correlation with hospitalization prior to the procedure. ****Appropriate ICD therapy before replacement was not entered into the multivariate model, owing to its correlation with ischemic cardiomyopathy.

Figure 1. Kaplan–Meier estimates of time to death from any cause according to independent risk factors and the survival curve of the whole population.

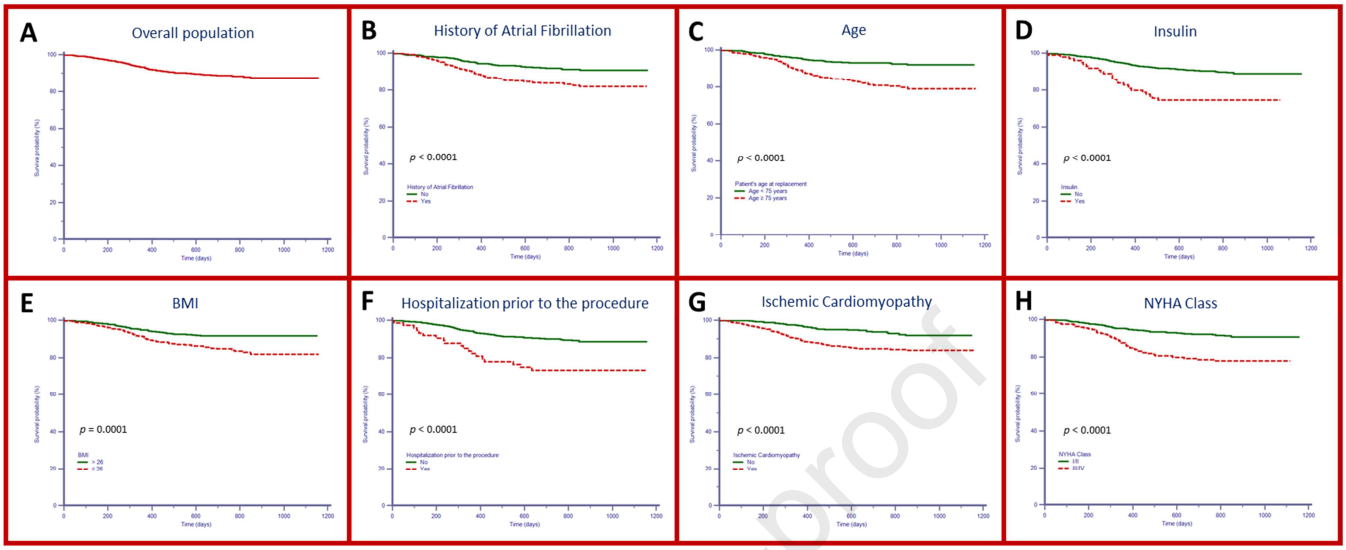
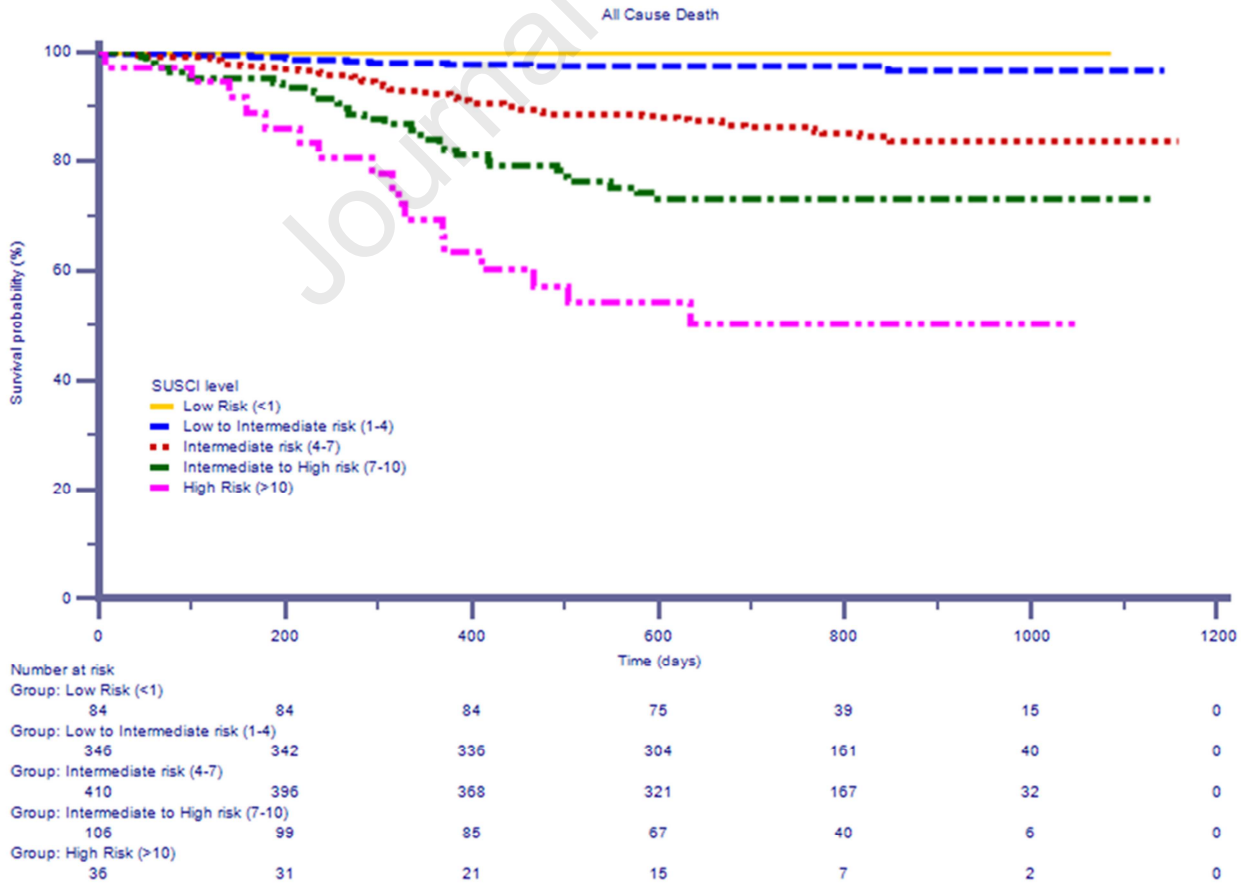


Figure 2. Kaplan–Meier estimates of time to death from any cause according to risk profile.



420 **Figure 3.** Percentages of deceased patients, of those with appropriate ICD therapy and of those with

421 both conditions, according to SUSCI risk level.

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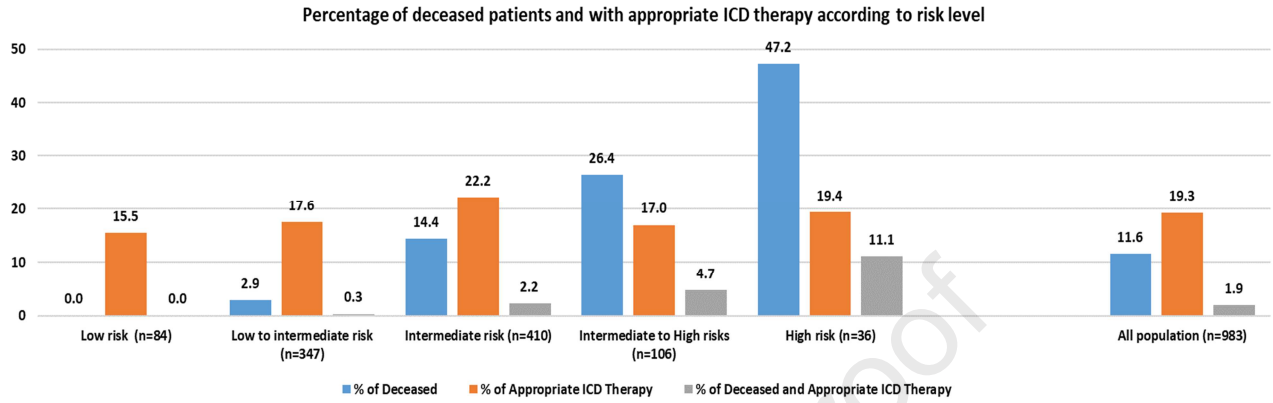

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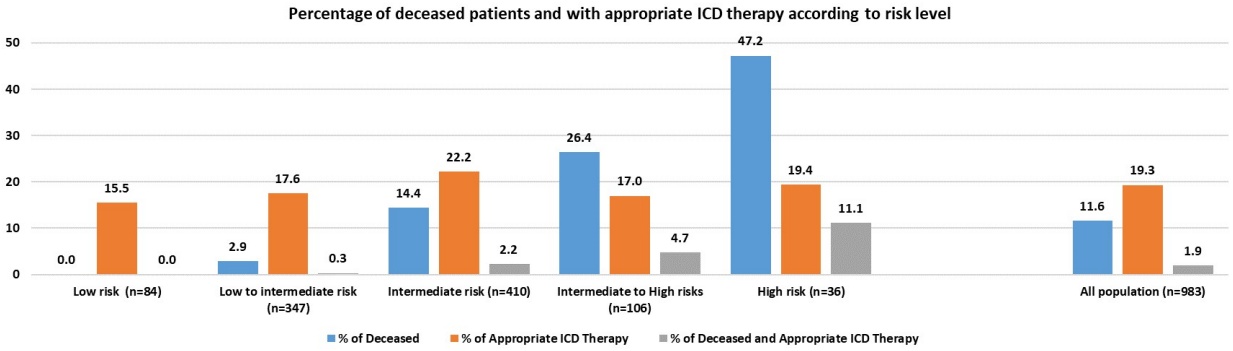

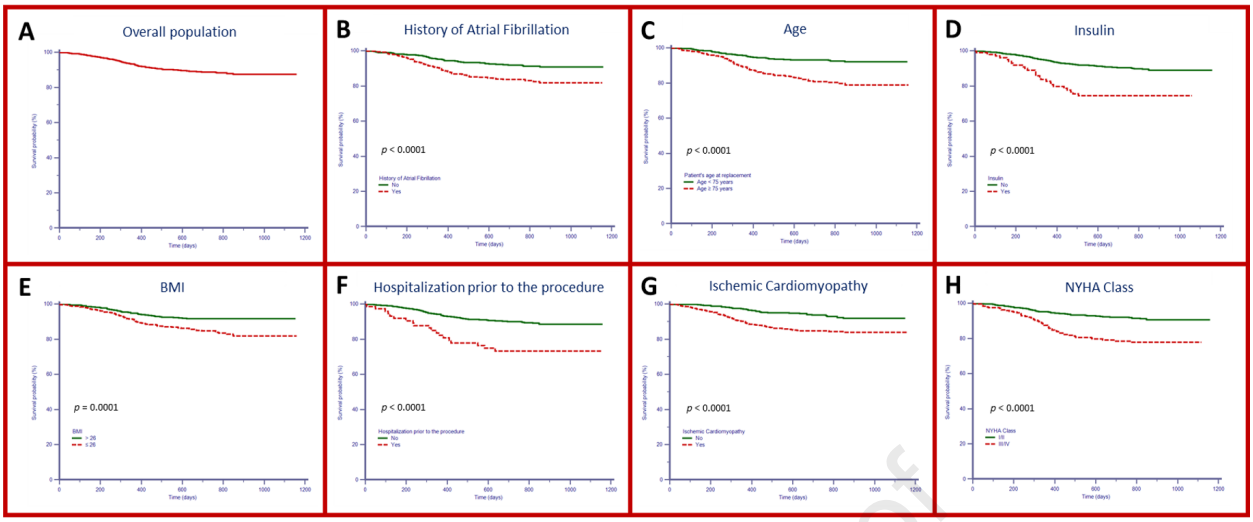

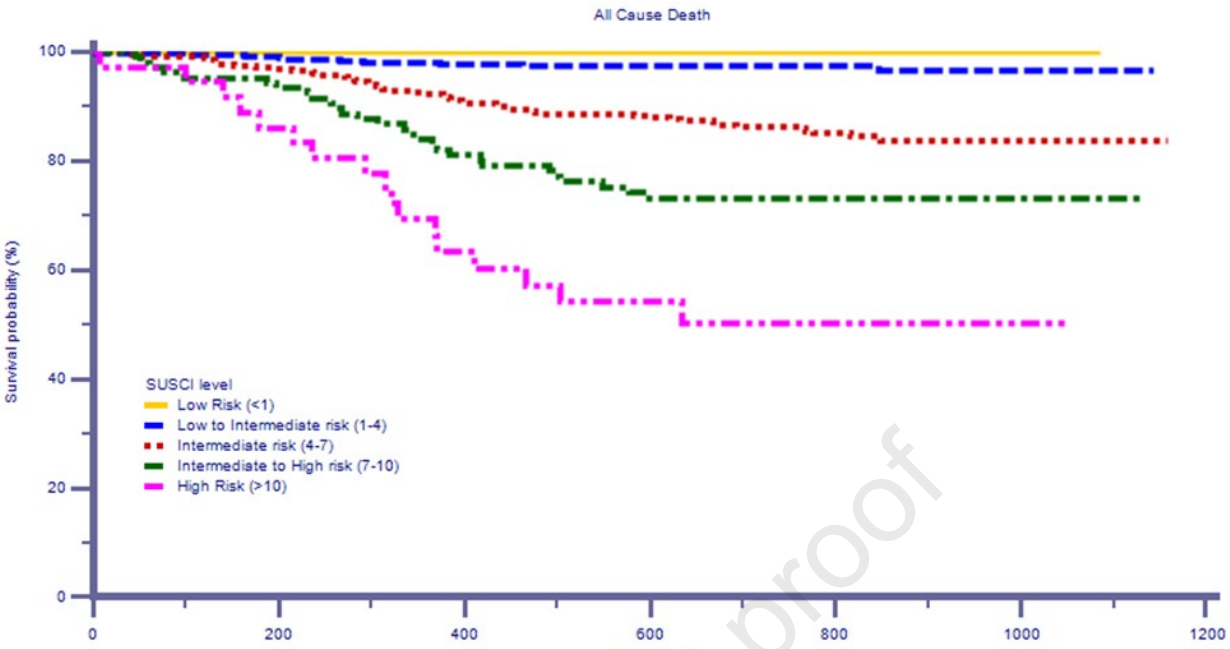

Number at risk

Group: Low Risk (<1)						
84	84	84	75	39	15	0
Group: Low to Intermediate risk (1-4)						
346	342	336	304	161	40	0
Group: Intermediate risk (4-7)						
410	396	368	321	167	32	0
Group: Intermediate to High risk (7-10)						
106	99	85	67	40	6	0
Group: High Risk (>10)						
36	31	21	15	7	2	0