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Survival and arrhythmic risk among ischemic and non-ischemic heart failure patients with prophylactic implantable cardioverter defibrillator only therapy: A propensity score-matched analysis

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ABSTRACT

Background: Concerns about the efficacy of prophylactic ICD in non-ischemic cardiomyopathy (NICM) heart failure (HF) patients are still present. We aimed to assess whether survival and arrhythmic risk were different among ischemic cardiomyopathy (ICM) and NICM ICD-only patients, along with specific predictors for mortality.
Methods: HF patients undergoing ICD-only implant were extracted from the nationwide multicenter UMBRELLA registry. Arrhythmic events were collected by remote monitoring and reviewed by a committee of experts.
Results: 782 patients (556 ICM; 226 NICM) were recruited: mean ejection fraction of 26.6%; 83.4% in NYHA class II-III; mean QRS duration of 108.9 ms (only 14.9% with QRS > 130 ms). After 4.35 years of mean follow-up, all-cause mortality rate was 4.2%/year. In propensity-score (PS) analysis no survival differences between ICM and NICM subgroups appeared (mortality rates: 19.4% vs. 20%, $p = 0.375$). Age (hazard ratio [HR] = 1.02, $p = 0.009$), diabetes (HR = 2.61, $p \leq 0.001$), chronic obstructive pulmonary disease (HR = 2.13, $p = 0.002$), and previous HF (HR = 2.28, $p = 0.027$) correlated with increased mortality for the entire population, however atrial fibrillation (AF) (HR = 2.68, p = 0.002) and chronic kidney disease (HR = 3.74, $p \leq 0.001$) emerged as specific predictors in NICM patients. At follow-up, 134 patients (17.1%) were delivered a first appropriate ICD therapy (5.1%/year) without significant differences between ICM and NICM patients in the PS analysis (17.6% vs. 15.8%, $p = 0.968$). ICD shocks were associated with a higher mortality (HR = 2.88, $p < 0.001$) but longer detection windows (HR = 0.57, $p = 0.042$) correlated with fewer appropriate therapies.
Conclusions: Mortality and arrhythmia free survival is similar among ICM and NICM HF patients undergoing ICD-only implant for primary prevention strategy.

1. Introduction

Prophylactic implantable cardioverter defibrillator (ICD) is a leading therapy in preventing sudden cardiac death (SCD) in heart failure (HF) patients with impaired left ventricular ejection fraction (LVEF) [1]. Randomized clinical trials (RCTs) have consistently shown that ICD therapy reduces morbidity and mortality as part of primary prevention strategy [2–5]. Nevertheless, concerns about the benefit in non-ischemic HF patients emerged since the first trials, as sudden death from arrhythmia

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but not all cause mortality was decreased by prophylactic implantation in non-ischemic cardiomyopathy (NICM) patients [3,6]. The discussion arose again, particularly after the publication of the DANISH trial, in which ICD did not significantly decrease the rates of all-cause death in NICM patients, even though SCD was effectively reduced [7]. The addition of cardiac resynchronization therapy (CRT) to an ICD device (58% of patients in both arms of DANISH trial carried CRT devices) not only modifies the possibilities to improve LVEF, especially in non-ischemic candidates, but can also reduce morbidity and mortality outcomes [8–11]. Pooled data from meta-analysis demonstrated, even after elimination of CRT trials, that ICD-only therapy accomplished a reduction in total mortality ranging between 26% and 31% in NICM patients [12,13]. Translation of this evidence into real-world increased the controversy, as several reports suggested that the efficacy of prophylactic ICD for HF patients with reduced LVEF seemed to be similar among RCTs and clinical practice. However, the same problem appeared, as population in these studies is heterogeneous and all of them include patients with wide QRS and high percentages of CRT carriers [14–18].

The present study tries to assess whether survival differs between ischemic and non-ischemic HF patients after ICD implant for primary prevention strategy. We also sought to define the rates of all-cause death and arrhythmia free survival, along with factors to be predictive of both events in a real-life cohort of ICD-only candidates (narrow QRS complex). Finally we try to look for specific predictors of mortality in ischemic and non-ischemic populations.

2. Methods

2.1. Patient selection

The present study was developed within the framework of the Scientific Cooperation Platform (SCOOP) supported within the UMBRELLA observational study (ClinicalTrials.gov/NCT01561144), which is a voluntary registry promoted by Medtronic Iberica that includes patients with Medtronic ICDs and follows them by remote monitoring (CareLink®) for both primary and secondary prevention. The institutional review board of the participating centers approved patient inclusion and all patients provided informed consent. Tachyarrhythmia detection and ICD settings were programmed at the discretion of local physicians.

All HF patients with reduced LVEF (≤35%) undergoing their first prophylactic ICD-only implant and enrolled in the UMBRELLA registry were selected (MADIT II-like and SCD-HeFT-like patients). People included in the database after a replacement procedure were excluded in order to avoid bias created by the collection of retrospective information. To achieve a homogeneous sample and to avoid the bias generated by improving LVEF, cardiac resynchronization therapy (CRT) carriers were not included.

2.2. Endpoints definition and follow-up

All cause death was the primary study endpoint. Data on the cause-specific mortality was also collected and classified into sudden, cardiovascular and non-cardiovascular origin. Follow-up time for each individual patient for the mortality endpoint, started from first ICD implantation until either the date of death or heart transplantation. Vital status of patients alive at data censored time-point (September 2017) was confirmed using the primary healthcare records of each participating centre. The last available contact by remote monitoring was considered the follow-up date in 15 patients, due to lack of clinical follow-up at data censored time-point.

Arrhythmia free survival (as a surrogate marker of SCD) was the secondary study endpoint. It was defined as survival free of first appropriate ICD therapy delivered in ventricular fibrillation (VF) detection zone (or in fast ventricular tachycardia (FVT) detection zone, only when programmed through VF window). Follow-up for this endpoint ran from ICD implantation to date of first appropriate delivered therapy.

2.3. Electrograms analysis and classification of arrhythmic events

A committee composed of six experts analyzed all electrograms stored in the CareLink® network. Two committee members reviewed each event in a double-blind manner, classifying the type of arrhythmia and the effectiveness of the delivered therapy. Type of arrhythmia was classified as ventricular, supraventricular, T-wave oversensing, false detection, or noise. Ventricular arrhythmia was further classified into sustained monomorphic ventricular tachycardia (SMVT), sustained polymorphic VT (SPVT), VF, or nonsustained ventricular arrhythmia. The appropriateness of every therapy delivered was then adjudicated for the events. If disagreement occurred between the first two reviewers, the event was referred to a third reviewer. If no agreement was reached between two of the three reviewers, the event was reassigned to a new pair of reviewers and, if necessary, a sixth reviewer. If consensus was not reached at this point, the event was classified in a joint meeting of all committee members.

2.4. Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD) and categorical data as numbers or percentages. Continuous variables were compared using the Student *t*-test when normally distributed and the Mann-Whitney *U* test when not normally distributed. Categorical variables were compared using χ^2, or the Fisher exact test when the conditions required for the former test were not met. Time to first appearance of the two study endpoints was described using Kaplan–Meier survival curves and significance, between ischemic and non-ischemic groups, was assessed by the log-rank test.

Because observational studies do not allow for randomization, we performed a propensity score (PS) matched analysis between ischemic and non-ischemic groups for both study endpoints. The PS was calculated using an ordered logistic regression model, taking HF etiology as the dependent variable and adopting a parsimonious approach. In a first step, all baseline characteristics were included in the univariable analysis. All variables with a $p < 0.2$ were entered into a multivariable ordered logistic regression model, which served to estimate the PS for each patient. Patient-matching was performed in a 1:1 ratio with the nearest neighbor method (caliper = 0.2 × SD[logitPs]).

Afterwards a stepwise multivariable Cox proportional analysis was performed in the overall population to avoid potential confounding factors, when searching predictors for both study endpoints. Variables with the potential to act as confounding factors were selected according to the following criteria: the clinical and biological plausibilities and, the statistical criterion of Mickey, excluding all variables that returned a *p*-value > 0.20 after univariable Cox regression analysis. Data were expressed as hazard ratios (HRs) and 95% confidence intervals (CIs). Statistical analysis was performed from the binomial distribution using the Statistical Package for Social Sciences (version 20.0, SPSS, Inc., Chicago, IL, USA). $P < 0.05$ was considered significant for all tests.

3. Results

3.1. Patient characteristics

We identified 782 patients in the UMBRELLA database who met the inclusion criteria and none of the exclusion criteria. First ICD implantation was performed from March 2006 until August 2015 in 23 different Spanish hospitals. Ischemic cardiomyopathy (ICM) accounted for 556 patients (71% of total population) while NICM was the etiology in the remaining 226 cases (29%). The baseline clinical characteristics of the overall population and propensity-matched patients are summarized in Table 1. As logical, patients with ICM had a significant higher burden of cardiovascular risk factors. On the other hand in NICM patients symptoms were more severe (NYHA class III or IV) and atrial fibrillation (AF) was more prevalent. No differences were found regarding HF medications, except for aldosterone antagonists, which were prescribed more often in NICM. Patient matching performed in a 1:1 ratio resulted in 310 patients (155 cases in each group).

Nearly two-thirds of the population underwent single-chamber device implant. The ICD settings are depicted in Table 2. Overall programming adjusted current recommendations, except for a high number of patients with ventricular tachycardia detection zone (dual zone) activated and a low percentage of long detection intervals programmed within the VF detection zone. No relevant differences appeared between study groups.

3.2. All-cause death

During a median follow-up of 4.2 years (interquartile range (IQR), 2.7–5.7 years) 142 patients died (18.2%), which meant an overall all-cause mortality rate of 4.2% per year. The mean follow-up was slightly shorter in NICM patients than in ICM ones (4.1 ± 2.1 vs. 4.4 ± 1.9 years, $p = 0.027$). The cause of death was unknown in 18 patients, 77 died from cardiovascular causes, 36 from non-cardiovascular causes, 3 from sudden death and 8 patients underwent transplantation.

In the PS matched analysis no survival differences appeared among ischemic and non-ischemic patients. All-cause death rates were similar between ICM and NICM patients (crude mortality rates: 19.4% vs. 20%, $p = 0.375$, log-rank test) as it is shown in Kaplan-Meier survival curves (panel A, Fig. 1).

The levels of significance for each variable in the univariable Cox proportional hazard analysis performed including the entire population are displayed in Supplementary material. In order to look for specific

Table 1
Baseline demographic and clinical characteristics of overall and propensity matched population.

	Overall population				Propensity matched population			
	Total ($N = 782$)	ICM ($N = 556$)	NICM ($N = 226$)	p value	Total ($N = 310$)	ICM ($N = 155$)	NICM (N = 155)	p value
Age (years)	61.1 ± 11.5	62.1 ± 10.4	58.4 ± 13.4	0.001	59.5 ± 12	59.6 ± 11.5	59.4 ± 12.6	0.874
Female gender	11.9%	8.8%	19.5%	<0.001	15.8%	14.8%	16.8%	0.640
Diabetes	35.6%	40.7%	23.1%	<0.001	26.5%	25.8%	27.1%	0.797
Hypertension	57.5%	62.8%	44.6%	<0.001	49.4%	50.3%	48.4%	0.733
Smoker	48.7%	51.3%	42.5%	0.033	44.2%	42.6%	45.8%	0.567
Dyslipidemia	56.6%	63.2%	40.6%	<0.001	46.5%	45.8%	47.1%	0.820
Stroke	6.5%	7.2%	4.8%	0.249	4.3%	5.4%	3.3%	0.368
COPD	13.1%	13%	13.2%	0.949	15.5%	14.4%	16.3%	0.710
Chronic kidney disease (GFR < 60 ml/min/1.73 m^2)	15.4%	14.5%	17.6%	0.280	16.5%	16.8%	16.1%	0.878
Atrial fibrillation	26.7%	23.1%	35.7%	<0.001	21.9%	21.3%	22.6%	0.784
NYHA class				0.036				0.336
I	16.1%	16.4%	15.7%		13.7%	12.5%	14.8%	
II	65.9%	67.2%	62.7%		68%	71.9%	64.1%	
III	17.5%	16.4%	20%		17.6%	15.6%	19.5%	
IV	0.5%	0%	1.6%		0.8%	0%	1.6%	
LBBB like pattern	13.8%	11.9%	18.6%	0.014	16.1%	16.1%	16.1%	1.000
Previous HF admission	76.6%	75.3%	80%	0.157	81.3%	81.9%	80.6%	0.771
Mean QRS duration (ms)	108.9 ± 24.7	107.5 ± 23.5	112.3 ± 27.3	0.109	109.6 ± 24.2	109.8 ± 23.3	109.3 ± 25	0.552
LVEF, mean (%)	26.6 ± 5.4	27.1 ± 5.3	26.6 ± 5.5	0.359	26.8 ± 5.7	26.9 ± 5.7	26.7 ± 5.7	0.551
Beta blockers	90.9%	91.9%	89%	0.268	88.6%	90.8%	86.8%	0.350
ACEI or ARB	84%	83.3%	85.5%	0.526	85.8%	86.7%	85.1%	0.734
Aldosterone antagonists	59.4%	56.7%	64.5%	0.090	62.6%	57.1%	66.9%	0.236

ACEi: angiotensin-converting enzyme inhibitors; ARB: angiotensin II receptor blockers; COPD: chronic obstructive pulmonary disease; GFR: glomerular filtration rate; HF: heart failure; ICM: ischemic cardiomyopathy; LBBB: left bundle branch block; LVEF: left ventricular ejection fraction; ms: milliseconds; NICM: non-ischemic cardiomyopathy.

predictors, interactions between cardiomyopathy origin and all of the following variables: AF, chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), diabetes mellitus (DM) and age, were also included in the final multivariable Cox model.

The multivariable Cox proportional regression analysis is shown in Table 3 and reveals that age, DM, COPD and previous HF strongly predicted all cause mortality for the entire population. Furthermore, AF and history of CKD were significantly associated with a higher risk of all-cause death but only in the subgroup of NICM patients (Fig. 1, panels C to F).

3.3. Arrhythmia free survival

At follow-up, 134 patients (17.1%) were delivered a first appropriate therapy within the VF detection zone, which meant an arrhythmic event rate of 5.1% per year. A vast majority of the arrhythmic episodes were due to SMVT ($n = 96$, 71.6%), whereas SPVT or VF accounted for the rest ($n = 38$, 28.4%). The mean tachycardia cycle length was 257.3 ± 37.6 milliseconds (ms) and the mean time from tachycardia detection to ICD intervention was 29.9 ± 85.4 s. High-energy shocks (cardioversion or defibrillation) were delivered and terminated most of the episodes ($n = 88$, 65.7%) while anti-tachycardia pacing (ATP) ended 46 events (34.3%). No differences regarding characteristic of the tachyarrhythmia episodes were found between ischemic and non-ischemic patients.

Kaplan-Meier analysis performed in the PS matched population, showed similar cumulative probability of first arrhythmic event between ICM and NICM populations (panel B, Fig. 1). Crude event rate did not differ among study groups (17.6% vs. 15.8% respectively, $p = 0.968$, log-rank test).

After multivariable Cox regression analysis (Table 3), first appropriate ICD therapy was associated with a 2.8-fold increased risk of all-cause mortality. Besides AF, history of stroke and lower LVEF strongly predicted first appropriate therapy. Finally, delayed programming (30 of 40 number of interval detection (NID) within the VF detection zone) emerged as a protective factor and was related to 42.3% lower risk of first appropriate ICD therapy without an increased risk of death ($p = 0.344$; Supplementary material). This was the only ICD setting related to a lower risk of appropriate therapies.

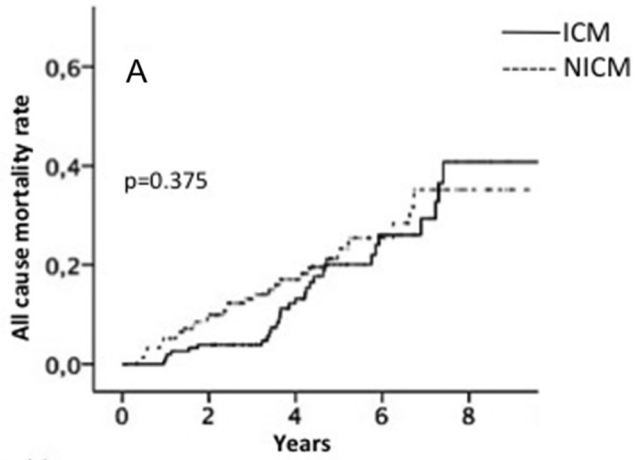
4. Discussion

The present study composed of a nationwide cohort of ICD-only patients focuses on the prognostic role that cardiomyopathy etiology plays

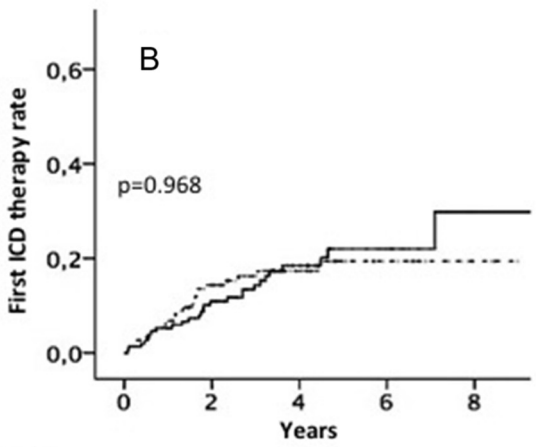
Table 2
ICD type and programming.

	Total ($n = 782$)	Ischemic ($n = 556$)	Non-ischemic ($n = 226$)	p value
ICD device				0.587
Single chamber	68.7%	69.2%	67.3%	
Dual chamber	31.3%	30.8%	32.7%	
VF detection zone cut-off > 188 bpm	94.9%	94.9%	94.9%	0.995
ATP[a]	96.7%	96.7%	96.8%	0.902
NID				0.314
<30 of 40	61.1%	59.9%	63.9%	
30 of 40	38.9%	40.1%	36.1%	
FVT programmed[b]	28.7%	28%	30.6%	0.480
FVT detection zone cut-off (mean) (ms)	266.7 ± 26.6	264.6 ± 24.9	271.8 ± 30	0.127
N° of ATP attempts (mean)	1.3 ± 0.5	1.3 ± 0.5	1.4 ± 0.5	0.263
Burst/ramp (first ATP attempt)[c]	99.8%/0.2%	100%/0%	97%/3%	0.095
Burst/ramp (second ATP attempt)[c]	29.5%/70.5%	32.7%/67.3%	24.1%/75.9%	0.425
VT zone programmed	50.7%	50.3%	51.9%	0.698
VT detection zone cut-off (mean) (ms)	356.4 ± 17.8	356.5 ± 20.8	356.1 ± 17.1	0.851
N° of ATP attempts (mean)	1.9 ± 1.7	1.9 ± 1.9	1.8 ± 0.5	0.505
Burst/ramp (first ATP attempt)[c]	99.7%/0.3%	99.6%/0.4%	100%/0%	1.000
Burst/ramp (second ATP attempt)[c]	15%/85%	16.9%/83.1%	10.2%/89.8%	0.158
Burst/ramp (third ATP attempt)[c]	14.3%/85.7%	12.5%/87.5%	20%/80%	0.238

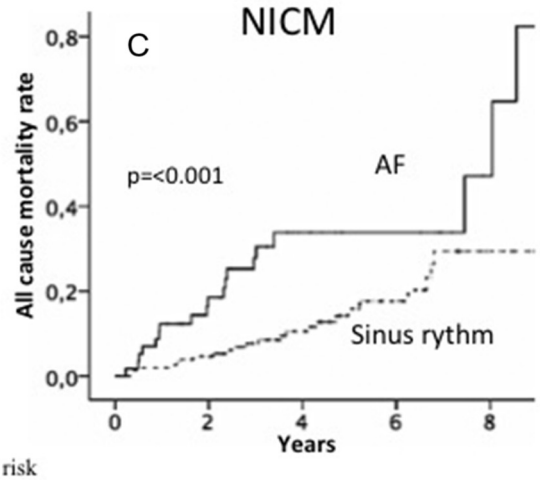
ATP: anti-tachycardia pacing; ICD: implantable cardioverter defibrillator; FVT: fast ventricular tachycardia; ms: milliseconds; HES: High-energy shock; NID: number of interval detection; VF: ventricular fibrillation; VT: ventricular tachycardia.
[a] During of before charging.
[b] Through VF detection zone.
[c] Proportions of total attempts programmed.



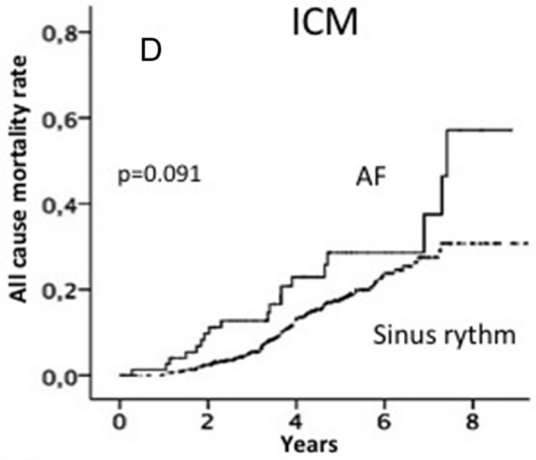
Nº at risk					
ICM	155	143	87	34	10
NICM	155	128	72	26	7



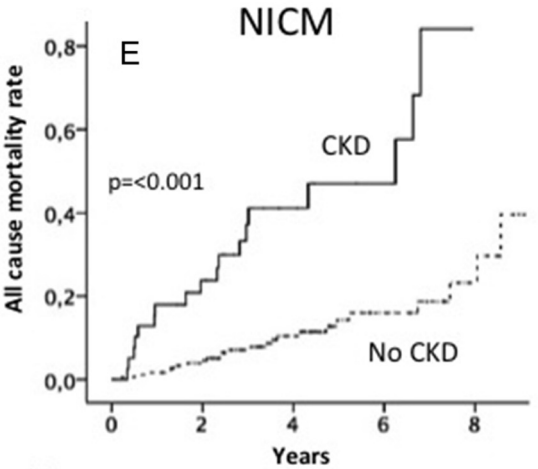
Nº at risk					
ICM	155	120	61	25	2
NICM	155	104	51	20	4



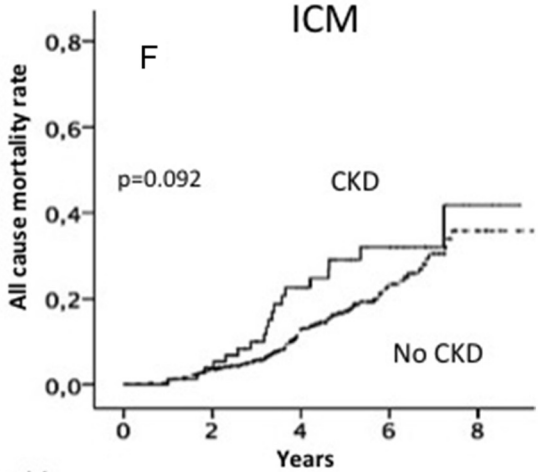
Nº at risk					
AF	56	39	16	9	3
Sinus rythm	151	137	85	36	10



Nº at risk					
AF	74	61	35	13	3
Sinus rythm	447	408	249	109	20



Nº at risk					
CKD	38	25	10	6	1
No CKD	181	161	92	40	11



Nº at risk					
CKD	77	68	38	19	3
No CKD	456	413	250	103	21

Table 3
Final Cox model for all-cause death and first ICD therapy in the overall population.

	Variable	HR (95% CI)	*p* value
Time to all-cause death	Age	1.028 (1.007–1.050)	0.009
	Diabetes	2.611 (1.723–3.958)	<0.001
	COPD	2.138 (1.321–3.453)	0.002
	Heart failure	2.284 (1.098–4.750)	0.027
	CKD * NICM	3.748 (2.051–6.851)	<0.001
	AF * NICM	2.682 (1.453–4.953)	0.002
Time to first appropriate ICD therapy	All-cause death	2.885 (1.844–4.514)	<0.001
	AF	2.002 (1.221–3.284)	0.006
	Previous stroke	2.335 (1.276–4.273)	0.006
	LVEF	0.941 (0.905–0.980)	0.003
	NID 30 of 40	0.577 (0.340–0.979)	0.042

AF: atrial fibrillation; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; LVEF: left ventricular ejection fraction; ms: milliseconds; NICM: non-ischemic cardiomyopathy; NID: number of interval detection.

regarding all-cause death and arrhythmic risk. All-cause mortality rates among ischemic and non-ischemic HF patients, receiving an ICD for primary prevention, were similar. Predictors of all-cause mortality were age, COPD, DM and previous HF admission, for the entire population, whereas AF and CKD were associated with death only in NICM patients. Moreover, rates of life-threatening arrhythmic events requiring ICD therapies were similar between ICM and NICM patients for primary prevention strategy. First appropriate therapy within the VF detection zone was strongly linked to an increased mortality risk at follow-up and also to the history of AF, stroke, and lower LVEF. Furthermore, longer interval detection windows were statistically associated with a lower risk of appropriate ICD interventions.

4.1. All-cause mortality

In our cohort composed of ICD-only candidates all-cause mortality was lower compared to mortality of patients randomized to the ICD arm in MADIT-II and SCD-HeFT trials [13] (18.2%, after 50.4 months of median follow-up vs. 14.2% after 20 months of mean follow-up vs. 22% after 45.5 months of median follow-up respectively). Over the past years, long-term prognosis of HF patients has improved. In the recent DANISH trial only 21.6% of patients in the ICD arm died after 67.7 months of median follow-up [7]. This trend has also been reported in contemporary cohorts of ICD carriers [17] and in HF patients regardless cardiac devices [19]. Several reasons appear: the patients included in older RCTs had a higher burden of comorbidities, proportions of patients taking betablockers, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers and aldosterone antagonists were higher in DANISH trial compared to older RCTs and finally, the increase in cardiovascular prevention strategies, the better medical management of coronary artery disease and the extend of coronary revascularization may also explain this phenomenon. Survival of our cohort of ICD patients is in agreement with survival found in current RCTs. Furthermore, the risk profile of our population is better compared to patients included in former RCTs but we also report more patients under optimal medical treatment. This is also in concordance with the profile of contemporary HF patients.

It should be noticed that a meaningful proportion of patients randomized to ICD therapy in MADIT-II [2], SCD-HeFT [3] and DEFINITE [6] trials had wide QRS complexes and consequently, they could have been potential candidates for concomitant CRT implant. This issue could have improved LVEF and therefore the final outcomes. The same problem is also observed in several real-world registries and in many risk models developed to predict mortality in primary prevention ICD patients: percentage of CRT carriers ranged from 31% to 53.8% and rate of patients with wide QRS complexes ranged from 37% to 69.5% [14–18]. Our population, selected from the UMBRELLA nationwide registry, represent a true population of HF patients in whom CRT has no potential benefit (median QRS duration of 100 ms, IQR: 90–120 ms). Only 14.9% of cases presented with QRS > 130 ms. This issue brings strength to the study findings, along with the fact that the prognostic role of HF etiology in narrow-QRS patients has not been specifically addressed in none of the previous reports.

Data extracted from clinical trials showed that an increasing number of comorbidities is related to higher mortality and less ICD benefit. MADIT-II risk score showed that efficacy was lower in patients with AF, CKD, wider QRS, elderly and NYHA class >II [20,21]. Furthermore in SCD-HeFT population, patients at high mortality risk obtained the smallest benefit [22]. In our study of ICD only patients, mortality was related to increasing age along with the fact that DM, COPD and HF increased more than twice the risk of all-cause death in the overall population. Predictors of mortality found in our population are also consistent with those reported in some observational risk scores [15–18], and they are particularly similar to the ones found in the SHOCKED model. It needs to be highlighted the predictive role of COPD, which is an issue not always taken into account at the decision making process [14]. Apart from the inclusion of CRT carriers and patients with wide QRS complexes, some of the mentioned models were developed using only ischemic patients and some also included secondary prevention ICDs. This is important, because in our homogeneous population, AF and CKD emerged as predictors of all-cause death only in NICM patients. To the best of our knowledge this is the first report about specific predictors of mortality in NICM patients compared to ICM ones. Predictors of death from any cause extracted from our national registry of contemporary ICD-only patients can help to select ischemic and non-ischemic narrow-QRS patients who would benefit more from ICD therapy.

4.2. Arrhythmia free survival

Annual rates of first appropriate ICD therapy in our cohort of primary prevention patients are also consistent with data from RCTs [13]. ICD interventions for life-threatening arrhythmia are just a surrogate for arrhythmic mortality, nevertheless it must be highlighted that event rates were similar among ischemic and non-ischemic populations despite no differences in the ICD settings. Even though myocardial fibrosis localized around scar regions in ischemic patients provides the main substrate for the initiation of reentrant circuits [23], we surprisingly found that rhythms leading to ICD intervention were rapid ventricular tachyarrhythmia in both groups (mean cycle length of 257.4 ± 36.4 vs. 257.2 ± 40.6 ms respectively, for ICM and NICM patients). All these findings offer important information for device programming

Fig. 1. Cumulative incidence of all-cause death (panel A) and first appropriate ICD therapy (panel B) in the propensity score matched population. Kaplan-Meier estimates on death from any cause according to history of AF in NICM (panel C) and ICM (panel D) groups; and according to CKD in NICM (panel E) and ICM (panel F) patients. *P* values correspond to log-rank test. CKD: chronic kidney disease; ICD: implantable cardioverter defibrillator; ICM: ischemic cardiomyopathy; NICM: non-ischemic cardiomyopathy.

and strongly suggest that arrhythmic risk in ICM and NICM ICD-only patients might not be different.

Several subgroup analysis of RCTs and observational reports suggest that patients at a higher risk of receiving appropriate ICD interventions have the worst prognosis, regardless of the implanted device [16,17,24]. Our results are consistent with the idea that appropriate ICD shocks may be a marker of disease progression because, survival free of an appropriate ICD therapy was independently associated with worse clinical characteristics such as AF, previous stroke and low LVEF. Physicians must be aware of these signs to enhance treatment-strategies in these patients.

Furthermore, ICD shocks have been associated with an increasing mortality in HF patients [25,26]. Because of this, for the past years several studies demonstrating the benefit of delayed programming have arisen [27–30]. The conclusions of these studies are congruent, but population included in them are heterogeneous. The ADVANCE III trial included both primary and secondary prevention patients, whereas only primary prevention patients were collected in the rest of the studies. The MADIT-RIT trial excluded patients with single-chamber ICD and finally, up to 45% of population included in these studies, received a CRT device added to the ICD [31]. The results of the present study reinforce the benefits of delayed programming when applied in a cohort of HF patients undergoing ICD-only implant for primary prevention. Appropriate ICD interventions are associated with a higher risk of all-cause mortality but delayed programming might reduce them without an increased risk of death.

4.3. Study limitations

Some limitations should be mentioned. The main problem is the observational nature and the potential for study population bias derived from unrecognized attitudes and approaches toward heart failure management. Data extracted from this nationwide registry comes from a preformatted sheet lacking of some specific important information as for example, severity of CKD. Device programming was performed at the discretion of the local physicians without pre-specified patterns. Nevertheless, all of them were expert electrophysiologists. It is relevant that some arrhythmic events could have been self-terminated without ICD intervention, specially the ones that happened in the beginning of the follow-up, when more aggressive programming was recommended. Therefore, it is not possible to determine whether the frequency of self-limiting events in ICM and NICM patients could have influenced the results. Finally, conclusions extracted from our study are based on ICD from only one manufacturer and extrapolation to other brands must be made with caution.

5. Conclusions

All-cause death and arrhythmia free survival among ischemic and non-ischemic HF patients undergoing ICD-only implant for primary prevention strategy are similar. Thus the benefit should not be restricted to ischemic patients. Age, DM and COPD strongly predict an increased mortality risk, whereas AF and CKD emerged as specific predictors in NICM patients. Although appropriate ICD therapies were associated with a lower survival, delayed programming appeared as a protective factor.

In HF patients with reduced LVEF and narrow QRS, the decision to implant an ICD for primary prevention must be individually made in patients with more comorbidity, and especially in NICM patients with AF or renal failure. This population should be programmed with longer detection windows to decrease the number of appropriate shocks.

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Disclosures

None of the authors declare any potential conflict of interest.

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