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Indication to cardioverter-defibrillator therapy and outcome in real world primary prevention. Data from the IRIDE [Italian registry of prophylactic implantation of defibrillators] study

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ABSTRACT

Aims: Several trials demonstrated the life saving role of implantable cardioverter-defibrillators (ICD) in primary prevention of sudden cardiac death (SCD). The aim was to evaluate the clinical characteristics and 4-year outcome of consecutive patients treated in clinical practice by prophylactic ICD implantation on the basis of class I recommendations and up-to-date ICD programming.

Methods and results: IRIDE multi-center, prospective and observational study enrolled 604 consecutive patients (mean age: 66±10 years) treated by ICD between 01/01/2006 and 30/06/2010. Main characteristics were similarly distributed among the inclusion criteria of MADIT II (24%), SCD-HeFT (24%), COMPANION (26%) and MADIT-CRT (18%) trials, while a small number of patients met the MUSTT and MADIT (7%) inclusion criteria. Single-chamber ICDs were implanted in 168 (28%) patients, dual-chamber in 167 (28%) and biventricular in 269 (43%) patients. ATP programming was activated in 546 (90%) patients. Overall survival and rate of appropriate ICD intervention by ATP and/or shock at 12–24–36–48 months of follow-up were 94%, 89%, 80%, 75% and 16%, 28%, 37% and 50%, respectively. No difference in mortality rate between the groups who received or did not receive appropriate ICD interventions was demonstrated (p = ns).

Conclusions: The IRIDE study confirms the effectiveness in real world practice of ICD implantation in patients at risk of SCD. The life saving role of ICD therapy increases as the duration of follow-up is prolonged and the survival benefit is similar in patients who received or did not receive appropriate device treatment, thus suggesting a beneficial effect of up-to-date device programming.

1. Introduction

Clinical efficacy of implantable cardioverter defibrillator (ICD) therapy in the setting of primary prevention was demonstrated in randomized trials [1–8] including patients at high risk due to low left ventricular ejection fraction (LVEF) [1,4–9], advanced NYHA class, presence of non-sustained ventricular tachycardia (VT) and inducibility of sustained VT [1,5,9]. Three trials enrolled patients with post-myocardial infarction ischemic heart disease [1,5,6], and other three involved patients with ischemic and/or non ischemic cardiomyopathy [2–4,7,8]. The life-saving role of ICD therapy in primary prevention has also been confirmed by a meta-analysis using individual patient data from randomized trials [10]. However, only few surveys have evaluated the application of large clinical trials and up-to-date guidelines to the real-world population [11–15], and most of them did not collect data on survival, number and type of appropriate and inappropriate ICD interventions.

The aim of the IRIDE prospective study was to compare clinical characteristics and outcome of patients undergoing prophylactic ICD implantation in clinical practice on the basis of class I recommendations

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of national [16] and international guidelines [17] with respect to the results of main trials. Of note, advanced ICD programming with antitachycardia pacing (ATP) in the VT window was strongly recommended, considering the emerging unfavorable prognostic role of ICD shock [2,18,19], the high efficacy of ATP for VT interruption and the better quality of life in patients treated with painless ICD therapy [20–22].

2. Methods

Patients were enrolled between 01/01/2006 and 30/06/2010 in 10 Italian hospitals (Appendix 1). The study was carried out with the approval of local ethics committees. Moreover, the authors certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology; all patients gave their informed consent before enrolment. The study population included consecutive patients treated for primary prevention on the basis of the inclusion criteria applied in the main randomized clinical trials [1–3,5,6,8]. Patients who simultaneously met the inclusion criteria of more than one trial were regarded as belonging to the category with the strictest criteria [1–3,5,8,23,24].

Primary end points were total mortality rate and rate of appropriate ICD interventions, as defined both by endocardial shock and/or VT interruption by ATP. Inappropriate ICD intervention was defined by ATP and/or shock due to sinus tachycardia, atrial tachyarrhythmias with fast ventricular response, lead noise and oversensing. Episodes of worsening heart failure, number of ICD replacements and device upgrading to Cardiac Resynchronization Therapy (CRT) were also considered in the follow-up.

On the basis of PAIN-FREE and PAIN-FREE II trials [20,21], detection of ventricular arrhythmic events required that 18 of the last 24 R–R intervals had a cycle length minor to the stated cut-off for some devices or at least 2.5 s of R–R intervals with a cycle length minor to the stated cut off for other device types. The majority of devices were programmed with two consecutive zones, including an antitachycardia pacing (ATP)/shock therapy in the VT window (188–220 bpm) and an initial shock zone in the VF window (≥220 bpm). In the ATP/shock zone, arrhythmias were treated by at least two bursts of ATP and with shock delivery, if ineffective. Classification of both appropriate and inappropriate ICD therapies stored in the device memory was adjudicated by trained electrophysiologists of participating centers. Electrical storm was defined as ≥3 appropriate ICD interventions in 24 h [25,26]. Patients were enrolled via the Internet (www.irideaiac.it) at the time of ICD implantation, and at the 12-, 24-, 36- and 48-month follow-up time.

3. Statistical methods

Survival curves and event-free curves for appropriate and inappropriate ICD interventions were calculated by using the Kaplan–Meier method in all series and in the different groups defined according to the main trial inclusion criteria. Comparison between the estimated curves was performed by means of the log-rank test.

A comparison between the study survival distribution with that of main randomized trials was performed applying Parmar et al.'s method [27]. P values less than 0.05 were considered statistically significant.

4. Results

4.1. Population characteristics (Table 1)

The total number of consecutively enrolled patients was 604 (mean age 66 ± 10 years). Main clinical and instrumental characteristics, cardiovascular risk factors, comorbidities and drug therapy in the whole study population and in the different groups are summarized in Table 1. Cardiovascular risk factors included obesity (body mass index ≥30), diabetes (fasting blood glucose ≥126 mg/dl and/or glycated hemoglobin ≥6.5%), hypertension, history of smoking and hypercholesterolemia (low density lipoprotein ≥130 mg/dl). Comorbidities included previous history of cerebrovascular disease (transient ischemic attack/stroke), chronic renal failure (serum creatinine level ≥1.5 mg/dl) and chronic obstructive pulmonary disease.

Specifically, 44 (7%) patients met the MADIT and MUSTT inclusion criteria, 147 (24%) MADIT II criteria, 144 (24%) SCD-HeFT criteria, 160 (26%) COMPANION criteria, and 109 (18%) patients met the MADIT-CRT criteria. The number of single-chamber ICDs implanted in patients was 168 (28%), dual-chamber 167 (28%) and biventricular 269 (45%). ATP programming was activated in 546 (90%) patients and in particular in 35 (80%) of the MUSTT–MADIT group, 129 (88%) of the MADIT II

Table 1
Main characteristics of the study population stratified according to the inclusion criteria of the main clinical trials.

	MADIT–MUSTT	MADIT II	SCD-HeFT	COMPANION	MADIT-CRT	TOTAL
No. of patients (%)	44 (7%)	147 (24%)	144 (24%)	160 (26%)	109 (18%)	604
Age (years)	65 ± 10	67 ± 9	62 ± 13	69 ± 8	66 ± 8	66 ± 10
Male (%)	42 (95%)	126 (86%)	119 (83%)	130 (81%)	87 (80%)	504 (83%)
LVEF (%)	35 ± 3	26 ± 4	28 ± 5	26 ± 5	27 ± 5	28 ± 7
Ischemic heart disease (%)	44 (100%)	147 (100%)	23 (16%)	58 (36%)	29 (27%)	294 (47%)
Obesity (%)	3 (9%)	26 (18%)	16 (11%)	19 (12%)	16 (15%)	80 (13%)
Smoking (%)	14 (32%)	32 (22%)	33 (23%)	25 (16%)	25 (23%)	129 (21%)
Diabetes (%)	7 (16%)	48 (33%)	27 (19%)	43 (27%)	20 (18%)	145 (23%)
Hypertension (%)	12 (27%)	61 (42%)	51 (35%)	63 (39%)	46 (42%)	233 (39%)
Hypercholesterolemia (%)	30 (68%)	90 (61%)	29 (20%)	57 (36%)	39 (36%)	245 (41%)
Chronic renal failure (%)	3 (7%)	18 (12%)	13 (9%)	26 (16%)	8 (7%)	68 (11%)
Cerebrovascular disease (%)	1 (2%)	15 (10%)	10 (7%)	5 (3%)	1 (1%)	32 (5%)
Respiratory disease (%)	5 (11%)	15 (10%)	18 (13%)	30 (19%)	8 (7%)	76 (13%)
NYHA class: I (%)	14 (32%)	4 (3%)	0	0	8 (7%)	26 (4%)
NYHA class: II (%)	28 (64%)	104 (71%)	109 (76%)	0	101 (93%)	342 (57%)
NYHA class: III (%)	1 (2%)	39 (27%)	35 (24%)	150 (94%)	0	225 (36%)
NYHA class: IV (%)	1 (2%)	0	0	10 (6%)	0	11 (2%)
Atrial tachyarrhythmias (%)	5 (11%)	36 (24%)	44 (31%)	68 (43%)	32 (29%)	173 (29%)
I–II–III AV block (%)	3 (7%)	12 (8%)	9 (6%)	11 (7%)	16 (15%)	51 (8.2%)
QRS ≥ 120 ms (%)	6 (14%)	32 (22%)	32 (22%)	124 (78%)	83 (76%)	277 (46%)
LBBB (%)	3 (7%)	18 (12%)	18 (13%)	111 (69%)	87 (80%)	237 (39%)
Non-sustained VT	20 (46%)	31 (21%)	54 (38%)	26 (16%)	19 (17%)	150 (25%)
Prior CABG (%)	11 (25%)	53 (36%)	13 (9%)	27 (17%)	19 (17%)	123 (20%)
Prior PTCA (%)	18 (41%)	56 (38%)	16 (11%)	28 (18%)	11 (10%)	129 (21%)
Beta-blocker usage (%)	33 (75%)	127 (86%)	111 (77%)	131 (82%)	91 (84%)	488 (81%)
ACEi/ARB usage (%)	33 (75%)	124 (84%)	116 (81%)	143 (89%)	86 (79%)	502 (83%)
Statins usage (%)	28 (64%)	89 (61%)	29 (20%)	54 (34%)	37 (34%)	237 (39%)
Diuretics usage (%)	27 (61%)	118 (80%)	112 (78%)	152 (95%)	90 (83%)	499 (83%)
Amiodarone usage (%)	8 (18%)	21 (14%)	29 (20%)	33 (21%)	10 (9%)	101 (17%)
Single-chamber ICD (%)	16 (36%)	80 (54%)	72 (50%)	–	–	168 (28%)
Dual-chamber ICD (%)	28 (64%)	67 (46%)	72 (50%)	–	–	167 (28%)
CRT-ICD (%)	–	–	–	160 (100%)	109 (100%)	269 (43%)
ATP activation in VT window	35 (80%)	129 (88%)	132 (92%)	150 (94%)	100 (92%)	546 (90%)

group, 132 (92%) of the SCD-HeFT group, 150 (94%) of the COMPANION group and 100 (92%) of the MADIT-CRT group.

4.2. Follow-up

During a mean follow-up of 24 ± 8 months (range 1–67) 60 (10%) patients died and 9 (1.5%) underwent heart transplantation. Overall survival curves in the whole population and in the different groups of patients stratified according to the inclusion criteria of the main randomized studies are shown in Fig. 1A and B. The patients who died had a mean age of 70 ± 8 years and a mean time to death of 23 ± 14 months. The cause of death was cardiac in 38 (63%) patients, of whom 33 underwent end-stage heart failure, 3 out-of-hospital sudden cardiac death and 2 in-hospital fatal and refractory ventricular tachyarrhythmias. In another 22 (37%) patients, death was due to stroke (3), cancer (8) or other causes (11). A total of 175 (29%) patients had a potentially life-threatening arrhythmia appropriately treated by ICD. The number of arrhythmic events requiring appropriate ICD intervention by ATP and/or shock was 785 (4.5 ± 15.6 per patient). In particular, 89 VF episodes occurred in 37 patients (2.4 ± 3.1 per patient), and 696 VT episodes in 138 patients (5.0 ± 11.7 per patient) of whom 481 were treated with ATP (119 patients) and 241 with ATP plus/or shock (47 patients) as shown in Table 2. At least one electrical storm due to appropriate ICD intervention was detected in 13 patients (2% of the total population), ranging from 1% to 3% in different groups (Table 2). The group of patients who received any type of appropriate ICD interventions showed a similar survival with respect to the group of patients who had no ICD intervention (Fig. 2A). Following first appropriate therapy, 2-year overall survival of the whole population was 80% and in particular it was 83% in patients treated by ATP only and 70% in patients treated by ATP and/or shock (p = ns) (Fig. 2B).

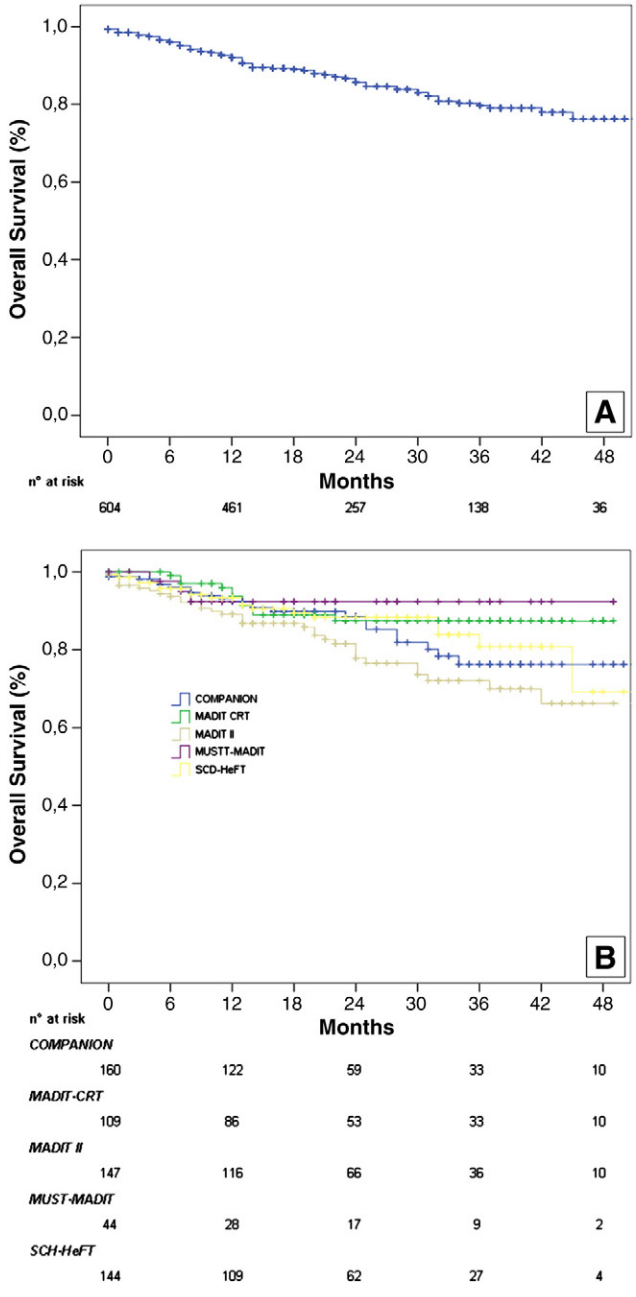

Fig. 1. Kaplan–Meier curves showing overall survival in the whole study population (A) and in patients stratified according to the inclusion criteria of the main trials (B).

Overall, 173 inappropriate device interventions (17% of all ICD interventions) occurred in 40 (7%) patients (4.3 ± 9.3 per patient), of whom 23 (4%) received only inappropriate shocks and 15 (2%) both appropriate and inappropriate interventions (Table 2). Appropriate and inappropriate intervention-free survival analyses in the whole population and in the different groups are reported in Figs. 3 and 4.

Episodes of relevant worsening heart failure were observed during the follow-up period in 24 (4%) patients, ranging from 1% to 8% in the different groups (Table 2).

5. Discussion

5.1. Main characteristics

In our population of 604 consecutive patients who underwent ICD implantation for primary prevention of SCD, the inclusion criteria were similarly distributed among the MADIT II (24%), SCD-HeFT (24%), COMPANION (26%) and MADIT-CRT (18%), while a smaller number of patients met the MUSTT and MADIT enrollment criteria (7%). We did not observe differences in mean age (66 ± 10 years) or sex distribution (83% males) in comparison with all major trials [1–3,5,6,8]. A distinctive observation is the large number of patients treated with CRT for ischemic/non-ischemic cardiomyopathies and left bundle branch block who were in NYHA classes I–II, thus anticipating the inclusion criteria of the MADIT-CRT [8] and REVERSE [28] trials. In the IRIDE registry, the percentages of patients treated with ACEi/ARB (83%) and beta-blockers (82%) were greater than in the main trials (60% and 26% in the MADIT trial, 72% and 29% in MUSTT, 68% and 70% in MADIT II), but not different from more recent randomized studies (94% and 69% in SCD-HeFT, 90% and 68% in COMPANION, 97% and 93% in MADIT-CRT). Amiodarone was administered to 17% of patients, a greater percentage than that reported in the MADIT (2%) and MADIT II (13%) trials, as a possible consequence of the high prevalence of atrial tachyarrhythmias (Table 1).

5.2. Survival analysis and ICD intervention

In the IRIDE study overall survival was 94%, 89%, 80% and 75% at 12, 24, 36 and 48 months, respectively (Fig. 1A). Patients who met the MUSTT–MADIT criteria [1,5] displayed a not-significantly different mortality rate from those enrolled in the original trials, being 8% at both 12 and 36 months vs 8% and 21% in the MADIT trial (p = ns) and 4% and 16% in the MUSTT trial (p = ns), respectively.

Not-significantly different mortality rate was also observed at 12, 24, 36 and 48 months of follow-up in patients enrolled on the basis of the MADIT II [6] and SCD-HeFT [2] inclusion criteria vs. original trials: 11%, 18%, 28% and 34% vs 8%, 15%, 21% and 23% for MADIT II (p = ns) and 6%, 11%, 18% and 31% vs 6%, 11%, 17% and 22% for SCD-HeFT (p = ns), respectively. Non significantly diverging results were also observed in patients who were treated by CRT devices on the basis of COMPANION [3] and MADIT-CRT [8] inclusion criteria: the mortality

Table 2
Number of arrhythmic events, appropriate/inappropriate ICD therapies, electrical storms and device replacement/upgrading in total population and in single groups stratified according to the inclusion criteria of the main randomized clinical trials.

	MADIT–MUSTT	MADIT II	SCD-HeFT	COMPANION	MADIT-CRT	TOTAL
Patients with appropriate ICD intervention only (%)	8 (18%)	36 (25%)	40 (28%)	30 (77%)	20 (18%)	134 (22%)
Patients with both appropriate and inappropriate ICD interventions (%)	0	6 (4%)	5 (4%)	1 (0.6%)	3 (3%)	15 (2%)
Patients with inappropriate ICD intervention only (%)	2 (5%)	4 (3%)	7 (5%)	6 (4%)	4 (4%)	23 (4%)
Ventricular fibrillation episodes (no. of patients)	15 (1)	29 (13)	29 (11)	8 (6)	8 (6)	89 (37)
Shocks for VF per treated patient (mean ± STD deviation)	–	2.5 ± 2.3	2.8 ± 3.2	1.5 ± 0.8	1.5 ± 1.2	2.6 ± 3.1
Ventricular tachycardia episodes (no. of patients)	72 (8)	110 (38)	166 (40)	114 (31)	234 (21)	696 (138)
ATP treatment for VT episodes (no. of patients)	52 (8)	101 (29)	144 (38)	77 (24)	107 (20)	481 (119)
Shocks for VT episodes (no. of patients)	33 (5)	25 (14)	33 (12)	18 (9)	132 (7)	241 (47)
ATP and/or shock for VT per treated patient (mean ± STD deviation)	6.6 ± 7.4	1.8 ± 1.7	2.8 ± 2.2	2.0 ± 1.3	18.9 ± 44.6	5.1 ± 17.2
Inappropriate ATP/shocks (no. of patients)	9 (2)	42 (10)	79 (12)	27 (7)	14 (7)	171 (38)
Patients with at least one electrical storm (%)	1 (2%)	2 (1%)	3 (2%)	4 (3%)	3 (3%)	13 (2%)
Patients with at least one episode of worsening heart failure (%)	2 (5%)	3 (2%)	2 (1%)	8 (5%)	9 (8%)	24 (4%)
Upgrade to CRT (%)	–	1 (0.6%)	2 (1%)	–	–	3 (0.5%)
Device replacement (%)	2 (5%)	2 (1%)	3 (2%)	3 (2%)	1 (1%)	11 (2%)

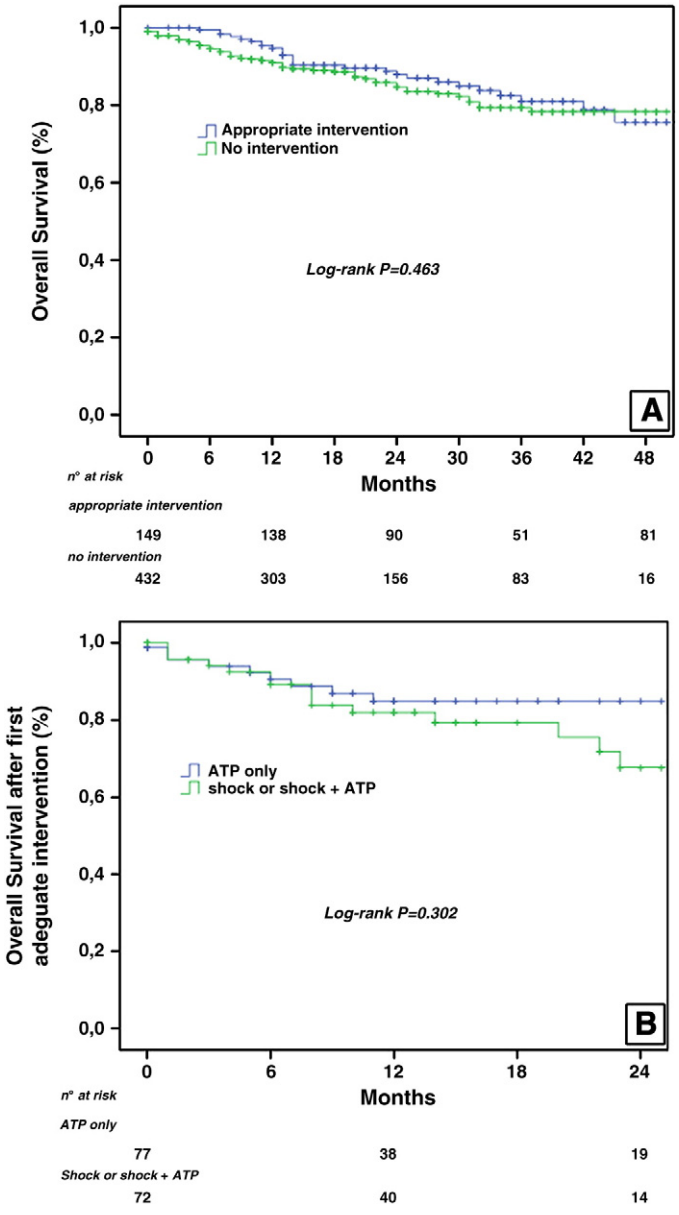

Fig. 2. Kaplan–Meier curves showing overall survival according to presence/absence of at least one appropriate ICD intervention (A) and survival after first appropriate therapy (B) in patients stratified according to type of therapy delivered.

rates where 7% and 24% vs. 18% and 31% at 12 and 36 months for COMPANION group and 8%, 13% and 13% vs. 8%, 13% and 18% at 12, 24 and 36 months for MADIT-CRT group, respectively.

Of note, in the IRIDE population we did not observe a different mortality rate between the group of patients who received appropriate ICD interventions and the group of patients who had no ICD intervention (Fig. 2A), also after the first appropriate intervention (Fig. 2B). Possible explanations may include the technological improvement in devices used in the IRIDE study and the high percentage of patients treated with ATP, and not with shock-only therapy (Table 2). By contrast, in the SCD-HeFT [2] and MADIT II [6] trials, appropriate ICD therapy was associated with higher mortality rates, possibly on account of the prevalent use of shock therapy in MADIT II and no provision for ATP programming in SCD-HeFT. The MADIT II investigators first raised the issue of worsening prognosis after ICD therapy [18], characterized by 3-fold increase of mortality rate, and higher rate of hospitalizations for heart failure. Analysis of the SCD-HeFT [2] data showed similar findings, suggesting the unfavorable role of myocardial damage induced by ICD shocks [29]. The additional benefit of ATP programming and of ventricular arrhythmia recognition window widening has been recently demonstrated in primary prevention both in patients with ischemic and non-ischemic dilated cardiomyopathy treated by single, dual and CRT-ICD devices [30,31].

The analysis of event-free survival curves showed that over 48 months of follow-up half of the patients (50%) had a potentially life-threatening arrhythmic event that required appropriate device intervention. These data are perfectly consistent with those reported in MADIT II (35% of appropriate interventions at 3 years vs. 36% in the IRIDE study, p = ns). All these data confirm the life-saving role of ICD therapy in the setting of class I recommendation for the primary prevention of sudden cardiac death. During the follow-up episodes of electrical storm were detected in a limited number of patients treated by ICD (2%), according to the main data reported in the setting of primary prevention by ICD therapy [25,26]. In our study population, patients who underwent CRT therapy following COMPANION and MADIT-CRT inclusion criteria showed a significantly lower ($p<0.05$) appropriate ICD intervention rate in comparison to patients treated on the basis of MADIT, MADIT II and SCD-HeFT criteria (Fig. 3B). This trend confirms the possible antiarrhythmic effect of the reverse remodeling obtained by CRT [32]. A great challenge for the future will be the identification in clinical practice of new and stricter risk-profiling strategies to select only high-risk patients who actually could benefit from ICD implantation [33].

One of the main criticisms of ICD therapy is the possible high rate of inappropriate interventions [34,35]. In our study population, 17% of all ICD interventions were inappropriately delivered in a small

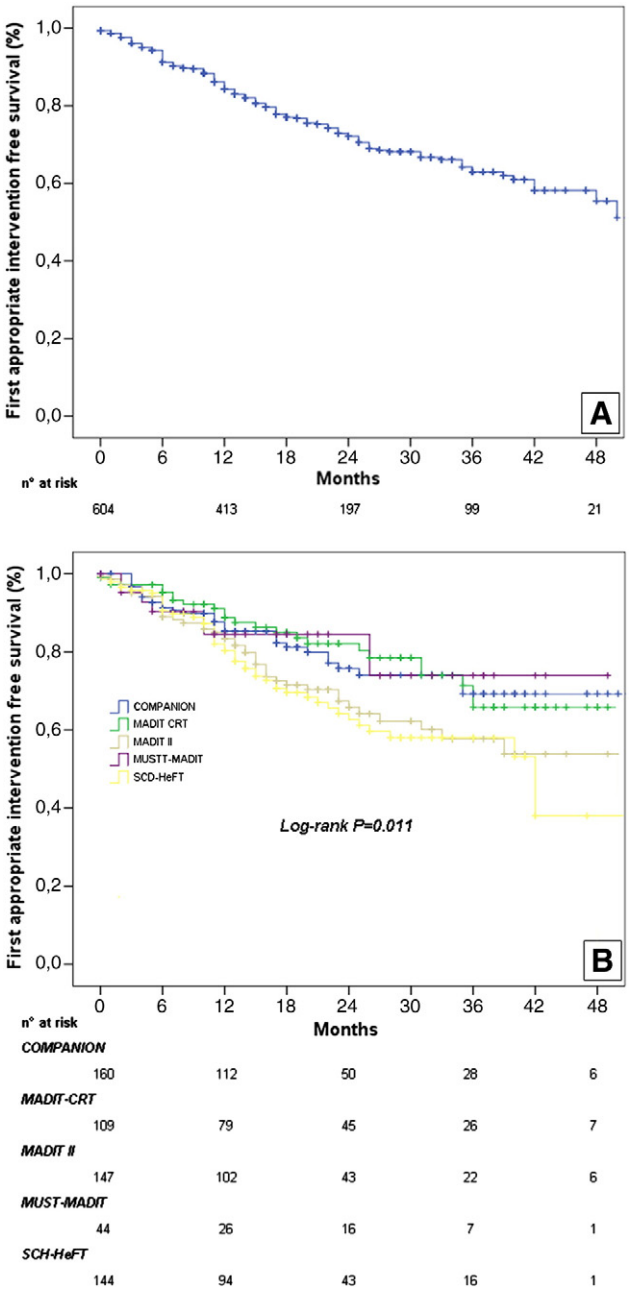

Fig. 3. Kaplan–Meier curves showing first appropriate ICD intervention-free survival in the whole population (A) and in patients stratified according to the inclusion criteria of the main trials (B).

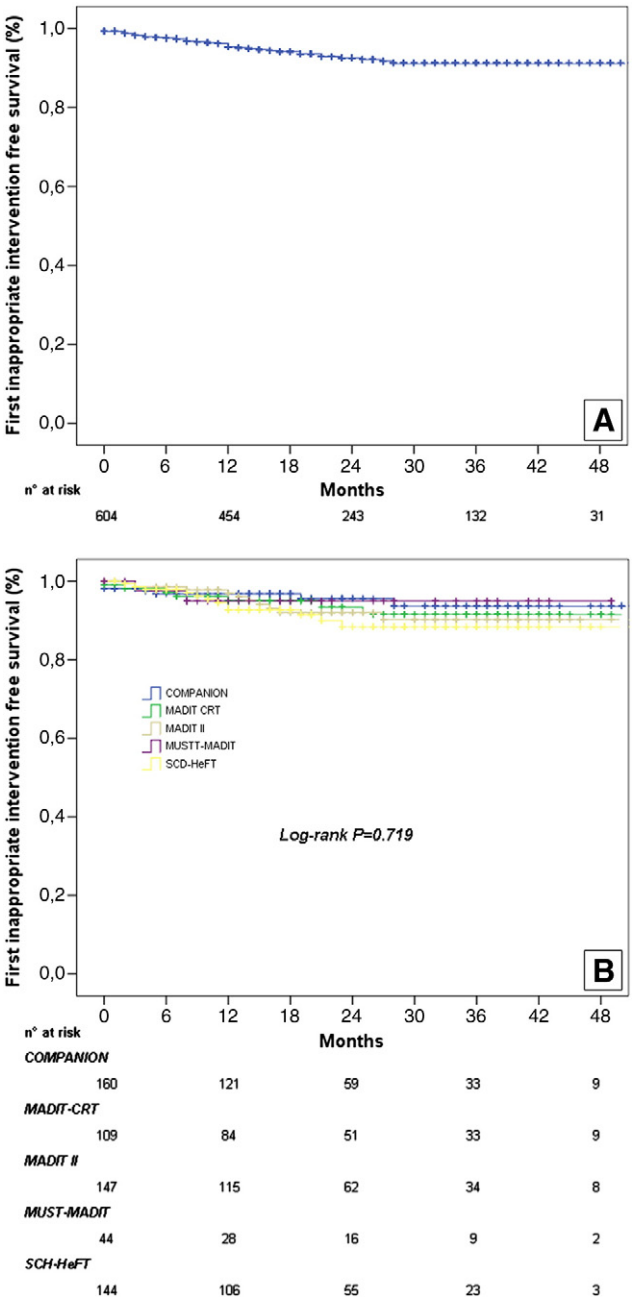

Fig. 4. Kaplan–Meier curves showing first inappropriate intervention-free survival in the whole population (A) and in patients stratified according to the inclusion criteria of the main trials (B).

number of patients (6%), many of whom (2%) also had appropriate ICD interventions. The probability of undergoing an inappropriate shock was similar according to the inclusion criteria of the main trials (log-rank p = ns) (Fig. 4A and B). The percentage of inappropriate shocks was comparable to that reported in the literature (10 to 24% of all ICD discharges) [34,35], but the number of patients who underwent inappropriate intervention in our series was lower as a possible consequence of the wide application of up-to-date discriminating algorithms [34,35].

5.3. Study limitations

As IRIDE was an observational study, it has some limitations:

1. Device programming was empirically left to single center preference, though the activation of ATP therapy on the basis of PAINFREE results [20,21] was strongly recommended in the majority of patients.
2. We have no data on the possible causes of inappropriate interventions, such as supraventricular tachyarrhythmias, T wave oversensing, lead fractures, myopotential oversensing and other interferences. However, the low number of patients who underwent inappropriate therapy reflects a careful follow-up in our series.
3. The IRIDE study used ICDs from several manufacturers, unlike the main trials in which devices from one or two manufacturers were used. This aspect, however, reflects normal clinical practice. Moreover, we used technologically advanced defibrillators with activation of the most recent pacing and discrimination algorithms.
4. We did not perform arrhythmic risk stratification for better selection of candidates to ICD therapy, as was proposed in the most recent retrospective analysis of MADIT II [23] and SCD-HeFT trials [19]. In this regard, we preferred to use the same selection criteria used in the original studies, as this approach is more in line with

evidence-based medicine than the findings of sub-analyses which require prospective validation.

6. Conclusions

Our study confirms in real world practice the effectiveness of ICD implantation in patients at risk of SCD, who meet the inclusion criteria validated in the main trials. Since IRIDE was an observational-prospective study with a relatively long-term follow-up, it yielded meaningful clinical information on primary ICD therapy that cannot be obtained from trials that are designed to terminate when statistical cutoffs are reached or when the time allocated for the trial expires. According to recent data [23,36], there is evidence that the life-saving role of ICD therapy increases as the duration of follow-up is prolonged.

We observed similar mortality rates in patients who received appropriate device treatment and in those who had no device intervention, suggesting that improved ICD programming (ATP therapy for VT) increases the long-term survival benefit. All our data on the life-prolonging benefit of ICD therapy provide support for a more widespread use of ICD in the setting of primary prevention.

Appendix 1. Participating centers

University Hospital S.M.M. — Udine
Hospital San Giovanni di Dio — Salerno
Hospital Antero Micone — Sestri Levante
University Hospital — Trieste
Hospital Bolognini — Seriate
Hospital Santa Chiara — Trento
Hospital Valduce — Como
Hospital S. M. Degli Angeli — Pordenone
Hospital S. M. Annunziata — Bagno a Ripoli
University Hospital San Raffaele — Milano

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