The First Firing after ICD Implantation: An Observational Multicentric Analysis of Clinical Reaction Time to ICD Therapy

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Abstract
Our research aimed to describe the management of patients after an implantable cardioverter defibrillator (ICD) shock in clinical practice and to evaluate if the delay between ICD shock and subsequent in-hospital visit may influence clinical outcomes. Twelve Italian cardiologic centers followed 976 consecutive ICD patients. During a mean follow-up of 27 months, 153 patients received at least an ICD shock. Among 153 patients with ICD shocks 20 (13%) died; mortality did not differ significantly between patients whose first shock was checked with a longer reaction time (>1 day) and patients whose first shock was checked with a shorter reaction time (≤ 1 day). After a shock, ICD reprogramming was performed for 62% of the appropriate shocks and 75% of the inappropriate shocks. Our data indicate that the reaction to ICD shocks was heterogeneous. Many ICD shocks were not evaluated in a timely manner (within 1 day) despite the observation that ICD re-programming is often needed; mortality, nevertheless, doesn’t seem to be associated with ICD shock reaction time.

Keywords — Implantable Cardiac Defibrillator; In-hospital and remote follow-up; Shock.

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I. INTRODUCTION

The use of implantable cardioverter-defibrillators (ICDs) for the prevention of sudden cardiac death increases the survival rate of patients treated for secondary (1-3) as well as primary prevention (4-8) indications.

An estimated 20% to 35% of patients who receive an ICD for primary prevention will experience an appropriate shock within 1 to 3 years of implantation (4-7), and one third of patients will experience an inappropriate shock (9). Forty-five percent of heart failure (HF) patients who survive a cardiac arrest and receive an ICD for secondary prevention will receive a shock within 1 year of implantation (1).

The correlation between ICD shocks, both appropriate and inappropriate, death and HF hospitalizations has been recently investigated. (10-12) Poole et al. (10) reported adverse long-term outcomes in patients who received ICD shocks. Sweeney et al. (11) demonstrated that each shock episode increases the relative risk of death by 20%. Moss et al (12) showed that programming ICD therapies only for ventricular tachyarrhythmias of 200 beats per minute or higher or even of 170 beats per minute or higher but with prolonged therapy delay, as compared with conventional programming, was associated with significantly reductions in inappropriate therapy and, importantly, in all-cause mortality during long-term follow-up.

ICD patients, after receiving a shock, report significant decreases in many aspects of quality of life (13), anxiety, depression and very low acceptance of the device (14). Despite the high frequency of shocks in the ICD population, the associated risks and the temporary effects on the quality of life, current practice guidelines do not offer a clear stepwise approach for the evaluation and treatment of patients who experience their initial ICD shock. For this reason, a large heterogeneity may characterize the reaction of both patients and cardiologists to the occurrence of ICD shocks.

The aim of our research was to describe the management of patients after an ICD shock event in Italian clinical practice and to evaluate if the delay between ICD shock and subsequent in-hospital visit may influence clinical outcomes.
In-hospital follow-up examinations were scheduled according to the clinical practice of each center. No patient was followed up with remote control.

Clinical management was performed at the judgment of expert cardiologists. ICDs were programmed in accordance with the clinical practice of each center, with careful attention to minimize inappropriate and unnecessary ICD therapies. At each scheduled or unscheduled visit, the ICD was interrogated, and the integrity and appropriate functioning of the implanted system was checked.

The stored electrogram (EGM) was used to classify all spontaneous episodes. All arrhythmic events were adjudicated by an Episode Review Board (ERB) composed of seven expert electrophysiologists. Each episode was reviewed by two different experts; in the case of disagreement, the episode was reviewed by the four ERB members in a plenary session.

The primary endpoint was the shock reaction time, i.e. the time between the first shock and the subsequent in-hospital visit. We also collected information about ICD re-programming after an ICD shock. Finally informations about clinical outcomes, such as hospitalizations and deaths, were collected during hospital visits or, in the case of missed scheduled visits, via telephone calls.

### II. METHODS

#### PATIENT POPULATION

Consecutive ICD patients were included and prospectively followed by 12 cardiovascular centers in the North-East regions of Italy. All centers participate in the Italian Clinical Service project, [http://clinicaltrials.gov/ct2/show/NCT01007474](http://clinicaltrials.gov/ct2/show/NCT01007474), a national medical care project that has been aimed at evaluating and improving the use of implantable cardiac devices in clinical practice since 2006. The project consists of a shared environment for collection, management, analysis and reporting of clinical and diagnostic data from patients wearing Medtronic (Minneapolis, MN) implantable devices. Each patient signed an informed consent form, which had been approved by the Institutional Review Board or Medical Director of each center. All patients received an implantable cardioverter defibrillator (ICD) or cardiac resynchronization therapy defibrillator (CRT-ICD) according to current secondary or primary prevention guidelines (15-16).

#### FOLLOW-UP AND DATA COLLECTION

The baseline assessment included demographics, medical history, cardiovascular medication, a standardized clinical examination, a 12-lead ECG, assessment of the New York Heart Association (NYHA) functional class and an echocardiographic evaluation.

Continuous data were expressed as an average±standard deviation (SD) for variables with a normal distribution, or as a median and 25th-75th percentile range (PR) for variables with skewed distributions. Categorical variables were expressed as absolute and relative frequencies.

To account for various follow-up durations in different subgroups of patients, the number of in-hospital visits and the number of shocks per patients were adjusted by considering the total number of patient-years of observation and by estimating annual rates. Comparisons of the shock reaction time between groups were performed using Mann-Whitney’s test.

Kaplan-Meier method was used to estimate the incidence of shocks.

Statistical analyses were performed by mean of SPSS 12.0 (SPSS Inc., Chicago, Illinois) and Stata SE9.0 (StataCorp, Texas, USA). A 2-sided p-value <0.05 was considered statistically significant.

#### TABLE I

**PATIENT CHARACTERISTICS**

<table>
<thead>
<tr>
<th>Patients characteristics</th>
<th>% mean±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>820 (84%)</td>
</tr>
<tr>
<td>Age (years mean±SD )</td>
<td>67 ± 10</td>
</tr>
<tr>
<td>Body Mass Index (mean±SD)</td>
<td>26 ± 4</td>
</tr>
<tr>
<td>NYHA class</td>
<td></td>
</tr>
<tr>
<td>NYHA I</td>
<td>78 (8%)</td>
</tr>
<tr>
<td>NYHA II</td>
<td>459 (47%)</td>
</tr>
<tr>
<td>NYHA III</td>
<td>429 (44%)</td>
</tr>
<tr>
<td>NYHA IV</td>
<td>10 (1%)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>820 (84%)</td>
</tr>
<tr>
<td>Left Ventricular Ejection Fraction (% mean±SD)</td>
<td>29±9</td>
</tr>
<tr>
<td>Hypertension</td>
<td>547 (56%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>234 (24%)</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>88 (9%)</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>90 (9%)</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>441 (45%)</td>
</tr>
</tbody>
</table>

#### III. RESULTS

From April 2004 to March 2010, 976 patients were included in 12 cardiovascular centers in the North-East regions of Italy.
Patients baseline characteristics are reported in table I. 732 patients (75%) had a primary prevention indication, while 244 patients underwent implantation for secondary prevention. During a mean follow-up of 27±18 months, 8128 ICD in-hospital visits were reported. The median number of visits for each patient was 4.5 per year [PR=3.1–7.1].

**VENTRICULAR ARRHYTHMIAS**
A total of 3848 spontaneous ventricular episodes were recorded by ICDs in 392 (40%) patients. 2429 episodes received therapy by the implanted ICD in 291 (30%) patients, of whom 138 (14%) patients were treated only with anti-tachycardia pacing therapy (ATP) while 153 (16%) patients received at least one ICD shock. Appropriate shocks occurred in 101 (10%) patients, while inappropriate shocks occurred in 72 (7%) patients. Twenty patients received both appropriate and inappropriate Shocks. The Kaplan-Meier incidences of appropriate and inappropriate shocks are shown in figure 1. The annual patient rates of appropriate and inappropriate shocks were 4.6 and 3.3 per 100 patient-years, respectively. The causes of inappropriate ICD shocks are shown in table II. The median time to the first appropriate ICD shock was 10 (PR=3-21) months, while the median time to the first inappropriate ICD shock was 6 (PR=2-19) months.

**SHOCK REACTION TIME**
The median reaction time for the first ICD shock was 5 days [PR 1-43 days]. The median time between the first ATP and the closer follow-up visit was 21 days [PR 1-64 days].

Median shock reaction times associated with the 7 cardiologic centers which followed patients with ICD shocks are shown in Table III. The comparison of these times among centers showed a statistically significant heterogeneity (p<0.004).
The median reaction time was 1 day [PR 1-3 days] for episodes with multiple shocks and 8 days [PR 2-60 days] for episodes with only one shock (p<0.001).

No statistically significant difference was found when comparing shock reaction times between appropriate versus inappropriate shocks.

The median reaction time for the second ICD shock was 11 days [PR 2-59 days, p=0.268 compared with first ICD shock reaction time].

**CLINICAL OUTCOMES**
During follow-up, 141 patients died, corresponding to a 6% yearly mortality rate. Among 153 patients with ICD shocks, 20 (13%) died during the observation period; we observed a non significative difference between mortality in patients whose first shock was checked with a longer reaction time (>1 day) compared with patients whose first shock was checked with a shorter reaction time (≤1 day) - 14/95 (15%) vs. 6/58 (10%), p=0.43. Among 153 patients with ICD shocks, 24 (17%) died or were hospitalized for HF during the observation period; patients whose first shock was checked with a longer reaction time (>1 day) were associated with a higher incidence, even if not statistically significant, of the endpoint composed by death or HF hospitalization compared with patients whose first shock was checked with a shorter reaction time (≤1 day) - 16/95 (17%) vs. 8/58 (14%), p=0.6. ICD shocks were associated with hospitalizations mainly to solve ventricular lead related problems, in 29 patients, or for multiple shocks, in 10 patients, while no hospitalization was induced by a single ICD shock.

**ICD REPROGRAMMING**
ICD reprogramming occurred in 67% of visits which followed an ICD shock; in particular, the percentage of visits with ICD reprogramming was 62% in case of appropriate shocks and 75% in case of inappropriate ICD shocks.

**IV. DISCUSSION**
Current guidelines indicate the use of implantable cardioverter-defibrillators to reduce the risk of sudden cardiac death in selected patients. Unfortunately guidelines do not specify a stepwise approach for the evaluation and treatment of patients who experience an ICD shock. This may cause a heterogeneous reaction to the occurrence of ICD shocks, either from a temporal or medical point of view. We aimed to describe reactions to ICD shocks, in terms of time delay between shock and subsequent visit and in term of ICD reprogramming, in the clinical practice of 12 Italian cardiovascular centers. We also aimed to evaluate if ICD shock reaction time may influence clinical outcomes. To the best of our knowledge, this is the first large multicenter study that shows the time between a shock and the next in-hospital visit.

The main results of our research were 1) ICD shocks reaction times were characterized by a significant heterogeneity; 2) in-hospital visits after the first ICD shock were performed within 1 day only in 25% of patients; 3) most post-shock in-hospital visits required ICD reprogramming; 4) a non-significative difference toward higher mortality incidence was observed in patients whose ICD shocks were reviewed.
after longer times (> 1 day) compared with shorter reaction times (≤ 1 day).

**VENTRICULAR ARRHYTHMIAS**

Our patient population received an ICD for primary (75%) or secondary (25%) prevention of sudden death. This distribution reflects the current trend in implant indications in Italy. During a mean follow-up of 27 months, 30% of our patients had ICD-treated ventricular arrhythmias and 16% of patients suffered ICD shocks, in particular 10% received an appropriate shock and 7% received an inappropriate shock. These percentages show that our ICD recipients had a lower incidence of shocks in comparison with previous primary and secondary prevention studies. (1-8) Considering only the most important recent primary prevention trials, the percentage of patients suffering ICD shocks was 29% in the MADIT II (7) trial during a mean observation period of 22 months and 33% in the SCD-HeFT (4) trial in a mean follow-up of 45 months. In our research the annual rates of patients with appropriate shocks was 4.6 per 100 patient-years while it was 3.3 per 100 patient-years for inappropriate shocks. The latter may be compared with 6.9 per 100 patient-years reported by MADIT II (7), with 4.6 per 100 patient-years reported by SCD-HeFT (4) and with 2.7 per 100 patient-years reported by MADIT RIT (12). A possible explanation of the difference in the percentage of patients receiving shocks between our project and MADIT II and SCD-HeFT could depend on the ICD programming. In fact, the SCD-HeFT study was designed to provide shock therapy for rapid, sustained ventricular tachycardia (VT) or ventricular fibrillation (VF) and ATP therapy was not allowed. In the MADIT-II study, alongside shock therapy, ATP was activated in 62% of patients. In our population, with the aim of reduce unnecessary and inappropriate shocks ATP was enabled in 92% of patients both in VT and fast VT detection zones.

**SHOCK REACTION TIME**

First ICD shock reaction time showed a significant heterogeneity; we observed a wide variability among the different centers which participated to the research (table III). This finding suggests the existence of different methodological approaches to the occurrence of shocks among different cardiologists and confirms that in real clinical practice there is not a shared conduct, despite a fair amount of evidence suggesting that patients who receive an ICD shock are at an increased risk of HF and death.

In-hospital visits after the first ICD shock were performed within 1 day only in 25% of patients and within 5 days only in 50% of patients. These findings are surprising because the first shock is usually perceived by patients as very important events in their life and because an un-reviewed shock of unknown etiology may expose patients to unnecessary risks of further shocks. Very few studies have reported about ICD shock reaction times. Lunati et al. (17) measured the time occurring between an ICD shock and the following device in-hospital visits finding that 80% of shock episodes were followed by an in-hospital visit within five days of the shock. The Connect trial (18), which showed that wireless remote monitoring with automatic clinician alerts significantly reduces the time to make a clinical decision in response to clinically relevant events as compared with a standard in-office follow-up, reported that the median time between the occurrence of 2 shocks delivered in an episode and the related clinical decision in the standard in-hospital follow-up arm was less than 24 hours, with an interquartile range of (0–2) days. This result, compared to our findings in terms of ICD shock reaction times, outlines the fact that real practice induces large variability compared to the results of controlled clinical trials.

Faster reaction times were observed for the first ICD shocks compared with the subsequent ones. This result may be explained by the fact that the first shock was unexpected, and could change patient’s perception of the disease.

Finally isolated shocks had slower reaction times than multiple shocks. These findings are expected because patients react differently to single or multiple shocks and because clusters or storms of episodes have been associated with worse prognosis (19).

**CLINICAL OUTCOMES AND IMPLICATIONS**

The correlation between ICD shocks, both appropriate and inappropriate, death and HF hospitalizations has been recently investigated. (10-12) Poole et al. (10) reported adverse long-term outcomes in patients who received ICD shocks. Sweeney et al. (11) demonstrated that each shock episode increases the relative risk of death by 20%. Moss et al (12) showed that programming ICD therapies only for ventricular tachyarrhythmias of 200 beats per minute or higher or even of 170 beats per minute or higher but with prolonged therapy delay, as compared with conventional programming, was associated with significantly reductions in inappropriate therapy and, importantly, in all-cause mortality during long-term follow-up.

The poor prognosis after an ICD shock (10-11) seems to warrant careful and fast monitoring of these patients. For this reason, in our observational research we aimed to compare incidence of death, and incidence of the endpoint composed by death or HF hospitalization, in patients whose ICD shocks were controlled after a short or long delay. We found that raw incidence of death was 15% in patients whose first shock was checked with a longer reaction time (>1 day) compared with 10% in patients whose first shock was checked with a shorter reaction time (≤1 day). We also found that the incidence of the endpoint composed by death or HF hospitalizations was 17% in patients whose first shock was checked with a longer reaction time (>1 day) compared with 6.9 per 100 patient-years reported by SCD-HeFT (4) and with 2.7 per 100 patient-years reported by MADIT RIT (12). A possible explanation of the difference in the percentage of patients receiving shocks between our project and MADIT II and SCD-HeFT could depend on the ICD programming. In fact, the SCD-HeFT study was designed to provide shock therapy for rapid, sustained ventricular tachycardia (VT) or ventricular fibrillation (VF) and ATP therapy was not allowed. In the MADIT-II study, alongside shock therapy, ATP was activated in 62% of patients. In our population, with the aim of reduce unnecessary and inappropriate shocks ATP was enabled in 92% of patients both in VT and fast VT detection zones.

**TABLE III**

<table>
<thead>
<tr>
<th>Center</th>
<th>First Shock reaction Time Days (25th and 75th percentile)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Center1</td>
<td>5 (4-5)</td>
</tr>
<tr>
<td>Center2</td>
<td>13 (1-28)</td>
</tr>
<tr>
<td>Center3</td>
<td>4 (2-22)</td>
</tr>
<tr>
<td>Center4</td>
<td>5 (2-218)</td>
</tr>
<tr>
<td>Center5</td>
<td>4 (1-36)</td>
</tr>
<tr>
<td>Center6</td>
<td>20 (2-92)</td>
</tr>
<tr>
<td>Center7</td>
<td>10 (1-38)</td>
</tr>
</tbody>
</table>
time (>1 day) compared with 14% in patients whose first shock was checked with a shorter reaction time (≤ 1 day). Our research, being an observational one, was not powered to test a statistical difference in mortality as a function of ICD reaction times; anyhow the mentioned trends confirm the importance of careful and fast monitoring after ICD shocks.

No significant differences in mortality were reported among the participating centers.

Mishkin et al. (20) suggested, in particular for HF patients receiving a shock, close surveillance throughout the following year for early signs and symptoms of impending decompensated HF. During this period, careful monitoring for recurrent AF (especially in patients who received inappropriate shocks) and titration of beta-blockers to the optimal dosage have been proposed. Monitoring of patients who suffered ICD shocks should include a combination of more frequent clinical encounters, titration of established HF therapy as tolerated and close attention to volume status. A multidisciplinary approach involving the primary care physician, the HF specialist, and the electrophysiologist could be employed. Gehi et al. (21) explained that management of a single ICD shock does not necessarily require an emergency office or emergency department visit. Although an ICD shock can be a frightening experience for the patient, occasional shocks are to be expected. When a single shock occurs, the physician should reassure the patient and refer him or her to a clinical electrophysiologist for evaluation within a week. However, if the shock is preceded or associated with syncope, shortness of breath, persistent palpitations, or chest pain, an emergency department visit would be required. In these cases the physician must consider the possibility that an arrhythmic process may have been triggered by a change in the clinical status of the patient, such as active coronary disease, worsening heart failure, or electrolyte imbalance. At the time of evaluation by the electrophysiologist, the appropriateness of ICD therapy can be determined by evaluating the stored electrograms. In our analysis no statistically significant difference has been found in the time that occurred between shock delivery and the first in-office visit in the case of appropriate versus inappropriate shocks, although the mean time is shorter when managing the first shock versus the subsequent shocks.

**FOLLOW-UP MANAGEMENT**

The majority of first shock episodes produced unscheduled urgent visits with a significant impact on costs and health care system resource allocation.

The fact that ICD reprogramming occurred in 67% of visits which followed an ICD shock - in particular, 62% for appropriate shocks and 75% for inappropriate ICD shocks – may lead to two apparently different conclusions. On one hand it could be stated that the need for reprogramming is frequent therefore it represents an added reason to have the patient in-hospital in addition to the possibility to perform a complete check-up. On the other hand, one third of shock-induced visits did not involve reprogramming, suggesting that those visits could have been performed remotely.

Lunati et al. (17) found even higher percentages - 49% - of clinical events where ICD shocks did not require device reprogramming.

The use of internet-based remote monitoring for a preliminary control of ICD shocks could prevent between one third and a half of unscheduled visits as well as patient travels while allowing a complete view on device diagnostic information, on ventricular arrhythmias and on ICD shock nature.

Taking into consideration the on-going increase in ICD indications and the rise in the number of implantations worldwide, the challenge for cardiologists in every day clinical practice will be to identify effective means of handling the growing ICD follow-up burden while discriminating between events which can be managed remotely and events which warrant careful in-hospital evaluation.

**LIMITATIONS**

The presented results come from a retrospective analysis of prospectively collected data. Research objectives were pre-specified before opening the database.

The research was not powered to test differences in clinical outcomes as a function of ICD shock reaction times, anyhow this specific objective could not be studied in a randomized controlled study therefore we believe that our observational research adds valuable information about factors which may influence clinical outcomes in real life practice.

The non-standardized device management among centers (e.g. frequency of routine follow-up or ICD shock reaction times) should not be considered as a limitation, rather represents one of the aspects, that our research wanted to evaluate, which characterize the real clinical practice of the involved centers. Moreover this characteristic allowed us to compare clinical outcomes in different ICD management approaches and to propose actionable clinical recommendations.

Only Medtronic devices were included in the project but this should not bias either patient population characteristics or
research results since the project included consecutive patients. Anyhow we consider that our results could not be applicable to devices from different manufacturers, or to institutions adopting specific approaches to post-shock device management.

V. CONCLUSIONS

ICD therapy is part of standard medical care to reduce the risk of sudden cardiac death in patients, both in primary and in secondary prevention. Despite the fact that shocks are quite frequent events in ICD patients and that evidence is increasing about the association between shocks and worse prognosis, we showed that in clinical practice the management of ICD shocks is characterized by a high heterogeneity; in terms of ICD shock reaction times, only 25% of patients were controlled within 24 hours from their first ICD shock. We also showed that many post-shock visits needed ICD reprogramming and that death incidence was higher, even if not statistically significant, in patients treated with longer delay after a shock. ICD management best practice should outline the importance of a fast reaction to first ICD shock in terms of identifying the shock etiology and causes, monitoring patient status and eventually intervening on patient therapy.

VI. ACKNOWLEDGMENTS

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APPENDIX

Centers and investigators participating in the Triveneto project are listed below.


REFERENCES


