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Determinants of inappropriate implantable cardioverter-defibrillator shocks: the German Device Registry perspective

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Abstract

Background In the present study, we have focused upon rates and clinical determinants of inappropriate shock (IS) after implantable cardioverter-defibrillator (ICD).

Methods Data were collected prospectively in the German Device II Registry.

Results A total of 783 patients were included. Three sub-groups were identified: non-shock (NS) included 725 patients (92.6%), IS 24 (3.1%), and appropriate shock (AS) 34 (4.3%). IS patients were younger (AS 68 (58–77); IS 59 (51–68); NS 66 (56–75) years; $p = 0.03$), had been mainly referred for primary prophylaxis (AS 42.4%; IS 70.8%; NS 67.3%; $p = 0.01$), had a higher resting heart rate (AS 70 (63–80); IS 80 (71–98); NS 70 (60–81) BPM; $p = 0.003$), had more often atrial fibrillation (AF) (AS 14.7%; IS 45.8%; NS 18.8%; $p = 0.006$), and shorter QRS duration (AS 100 (90–120); IS 95 (90–100); NS 120 (98–150) msec.; $p = 0.001$). VVI-ICD was more common in IS (AS 64.7%; IS 83.3%; NS 49.8%; $p = 0.002$). At a follow-up of 18.2 months (75% IQR 13.6–22.4), no deaths were observed in the IS group, one (2.9%) in the AS, and 36 (4.9%) in the NS ($p = 0.9$). At logistic regression, VVI-ICD implantation was the strongest IS independent determinant (OR 5.0; 95% CI 1.6–15.9; $p = 0.004$) together with age < 70 years (OR 4.6; CI 1.4–14.7; $p = 0.009$), AF at time of ICD implantation (OR 3.5; CI 1.3–9.1; $p = 0.01$), and resting heart rate > 70/min (OR 2.8; CI 1.0–7.3; $p = 0.03$).

Conclusion In a contemporary setting, some specific conditions such as VVI-ICD, younger age, and faster resting heart rates remain important IS determinants after ICD implantation.

Keywords Inappropriate · Shock · Cardioverter · Defibrillator

1 Introduction

Although implantable cardioverter-defibrillator (ICD) provides a significant mortality reduction in sudden cardiac arrest survivors and in patients with advanced cardiovascular disease [1–4], delivery of inappropriate shocks (IS) may increase morbidity and mortality and have impact on patients' quality of life.

All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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A better understanding of the etiology and independent predictors of IS could help reduce their occurrence, particularly in patients implanted with ICD at a younger age and for primary prevention. In the present study, we have focused upon rates and clinical determinants of IS within the premises of a multicenter, prospective, real-world registry, i.e., the German Device II Registry.

2 Methods

The German DEVICE-II registry is one of the largest European databases for cardiac implantable electronic devices (CIED) and includes patients implanted with ICD and cardiac resynchronization therapy (CRT) devices. Data are collected prospectively in a computerized database and are analyzed retrospectively, on the basis of the research queries formulated by the participating centers. The registry has been supported by "Stiftung Institut für Herzinfarktforschung (IHF)" and by Biotronik, Medtronic, and St. Jude Medical. Patients discussed in the present manuscript were treated during the period February 2011–February 2014. All patients gave written informed consent and data were collected via web-based electronic case report forms. A positive vote was obtained from the ethics committee of the Landesaerztekammer Rheinland-Pfalz in April 2011.

All centers were encouraged to enroll consecutive patients who received a first implantation of ICD or CRT and who gave informed consent. However, the actual enrolment periods and enrolment size varied across centers. A clinical and technical (device) follow-up has been routinely performed by the implanting centers, and findings have been forwarded to a central database at preestablished time points. If necessary, information on clinical events was supplemented by telephone calls from the IHF at 1 year after inclusion. Complete data from device interrogations could be obtained only from 6 of the 14 participating centers of the German Device Registry. The present analysis includes only those patients that had undergone a documented device interrogation. No specific information concerning the different institutional policies for ICD programming has been provided. A shock not delivered for ventricular tachycardia (VT) or ventricular fibrillation (VF) was deemed IS. An IS episode has been defined as an episode during which 1 or more IS occurred; another inappropriate ICD episode occurring within 5 min has not been accounted for. Finally, the time of occurrence and the reason for device therapy have not been reported.

2.1 Statistical analysis

In a first analysis, we have compared patients that had experienced appropriate shocks (AS), IS, and no shocks (NS) as documented by the device follow-up interrogation. Categorical variables are presented by absolute numbers and percentages and are compared by chi-square tests. Continuous variables are expressed as means with standard deviations or medians with interquartile ranges and are compared by Mann-Whitney-Wilcoxon tests. The cumulative 1-year incidence of mortality has been estimated by the Kaplan-Meier method with log-rank testing.

In a second step, we have tried to identify independent determinants for inappropriate shocks by means of backward and forward stepwise logistic regression.

All tests were two tailed and p values < 0.05 were considered significant. SAS statistical package version 9.3 (Cary, NC, USA) was used for the computations.

3 Results

The Device II Registry includes a cohort of 1018 ICD patients. The present study focuses only on those 783 patients who underwent at least one clinical follow-up visit and device interrogation within the premises of the implanting center. Preoperative and perioperative data in the 3 sub-groups are summarized in Table 1. The NS group included 725 patients (92.6%), the IS 24 (3.1%), and the AS 34 (4.3%). Only 4 out of 783 patients (0.5%) experienced both AS and IS. Due to the limited number of combined events, we did not think it valuable to perform a sub-analysis to identify additional predictors of events in this sub-group.

Patients experiencing IS were significantly younger ($p = 0.03$), had been more often referred for primary prophylaxis ($p = 0.01$), had a significantly higher resting heart rate ($p = 0.003$), had been more often in atrial fibrillation (AF) ($p = 0.006$), and had a shorter QRS complex duration on routine 12-lead ECG ($p = 0.001$). Operation duration was significantly longer in the NS patients ($p = 0.004$). Implantation of a single-lead ICD (VVI-ICD) was more common in the IS group ($p = 0.002$). In-hospital morbidity and mortality were similar in the 3 groups. At a median follow-up of 18.2 months (75% IQR 13.6–22.4 months), no mortalities were observed in the IS group, one (2.9%) in the AS group, and 36 (4.9%) in the NS group ($p = 0.9$) (Table 2). Kaplan-Meier-estimated 1-year survival was similar in the 3 groups ($p = 0.7$). Hospital readmissions for cardiovascular reasons (including ICD revisions) and visits to the outpatient cardiology departments were both significantly more common in patients experiencing IS. A total of 92 ICD shocks were experienced in the AS group and 91 in the IS group. More specific ICD recordings at follow-up, including additional ICD therapy (anti-tachycardia pacing (ATP)) and AF episodes, are reported in Table 2. Of note, patients experiencing AS had also more often experienced ATP ($p < 0.0001$). Moreover, in patients with IS, recording of AF episodes was significantly more common ($p < 0.001$).

Table 1 Device II German Registry. Preprocedural and periprocedural features of the 3 sub-groups (appropriate, inappropriate, and no shock at follow-up). Numbers refer to rates (discrete variables) and median and interquartile range (IQR) (continuous variables)

	Appropriate shock 34 patients (4.3%)	Inappropriate shock 24 patients (3.1%)	No shock 725 patients (92.6%)	*p* value
Age (years)	68 (58–77)	59 (51–68)	66 (56–75)	0.03
Female gender	5.9%	16.7%	20.4%	0.09
BMI	27.0 (24.5–30.0)	30.8 (25.9–34.8)	26.6 (24.0–29.8)	0.4
Primary prophylaxis	42.4%	70.8%	67.3%	0.01
CAD	67.6%	50.0%	57.1%	0.3
Valve disease	23.5%	29.2%	21.2%	0.5
Dilatative CMP	29.4%	54.2%	39.6%	0.1
Hypertensive CMP	8.8%	0	3.7%	0.2
Primary electrical disorder and CMP	2.9%	0	1.7%	0.6
CHF	29.4%	50.0%	47.7%	0.1
LVEF%	32 (25–41)	28 (20–33)	30 (25–37)	0.3
AF at admission	14.7%	45.8%	18.8%	0.006
HR at admission	70 (63–80)	80 (71–98)	70 (60–81)	0.003
LBB at admission	17.6%	8.3%	34.5%	0.004
QRS (ms.)	100 (90–120)	95 (90–100)	120 (98–150)	0.003
ICD (VVI)	64.7%	83.3%	49.8%	0.002
ICD (DDD)	17.6%	8.3%	19.9%	0.4
CRT-D	14.7%	8.3%	29.5%	0.01
Implantation duration (min.)	55 (40–95)	50 (35–59)	80 (45–115)	0.004
Periprocedural complications	0	0	1.1%	1
In-hospital mortality	0	0	0.1%	1

BMI body mass index, *CMP* cardiomyopathy, *CAD* coronary artery disease, *CHF* congestive heart failure, *LVEF%* left ventricular ejection fraction %, *AF* atrial fibrillation, *HR* heart rate, *LBB* left bundle branch block, *ICD* implantable cardioverter-defibrillator, *CRT-D* cardiac resynchronization therapy-defibrillator

A satisfaction questionnaire was administered at follow-up, at time of device interrogation. Patients in the 3 sub-groups seemed equally satisfied with the treatment received. Furthermore, the perception of the ICD as a protection tool against sudden death and the level of fear generated by a potential ICD shock were similar within the 3 groups (Table 3).

At logistic regression analysis, age < 70 years, AF at time of ICD implantation, resting heart rate > 70/min at time of implantation, and implantation of a VVI-ICD were all independent determinants of IS at follow-up (Table 4).

4 Discussion

The present study has focused upon incidence, predictors, and outcome of IS in a large real-world multicenter setting. In this contemporary scenario of patients implanted with ICD for primary and secondary prophylaxis of sudden cardiac death, the cumulative incidence of IS at follow-up was below 5%. Although IS occurred with a rather low rate, they led to a significantly increased rate of re-hospitalizations and outpatient visits. However, mortality and quality of life did not seem to be impacted by the occurrence of IS. Finally, we have identified patients and treatment traits which showed a specific independent impact upon IS occurrence. They included patients' age younger than 70 years, presence of AF at time of ICD implantation, and implantation of a single-lead ICD.

Identification of determinants of IS after ICD implantation may be critical to minimize the risk of harm to the patient. This is of particular importance in patients of younger age implanted for primary prophylaxis.

Our findings in this real-world scenario partly confirm data published in the less and more recent literature, including results from national databases and multicenter trials [5–11]. In a recent Swiss multicenter study, Hofer et al. have reported an IS rate of 23% in 100 ICD patients during a long-term follow-up (11 years). Patients with younger age or previous supraventricular arrhythmias were at increased risk of IS. No association between IS and increased long-term follow-up mortality was disclosed [9]. In a larger Spanish multicenter cohort of over 1000 ICD patients, Fernández-Cisnal et al. have reported a 6.8% rate of IS. In their multivariate analysis, age < 65 years and history of AF were identified as the strongest IS

Table 2 Device II German Registry. Follow-up outcomes of the 3 sub-groups (appropriate, inappropriate, and no shock at follow-up). Numbers refer to rates (discrete variables), mean with standard deviation (continuous normally distributed variables), and median and interquartile range (IQR) (continuous not normally distributed variables)

	Appropriate shock 34 patients (4.3%)	Inappropriate shock 24 patients (3.1%)	No shock 725 patients (92.6%)	*p* value
Follow-up (months)	21.8 (18.9–25.2)	21.8 (16.1–26.5)	18.2 (14.3–22.2)	< 0.001
Follow-up survival	97.0%	100%	95.0%	0.9
1-year estimated mortality (K-M)	3.3%	0	2.2%	0.7
Observed MI	5.3%	0	0.9%	0.2
Observed CVA	0	0	0.9%	0.2
Observed device revision	3.0%	12.5%	2.6%	0.03
Observed re-hospitalization	61.5%	85.7%	34.4%	< 0.001
Cardiology clinic visits	2.0 (0–5.0)	3.0 (0–5.0)	0 (0–3.0)	0.004
Recorded ATP	66.7%	47.8%	3.6%	< 0.001
Recorded AF	50.0%	87.0%	11.4%	< 0.001
Medications:				
Ace-inhibitor/angiotensin II Rec. blockers	76.9%	100%	77.8%	0.1
Diuretics	65.4%	64.3%	62.2%	0.9
Aldosterone antagonists	34.6%	71.4%	39.2%	0.04
Beta blockers	88.5%	92.9%	87.7%	1
Anti-arrhythmic (I-III-IV)	26.9%	15.4%	13.4%	0.1
Anti-coagulants	34.6%	71.4%	40.4%	0.05

KM Kaplan-Meier, *MI* myocardial infarction, *CVA* cerebrovascular accident, *ATP* anti-tachycardia pacing, *AF* atrial fibrillation

predictors. Moreover, IS did not seem to be associated with re-hospitalization and/or all-cause mortality [10]. A less recent Dutch experience including over 1500 ICD patients has shown a long-term follow-up (< 4 years) IS rate of 13% [5]. The cumulative IS incidence increased to 18% at 5-year follow-up. Independent predictors of IS were history of AF and

Table 3 Device II German Registry. Patient's satisfaction questionnaire administered at follow-up to the 3 sub-groups (appropriate, inappropriate, and no shock at follow-up)

	Appropriate shock 30 patients	Inappropriate shock 18 patients	No shock 649 patients	*p* value
Patient satisfaction after ICD implantation				
Fully satisfied	96.0%	92.3%	92.1%	0.8
Partly satisfied	4.0%	7.7%	7.4%	
Not satisfied	0	0	0.6%	
Patient would choose again for ICD implantation				
Yes	68.0%	64.3%	83.7%	0.02
Possibly yes	28.0%	14.3%	10.9%	
Possibly no	0	14.3%	4.4%	
No	4.0%	7.1%	1.0%	
Patient perception of ICD as protection against sudden death				
Yes	76.0%	57.1%	79.7%	0.1
Possibly yes	24.0%	28.6%	15.3%	
Possibly no	0	14.3%	3.1%	
No	0	0	1.9%	
Patient fear of ICD shocks				
Yes	12.0%	7.1%	11.7%	0.7
Possibly yes	16.0%	21.4%	9.9%	
Possibly no	28.0%	21.4%	26.3%	
No	44.0%	50.0%	52.2%	

Table 4 Independent determinants of inappropriate shock as detected (backward stepwise logistic regression)

	Unadjusted odds ratio (95% CI)	Multivariable odds ratio (95% CI)	*p* value
Age < 70 years	3.5 (1.2–10.4)	4.6 (1.4–14.7)	0.009
Atrial fibrillation	3.6 (1.6–8.3)	3.5 (1.3–9.1)	0.01
Heart rate > 70/min	3.5 (1.3–8.9)	2.8 (1.0–7.3)	0.03
ICD-VVI	5.0 (1.7–14.8)	5.1 (1.6–15.9)	0.004

age younger than 70 years. Moreover, experiencing a single IS resulted in an increased risk of all-cause mortality, and mortality risk increased with every subsequent IS [5].

Frequency, mechanisms, predictors, and survival impact of IS have also been partly addressed in the MADIT II trial. This seminal trial has initially shown that although prophylactic ICD implantation improves survival in post-myocardial infarction patients with reduced LVEF%, inappropriate ICD shocks are common (11.5%) and lead to adverse consequences that may impair quality of life [11]. The investigators had initially reported that AF was the most common trigger for IS (in 44% of the cases) and that AF was actually one of the strongest independent predictors for IS [11]. In light of these initial findings, in the MADIT-RIT study, attention was focused on reducing IS and mortality by changing ICD programming [8].

Rate of IS was reduced from 19 to 3.6% just by changing the heart rate threshold (below or above 200 bpm) and therapy time delay. Conventional ICD programming was associated with more inappropriate therapy, as were younger age and history of atrial arrhythmia. High-rate and long-delay therapy significantly reduced the risk of IS [8]. As a consequence, since the publication of the MADIT-RIT, it seems clear that in more recent clinical experiences, adequate ICD programming has been able to reduce the occurrence of IS. At the same time, a not negligible rate of IS persists and is mainly related to specific demographic and clinical traits of the implanted patient.

All findings seem to suggest that younger patients with history of atrial tachyarrhythmias will have a significant higher chance of being inappropriately shocked. In fact most probably, these patients are in the very initial stages of their disease and have, for this reason, a minimal limitation of their daily functions. Maximal daily activity could lead to increased heart rates, including paroxysm of AF that may be "misinterpreted," by the implanted device, as a malignant tachyarrhythmia. Our findings show that most often, these patients have been implanted for primary prophylaxis with single-lead ICD. As supraventricular arrhythmias are the main cause of IS, the additional sensing operated by an atrial lead may facilitate discriminating the origin of the tachyarrhythmias and may eventually reduce the occurrence of IS. Of note, previously published reports have led to controversial conclusions. In particular, two prospective randomized studies have been aimed at defining the performance of tachyarrhythmia detection algorithms in single- and dual-chamber ICD. Although the goal was to understand whether optimally programmed dual-chamber ICD could lower the risk of IS, the two studies have come to different conclusions [12, 13]. A more recent meta-analysis of eight studies has demonstrated that there is no significant difference in inappropriate therapies among patients with single- or dual-chamber ICD [14]. Differently, the theoretical protective effect of a dual-chamber ICD has been confirmed in our study where implantation of an ICD-VVI was actually the strongest independent determinant of IS with an OR of over 5.

Although the present study was focused upon the identification of IS determinants, we should also discuss the AS occurrence rate. In our registry, a 3.1% aggregate incidence of AS during 2 years of study follow-up raises the issue of how representative is the present population of the general population receiving an ICD in daily practice. All patients treated with ICD within the German health care system must present clear and documented indications to treatment, according to European guidelines. The national system for reimbursement does monitor constantly the correct application of the guidelines. Cases treated outside of the guideline terms will be simply not reimbursed. In this sense, all cases presented in this series have been treated on the basis of correct international indications and should represent the *status quo* in developed health care systems. In truth, the rate of occurrence of device therapies may change according to the post-procedural patient's care and to the evolution of the initial cardiac condition (CHF).

Post-ICD implantation patient's care may vary, according to geographical regions and density of health care facilities/providers on the territory. As a result, the presented cohort may not necessarily represent at full the worldwide reality in terms of post-procedural management. The German institutions that have participated to the present registry have shown an advanced interest and structure for the treatment of CHF patients. In fact, they mainly have dedicated personnel (device and heart failure clinics) that allow for optimized and customized monitoring and treatment after ICD implantation. In addition, all patients were redirected to their referring cardiologist after ICD implantation in order to guarantee for a real-time and constant optimization of medical treatment and stabilization of CHF evolution. Finally, the 3.1% rate of AS at midterm follow-up presented in our registry does not differ much from recently published "real-world" data. In fact in a

contemporary cohort of over 2000 patients, the Israeli ICD registry has shown an AS rate at 30-month follow-up of 2.6% among patients who received an ICD for primary prevention and 7.4% among those who received a device for secondary prevention [15].

Some final comments should be given concerning the mid-term outcomes and the occurrence of IS in our study. The relationship between follow-up mortality and IS has been tested in different studies, as elucidated in the previous paragraphs, and remains controversial. Theoretically repeated IS may lead to myocardial injury, anxiety, and depression and finally exacerbate the deterioration of LVEF% resulting in an increased mortality rate. Although within the Device II Registry we did not report follow-up mortalities in the IS group, our findings are limited by the sample size and by the follow-up duration. However, it should be noted that in our experience, IS have resulted in an increased rate of re-hospitalizations and outpatient visits. Both these two eventualities may have resulted in a closer monitoring of the treated patients, in a constant optimization of their medical care and management, and may have had a final positive outcome in reducing the mortality risk. This is supported by the fact that our patients' satisfaction and quality of life questionnaires showed a high rate of patient satisfaction and ICD perception even in patients experiencing IS.

5 Limitations

The present study has a series of limitations that are mainly intrinsic to the database structure. In particular, no specific information concerning the programming of the implanted device is given. Moreover, the timing of and the reason for IS and AS are not reported in the database.

6 Conclusion

In a contemporary setting, the risk of IS after ICD implantation seems to be limited but still concrete. Very specific demographic and clinical conditions, such as implantation of VVI-ICD, younger age, and faster resting heart rates, are confirmed to enhance IS occurrence. Patient-tailored treatment and monitoring strategies should be tested with the aim of further reducing the eventuality of IS.

Authors' contributions All authors have contributed to database designing and patients' clinical management. GD, HI, JS, and MH have designed the study. GD has written the manuscript. MH has performed the analysis. LE and ES ha have given a first critical reading and correction to the original version of the manuscript. All other authors have read and approved the final version of the manuscript.

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Data availability This is a multicenter study and data are protected by local patients' privacy regulations. In any case, data will be made available upon request.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethics approval and consent to participate A positive vote was obtained from the ethics committee of the Landesaerztekammer Rheinland-Pfalz in April 2011. All patients have given written informed consent to data collection and publication.

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