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Appropriate and inappropriate implantable cardioverter defibrillator interventions during secondary prevention

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Background — ICD therapy is established therapy for secondary prevention after aborted sudden death or ventricular tachycardia. Long-term data on the incidence of appropriate and inappropriate interventions are scarce.

Methods and results — We retrospectively studied 391 patients with an ICD for secondary prophylaxis: 247 (63%) with ischaemic heart disease (IHD) and 144 without IHD (37%). Fifty-four patients were free from left ventricular structural disease. Mean follow-up was 30.8 months. Kaplan-Meier methodology was used for survival analysis.

The use of beta-blockers was high and similar in both groups (85% IHD; 88% non-IHD; $P = 0.36$). The incidence of appropriate interventions was identical in IHD and non-IHD (42.7% and 47.8% at 4y; HR 1.0, $P = 0.99$). There was a yearly rate of first intervention around 5% even in the fourth and fifth year after implantation. The incidence of inappropriate interventions was about half that of appropriate ICD interventions (21.4% at 4 y). It was higher in patients who also had received appropriate therapy (HR: 2.73 in the IHD group, 1.61 in the non-IHD group, $P < 0.001$ for both). Atrial fibrillation was the most common cause of inappropriate interventions in IHD, and sinus tachycardia in those without LV disease. The incidence of inappropriate interventions was not dependent on the type of ICD (VVI vs. DDD), in any group.

Conclusions — Patients with an ICD for secondary prophylaxis have a high rate of appropriate interventions, and remain at risk for developing a first intervention several years after implantation. Inappropriate interventions constitute a significant burden. Taking preventive measures (AV nodal slowing drugs, device selection and programming, patient counseling regarding allowable physical activity) is required to optimize the quality-of-life adjusted life-saving potential of ICDs.

Keywords: *implantable cardioverter defibrillator – sudden death – ventricular arrhythmias – appropriate – inappropriate – interventions.*

Introduction

In the early 1980 s the automatic implantable cardioverter defibrillator (ICD) emerged in clinical practice[1]. ICDs are now an established therapy for secondary prevention after aborted sudden death or ventricular arrhythmias[2-4]. The majority of ICD patients have underlying structural heart disease, most often ischaemic heart disease (IHD). ICD interventions triggered by ventricular tachycardia (VT) or ventricular fibrillation (VF) are considered appropriate since they may prevent death. However, events such as electromagnetic interference, sinus tachycardia, atrial fibrillation or T-wave oversensing may trigger inappropriate device therapy. Inappropriate antitachypacing may pass by unnoticed, but it is not without danger (e.g. arrhythmia induction or acceleration) and inappropriate DC shocks can be a frightening experience. Studies have shown a correlation between delivery of DC shocks and lower quality of life scores[5,6]. Moreover, inappropriate interventions can be dangerous since they may trigger life-threatening arrhythmias by themselves. Reducing inappropriate therapy therefore is a major aspect of ICD patient management. Data on the incidence of inappropriate interventions, their cause and their relation to

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the underlying heart disease, are still relatively scarce. A wide range in incidence between 3 to 45% per year has been reported[7-11].

The aim of this study was to evaluate: (i) the long-term incidence of appropriate and inappropriate interventions in patients who underwent ICD implantation for secondary prevention; (ii) whether this incidence depends on the nature of the underlying heart disease; (iii) the relationship between device interventions and left ventricular ejection fraction (LVEF), and (iv) the reasons for inappropriate interventions.

Methods

Patients

We retrospectively studied the occurrence of appropriate and inappropriate ICD interventions in 391 patients who received a first ICD for secondary prevention in our centre between January 1995 and May 2005. Sixty-five patients who received prophylactic implants during the same time period were excluded from this study. Mean follow-up was 30.8 months (range 1-60) and was similar in both groups. Outcome was compared between 247 patients (63%) with ischaemic heart disease (IHD) and 144 patients (37%) with non-IHD. Ninety of the 144 non-IHD patients had manifest structural heart disease: 39 patients with idiopathic dilated cardiomyopathy (27%), 18 with Fallot's tetralogy (12%), 3 with other types of congenital heart disease (2%), 11 with hypertrophic cardiomyopathy (8%), 10 with valvular pathology (7%), 4 with sarcoidosis (3%), 3 with Steinert's disease (2%), and 2 with myocarditis (1%). Fifty-four of the non-IHD patients (37.5%) were also free from LV structural disease: 37 had a primary electrical problem (Brugada syndrome, long QT syndrome or undefined electrical disease), and 17 had right ventricular cardiomyopathy but without evidence for LV involvement.

Rhythm classification

All ICDs provided extensive data information and stored endocardiac electrograms. The VF-zone was programmed for rates above 182 or 188 bpm, sometimes including a fast-VT zone to allow for antitachypacing before shock delivery. If any spontaneous or induced VT was documented, a VT-zone was programmed from 20 bpm below the documented VT rate. To minimize short- and long-term lead complications, we have implanted primarily single-chamber ICDs (in 279 patients, 71.4%; table 1). Discriminative detection enhancements (like sudden onset, stability or electrogram morphology) were not routinely activated, but only (i) when the VT rate was overlapping with potential sinus tachycardia rates (determined by 220 - age) or (ii) after an inappropriate shock for which post-hoc evaluation showed that additional discriminators could have been useful in its prevention. Overall, one or more discriminators were activated in 21 of the 391 patients (5.4%) and in only 10 at implant (2.6%). In all patients, the ICD was programmed to store a far-field electrogram to facilitate evaluation of the appropriateness of interventions. Evaluation of appropriateness of therapy was based on stored electrograms and/or other available information (such as clinical history, data from prior electrophysiological studies, data from prior interventions). An intervention triggered by VT or VF was considered appropriate; an intervention was classified as inappropriate when triggered due to other causes. In case of doubt, the intervention was coded as appropriate. The classification was entered in a prospective database by the electrophysiologist during the in-hospital ICD follow-up of the patient. There was no prospective logging of doubtful classification.

Table 1. – *Demographic characteristics*

	IHD (n = 247)	Non-IHD (n = 144)	*P*-value
Age (y)	66 ± 9	46 ± 17	< 0.001
Male sex (%)	89.5	72.4	< 0.001
Average follow-up (m)	30.9 ± 21.7	31.6 ± 21.7	NS
Median & IQR	26 (50)	31.5 (46.5)	NS
Ejection fraction (%)			< 0.001
< 30%	21.8	15.3	
30 – 45%	42.5	20.1	
> 45%	35.7	64.6	
NYHA class (%)			0.88
I	72.9	73.6	
II	25.5	22.9	
III	1.6	3.5	
Indication ICD (%)			0.13
VF or VT with collaps	57.1	61.8	
VT without collaps	32.0	25.7	
Nonsustained VT*	10.9	12.5	
ICD type			0.05
Single chamber	68.2%	77.4%	
Dual chamber	16.7%	13.7%	
CRT	15.1%	9%	
Betablockade (%)	84.9	87.7%	0.36
Amiodarone (%)	44.8%	23.1%	< 0.001
Amiodarone or BB	96.3%	92%	0.04
ACEI/ARB	80.6%	39.6%	< 0.0001

VT: sustained monomorphic ventricular tachycardia; VF: ventricular fibrillation; CRT: cardiac resynchronization therapy device; BB: beta blockers; ACEI: angiotensin-converting enzyme inhibitors; ARB: angiotensin receptor blocker.
*: documented on Holter or electrophysiological study, but with a history of syncope of presumed arrhythmic aetiology.

Statistical analysis

Demographic data are summarized as mean ± SD. Freedom from a first appropriate or inappropriate intervention was calculated with the Kaplan-Meier

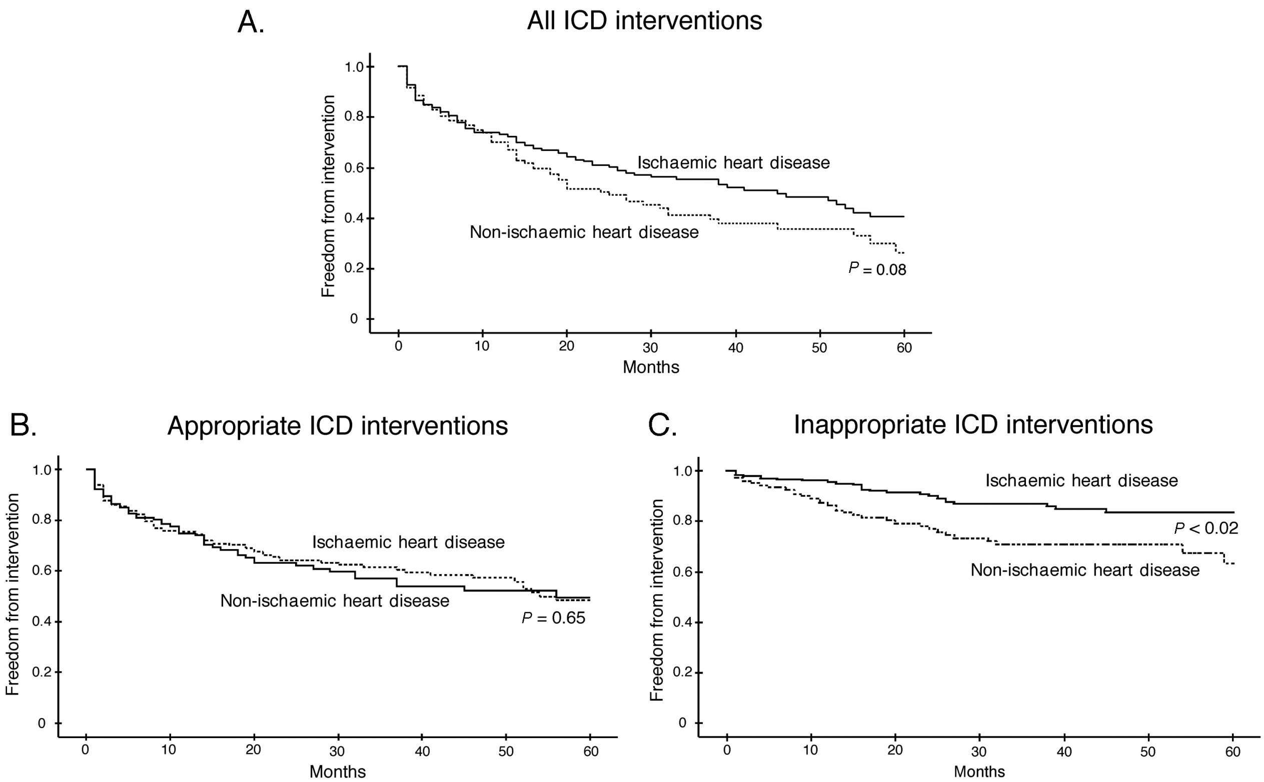

Fig. 1. – Kaplan-Meier curves showing freedom from all ICD interventions (panel A), from appropriate interventions (panel B) and from inappropriate interventions (panel C) in patients with and without ischaemic heart disease (IHD, n = 247; non-IHD, n = 144).

method. Data were censored if the patient died, underwent cardiac transplantation or reached the end of the follow-up period. Log rank testing was used to compare outcome in IHD and non-IHD patients. A P-value < 0.05 was considered significant. The Cox regression method was used to calculate hazard ratios (HR). Statistical analysis was performed with SPSS (version 12.0).

Results

Study population

The baseline clinical characteristics of the 247 IHD (63%) and the 144 non-IHD (37%) patient groups are provided in table 1. As expected, the IHD patients were significantly older (66.2 y vs. 46.3 y, $P < 0.001$). Non-IHD patients with and without LV structural heart disease had the same mean age. Both IHD and non-IHD groups had a clear predominance of men but their proportion was significantly higher in the IHD patients (89.5% vs. 72.4%, $P < 0.001$). The arrhythmic indication for ICD implantation was also similar in both groups. Single-chamber ICDs were implanted in the majority, more often in non-IHD patients (77.4% vs. 68.2% (table 1; $P = 0.05$). The use of beta-blockers was high and not different in both groups (86.1% overall; $P = 0.36$). Amiodarone (usually at a low dose, ≤ 200 mg/day) and angiotensin-converting enzyme inhibitors or receptor blockers were used more often in IHD.

Appropriate ICD interventions

The proportion of patients receiving an appropriate intervention and the time to this first intervention were similar in the patients with and without IHD (figure 1; hazard ratio 1.0; $P = 0.99$). After 48 months, the incidence of appropriate interventions was 42.7% in IHD and 47.8% in non-IHD patients. The average time till the first appropriate intervention was 362 days in IHD patients vs. 346 days in non-IHD patients (NS). The incidence of appropriate interventions was not dependent on the type of ICD (VVI vs. DDD or CRT).

In the IHD group, there was a trend for a relationship between the LVEF at the time of ICD implantation and the risk of receiving an appropriate intervention during follow-up (figure 2). In patients with an LVEF > 45%, 39.8% received an appropriate intervention, compared to 59.7% of those with an LVEF of 30 to 45% and even 83.2% of the patients with an LVEF < 30% ($P = 0.07$). The group with LVEF < 30% had a hazard ratio of 1.57 for receiving an appropriate intervention compared to those with LVEF ≥ 30% ($P = 0.07$). Even in IHD patients with an LVEF > 45%, the risk for receiving an appropriate therapy within

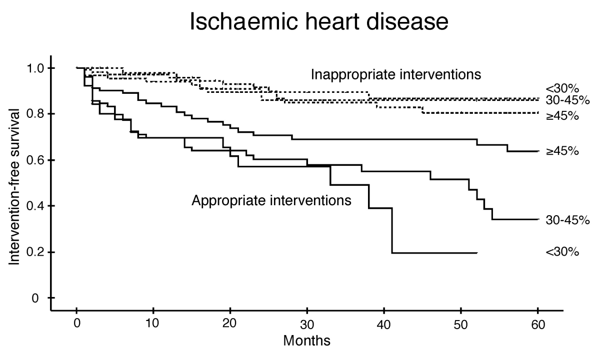

Fig. 2. – Freedom from appropriate and inappropriate interventions in patients with IHD according to the left ventricular ejection fraction (LVEF) at the time of implantation (n = 88 with LVEF > 45%; n = 105 for LVEF 30-45%; n = 54 for LVEF < 30%).

5 years (i.e. the average life time of an ICD) was still 36.2% (figure 2).

Inappropriate ICD interventions

Overall, the incidence of inappropriate interventions was about half that of appropriate interventions (incidence after 48 months of 21.4% vs. 44.7%). In contrast to appropriate interventions, there was a significant difference in the occurrence of inappropriate interventions depending on the underlying aetiology: the hazard ratio was 2.38 in non IHD compared to IHD patients ($P < 0.02$). Figure 1 shows that within 48 months, 29.3% of the non IHD patients had received at least 1 inappropriate intervention vs. only 16.5% in the IHD group. The average time till a first inappropriate intervention was not statistically different in both groups (447 days in non IHD vs. 478 days in IHD; $P = 0.85$). The patients with inappropriate shocks were younger (50.9 y vs. 58.5 y, $P = 0.02$). Comparing non-IHD and IHD patients, non-IHD patients tended to receive more first inappropriate shocks regardless of age: the HR was 1.93 in the age group below 58 y ($P = 0.12$) and 2.31 in patients older than 58 y ($P < 0.05$).

In both groups, approximately half of the patients who received inappropriate interventions also received an appropriate intervention (12/26 = 46.2% in the IHD group; 20/33 = 60.6% in the non-IHD group; $P = 0.35$).

Conversely, those who received appropriate therapy had a hazard ratio of 2.11 to receive inappropriate therapy, and more so in the patients with IHD (HR: 2.73 in the IHD group, 1.61 in the non-IHD group, $P < 0.001$ for both). From the patients who experienced an appropriate intervention (n = 141), 31.9% also received inappropriate ICD therapy, but significantly more often in the non-IHD group (33/54, 61.1%) than in the IHD group (25/87, 28.7%, $P < 0.001$). In contrast to the appropriate interventions, the occurrence of inappropriate interventions was not dependent on the LVEF in IHD patients ($P = 0.78$; figure 2).

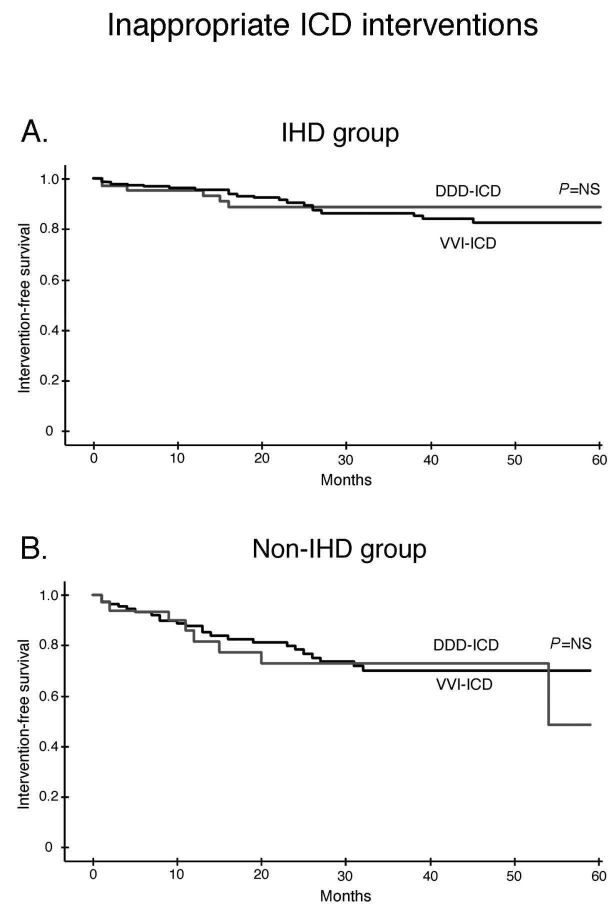

Fig. 3. – The incidence of inappropriate ICD interventions was not different in patients with VVI-ICDs compared to those with DDD devices, in either patient subgroup.

The incidence of inappropriate interventions was not dependent on the type of ICD (VVI vs. DDD or CRT), neither in the IHD nor in the non-IHD patients (figure 3).

The causes of inappropriate therapies are shown in figure 4, each as a proportion of the total number of interventions within the group. The distribution of causes was significantly different in IHD and non-IHD patients ($P = 0.04$). In non-IHD patients, especially those without structural LV disease, sinus tachycardia was the most common cause, whereas in patients with structural heart disease (ischaemic or non-ischaemic) inappropriate shocks were mainly due to atrial fibrillation or atrial tachycardia.

Discussion

Main findings

The main findings of our study are: (1) patients with an ICD for secondary prophylaxis experience appropriate interventions in about 45% within 4 years,

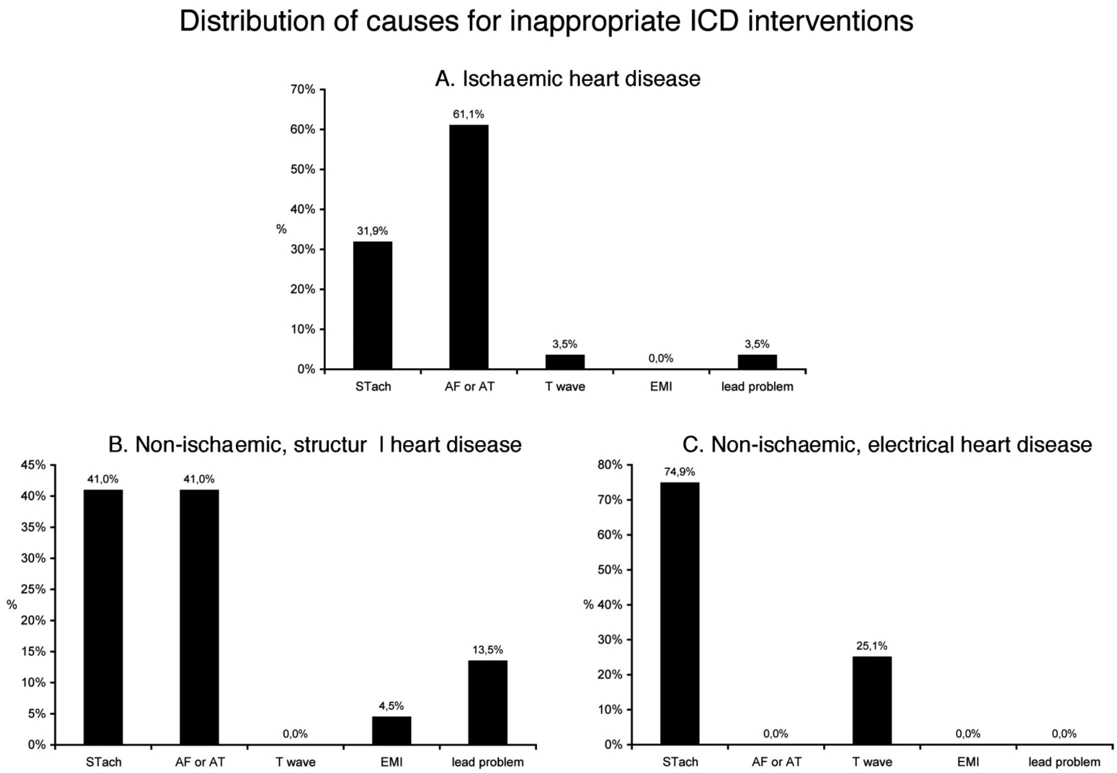

Fig. 4. – Proportional distribution of causes of inappropriate ICD interventions, in patients with ischaemic heart disease (panel A), without ischaemic heart disease but with LV structural abnormalities (panel B), and with electrical heart disease (panel C). STach = sinus tachycardia; AF = atrial fibrillation; AT: atrial tachycardia; T wave = T wave oversensing; EMI = electromagnetic interference; Lead problem = ICD lead defect; SHD = structural heart disease.

regardless of aetiology; (2) inappropriate interventions constitute a significant burden, occurring in about 21% of the patients within 4 years, mainly in non-ischaemic patients (HR 2.38) and in patients who also had experienced appropriate shocks (HR 2.73 in IHD and 1.61 in non-IHD); and (3) atrial arrhythmias are the main cause for inappropriate shocks in patients with structural LV disease (ischaemic or non-ischaemic), whereas sinus tachycardia is the major cause in those without.

The incidence of appropriate shocks in our secondary prevention patient population is comparable to that described in other secondary prevention trials[2-4,7,12,13]. The SCD-HeFT trial, a primary prevention trial including heart failure patients with or without ischaemic heart disease (52% and 48%, respectively) showed a smaller mortality rate in non-ischaemic patients, but no data on appropriate device therapy are available so far[14]. We showed that after 5 years, about half of the patients with a history of sudden death or sustained VT have had an appropriate intervention, and that this proportion is similar in patients with and without ischaemic heart disease. The higher incidence of appropriate ICD therapies in patients with lower LVEF confirms the higher benefit of ICD therapy in these patients[15]. Although therapy delivery mainly occurs during the initial 2 years after implantation, there is a yearly rate of first intervention around 5% even in the fourth and fifth year after implant. Therefore, secondary prevention ICD patients remain at risk, underscoring the practice that replacement of the first device is warranted after battery depletion, even when no appropriate therapy delivery has been delivered by the first device.

The incidence of inappropriate shock delivery that we observed was similar or somewhat lower than in other secondary prevention trials[7,12,13,16,17,18,19]. Since our series consisted mainly of first ICD implants (and thus young leads) it can be anticipated that the proportion of lead problems increases over time[20]. A high rate of inappropriate therapy will reduce the perceived ICD benefit ("quality-adjusted life years gained"). Reduction of inappropriate therapy therefore is an important therapeutic goal. More intensive monitoring of exercise-induced sinus tachycardia and atrial arrhythmias, with adjustment of drug treatment or ICD programming if necessary, could reduce the incidence of inappropriate interventions. In ICD patients enrolled in a revalidation programme, we have observed a very low rate of inappropriate interventions during the training sessions ($< 1\%$)[21]. Some patients, however, should be instructed to refrain from medium to high intensity physical activity, even recreational in nature[22].

Ablation of atrial flutter and ablation of the AV-node have been shown to be highly effective in the event of drug-refractory inappropriate ICD therapies[23], but the potentially negative haemodynamic effect of the mandatory ventricular pacing associated with the latter should carefully be weighed against the need for AV nodal ablation.

Our results show an important association between appropriate and inappropriate ICD therapy and there is only a small percentage of patients who only received inappropriate therapy. This association has two important practical implications: 1) medical therapy that reduces both supraventricular and ventricular arrhythmias will often be the preferred choice. This concept explains the high proportion of our patients on amiodarone and/or beta blockers as adjunctive therapy; 2) programming algorithms which increase specificity of SVT discrimination[24] may lead to a decreased sensitivity for VT detection, and therefore should be used with caution since many patients will have both. The proportion of single-chamber ICDs in our population is higher than in most reported secondary prophylaxis series. Dual-chamber detection algorithms do not reduce the incidence of inappropriate shocks, as our data show and as has been shown by others[25-28]. Ventricular pacing due to a dual-chamber ICD may even lead to higher propensity for heart failure and atrial fibrillation[29].

Limitations

Due to the retrospective nature of our study, programming of ICDs was not standardized. The technology for arrhythmia differentiation (automatic algorithms; stored electrograms available for review during an ICD interrogation) has evolved over the evaluation period used for the study. Moreover, it can not be excluded that the introduction and application of concomitant therapy has altered the natural history over time for the underlying disease groups. The group of non-IHD is heterogeneous and pooled a number of different aetiologies. We divided this group in patients with or without structural LV disease where we considered this useful for the analysis. Making smaller subgroups, however, was not meaningful for statistical reasons. On the other hand, our data describe the real-life outcome in a large cohort of patients in a third-line cardiology centre.

Our database contained no option to log “doubtful” coding of ICD interventions but forced the electrophysiologist to consider the episode as appropriate or inappropriate. Therefore we can not evaluate which proportion of interventions fell into this category. The fact, however, that there was no difference in the incidence of appropriate interventions in VVI vs. dual-chamber ICDs suggest that this proportion may not have had an impact on the overall results.

Given the very small number, evaluating the impact of additional arrhythmia discriminators on inappropriate shock delivery was not statistically meaningful in this study. The incidence of inappropriate therapies might have been lower with more systematic activation of discrimination algorithms, as some studies suggest, although the data remain scarce in single-chamber ICDs[24].

Conclusion

The benefit of ICD therapy as secondary prophylaxis (with a first appropriate intervention often many years after implantation) is compromised by a high incidence of inappropriate shocks during follow-up. Preventive measures are mandatory to preserve the confidence of patients in their ICD safeguard. Preimplant and follow-up information, including exercise testing and electrophysiological study will allow adequate follow-up: appropiate device programming, efficient use of antiarrhythmic drugs and counselling about allowable level of physical activity.

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