

Prognostic Importance of Atrial Fibrillation in Implantable Cardioverter-Defibrillator Patients

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- Objectives** This study aimed to assess the prevalence of different types of atrial fibrillation (AF) and their prognostic importance in implantable cardioverter-defibrillator (ICD) patients.
- Background** The prevalence of AF has taken epidemic proportions in the population with cardiovascular disease. The prognostic importance of different types of AF in ICD patients remains unclear.
- Methods** Data on 913 consecutive patients (79% men, mean age 62 ± 13 years) receiving an ICD at the Leiden University Medical Center were prospectively collected. Among other characteristics, the existence and type of AF (paroxysmal, persistent, or permanent) were assessed at implantation. During follow-up, the occurrence of appropriate or inappropriate device therapy as well as mortality was noted.
- Results** At implantation, 73% of patients had no history of AF, 9% had a history of paroxysmal AF, 7% had a history of persistent AF, and 11% had permanent AF. During 833 ± 394 days of follow-up, 117 (13%) patients died, 228 (25%) patients experienced appropriate device discharge, and 139 (15%) patients received inappropriate shocks. Patients with permanent AF exhibited more than double the risk of mortality, ventricular arrhythmias triggering device discharge, and inappropriate device therapy. Patients with paroxysmal or persistent AF did not show a significant increased risk of mortality or appropriate device therapy but demonstrated almost 3 times the risk of inappropriate device therapy.
- Conclusions** In the population currently receiving ICD treatment outside the setting of clinical trials, a large portion has either a history of AF or permanent AF. Both types of AF have prognostic implications for mortality and appropriate as well as inappropriate device discharge. (J Am Coll Cardiol 2010;55:879–85) © 2010 by the American College of Cardiology Foundation

Large randomized trials have shown a beneficial effect of implantable cardioverter-defibrillator (ICD) therapy, initially in survivors of life-threatening arrhythmias (1–3), but also more recently in the primary prevention of sudden arrhythmic death in selected ischemic and nonischemic patients at high risk, based solely on a poor left ventricular ejection fraction (LVEF) (4–7). The implementations of these results in the international guidelines have caused, in addition to a considerable increase in the number of implants, a significant change in the population considered for ICD therapy because the majority of implantations now

occurs in patients with a low LVEF and symptoms of heart failure (primary prevention patients) (8).

Atrial fibrillation (AF) is common in patients with low LVEF and symptoms of heart failure, with a reported prevalence of AF in congestive heart failure patients of as high as 50% in patients with New York Heart Association (NYHA) functional class IV (9–12). Furthermore, AF is associated with significant morbidity and mortality, both in the general population and more specifically in patients with heart failure (13,14).

As the number of ICD implants in patients with a low LVEF and heart failure is increasing, it can be expected that more patients with paroxysmal, persistent, or permanent AF will receive an ICD. So far, most studies have focused on a single type of AF (e.g., paroxysmal/persistent or permanent AF) and were often conducted in the setting of a clinical trial (15–19). The prevalence and prognostic implications of a history of AF at ICD implantation remain unclear. The present study aims to provide insight into the effects of AF on

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Abbreviations and Acronyms

AF = atrial fibrillation
ATP = antitachycardia pacing
CI = confidence interval
ICD = implantable cardioverter-defibrillator
LVEF = left ventricular ejection fraction
NYHA = New York Heart Association

mortality, the occurrence of ventricular arrhythmias, and inappropriate device therapy during long-term follow-up in a large cohort of ICD patients.

Methods

Patients and study protocol.

Since 1996, all patients receiving an ICD at the Leiden University Medical Center were prospectively collected in the departmental Cardiology Information

System (EPD-Vision, Leiden University Medical Center, Leiden, the Netherlands). Characteristics at baseline, data of the implant procedure, and data for all follow-up visits were recorded.

Eligibility for ICD implantation in this population was based on international guidelines that, due to evolving guidelines, might have changed over time. Patients underwent ICD implantation after surviving life-threatening ventricular arrhythmias or in the presence of a depressed LVEF with or without nonsustained ventricular tachycardia (8,20).

AF. At baseline, patients were grouped according to the type of AF. This resulted in the following 4 groups: 1) patients without a history of (documented) AF, the no AF group; 2) patients with a history of paroxysmal AF as documented by electrocardiography; 3) patients with a history of persistent AF as documented on electrocardiography; and 4) patients with permanent, accepted AF.

If the arrhythmia terminated spontaneously and within 7 days, AF was designated paroxysmal; when sustained beyond 7 days or being terminated by pharmacological or electrical cardioversion, AF was termed persistent. The category of persistent AF also includes cases of long-standing AF, usually leading to permanent AF, in which cardioversion has failed or has been foregone (10,21).

Device implantation. All defibrillator systems used were implanted transvenously and without thoracotomy. During the implantation procedure, testing of sensing and pacing thresholds and defibrillation threshold testing was performed. The systems used were manufactured by Biotronik (Berlin, Germany), Medtronic (Minneapolis, Minnesota), Boston Scientific (Natick, Massachusetts) (formerly CPI, Guidant, St. Paul, Minnesota), and St. Jude Medical/Ventritex (St. Paul, Minnesota).

Long-term follow-up. Patient check-ups were scheduled every 3 to 6 months. Device interrogation printouts were checked for appropriate and inappropriate ICD therapy (antitachycardia pacing [ATP] or shocks). Therapies were classified as appropriate when they occurred in response to ventricular tachycardia or ventricular fibrillation and as inappropriate when triggered by sinus or supraventricular tachycardia, T-wave oversensing, or electrode dysfunction. Furthermore, follow-up included all-cause mortality.

In the Dutch health care system, all patients are followed by the implantation center. Because periodic follow-up was performed every 3 to 6 months, patients without data for the past 6 months were considered lost to follow-up.

Statistical analysis. Continuous data are expressed as mean \pm SD; dichotomous data are presented as numbers and percentages. Comparison of continuous or dichotomous data was performed with the Student *t* test for paired and unpaired data and chi-square tests with Yates correction when appropriate. Nonparametric data (NYHA functional class) were compared using the Mann-Whitney *U* test. Cumulative event rates (all-cause mortality, appropriate device therapy, appropriate device shocks, and inappropriate device shocks) were analyzed by the Kaplan-Meier method. The relationship between different types of AF at baseline and the occurrence of end points was assessed using a Cox proportional hazard model, calculating a hazard ratio (HR) with a 95% confidence interval (CI) and adjusting for age, sex, renal clearance, LVEF, QRS duration, NYHA functional class, and use of beta-blockers. For all tests, a *p* value <0.05 was considered significant.

Results

Baseline characteristics. Data for 955 consecutive patients receiving an ICD in the Leiden University Medical Center were prospectively collected. Forty-two (4.4%) patients were lost to follow-up. The remaining 913 ICD recipients were included in the analysis. The mean follow-up time was 833 ± 394 days.

The majority of patients (79% men, mean age 62 ± 13 years) had a depressed LVEF ($32 \pm 14\%$), wide QRS complex (127 ± 35 ms), and poor renal function (renal clearance 83 ± 38 ml/min). Medications included beta-blockers in 76%, angiotensin-converting enzyme inhibitors or AT antagonists in 82%, and diuretics for heart failure in 70%. Baseline characteristics are summarized in Table 1.

A total of 663 (73%) out of all 913 patients had no history of AF (no AF), 84 (9%) patients had a history of paroxysmal AF, 64 (7%) patients had a history of persistent AF, and the remaining 102 (11%) patients had permanent AF. All patients with a history of paroxysmal or persistent AF were in sinus rhythm at discharge after device implantation. As is shown in Table 1, when compared with patients without a history of AF, patients with AF were older, had higher NYHA functional class, and were more often treated with diuretics, amiodarone, and oral anticoagulants.

Mortality. During a mean follow-up of 833 ± 394 days, 117 (13%) patients died. The study population mortality rates were 5% (95% CI: 4% to 7%) at 1 year, 11% (95% CI: 8% to 13%) at 2 years, and 15% (95% CI: 12% to 17%) at 3 years of follow-up. Comparing the 4 groups, survival analysis showed a 3-year cumulative event rate for mortality of 12% (95% CI: 9% to 15%) for no AF, 15% (95% CI: 8% to 24%) for paroxysmal AF, 17% (95% CI: 7% to 27%) for

Table 1 Baseline Characteristics

Clinical Parameters	All (n = 913)	No AF (n = 663)	Paroxysmal AF (n = 84)	Persistent AF (n = 64)	Permanent AF (n = 102)
Male sex	722 (79%)	515 (78%)	64 (76%)	53 (83%)	90 (88%)*
Age (yrs)	62 ± 13	61 ± 13	64 ± 11†	66 ± 10*	67 ± 10‡
Secondary prevention	140 (15%)	94 (14%)	22 (26%)*	9 (14%)	15 (15%)
History of VT	93 (66%)	62 (66%)	15 (68%)	7 (78%)	9 (60%)
History of VF	47 (34%)	32 (34%)	7 (32%)	2 (22%)§	6 (40%)
Primary prevention	773 (85%)	569 (86%)	62 (74%)*	55 (86%)	87 (85%)
History of nsVT	201 (26%)	150 (26%)	17 (27%)	15 (27%)	19 (22%)
Ischemic heart disease	561 (61%)	423 (64%)	49 (58%)	39 (61%)	50 (49%)*
NYHA functional class					
I	228 (25%)	188 (28%)	17 (20%)	10 (16%)†	13 (13%)‡
II	346 (38%)	253 (38%)	37 (44%)	24 (38%)	32 (31%)
III	320 (35%)	208 (31%)	28 (33%)	30 (47%)†	54 (53%)‡
IV	19 (2%)	14 (2%)	2 (2%)§	0 (0%)§	3 (3%)§
Renal clearance (ml/min)	83 ± 38	86 ± 38	75 ± 39*	77 ± 43	72 ± 29‡
QRS duration (ms)	127 ± 35	125 ± 34	123 ± 33	129 ± 35	140 ± 34‡
LVEF (%)	32 ± 14	33 ± 14	32 ± 15	32 ± 14	30 ± 12
Diabetes	177 (19%)	127 (19%)	16 (19%)	14 (22%)	20 (20%)
History of smoking	380 (42%)	287 (43%)	36 (43%)	24 (38%)	33 (32%)†
Body mass index (kg/m ²)	26 ± 4	26 ± 4	26 ± 4	26 ± 4	26 ± 4
Device type					
Single-chamber	43 (5%)	20 (3%)	4 (5%)§	2 (3%)§	17 (17%)‡§
Dual-chamber	409 (45%)	234 (49%)	39 (46%)	26 (41%)	20 (20%)
CRT-D	461 (51%)	319 (48%)	41 (49%)	36 (56%)	65 (64%)*
Medication					
Beta-blockers	691 (76%)	510 (77%)	63 (75%)	46 (72%)	72 (71%)
ACE inhibitors/AT antagonist	750 (82%)	548 (83%)	66 (79%)	49 (77%)	87 (85%)
Calcium antagonists	64 (7%)	52 (8%)	3 (4%)	3 (5%)§	6 (6%)
Diuretics	641 (70%)	440 (66%)	65 (77%)†	47 (73%)	89 (87%)‡
Statins	594 (65%)	445 (67%)	53 (63%)	44 (69%)	52 (51%)‡
Amiodarone	125 (14%)	68 (10%)	19 (23%)‡	15 (23%)*	23 (23%)‡
Aspirin	364 (40%)	300 (45%)	32 (38%)	22 (34%)	10 (10%)‡
Oral anticoagulants	504 (55%)	316 (48%)	51 (61%)†	42 (66%)*	95 (93%)‡

*p < 0.01; †p < 0.05; ‡p < 0.001; all compared with no AF group. §Comparison was performed with Yates correction.
 ACE = angiotensin-converting enzyme; AF = atrial fibrillation; AT = angiotensin; CRT-D = cardiac resynchronization therapy-defibrillator; LVEF = left ventricular ejection fraction; nsVT = nonsustained ventricular tachycardia; NYHA = New York Heart Association; VF = ventricular fibrillation; VT = ventricular tachycardia.

persistent AF, and 32% (95% CI: 20% to 43%) for permanent AF (Fig. 1).

Of interest, patients with paroxysmal AF or persistent AF did not demonstrate a significant higher risk of mortality. However, patients with permanent AF exhibited a 70% increased risk of mortality (adjusted HR: 1.7, 95% CI: 1.0 to 2.7, p = 0.033).

Appropriate device therapy. During follow-up, ventricular arrhythmias causing appropriate device therapy (ATP or shock) were observed in 228 (25%) patients. A total of 5,116 episodes were noted, consisting of 4,793 (range 1 to 2,194) episodes terminated with ATP in 166 patients and 304 (range 1 to 33) episodes terminated by ICD shock in 112 patients.

The cumulative event rates for appropriate device therapy (ATP or shock) were 15% (95% CI: 13% to 18%) at 1 year, 24% (95% CI: 21% to 27%) at 2 years, and 30% (95% CI: 24% to 34%) at 3 years of follow-up.

As shown in Figure 2, the 3-year cumulative event rates for appropriate device therapy were 29% (95% CI: 24% to 33%) for no AF, 26% (95% CI: 14% to 39%) for paroxysmal AF, 26% (95% CI: 13% to 38%) for persistent AF, and 49% (95% CI: 36% to 61%) for permanent AF. Patients with permanent AF exhibited twice the risk of appropriate therapy compared with patients without a history of AF (adjusted HR: 2.2, 95% CI: 1.6 to 3.2, p < 0.001). The no AF group demonstrated event rates similar to those of patients with a history of paroxysmal or persistent AF.

As shown in Figure 3 and Table 2, the occurrence of appropriate shocks alone showed a distribution similar to that of the occurrence of all appropriate therapy among the 4 groups. No differences were observed between patients without a history of AF and those with a history of paroxysmal or persistent AF. Moreover, a doubled risk of appropriate shocks was observed in the permanent AF group compared with

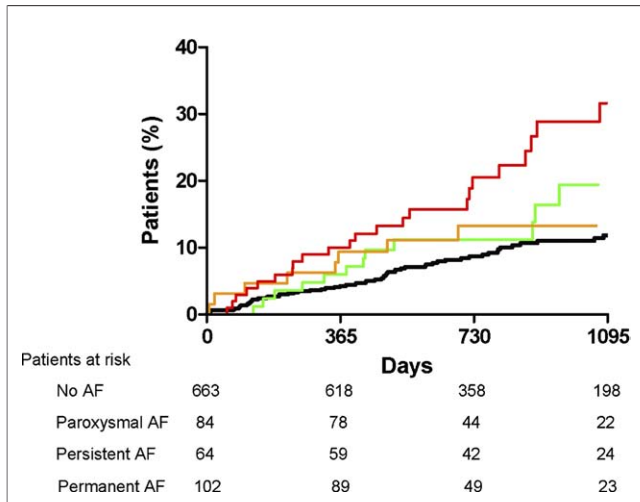


Figure 1 All-Cause Mortality

Kaplan-Meier curve for all-cause mortality in patients without a history of atrial fibrillation (AF) (no AF, black line), paroxysmal AF (green line), persistent AF (orange line), or permanent AF (red line).

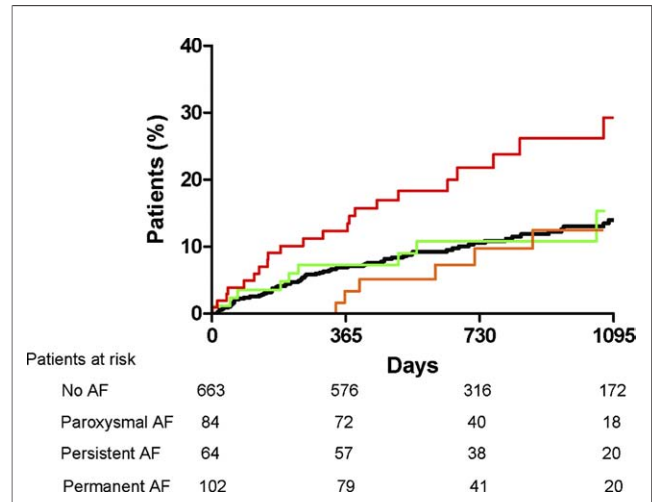


Figure 3 Appropriate Device Shock

Kaplan-Meier curve for the occurrence of first appropriate shock in patients without a history of atrial fibrillation (AF) (no AF, black line), paroxysmal AF (green line), persistent AF (orange line), or permanent AF (red line).

patients with no history of AF (adjusted HR: 2.4, 95% CI: 1.5 to 4.0, $p < 0.001$).

Inappropriate device shocks. A total of 139 (15%) patients experienced at least 1 inappropriate device discharge. When comparing the 4 groups, major differences in event rates were observed. Three-year event rates for inappropriate shocks were 13% (95% CI: 10% to 17%) for no AF, 28% (95% CI: 15% to 40%) for paroxysmal AF, 18% (95% CI: 15% to 41%) for persistent AF, and 32% (95% CI: 19% to 45%) for permanent AF (Fig. 4). Compared with the no AF group, the permanent AF group showed more than double the risk of the inappropriate shocks (adjusted HR: 2.7, 95%

CI: 1.7 to 4.4, $p < 0.001$). Patients with a history of paroxysmal AF had the highest risk of inappropriate device shocks (adjusted HR: 2.9, 95% CI: 1.7 to 4.8, $p < 0.001$) during follow-up. It is of note that in the no AF group, new-onset AF during follow-up was the cause of inappropriate device shocks in 27 (4%) patients.

Discussion

The main findings of the current study on the prognostic importance of AF in ICD patients can be summarized as follows: 1) in the population currently receiving ICD treatment, 9% have a history of paroxysmal AF, 7% have a history of persistent AF, and 11% have permanent AF; 2) patients with permanent AF exhibited more than double the risk of mortality, ventricular arrhythmias triggering device discharge, and inappropriate device shocks than patients without AF; and 3) patients with a history of paroxysmal or persistent AF did not show a significantly increased risk of mortality or appropriate device therapy but demonstrated almost triple the risk of inappropriate device shocks.

The present analysis adds to the previous literature in that it distinguishes between different types of AF and assesses the population currently considered for ICD treatment outside the setting of clinical trial.

Mortality. Previous trials demonstrated the importance of AF in the general population as well as in a population with symptomatic or asymptomatic heart failure (13,14). Benjamin et al. (13) showed that the occurrence of AF was associated with a 1.5- to 1.9-fold risk of all-cause mortality, even after adjustment for further cardiovascular conditions related to AF. These findings seem comparable to the 1.7 times increased risk of mortality in patients with permanent

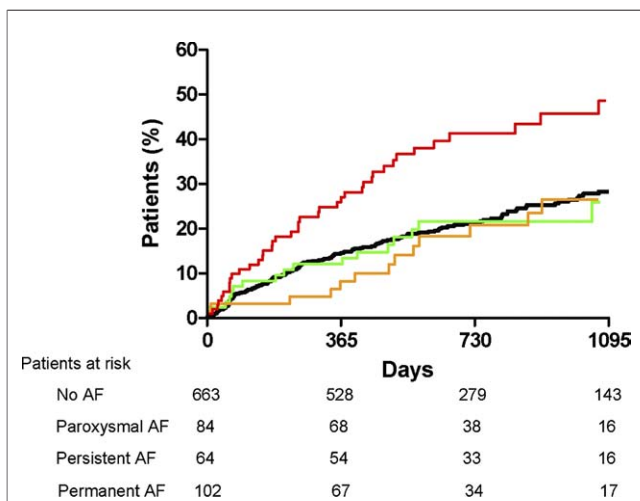


Figure 2 Appropriate Device Therapy

Kaplan-Meier curve for the occurrence of first appropriate device therapy in patients without a history of atrial fibrillation (AF) (no AF, black line), paroxysmal AF (green line), persistent AF (orange line), or permanent AF (red line).

	No AF (n = 663)		Paroxysmal AF (n = 84)		Persistent AF (n = 64)		Permanent AF (n = 102)		Adjusted HR (95% CI)*	
	n (%)	HR (95% CI)	n (%)	HR (95% CI)	n (%)	HR (95% CI)	n (%)	HR (95% CI)	HR (95% CI)	Adjusted HR (95% CI)*
All-cause mortality	69 (10%)	1.3 (0.7-2.5)	11 (13%)	1.2 (0.6-2.3)	12 (19%)	1.6 (0.9-4.1)	25 (25%)	2.6 (1.6-4.1)	1.2 (0.6-2.2)	1.7 (1.0-2.7)
Appropriate therapy	154 (23%)	1.0 (0.6-1.6)	18 (21%)	1.0 (0.6-1.6)	14 (22%)	0.9 (0.5-1.5)	42 (41%)	2.1 (1.5-2.9)	0.9 (0.5-1.6)	2.2 (1.6-3.2)
Appropriate shock	72 (11%)	1.2 (0.6-2.2)	10 (12%)	1.2 (0.6-2.4)	8 (13%)	1.0 (0.5-2.2)	22 (22%)	2.2 (1.4-3.6)	1.1 (0.5-2.4)	2.4 (1.5-4.0)
Inappropriate shock	78 (12%)	2.5 (1.6-4.1)	21 (25%)	2.9 (1.7-4.8)	15 (23%)	1.9 (1.1-3.4)	25 (25%)	2.2 (1.4-3.5)	2.5 (1.4-4.4)	2.7 (1.7-4.4)

*Hazard ratio (HR) adjusted for age, sex, renal clearance, left ventricular ejection fraction, QRS duration, New York Heart Association functional class, and use of beta-blocker. CI = confidence interval.

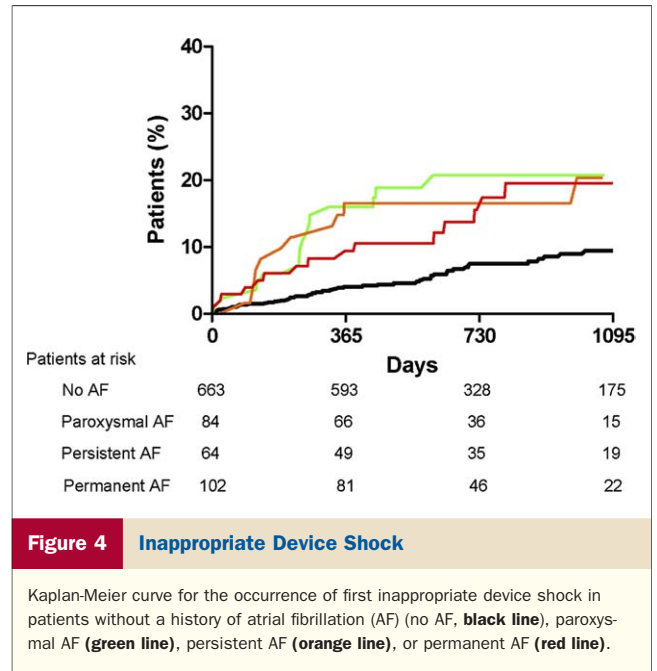


Figure 4 Inappropriate Device Shock

Kaplan-Meier curve for the occurrence of first inappropriate device shock in patients without a history of atrial fibrillation (AF) (no AF, black line), paroxysmal AF (green line), persistent AF (orange line), or permanent AF (red line).

AF, as observed in the current analysis. However, when specifically assessing a population with symptoms of heart failure, findings in current literature are inconsistent regarding the potential relationship between AF and the risk of mortality (14,22-25). In a post hoc analysis of the MADIT II (Multicenter Automatic Defibrillator Implantation Trial), Zareba et al. (7,19) compared patients with sinus rhythm and those with AF. Because AF was defined by its presence on the electrocardiogram at enrollment, one might assume that all the patients identified with AF have permanent AF and those with paroxysmal or persistent AF, if not coincidentally present at enrollment, will have been classified as having sinus rhythm. Furthermore, the trial only included primary prevention ICD recipients with a previous myocardial infarction. In contrast to the current study, Zareba et al. (19) did not find a relationship between AF and mortality after adjustment for other variables.

Appropriate ICD therapy. One might hypothesize that the occurrence of any type of AF is a marker for worse general cardiac status and therefore that AF will be positively correlated with the occurrence of ventricular arrhythmias. On the other hand, AF could initiate episodes of ventricular arrhythmias and might therefore directly influence the occurrence of ventricular arrhythmias and consequent appropriate device therapy. The facilitation of AF in the initiation of ventricular tachyarrhythmias was observed by Roy et al. (26) during an electrophysiological study. Later, Stein et al. (27) observed that 8.9% of the episodes of ventricular arrhythmia were accompanied by AF. Earlier studies suggested that ventricular arrhythmias are evoked by rapid and uncontrolled atrioventricular conduction (28-30). More recently, Grönefeld et al. (16) suggested that the atrioventricular nodal conduction pattern preceding ventricular tachyarrhythmia were short-long-short sequences

rather than solely a rapid conduction. The irregular ventricular excitation leads to heterogeneous depolarization that subsequently renders the myocardium more susceptible to ventricular arrhythmias (31,32). In line with the current findings, previous studies confirm AF to have a positive correlation with the occurrence of ventricular arrhythmias (16–18). Interestingly, a post hoc analysis of the MADIT II trial did not demonstrate a difference in the occurrence of appropriate therapy when comparing (mostly permanent) AF with patients in sinus rhythm (19). A possible explanation for this difference could be that the permanent AF group in the current study is sicker in a manner not completely accounted for by post hoc statistical adjustment. The present study did not show an increase in appropriate device therapy in the groups with a history of paroxysmal or persistent AF, which could imply that these patients do not have a deterioration of their general cardiac status of such magnitude to consequently cause a higher occurrence of ventricular arrhythmia. Thus far, no analysis had been reported of the prognostic implications of the different types of AF.

Inappropriate ICD shocks. Previous studies have demonstrated the relationship between the existence of AF and inappropriate device discharge and the consequent negative effect of inappropriate device discharge on patient quality of life (33–35). Furthermore, recent research has demonstrated the impact of inappropriate shock delivery on mortality (33,36). These findings stress the importance of clear identification of patients at high risk of inappropriate shocks to better inform patients and to optimize individual patient treatment. The current study maps the importance of different types of AF on the occurrence of inappropriate shocks and highlights the high event rate in patients with persistent, permanent, and, most importantly, paroxysmal AF. A potential explanation of the higher event rate in the paroxysmal AF group, even when compared with the group with permanent AF, can be explained by the fact that clinicians will more often adjust their treatment (such as atrioventricular node ablation) if AF is ongoing. Additionally, the higher occurrence of ventricular arrhythmias in the group with permanent AF might cause a more aggressive pharmacological antiarrhythmic treatment.

Study limitations. This was a nonrandomized, prospective, observational cohort study performed to assess the long-term follow-up in ICD patients outside the setting of a clinical trial. Because patients were collected over a 4-year period, expanding guidelines for the implantation of ICDs, treatment of acute myocardial infarction, and pharmacological antiarrhythmic therapy could have created a heterogeneous population. Furthermore, standard ICD settings at discharge could have been altered during follow-up. Finally, applying a different classification of AF might have altered the results.

Conclusions

In the population currently receiving ICD treatment outside the setting of a clinical trial, 11% has permanent AF and 16% has a history of paroxysmal or persistent AF. The existence of permanent AF doubles the risk of mortality and appropriate as well as inappropriate device therapy. Paroxysmal and persistent AF did not prove to have an effect on mortality or the occurrence of appropriate device discharge. However, the rate of inappropriate shocks is significantly increased in this group.

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