Europace (2006) **8**, 566–572
doi:10.1093/europace/eul081

Atrial fibrillation predicts appropriate shocks in primary prevention implantable cardioverter-defibrillator patients

Marcelle D. Smit, Pascal F.H.M. Van Dessel, Michiel Rienstra, Wybe Nieuwland, Ans C.P. Wiesfeld, Eng S. Tan, Rutger L. Anthonio, Dirk J. Van Veldhuisen, and Isabelle C. Van Gelder*

Department of Cardiology, Thoraxcenter, University Medical Center Groningen, University of Groningen, P.O. Box 30.001, 9700 RB Groningen, The Netherlands

Received 21 October 2005; accepted after revision 4 May 2006

KEYWORDS
Atrial fibrillation;
Implantable cardioverter-defibrillators;
Primary prevention;
Sudden cardiac death;
Appropriate shocks

Aims Atrial fibrillation (AF) is often present in patients with left ventricular dysfunction who receive an implantable cardioverter-defibrillator (ICD). The purpose of this study was to investigate whether AF is associated with appropriate shocks and cardiovascular mortality in primary prevention ICD patients with left ventricular dysfunction.

Methods and results We included 80 primary prevention ICD patients with left ventricular dysfunction and compared the outcome between patients with a history of AF ($n = 29$) and patients with no history of AF ($n = 51$). The primary endpoint was occurrence of appropriate shocks. Secondary endpoints were: (1) the composite of cardiovascular mortality/appropriate shocks; and (2) inappropriate shocks. During follow-up (median 8 months, range 1–60), patients with a history of AF more often received appropriate shocks than patients with no history of AF (24 vs. 6%, $P = 0.03$). The composite endpoint of cardiovascular mortality/appropriate shocks was also more likely to occur in patients with a history of AF (34 vs. 12%, $P = 0.02$). History of AF predicted appropriate shocks (HR 6.9, 95% CI 1.7–27.5, $P = 0.006$) and the composite endpoint of cardiovascular mortality/appropriate shocks (adjusted HR 5.1, 95% CI 1.7–15.1, $P = 0.003$). There were no differences in occurrence of inappropriate shocks.

Conclusion Our study demonstrates that history of AF is associated with increased risk of appropriate shocks and cardiovascular mortality in primary prevention ICD patients with left ventricular dysfunction.

Introduction

Patients with impaired left ventricular function have an increased risk of cardiovascular morbidity and mortality, despite new pharmacological strategies over the past years, these patients still have a poor prognosis.[1] One approach to increase survival of heart failure patients is to reduce sudden cardiac death by implantable cardioverter-defibrillator (ICD) therapy. Initially developed for secondary prevention of sudden death,[2] ICD therapy has now been shown to be effective for primary prevention with left ventricular dysfunction.[3–7] As a result, increasing numbers of these patients receive an ICD for primary prevention of sudden death. However, better risk stratification for patient selection would be beneficial to avoid ICD implantation in patients who do not need ICD therapy.

Atrial fibrillation (AF) is highly prevalent in patients with impaired left ventricular function. Several studies have shown that AF is associated with an increased risk of mortality.[8–12] However, this observation has been contradicted by other studies, in which AF was not an independent risk factor for mortality.[13–16] In particular, it is uncertain whether AF is associated with life-threatening ventricular arrhythmias and, consequently, with sudden cardiac death. If this is the case, it may be of help in the selection of patients qualifying for primary prevention ICD implantation. Therefore, the purpose of this study was to investigate whether AF is associated with appropriate ICD shocks and cardiovascular mortality in primary prevention ICD patients with left ventricular dysfunction.

Methods

Patient population

We retrospectively evaluated all consecutive patients who underwent a first ICD implantation for primary prevention of sudden

* Corresponding author. Tel: +31 50 3612355; fax: +31 50 3614391.
E-mail address: i.c.van.gelder@thorax.umcg.nl

cardiac death in the University Medical Center of Groningen until January 2005. Patients were included if they had ischaemic or non-ischaemic cardiomyopathy and left ventricular ejection fraction (LVEF) $\leq$35%. The indication for device implantation was based on guidelines of the European Society of Cardiology and American College of Cardiology/American Heart Association for the use of ICDs in the primary prevention of sudden cardiac death.[17–20] Over the period of enrolment, indications for ICD implantation became more liberal as a result of the publication of important primary prevention ICD trials such as the Multicenter Automatic Defibrillator Implantation Trial (MADIT) II and the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) Trial.[6,21] Our evaluation protocol for patients who were candidates for ICD implantation includes 12-lead electrocardiogram, transthoracic echocardiography, exercise test, 24-h Holter monitoring, LVEF assessment (using radionuclide scanning, angiography, or transthoracic echocardiography), and coronary angiography.[22] Clinical history and characteristics were retrieved using patient medical records. History of AF was determined using electrocardiograms stored in medical records, and was defined as AF ever documented on electrocardiogram, including AF at baseline.

We used a consistent protocol for ICD programming. Shocks for ventricular fibrillation (VF) were usually set at a rate >200 bpm and therapy for ventricular tachycardia (VT) usually at >150 bpm. Routinely, we use antitachycardia pacing in this zone, which consists of two bursts and two ramps, followed by shocks. For detection, an arrhythmia needed to persist for 1–3 s for Guidant devices, whereas Medtronic devices were programmed to require 18 of 24 beats to be below the programmed VF detection cycle length. Supraventricular tachycardia and VT discrimination algorithms were routinely used. There were no systematic differences in programming between patients with a history of AF and patients with no history of AF.

Follow-up

Patients were routinely seen every 6 months. In case of shock delivery they were seen within 48 h. Duration of follow-up was computed from the time of ICD implantation to death or heart transplantation when applicable, or to the date when the last follow-up data were obtained.

Endpoint definitions

The primary endpoint was the occurrence of appropriate ICD shocks. Appropriate shocks were defined as shocks delivered by the ICD to terminate ventricular arrhythmias documented by stored ICD electrograms. All ICD-stored electrograms from delivered therapies were printed out as hardcopies and reviewed by two experienced electrophysiologists blinded for the presence or absence of AF to assess the type of clinical arrhythmia and to confirm appropriateness of the ICD intervention. The findings of this retrospective analysis were compared with the analysis made by the electrophysiologist after interrogation of the device immediately after the shock.

Secondary endpoints included: (1) the composite endpoint of cardiovascular mortality and appropriate ICD shocks; and (2) inappropriate shocks. We defined cardiovascular mortality as death due to sudden cardiac death, heart failure, or other cardiovascular causes, and heart transplantation. Sudden cardiac death was defined as natural death due to cardiac causes, heralded by abrupt loss of consciousness within 1 h of the onset of acute symptoms. Pre-existing heart disease was known to be present, but the time and mode of death are unexpected.[23] Inappropriate ICD shocks were defined as shocks which were not delivered for ventricular arrhythmias, for example during AF with a high ventricular response, or because of over-sensing due to lead problems such as lead fractures or lead dislocation.

Other definitions

Valve disease is defined as moderate or severe valve regurgitation/stenosis. Paroxysmal AF is defined as self-terminating, recurrent AF, in which the episodes of AF usually last less than 48 h (with a maximum of 7 days). Persistent AF is defined as AF that fails to terminate spontaneously and can be cardioverted to sinus rhythm, and in permanent AF electrical cardioversion is unsuccessful or deemed unnecessary.[24]

Statistical analysis

Baseline descriptive statistics are presented as mean $\pm$ SD or median (range) for continuous variables and numbers with percentages for categorical variables. We evaluated differences between variables in patients with a history of AF vs. patients with no history of AF using χ^2 test and Fisher's exact test for categorical data, and Student's *t*-test and Mann–Whitney *U* test for continuous data, according to the normality of distribution of the data.

Cumulative event proportions were calculated using Kaplan–Meier analysis and the log-rank test was used to compare survival curves between the two study groups. We calculated adjusted hazard ratios (HRs) for all baseline variables with Cox proportional hazard regression models. Multivariate analysis was performed using all variables with $P < 0.1$ in univariate analysis. A stepwise approach was used and first-line interactions were investigated. In all analyses $P < 0.05$ was considered statistically significant.

Results

Patient characteristics

Between January 2000 and January 2005, 80 patients with ischaemic or non-ischaemic cardiomyopathy and LVEF $\leq$ 35% received an ICD for primary prevention. A total of 15 patients (19%) received a single-chamber device, 40 patients (50%) received a dual-chamber device, and a biventricular device was implanted in 25 patients (31%).

Baseline characteristics of the patients are depicted in *Table 1*. Drug therapy at hospital discharge is shown in *Table 2*. Mean LVEF was 24 $\pm$ 8%. Reasons for ICD implantation were non-sustained VTs ($n = 49$) or LVEF $\leq$ 30% without VTs ($n = 31$).

A total of 29 patients (36%) had a history of AF and 51 patients (64%) had no history of AF. Patients with a history of AF more often had a single-chamber ICD than patients with no history of AF [10 of 29 patients (34%) vs. 5 of 51 patients (10%), $P = 0.004$]. They also more often had previous cardiac surgery [12 of 29 patients (41%) vs. 10 of 51 patients (20%), $P = 0.04$], and at echocardiography they had a larger left atrium, parasternal axis (52 $\pm$ 6 vs. 47 $\pm$ 9 mm, $P = 0.04$). In addition, patients with a history of AF more often took oral anticoagulation [28 of 29 patients (97%) vs. 39 of 51 patients (76%), $P = 0.03$] at baseline.

Ten patients had either paroxysmal or persistent AF at baseline, i.e. at the time of implantation. None of the patients had permanent AF. Baseline variables between patients with and without AF at baseline were comparable, except that patients with AF at baseline more often had a single-chamber ICD than patients with sinus rhythm at baseline [8 of 10 AF at baseline patients (80%) vs. 7 of 70 no AF at baseline patients (10%), $P < 0.001$].

Follow-up

Median follow-up was 8 months (range 1–60 months). During follow-up, one of 80 patients (1%) received an ICD

Table 1 Clinical characteristics of the patients at baseline

Clinical characteristic	Total population ($n = 80$)	History of AF ($n = 29$)	No history of AF ($n = 51$)	*P*-value
Age (years)	61 ± 15	63 ± 14	56 ± 14	0.05
Male sex	63 (79%)	23 (79%)	40 (78%)	0.93
Ischaemic cardiomyopathy	48 (60%)	19 (66%)	29 (57%)	0.45
Angina pectoris	30 (38%)	11 (38%)	19 (37%)	0.95
Previous MI	45 (56%)	18 (62%)	27 (53%)	0.43
Time between MI and ICD implantation (months)	95 (1–421)	90 (1–354)	104 (1–421)	0.80
Non-ischaemic dilated cardiomyopathy	32 (40%)	10 (34%)	22 (43%)	0.45
History of valve disease	29 (36%)	13 (45%)	16 (31%)	0.23
Mitral valve regurgitation	27 (34%)	11 (38%)	16 (31%)	0.55
Aortic valve regurgitation/stenosis	1/1 (1/1%)	1 (3%)	1 (2%)	1.00
Tricuspid valve regurgitation	6 (8%)	4 (14%)	2 (4%)	0.18
History of hypertension	22 (28%)	10 (34%)	12 (24%)	0.29
Diabetes mellitus	13 (16%)	7 (24%)	6 (12%)	0.21
Previous cardiac surgery	22 (28%)	12 (41%)	10 (20%)	0.04
History of AF	29 (36%)	29 (100%)	–	
Paroxysmal AF	10 (13%)	10 (34%)	–	
Persistent AF	19 (24%)	19 (66%)	–	
NYHA functional class				0.78
I	13 (16%)	4 (14%)	9 (18%)	
II	34 (43%)	12 (41%)	22 (43%)	
III	32 (40%)	13 (45%)	19 (37%)	
IV	1 (1%)	–	1 (2%)	
Index arrhythmia				0.72
Non-sustained VT	49 (61%)	17 (59%)	32 (63%)	
None	31 (39%)	12 (41%)	19 (37%)	
Number of chambers with leads implanted				
Single	15 (19%)	10 (34%)	5 (10%)	0.004
Dual	40 (50%)	10 (34%)	30 (59%)	
Biventricular	25 (31%)	9 (31%)	16 (31%)	0.78
Rhythm at baseline				<0.001
Sinus rhythm	70 (88%)	19 (66%)	51 (100%)	
AF	10 (13%)	10 (34%)	–	
Heart rate (bpm)	73 ± 15	76 ± 17	70 ± 14	0.11
Blood pressure (mmHg)				
Systolic	120 ± 22	119 ± 22	121 ± 22	0.65
Diastolic	70 ± 13	69 ± 15	70 ± 12	0.70
Echocardiography				
Septal wall thickness (mm)	10 ± 2	10 ± 1	9 ± 2	0.05
Posterior wall thickness (mm)	9 ± 1	9 ± 1	9 ± 1	1.00
Left ventricular end-diastolic diameter (mm)	68 ± 13	68 ± 12	69 ± 13	0.75
Left ventricular end-systolic diameter (mm	59 ± 14	58 ± 13	59 ± 14	0.63
Left atrial parasternal axis (mm)	49 ± 9	52 ± 6	47 ± 9	0.04
Fractional shortening (%)	13 (2–46)	13 (5–46)	12 (2–33)	0.83
Left ventricular ejection fraction (%)	24 ± 8	24 ± 8	24 ± 8	0.64

Data expressed as mean ± SD, median (range) or number (%), as required. The *P*-values relate to the comparison between patients with a history of AF and patients with no history of AF. MI, myocardial infarction; NYHA, New York Heart Association functional classification.

replacement because of premature end-of-life. Complications because of ICD implantation occurred in five of 80 patients (6%). Four atrial lead dislocations (5%) occurred and one patient (1%) developed a pneumothorax requiring intervention. No patient was lost to follow-up.

Appropriate ICD shocks

Retrospective analysis regarding appropriateness of the shocks was the same between the two electrophysiologists in all cases. It was also comparable with the analysis made immediately after interrogation of the ICD. Ten of 80 patients (12%) received a median of 1 (range 1–3) appropriate ICD shocks during follow-up. The first appropriate shock occurred after a median of 7 months (range 1–15 months). Four patients received more than one appropriate shock, of which three patients experienced repeated shocks occurring within 1 h. All but one appropriate shock were due to monomorphic fast VTs with a mean rate of 203 ± 9 bpm; one patient in the no history of AF group received a shock for VF.

In the history of AF group more patients received appropriate shocks than in the no history of AF group [7 of 29 patients (24%) vs. 3 of 51 patients (6%), $P = 0.03$] (*Table 3* and *Figure 1A*). AF preceded the fast VT requiring a shock in two patients. Both patients had AF at baseline. One of the patients in whom AF preceded the fast VT was

Table 2 Drug therapy at hospital discharge

Treatment	Total population ($n = 80$)	History of AF ($n = 29$)	No history of AF ($n = 51$)	*P*-value
β-blocker	68 (85%)	24 (83%)	44 (86%)	0.75
ACE-inhibitor or ARB	76 (95%)	29 (100%)	47 (92%)	0.29
Diuretic	63 (79%)	24 (83%)	39 (76%)	0.51
Digitalis	21 (26%)	10 (34%)	11 (22%)	0.21
Oral anticoagulation	67 (84%)	28 (97%)	39 (76%)	0.03
Aspirin	9 (11%)	1 (3%)	8 (16%)	0.15
Calcium channel blocker	5 (6%)	4 (14%)	1 (2%)	0.06
Class III antiarrhythmic agent	16 (20%)	7 (24%)	9 (18%)	0.49
Statin	45 (56%)	16 (55%)	29 (57%)	0.88

Data are expressed as number (%). The *P*-values relate to the comparison between patients with a history of AF and patients with no history of AF. ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker.

Table 3 Events during follow-up

Events	Total population ($n = 80$)	History of AF ($n = 29$)	No history of AF ($n = 51$)	*P*-value
Appropriate shocks	10 (12%)	7 (24%)	3 (6%)	0.03
Cardiovascular mortality + appropriate shocks	16 (20%)	10 (34%)	6 (12%)	0.02
Cardiovascular mortality	6 (8%)	3 (10%)	3 (6%)	0.66
Heart transplantation	1 (1%)	1 (3%)	—	
Heart failure	5 (6%)	2 (7%)	3 (6%)	
Non-cardiac death	1 (1%)	1 (3%)	1 (2%)	1.00
Inappropriate shocks	3 (4%)	2 (7%)	1 (2%)	0.30

Data are expressed as number (%). The *P*-values relate to the comparison between patients with a history of AF and patients with no history of AF.

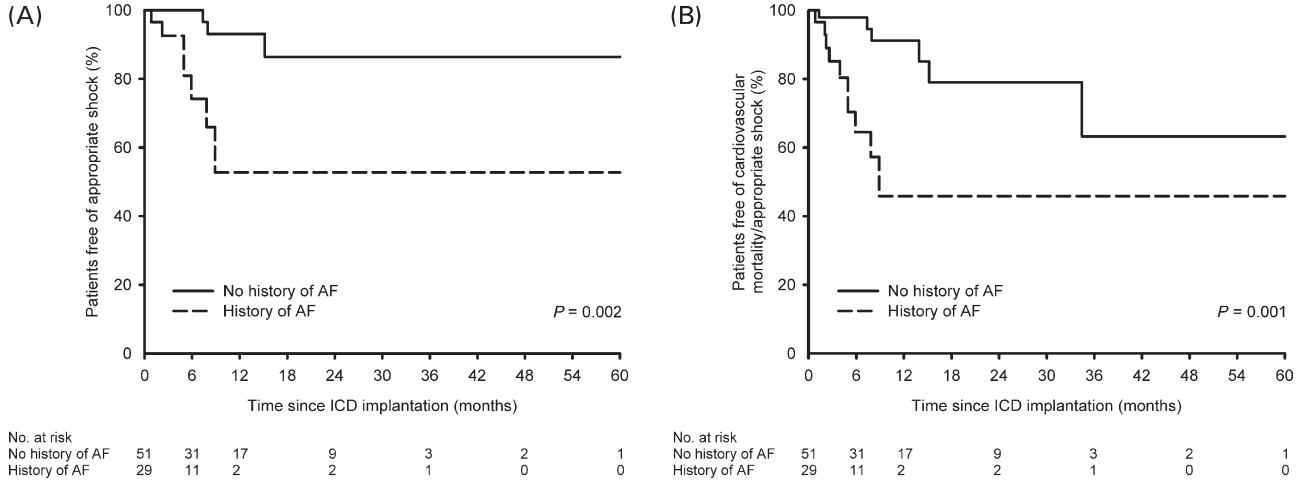

Figure 1 (*A*) Kaplan–Meier survival curve of time to first appropriate shock according to presence of history of AF or no history of AF. (*B*) Kaplan–Meier survival curve of time to composite endpoint of cardiovascular mortality and appropriate shock according to presence of history of AF or no history of AF.

known to have paroxysmal AF, and the other had persistent AF. There was no difference in occurrence of appropriate shocks between paroxysmal and persistent AF patients [2 of 10 paroxysmal AF patients (20%) vs. 5 of 19 persistent AF patients (26%), $P = \text{ns}$).

According to Cox proportional hazard regression models, baseline characteristics that were significantly different between patients with a history of AF and patients with no history of AF were not associated with the occurrence of appropriate shocks. In contrast, history of AF was the only

univariate predictor of appropriate shocks (HR 6.9, 95% CI 1.7–27.5, $P = 0.006$) (*Table 4A*). All other baseline variables including drugs of patients with appropriate shocks during follow-up were comparable with baseline variables of patients without appropriate shocks during follow-up.

Cardiovascular mortality and appropriate ICD shocks

Cardiovascular mortality occurred in 6 of 80 patients (8%) (*Table 3*). One patient (1%) underwent heart transplantation due to end-stage heart failure and five patients (6%) died because of end-stage heart failure. There were no differences between the history of AF and no history of AF groups with respect to cardiovascular mortality.

The composite endpoint of cardiovascular mortality and appropriate shocks occurred in 16 patients (20%) and was more likely to occur in patients with a history of AF [10 of 29 patients (34%) vs. 6 of 51 patients (12%), $P = 0.02$] (*Figure 1B*).

Baseline characteristics that were significantly different between patients with a history of AF and patients with no history of AF were not associated with the occurrence of the composite endpoint according to Cox proportional hazards regression models. History of AF was an independent predictor of the composite endpoint of cardiovascular mortality and appropriate shocks (adjusted HR 5.1, 95% CI 1.7–15.1, $P = 0.003$) (*Table 4B*). In addition, presence of tricuspid valve regurgitation also independently predicted the occurrence of the composite endpoint (adjusted HR 4.9, 95% CI 1.5–16.1, $P = 0.009$).

Inappropriate ICD shocks

A total of three of 80 patients (4%) experienced a median of 3 (range 2–8) inappropriate shocks during follow-up. Median time until the first inappropriate shock was 3 months (range 0–22 months). In two patients (3%) inappropriate shocks were because of lead problems (lead fracture, $n = 1$; lead over-sensing, $n = 1$), whereas in the other patient (1%) inappropriate shocks were caused by AF. There was no difference in the occurrence of inappropriate shocks between the history of AF and no history of AF groups [2 of 29 patients (7%) vs. 1 of 51 patients (2%), $P =$ ns] (*Table 3*).

Discussion

Our study shows that in primary prevention ICD patients, patients with a history of AF are more likely to receive appropriate shocks than patients with no history of AF.

AF and appropriate shocks

Two other studies have also shown an association between AF and appropriate ICD interventions. Grönefeld *et al.*[25] identified AF as an independent predictor of appropriate ICD therapy in predominantly secondary prevention ICD patients. Grimm *et al.*[26] studied idiopathic dilated cardiomyopathy patients who underwent ICD implantation. During a mean follow-up of 36 months, 35% of the patients experienced an appropriate ICD intervention (including antitachycardia pacing). Multivariate Cox regression analysis identified LVEF, history of sustained VT or VF, and AF as independent predictors of appropriate interventions. We also observed this association between AF and ICD shocks, but in contrast to the above-mentioned studies, only in a population without previous haemodynamically significant ventricular tachyarrhythmias.

Stein *et al.*[27] found a time relation between AF and ventricular tachyarrhythmias in patients with an ICD. In this study, 8.6% of all VT/VF episodes were preceded by paroxysmal atrial tachycardia or AF. The median duration of atrial tachycardia or AF preceding VT or VF was approximately 1 h. In our study, taking into account the small number of patients with a history of AF, appropriate shocks while in AF occurred in only 2 of 10 patients. Although the numbers are too small to draw any conclusions, it suggests that AF is merely an epiphenomenon, being a marker of more advanced disease, rather than the cause of the ventricular arrhythmia.

It has been questioned whether AF influences survival in patients with heart failure.[10,13,15] Data suggest that especially in moderate heart failure AF might be associated with impaired prognosis.[28] This idea is supported by our finding that AF independently predicted the occurrence of cardiovascular mortality and/or appropriate shocks. Our study was too small to investigate whether the influence of AF on outcome differed according to severity of heart

Table 4A Predictors of appropriate shocks

	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
History of AF	6.9	1.7–27.5	0.006	6.9	1.7–27.5	0.006

Table 4B Predictors of cardiovascular mortality and appropriate shocks

	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
History of AF	4.8	1.7–13.6	0.003	5.1	1.7–15.1	0.003
Tricuspid valve regurgitation	4.6	1.5–14.7	0.009	4.9	1.5–16.1	0.009

failure (i.e. lower ejection fraction or higher New York Heart Association functional class).

A possible explanation for the association between AF and appropriate shocks might be that AF and ventricular arrhythmias have shared risk factors, such as ischaemia, increased sympathetic tone, or increased left ventricular filling pressure. Secondly, haemodynamic changes caused by AF (e.g. decreased cardiac output) might affect ventricular electrophysiological properties and therefore induce ventricular arrhythmias.[29] A third possibility is that the irregular rhythm during AF leads to short-long-short sequences, which can have a pro-arrhythmic effect.[30] In the present study, however, appropriate shocks while in AF occurred in only two of 10 patients.

Study limitations

The retrospective observational design was a major limitation of our study. Furthermore, it remains a problem to classify shocks accurately as appropriate or inappropriate, especially for patients with single-chamber ICDs. Because patients with a history of AF were more likely to have single-chamber ICDs, there may have been more false positive events in the history of AF group. However, the ICD electrograms were examined carefully to determine appropriateness of the ICD shocks and we did not encounter ambiguous cases.

Over the broad period of enrolment in our study (2000–05), indications for ICD implantation changed. The most dramatic change in indications took place after publication of MADIT-II.[6] After publication, indications for primary prevention ICD therapy became more liberal and the presence of non-sustained VTs became no longer an obligate criterion in our centre. Therefore, in the present primary prevention study, an increasing number of patients received an ICD after publication of MADIT-II [70 patients (88%) after publication vs. 10 patients (13%) before publication]. However, this change in indication did not influence outcome in our study because the index arrhythmia (non-sustained VT or no VT) was no predictor of cardiovascular mortality and/or appropriate shocks.

Another limitation of our study was the modest population size, which explains why Cox proportional hazard regression analysis showed large confidence intervals. However, the study group was relatively homogeneous, because we included all consecutive primary prevention patients in our centre, if they had ischaemic or non-ischaemic cardiomyopathy and LVEF $\leq$ 35%. Furthermore, even though the history of AF and no history of AF groups were small, they were well comparable. The short follow-up duration of the study was also a limitation. On the whole, the retrospective design, small patient numbers, and short follow-up preclude definite conclusions.

Conclusion

Our study demonstrates that in primary prevention ICD patients with left ventricular dysfunction, AF seems to be a factor that contributes to the occurrence of appropriate shocks and cardiovascular mortality. Although the reason why AF plays a role is still unknown, it is intriguing to speculate on the possible role of AF in the selection of patients qualifying for primary prevention ICD implantation. This definitely warrants prospective studies.

References

1. MacIntyre K, Capewell S, Stewart S *et al*. Evidence of improving prognosis in heart failure: trends in case fatality in 66 547 patients hospitalized between 1986 and 1995. *Circulation* 2000;**102**:1126–31.
2. Tchou PJ, Kadri N, Anderson J *et al*. Automatic implantable cardioverter defibrillators and survival of patients with left ventricular dysfunction and malignant ventricular arrhythmias. *Ann Intern Med* 1988;**109**:529–34.
3. Moss AJ, Hall WJ, Cannom DS *et al*. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. Multicenter Automatic Defibrillator Implantation Trial Investigators. *N Engl J Med* 1996;**335**:1933–40.
4. Bigger JT Jr. Prophylactic use of implanted cardiac defibrillators in patients at high risk for ventricular arrhythmias after coronary-artery bypass graft surgery. Coronary Artery Bypass Graft (CABG) Patch Trial Investigators. *N Engl J Med* 1997;**337**:1569–75.
5. Buxton AE, Lee KL, Fisher JD *et al*. A randomized study of the prevention of sudden death in patients with coronary artery disease. Multicenter Unsustained Tachycardia Trial Investigators. *N Engl J Med* 1999;**341**: 1882–90.
6. Moss AJ, Zareba W, Hall WJ *et al*. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med* 2002;**346**:877–83.
7. Hohnloser SH, Kuck KH, Dorian P *et al*. Prophylactic use of an implantable cardioverter-defibrillator after acute myocardial infarction. *N Engl J Med* 2004;**351**:2481–8.
8. Middlekauff HR, Stevenson WG, Stevenson LW. Prognostic significance of atrial fibrillation in advanced heart failure. A study of 390 patients. *Circulation* 1991;**84**:40–48.
9. Stevenson WG, Stevenson LW, Middlekauff HR *et al*. Improving survival for patients with atrial fibrillation and advanced heart failure. *J Am Coll Cardiol* 1996;**28**:1458–63.
10. Dries DL, Exner DV, Gersh BJ *et al*. Atrial fibrillation is associated with an increased risk for mortality and heart failure progression in patients with asymptomatic and symptomatic left ventricular systolic dysfunction: A retrospective analysis of the SOLVD trials. *J Am Coll Cardiol* 1998;**32**: 695–703.
11. Wyse DG, Love JC, Yao Q *et al*. Atrial fibrillation: a risk factor for increased mortality—an AVID registry analysis. *J Interv Card Electrophysiol* 2001;**5**:267–73.
12. Wang TJ, Larson MG, Levy D *et al*. Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: the Framingham Heart Study. *Circulation* 2003;**107**:2920–5.
13. Carson PE, Johnson GR, Dunkman WB *et al*. The influence of atrial-fibrillation on prognosis in mild-to-moderate heart-failure—the V-heft studies. *Circulation* 1993;**87**:102–10.
14. Mahoney P, Kimmel S, DeNofrio D, Wahl P, Loh E. Prognostic significance of atrial fibrillation in patients at a tertiary medical center referred for heart transplantation because of severe heart failure. *Am J Cardiol* 1999;**83**:1544–7.
15. Crijns HJGM, Tjeerdsma G, De Kam PJ *et al*. Prognostic value of the presence and development of atrial fibrillation in patients with advanced chronic heart failure. *Eur Heart J* 2000;**21**:1238–45.
16. Stevenson WG, Stevenson LW. Atrial fibrillation and heart failure—five more years. *N Engl J Med* 2004;**351**:2437–40.
17. Gregoratos G, Cheitlin MD, Conill A *et al*. ACC/AHA guidelines for implantation of cardiac pacemakers and antiarrhythmia devices—A report of the American College of Cardiology American Heart Association Task Force on Practice Guidelines (Committee on Pacemaker Implantation). *J Am Coll Cardiol* 1998;**31**:1175–206.
18. Gregoratos G, Abrams J, Epstein AE *et al*. ACC/AHA/NASPE 2002 Guideline update for implantation of cardiac pacemakers and antiarrhythmia devices: Summary article—A report of the American college of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/NASPE Committee to Update the 1998 Pacemaker, Guidelines). *J Cardiovasc Electrophysiol* 2002;**13**:1183–99.
19. Priori SG, Aliot E, Blomström-Lundqvist C *et al*. Task Force on Sudden Cardiac Death of the European Society of Cardiology. *Eur Heart J* 2001;**22**:1374–450.
20. Priori SG, Aliot E, Blomström-Lundqvist C *et al*. Update of the guidelines on sudden cardiac death of the European Society of Cardiology. *Eur Heart J* 2003;**24**:13–15.

21. Bristow MR, Saxon LA, Boehmer J *et al*. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med* 2004;**350**:2140–50.
22. Wiesfeld AC, Crijns HJ, Hillege HL, Tuininga YS, Lie KL. The clinical significance of coronary anatomy in post-infarct patients with late sustained ventricular tachycardia or ventricular fibrillation. *Eur Heart J* 1995; **16**:818–24.
23. Myerburg RJ, Castellanos A. Cardiac arrest and sudden cardiac death. In: Braunwald E, ed. *Heart Disease: A Textbook of Cardiovascular Medicine*. New York: WB Saunders Publishing Co.; 1997. p742–79.
24. Sopher SM, Camm AJ. Atrial fibrillation: maintenance of sinus rhythm versus rate control. *Am J Cardiol* 1996;**77**:A24–A37.
25. Grönefeld GC, Mauss O, Li YG, Klingenheben T, Hohnloser SH. Association between atrial fibrillation and appropriate implantable cardioverter defibrillator therapy: results from a prospective study. *J Cardiovasc Electrophysiol* 2000;**11**:1208–14.
26. Grimm W, Hoffmann JJ, Muller HH, Maisch B. Implantable defibrillator event rates in patients with idiopathic dilated cardiomyopathy, non-sustained ventricular tachycardia on Holter and a left ventricular ejection fraction below 30%. *J Am Coll Cardiol* 2002; **39**:780–7.
27. Stein KM, Euler DE, Mehra R *et al*. Do atrial tachyarrhythmias beget ventricular tachyarrhythmias in defibrillator recipients? *J Am Coll Cardiol* 2002;**40**:335–40.
28. Van den Berg MP, Van Gelder IC, Van Veldhuisen DJ. Impact of atrial fibrillation on mortality in patients with chronic heart failure. *Eur J Heart Fail* 2002;**4**:571–5.
29. Lerman BB. Mechanoelectrical feedback: maturation of a concept. *J Cardiovasc Electrophysiol* 1996;**7**:17–19.
30. Denker S, Lehmann M, Mahmud R, Gilbert C, Akhtar M. Facilitation of ventricular-tachycardia induction with abrupt changes in ventricular cycle length. *Am J Cardiol* 1984;**53**:508–15.