Implantable cardioverter defibrillator treatment : benefits and pitfalls in the currently indicated population

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Chapter 3

Recurrence of Ventricular Arrhythmias in Ischemic Secondary Prevention ICD Recipients: Long-term Follow-up of the Leiden Out-of-Hospital Cardiac Arrest Study (LOHCAT)

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Abstract

Aims: To assess the long-term rate of mortality and the recurrence of potentially life-threatening ventricular arrhythmias in secondary prevention implantable cardioverter defibrillator (ICD) patients and to construct a model for baseline risk stratification.

Methods and results: Since 1996, all patients with ischemic heart disease, receiving ICD therapy for secondary prevention of sudden death were included in the current study. Patients were evaluated at implantation and during long-term follow-up. A total of 456 patients were included in the analysis and followed for 54±35 months. During follow-up, 100 (22%) patients died and ICD therapy was noted in 216 (47%) patients of which 138 (30%) for fast, potentially life-threatening ventricular arrhythmia. Multivariate analysis revealed a history of atrial fibrillation or flutter (AF), ventricular tachycardia as presenting arrhythmia, wide QRS and poor left ventricular ejection fraction as independent predictors of life-threatening ventricular arrhythmias. The strongest predictor was AF with a hazard ratio of 2.1 (95% CI: 1.3-3.2). Based on the available clinical data it was not possible to identify a group which exhibited no risk on recurrence of potentially life-threatening ventricular arrhythmias.

Conclusions: Ischemic secondary prevention ICD recipients exhibit a high recurrence rate of potentially life-threatening ventricular arrhythmias. Factors, increasing risk can be identified but, even with these factors, it was not possible to distinguish a recurrence-free group.

Introduction

Sudden cardiac death, mainly caused by ventricular arrhythmias in a population with coronary artery disease, is a major cause of mortality in the western world.[1, 2] Large randomised trials have proven the beneficial effect of implantable cardioverter defibrillator (ICD) therapy in survivors of these life-threatening ventricular arrhythmias.[3-5] Although implantation of a defibrillator has become common practice, little is known about the long-term recurrence rate of potentially life-threatening ventricular arrhythmias, mortality and device-related adverse events in this population outside the setting of a clinical trial. Furthermore, results from these randomised trials seldom differentiate in the type of arrhythmia, causing the need for appropriate device therapy. Finally, an attempt to identify a recurrence-free group within this high risk population has not yet been made.

Since 1996, all survivors of life-threatening arrhythmias were screened according to the protocol of the Leiden Out of Hospital Cardiac Arrest STudy (LOHCAT).[6] This well-defined cohort offers a unique opportunity to study the rate of recurrence and mortality after a life-threatening ventricular arrhythmia in patients with ischemic heart disease and to assess the possibility to identify a recurrence-free population.

Methods

Patients and study protocol

Since 1996, all consecutive survivors of life-threatening ventricular arrhythmias at our hospital were evaluated systematically according to a standardised protocol as previously described.[6, 7] All patients with ischemic heart disease, treated by implantation of an ICD, were included in the current evaluation. Life-threatening ventricular arrhythmias were defined similarly to previous large randomised trials as ventricular arrhythmias causing loss of consciousness, requiring pharmacological or electrical cardioversion, or lasting longer than 30 seconds.[3, 4] Patients with ventricular tachycardia (VT) or ventricular arrhythmia due to myocardial infarction (<48 hours), patients with Wolff-Parkinson-White, and patients with adverse drug reactions were excluded from the current evaluation. An acute myocardial infarction was defined as the presence of persistent ST-segment elevation or electrocardiographic signs of evolving myocardial infarction. Patients with minimally elevated creatinin kinase-MB (less than twice the upper limit of normal) were not considered to be patients with acute myocardial infarction.[2] Ischemic heart disease was defined in the presence of significant coronary artery disease (a diameter stenosis of at least 50% in at least one coronary artery).

At inclusion, the following variables were obtained: patient demographics, cardiovascular history, co-morbidity, cardiovascular risk factors and medication. Additionally, an

electrocardiogram was acquired for determination of QRS duration, left ventricular ejection fraction (LVEF) was defined by echocardiography or single photon emission computed tomography and coronary anatomy was investigated by coronary angiography.[6]

Device interrogation/long-term follow-up

Device interrogation was scheduled every three-six months. All printouts were checked for appropriate and inappropriate ICD therapy (anti tachycardia pacing [ATP] or shocks). Therapies were classified as appropriate when they occurred in response to VT or ventricular fibrillation (VF) and as inappropriate when triggered by sinus or supraventricular tachycardia, T-wave oversensing, or electrode dysfunction. In addition cycle length of all ventricular arrhythmias causing device therapy, were noted. Furthermore, follow-up included all-cause mortality, device infections, and device replacements.

In the Dutch health care system, all patients are followed by the implanting centre. Since periodical follow-up was performed every three to six months, patients without data on the past six months were considered as lost to follow-up.

End points

Our primary end-point was the occurrence of a potentially life-threatening ventricular arrhythmia, defined as a ventricular arrhythmia faster than 188 bpm. Secondary end-points were the occurrence of any appropriate ICD therapy (ATP or shock) and all-cause mortality. Furthermore, pocket infection, revascularization and device replacement were noted.

Statistical analysis

Continuous data are expressed as mean ± SD or median with 25th and 75th percentile where appropriate; dichotomous data are presented as numbers and percentages. Cumulative event rates were analyzed by method of Kaplan-Meier and log-rank test. Univariate relationships between baseline parameters and end-points were assessed with Cox proportional hazard regression analysis. For each variable a hazard ratio (HR) with a 95% confidence interval (95% CI) was calculated. Variables with a p-value <0.10 were further evaluated in a multivariate model, using backward stepwise selection. At each step, the least significant variable was discarded from the model, until all variables in the model reached a p-value <0.25. All analyses were performed with SPSS for Windows, version 16.0 (SPSS, Chicago, IL). For all tests, a p-value <0.05 was considered statistically significant.

Results

Baseline characteristics

During the study period, 875 survivors of a life-threatening ventricular were screened according to the LOHCAT protocol. Two-hundred-and-eighty patients (32%) did not show ischemic heart disease and were therefore excluded from the current analysis. Of the population with ischemic heart disease, 119 (20%) patients were not treated with an ICD because of diagnosed acute myocardial infarction (108 patients) or patient's refusal to receive ICD treatment (11 patients). The remaining 476 patients were treated with an ICD in the Leiden University Medical Center. Twenty patients (4.2%) were lost to follow-up. Of these patients, 3 (15%) died during an average follow-up of 21±25 months. No data on device interrogations could be obtained in these patients. The remaining 456 patient were included in the analysis. One-hundred-eighty-eight patients (41%) required cardiopulmonary resuscitation at baseline before ICD implantation. Sixty percent of included patients were implanted after 2002 and mean follow-up was 54±35 months.

The majority of patient (86% men, mean age 65 years, range 33 to 86 years), had a depressed LVEF (35±14%), wide QRS (119±30 ms), and a VT as the presenting arrhythmia (286, 63%). Medication at discharge included diuretics in 53%, beta-blockers (without sotalol) in 47%, sotalol in 20% and amiodarone in 32%. All baseline characteristics are summarised in Table 1.

Occurrence of potentially life-threatening ventricular arrhythmias

Life-threatening ventricular arrhythmias (>188 bpm), triggering device therapy, occurred 470 (range per individual patient: 1-59) times in 138 (30%) out of 456 patients. Cumulative incidences of device therapy for life-threatening ventricular arrhythmias at one, five and eight years are 13%, 35% and 45% respectively (Figure 1).

The chance of a first occurrence of life-threatening ventricular arrhythmias causing an ICD therapy decreased during time following implantation. Still, 12% of patients experiencing a life-threatening ventricular arrhythmia during follow-up had their first occurrence more than 60 months after implantation, as shown in Figure 2.

The multivariate Cox regression model (Figure 3) for the occurrence of life-threatening ventricular arrhythmias revealed the following variables as independent predictors: a history of atrial fibrillation or flutter (AF), VT as presenting arrhythmia (as compared to VF), wide QRS and poor LVEF. The strongest predictor was AF with a HR of 2.1 (95% CI: 1.3-3.2).

Based on the available clinical data it was not possible to identify a group which exhibited no risk on recurrence of potentially life-threatening, fast ventricular arrhythmias.

Table 1. Baseline characteristics

	All patients (n=456)
Clinical parameters	
Male gender	393 (86%)
Age (yrs)	65±10
Presenting arrhythmia is VT	286 (63%)
Creatinin (μmol/L)	110±53
Renal clearance (ml/min)*	75±39
QRS-duration (ms)	119±30
LVEF (%)	35±14
Medication	
Beta-blockers (without sotalol)	212 (47%)
Sotalol	90 (20%)
Ca-antagonist	47 (10%)
Nitrates	145 (32%)
ACE inhibitors / AT antagonist	362 (79%)
Statins	325 (71%)
Diuretics	241 (53%)
Amiodarone	146 (32%)
Aspirin / calcium carbasalate / ASA	186 (41%)
Oral anticoagulant therapy	262 (58%)
Cardiovascular history	
History of atrial fibrillation or flutter	60 (13%)
Previous infarction	424 (93%)
Previous PCI	143 (31%)
Previous CABG	154 (34%)
Risk factors	
Hypertension	153 (34%)
Diabetes	77 (17%)
Hypercholesterolemia	264 (58%)
(History of) nicotine abuse	337 (74%)

* Renal clearance was determined with the formula of Cockroft-Gault.
ACE = angiotensin-converting enzyme; ASA =acetylsalycic acid; AT = angiotensin; CABG = coronary artery bypass graft; LVEF = left ventricular ejection fraction; PCI = percutaneous coronary intervention; VT = ventricular tachycardia

Appropriate device therapy

Ventricular arrhythmias, followed by any ICD therapy (ATP or shock) were noted in 216 (47%) patients. In this group, a total number of 6500 ICD therapies was noted. These consisted of 5890 (range per individual patient: 1-1948) episodes of ATP in 142 patients and 610 (range per individual patient: 1-59) shocks in 152 patients. Cumulative incidences of appropriate therapy at one, five and eight years are 24%, 52% and 61% respectively (Figure 1).

Seventy-nine patients (17%) received appropriate device therapy within six months following ICD implantation. Patients receiving device therapy within six months demonstrate

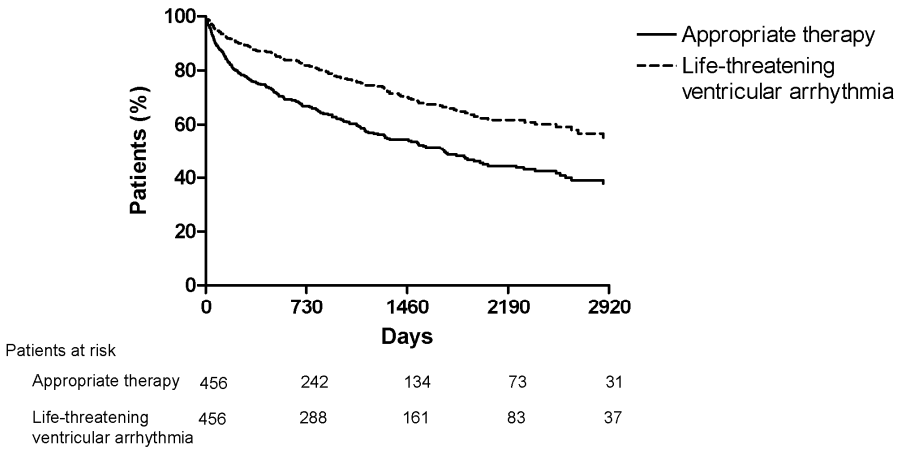

Figure 1. Kaplan-Meier curve for appropriate therapy-free follow-up (bold line) and appropriate therapy for life-threatening VT-free follow-up (dashed line).

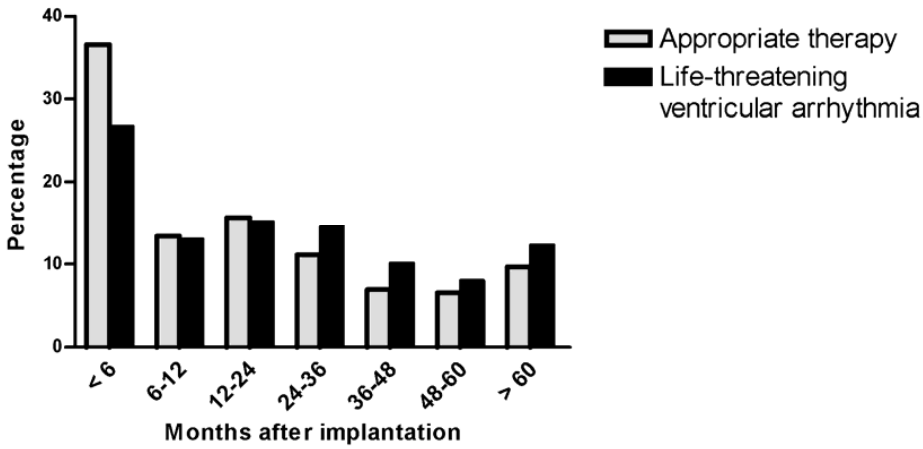

Figure 2. First appropriate therapy or therapy for life-threatening ventricular arrhythmia after ICD-implantation.

an increased risk of subsequent device therapy during further follow-up. Early therapy exhibits a HR of 3.3 (95% CI: 2.4-4.6) when compared to patients without early therapy (Figure 4). Of interest, early device therapy had no negative effect on survival (HR 1.1, 95% CI: 0.6-2.0).

All-cause mortality

Figure 5 shows the survival rates and the number of patient at risk. During follow-up, 100 (22%) patients died 41±30 months after implantation. One, five and eight-year mortality rate was 4%, 20% and 36% respectively.

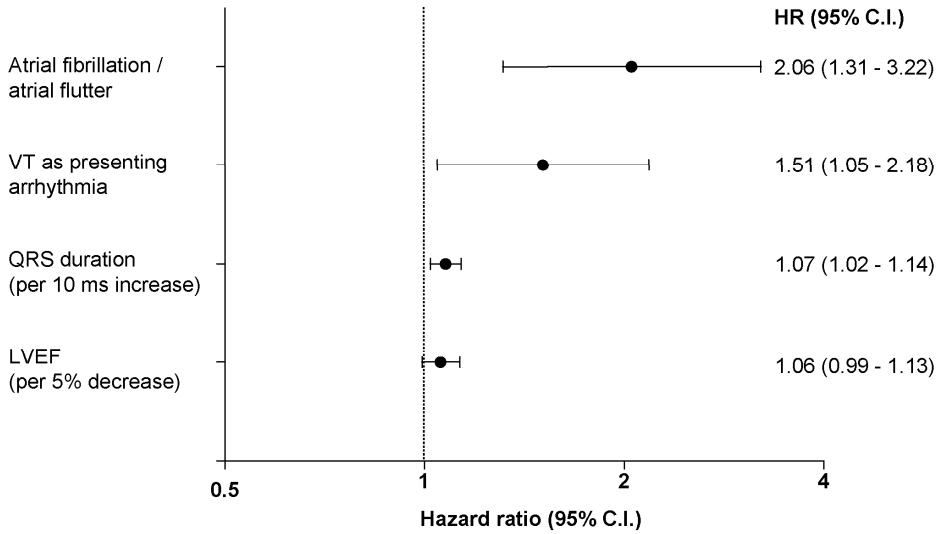

Figure 3. Multivariate Cox proportional hazard model for therapy for life-threatening ventricular arrhythmias.

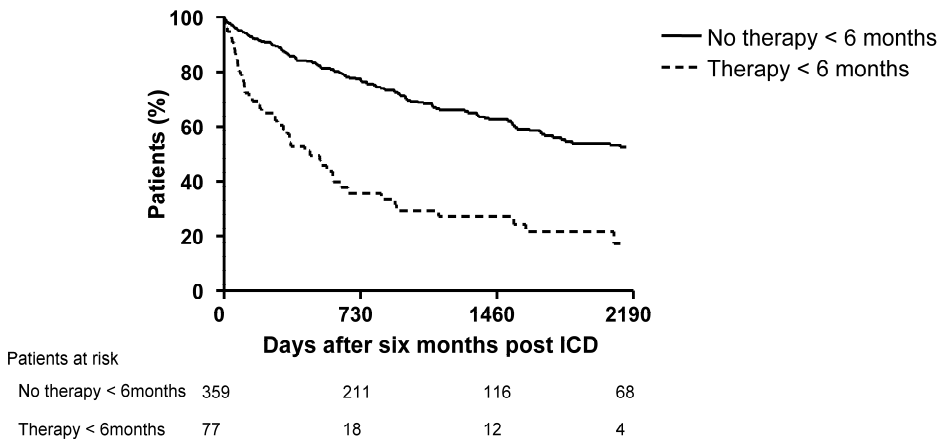

Figure 4. Cumulative appropriate device therapy-free period in patients with vs. without early therapy.

A multivariate Cox regression model for the relation between patient characteristics and death is shown in Figure 6. AF, no statin usage, diuretics for congestive heart failure, diabetes, high age, poor renal function, and wide QRS were independent predictors of mortality.

Infections, revascularizations, inappropriate shocks and device replacement

Screening for adverse events related to ICD implantation, included pocket infections, revascularizations and inappropriate shocks. Pocket infections occurred in eight patients

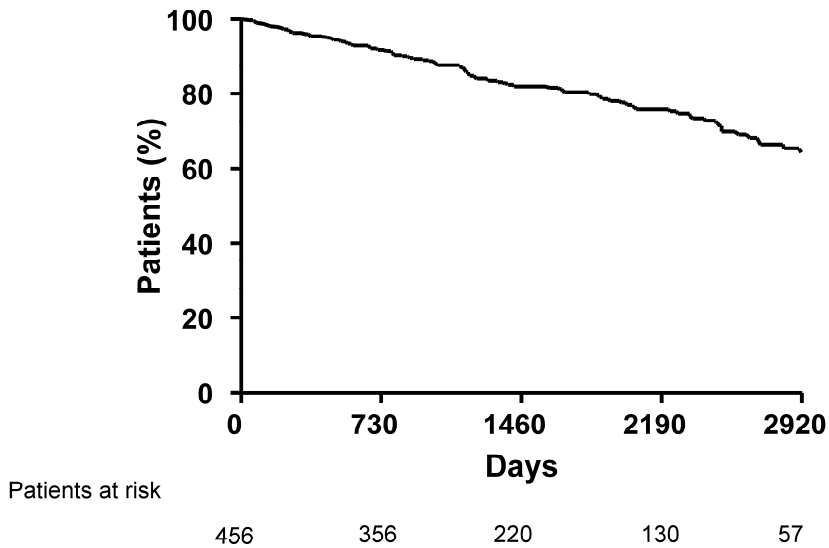

Figure 5. Kaplan-Meier curve for survival.

(1.8%). Thus, with a mean follow-up of 54 months, the rate of pocket infections was 3.9 per 1000 patient-years.

During follow-up, a total of 33 (7%) patients required revascularization. These procedures included 19 cases of percutaneous coronary angioplasty, 13 cases of coronary artery bypass graft and one patient received both types of revascularization.

Two-hundred-and-ten episodes of inappropriate shocks, not caused by VT or VF, were noted in 75 (16%) patients. This brings the rate of inappropriate shocks to 102 per 1000 patient-years. Of notice in patients receiving inappropriate shock therapy, 36% also received appropriate therapy for life-threatening ventricular arrhythmias, whereas 64% did not.

One-hundred-sixty-seven (37%) patients outlived the longevity of their first device and needed a replacement. Of these, 39 patients got a second replacement and 5 patients even received a fourth device. This gives a mean number of 1.5 ICDs per person during our follow-up or 325 ICDs per 1000 patient-years.

Discussion

In the current study on the long-term follow-up of ischemic secondary prevention ICD recipients, findings can be summarised as follows: 1) Ventricular arrhythmia, triggering device therapy occurred in 47% of patient with a cumulative incidence of 61% after eight years; 2) Device therapy for a fast, potentially life-threatening VT occurred in 30% with a cumulative incidence of 45% after eight years; 3) Factors independently correlated with an

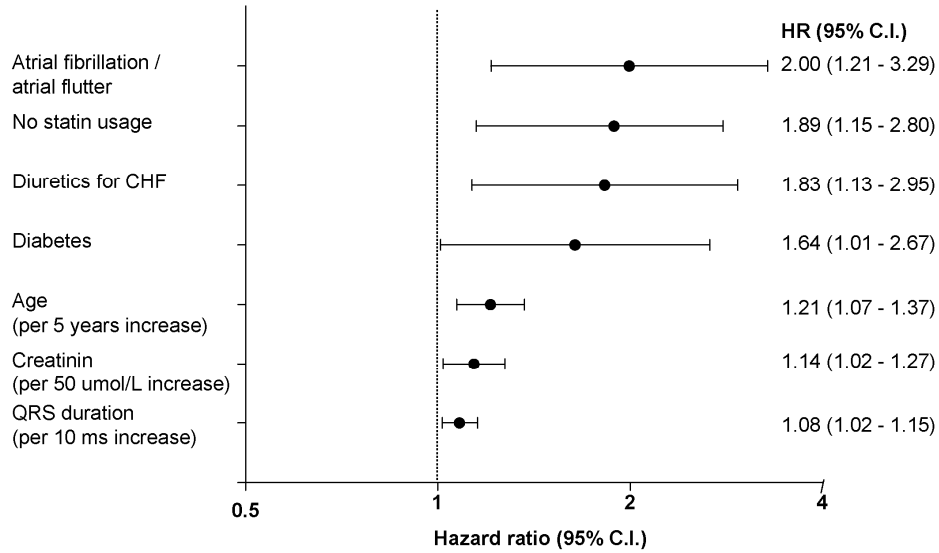

Figure 6. Multivariate Cox proportional hazard model for all-cause mortality.

increase in the risk of potentially life-threatening VT are a history of AF, a VT as the presenting arrhythmia, wide QRS and poor LVEF; 4) No recurrence-free group could be identified; 5) Cumulative mortality was approximately 5% per year; 6) Factors that independently increased mortality were a history of AF, no statin usage, diuretics for congestive heart failure, diabetes, high age, poor renal function and wide QRS.

Potentially life-threatening ventricular arrhythmia

Since previous studies demonstrated that device therapy should not be used as a surrogate end-point for death in case the ICD had not been implanted,[8] it is hard to identify which part of the implanted population actually owns its life to the device. As done previously,[9, 10] the current study used cycle length to differentiate between possible life-threatening ventricular arrhythmias and slower, less dangerous arrhythmias. Given the fact that that all patients received an ICD as secondary prevention, use of potentially life-threatening arrhythmias as an end-point makes it possible to study the predicting factors of recurrence of these dangerous arrhythmias. The factors influencing the risk on recurrence of potentially life-threatening VT are AF, VT as presenting arrhythmia (as compared to VF), wide QRS and poor LVEF. No previous studies have been conducted on the prediction of fast ventricular arrhythmias in secondary prevention. Factors, described in predicting any appropriate device therapy in secondary prevention ICD recipients are poor LVEF, VT as presenting arrhythmia (as compared to VF).[11] A history of AF and wide QRS have not yet been described in the context of secondary prevention, but are known risk factors in the occurrence of ventricular arrhythmia in primary prevention.[12, 13] Even with knowledge of these risk factors, it was still not possible to identify patients who would not have a recurrence of life-threatening VT at

follow-up, in which case device implantation might not have been necessary. This finding emphasises the importance of a defibrillator in all patients with ischemic heart disease, surviving sudden death or sustained VT.

Appropriate device therapy

During follow-up, 216 (47%) patients experienced appropriate device therapy (ATP or shock), triggered by ventricular arrhythmias. As expected in this high risk population, occurrence of ventricular arrhythmias is higher than observed in large trials on the effect of primary prevention, such as the MADIT II (cumulative event-rate at three years LOHCAT: 40% vs. MADIT II: 35%).[14] Previous studies on secondary prevention show a wide range in the need for defibrillator back-up during follow-up. One of the first large randomised trials, the Antiarrhythmics versus Implantable Defibrillator (AVID) trial, displays an incidence of up to 68% in 18 months and a cumulative incidence of 73% at three years.[3, 8] A possible explanation for this much higher device therapy rate is the fact that the single-chamber ICDs used in AVID made it hard to discriminate between appropriate and inappropriate therapy. Furthermore, AVID used the composed end-point of device therapy and possible arrhythmic death, increasing event rates.[15] Further studies on the follow-up in secondary prevention ICD recipients demonstrate an occurrence of 27% to 49% during a mean follow-up of 11 to 32 months, which is in line with our findings.[7, 9-11, 16]

The increased risk of recurrent ventricular arrhythmias in patients with early ventricular arrhythmia was previously described by Freedberg and co-workers, who noted subsequent ventricular arrhythmias in 79% of patients receiving initial therapy.[11] Additionally, even though the annual rate of first appropriate device therapy decreases in the time following implantation, the risk for device therapy persists during the entire follow-up, as previously described.[17] The fact that patients receiving appropriate device therapy are at such an increased risk of recurrence stresses the need for close follow-up of this high risk population

Mortality

Cumulative mortality was approximately 5% per year. Previously studied similar cohorts exhibit comparable yearly mortality rates ranging from 4.6% to 8.4%.[4, 5, 7, 9, 16] Two trials describe a significant higher yearly mortality rate of 10%, which could be explained by the short follow-up of eleven and 18 months.[3, 10] With such a short follow-up, the relatively high in-hospital mortality has a greater effect on the calculated yearly death rate than in trials with a longer follow-up.

Baseline characteristics of independent value in the risk stratification on mortality are a history of AF, no statin usage, diuretics for congestive heart failure, diabetes, high age, poor renal function, and wide QRS. Most factors are markers for more severe cardiac dysfunction and all factors are known to increase mortality in a population with ischemic heart dise

Limitations

This was a non-randomised prospective observational study, performed to assess the long-term follow-up in ICD recipients at high risk for recurrence and to construct a model for the risk stratification of this population. Since previous large trials have shown the benefit of defibrillator implantation in this population, no control group could be used. Therefore, irrespectively of the end-point chosen to mark recurrence of life-threatening arrhythmia, this will never perfectly represent the occurrence of potentially life-threatening events in case the ICD would not have been implanted. This also holds true for a sustained VT at baseline which causes the patient to be labelled as secondary prevention ICD recipient but would not necessarily have degenerated in VF, causing arrhythmic death. Furthermore, since patients were collected over a period of eleven years, expanding guidelines for the implantation of defibrillators, treatment of acute myocardial infarction, and pharmacological antiarrhythmic therapy could have created a heterogeneous population.

Conclusion

Ischemic secondary prevention ICD recipients exhibit a high risk of recurrence of potentially life-threatening ventricular arrhythmia. The need for defibrillator back-up is highest in the first period following implantation but persists during long-term follow-up. Factors, increasing risk can be identified but no recurrence-free group can be distinguished.

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