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COOPERATIVE STUDIES

Determinants of Prognosis in Symptomatic Ventricular Tachycardia or Ventricular Fibrillation Late After Myocardial Infarction

ALBERT R. WILLEMS, MD,* JAN G. P. TIJSSEN, PHD,† FRANS J. L. VAN CAPELLE, PHD,* J. HERRE KINGMA, MD, PHD,‡ RICHARD N. W. HAUER, MD,§ FREDDY E. E. VERMEULEN, MD,‡ PEDRO BRUGADA, MD,‖ DIEDERICK C. A. VAN HOOGENHUYZE, MD,¶ MICHIEL J. JANSE, MD,* ON BEHALF OF THE DUTCH VENTRICULAR TACHYCARDIA STUDY GROUP OF THE INTERUNIVERSITY CARDIOLOGY INSTITUTE OF THE NETHERLANDS

Amsterdam, Rotterdam, Nieuwegein, Utrecht and Maastricht, The Netherlands

In a multicenter study, 390 patients with sustained symptomatic ventricular tachycardia or ventricular fibrillation late after acute myocardial infarction were prospectively followed up to assess determinants of mortality and recurrence of arrhythmic events. Patients were given standard antiarrhythmic treatment, which consisted primarily of drug therapy. During a mean follow-up period of 1.9 years, 133 patients (34%) died; arrhythmic events and heart failure were the most common cause of death (41 patients [11%] died suddenly, 31 [8%] died because of recurrent ventricular tachycardia or ventricular fibrillation and 23 [6%] died of heart failure). One hundred ninety-two patients (49%) had at least one recurrent arrhythmic event; 85% of first recurrent arrhythmic events were nonfatal.

Multivariate analysis of data from patients who developed the arrhythmia <6 weeks after infarction identified five variables as independent determinants of total mortality: 1) age >70 years (risk ratio 4.5); 2) Killip class III or IV in the subacute phase of infarction (risk ratio 3.5); 3) cardiac arrest during the index arrhythmia (risk ratio 1.7); 4) anterior infarction (risk ratio 2.2); and 5) multiple previous infarctions (risk ratio 1.6). Multivariate analysis of data from patients developing the arrhythmia >6 weeks after infarction identified four variables as independently predictive of total mortality: 1) Q wave infarction (risk ratio 2.1); 2) cardiac arrest during the index arrhythmia (risk ratio 1.7); 3) Killip class III or IV in the subacute phase of infarction (risk ratio 1.7); and 4) multiple previous infarctions (risk ratio 1.4).

The results of the two multivariate analyses were used in a model for prediction of mortality at 1 year. The average predicted mortality rate varied considerably according to the model: for 243 patients (62%) with the lowest risk, it was 13%, corresponding to an observed mortality rate of 12%; for 92 patients (24%) with intermediate risk, it was 27%, corresponding to an observed rate of 28%; for 55 patients (14%) with the highest risk, it was 64%, corresponding to an observed rate of 54%.

This study shows that patients with symptomatic ventricular tachycardia or ventricular fibrillation late after myocardial infarction who are given standard antiarrhythmic treatment have a high mortality rate. The predictive model presented identifies patients at low, intermediate and high risk of death and can be of help in designing the appropriate diagnostic and therapeutic strategy for the individual patient.

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The prognosis of patients developing ventricular tachycardia or ventricular fibrillation ≥48 h after acute myocardial infarction is poor, with mortality rates after 6 months to 3 years of follow-up study ranging from 31% to 66% (1–6). The mortality rate is even higher if the arrhythmia occurs relatively early after the onset of infarction. Wellens et al. (7) reported an 83% mortality rate after a mean follow-up period of 0.7 year if sustained ventricular tachycardia had occurred within 8 weeks. Different methods are available to identify patients at high risk of sudden cardiac death, including ambulatory Holter electrocardiographic (ECG) monitoring

From the *Department of Experimental Cardiology, Academic Medical Center, Amsterdam; †Thoraxcenter, Erasmus University, Rotterdam; ‡Departments of Cardiology and Cardiac Surgery, St. Antonius Hospital, Nieuwegein; §Department of Cardiology, University Hospital Utrecht, Utrecht; ‖Department of Cardiology, University Hospital Maastricht, Maastricht and ¶Department of Cardiology, Zuiderziekenhuis, Rotterdam, The Netherlands. This work was supported by Grants 8362 and 86019 from the Dutch Heart Foundation, The Hague, The Netherlands and by Knoll Pharmaceuticals, Amsterdam.

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Address for reprints: Albert R. Willems, MD, Department of Experimental Cardiology, M053, Academic Medical Center, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands.

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and programmed electrical stimulation (8–14). However, the role of the clinical history and 12 lead ECG in determining prognosis is not well established.

Therefore, the present Dutch multicenter study was initiated in 1984. Its aims were 1) to assess prognosis in patients with symptomatic ventricular tachycardia or ventricular fibrillation late after infarction, and 2) to identify those baseline characteristics that independently determine prognosis; both evaluations were limited to patients receiving standard antiarrhythmic treatment. The study was designed as a prospective nonrandomized follow-up investigation.

Methods

Organization. The study was carried out under the auspices of the Interuniversity Cardiology Institute of The Netherlands. Thirteen cardiology departments participated (see Appendix). The first patient was enrolled on April 1, 1984 and the last on April 1, 1987. Central registry and processing of the data were done at the Department of Clinical and Experimental Cardiology of the Academic Medical Center in Amsterdam. A steering committee was responsible for the scientific conduct of the study.

Patient selection. Patients with documented sustained ventricular tachycardia or fibrillation occurring ≥48 h after the onset of myocardial infarction were eligible for the study, provided that at least one of the following symptoms occurred during the arrhythmia: palpitation, chest pain, dyspnea, dizziness, syncope or cardiac arrest. The diagnosis of (previous) myocardial infarction was based on the presence of at least two of the following criteria: 1) pathologic Q waves on the ECG meeting Minnesota Code Manual criteria (15); 2) elevation of cardiac serum enzymes; and 3) abnormal wall motion as documented by echocardiography, scintigraphy or angiography. Patients were not registered if the attending cardiologist attributed the ventricular tachyarrhythmia to pump failure, ischemia or imbalance of serum electrolytes. In addition, participating cardiologists did not register patients if the arrhythmia was considered to be caused by proarrhythmic effects of an antiarrhythmic drug. Proarrhythmic effects of drugs were considered in cases in which ventricular fibrillation or a ventricular tachycardia with a rate >250 beats/min occurred within 30 days after the prescription of the drug (16). The records of all patients were retrospectively reviewed by the study coordinator (A. R. W.); patients whose entry criteria had been unequivocally violated were removed from the registry.

Treatment and follow-up. Patients were initially treated with an antiarrhythmic drug; if this failed, a second drug was prescribed; and if that failed, a third drug was given. The first two drugs were preferably class I antiarrhythmic drugs (17), such as procainamide, quinidine, disopyramide, flecainide and propafenone. Amiodarone was the drug of choice in the third phase. Participating cardiologists were not restricted in guiding drug therapy. In addition, some departments used "parallel testing of drugs." Nonpharmacologic treatment was undertaken in patients who had ventricular tachycardia or ventricular fibrillation refractory to drug treatment.

Patients were prospectively followed up from entry in the study until April 1, 1988. All patients attended an outpatient clinic at regular intervals. At entry, data on clinical history, physical examination and the index arrhythmia were collected. In addition, information concerning the previous infarction and its complications were retrospectively obtained. Therefore in some cases no clinical information was available with regard to the previous infarction. During follow-up study, symptomatic recurrent arrhythmic events and the different forms of antiarrhythmic treatment were documented. Moreover, causes and circumstances of death were ascertained for all patients who died.

Definition of outcome events. Total mortality was the main outcome event in this study. Recurrence of an arrhythmic event (sudden death, fatal or nonfatal symptomatic sustained ventricular tachycardia or ventricular fibrillation) was considered a secondary outcome event. All deaths were categorized by two experienced cardiologists. Sudden death was defined as witnessed death within 1 h after the onset of (new) symptoms, unwitnessed but unexpected death and death occurring during sleep. Documented fatal recurrent ventricular tachycardia or ventricular fibrillation was considered a separate category. Sudden death and fatal documented recurrent ventricular tachyarrhythmias were considered arrhythmic deaths.

Data analysis. The occurrence of death is presented as cumulative incidences derived from actuarial survival curves and as incidence rates, which are defined as the total number of deaths divided by the total number of patient-years of follow-up study. The incidence rate quantifies the occurrence of new events in relation to time and allows an adequate (and simple) description of differences in mortality rates between groups with different durations of follow-up study (19).

In the univariate analysis, the effect of a baseline characteristic is quantified by the risk ratio, defined as the ratio of two incidence rates; 95% confidence intervals were calculated to indicate the precision of the risk ratio estimate. If the 95% confidence interval is >1, the association of the respective variable with the mortality risk is statistically significant at a 5% level ($p < 0.05$).

In the multivariate analysis, Cox survival analysis (proportional hazards model) is used (20). The goal of this analysis is to predict survival from a set of independent (risk) factors within the baseline characteristics.

Actuarial survival curves are estimated with the Kaplan-Meier method (21).

Definitions of baseline characteristics. The following definitions were used. *Ventricular tachycardia:* tachycardia

consisting of at least three consecutive ventricular complexes with a mean rate >100 beats/min.

Nonsustained ventricular tachycardia: ventricular tachycardia lasting <30 s and not leading to hemodynamic collapse.

Sustained ventricular tachycardia: ventricular tachycardia lasting ≥30 s or leading to hemodynamic collapse.

Ventricular fibrillation: chaotic ventricular rhythm without identifiable QRS complexes on the surface ECG.

Primary ventricular tachycardia or ventricular fibrillation: ventricular tachycardia or ventricular fibrillation within 48 h after the onset of infarction and not related to pulmonary edema or cardiogenic shock.

Cardiac arrest: a clinical condition during ventricular tachycardia or ventricular fibrillation requiring cardiopulmonary resuscitation.

Index arrhythmia: the arrhythmia that led to registration of the patient in the study; it was not necessarily the first episode of ventricular tachycardia or ventricular fibrillation after myocardial infarction.

Nonreferred patients: patients under treatment in one of the participating centers at the time of the index arrhythmia.

Referred patients: patients referred to the participating centers for diagnostic or therapeutic evaluation at the time of the index arrhythmia.

Q wave infarction: infarction with pathologic Q waves on the ECG, that is, Q waves >30 ms in two or more of anterior (V_1 to V_4), inferior (II, III or aVF) or lateral (V_5, V_6, I or aVL) leads. Minimal amplitude R waves (≤0.025 mV) in infarct-related ECG leads and an R/S ratio ≥1 in lead V_1 were considered synonymous with pathologic Q waves.

Non-Q wave infarction: infarction without pathologic Q waves, as just defined.

Undetermined infarction: infarction in the presence of left bundle branch block.

Results

Patient registry and follow-up. Of 473 patients registered, 83 were excluded because of violations of the admission protocol, such as no documentation of the ventricular tachyarrhythmia or nonsustained ventricular tachycardia (n = 41); retrospective registration (n = 26); arrhythmia related to ischemia (n = 1), pump failure (n = 8) or both (n = 1); no evidence of infarction (n = 2); asymptomatic tachycardia (n = 3); and tachycardia of supraventricular instead of ventricular origin (n = 1). Ultimately, 390 patients were available for data analysis. The mean follow-up period (±1 SD) was 1.9 ± 1.2 years (range 1 to 4). No patient was lost to follow-up study.

Clinical profile of the study group (Table 1). The following characteristics are of note: 1) 24% of the index arrhythmias occurred after multiple myocardial infarctions but the infarction preceding the arrhythmia was typically located in the anterior wall; 2) the most severe clinical condition in the first 6 weeks after the infarction (not during the arrhythmia), estimated according to the Killip classification (22), was class III or IV in only 13%; the majority of patients (77%), however, were in relatively good clinical condition; 3) primary sustained ventricular tachycardia or ventricular fibrillation had occurred during the acute phase of the infarction in 17% of patients; 4) the infarction was complicated by second degree atrioventricular (AV) heart block in 10%, and right bundle branch block, left bundle branch block and complete heart block had occurred in 12%, 4% and 5%, respectively; 5) 26 of 137 patients whose index arrhythmia was ventricular fibrillation or ventricular tachycardia with a mean rate >250 beats/min developed the arrhythmia while receiving antiarrhythmic drug treatment for reasons other than symptomatic ventricular tachyarrhythmias as defined earlier. However, 9 of these 26 patients had received this treatment for >30 days, suggesting no relation between drug prescription and occurrence of the arrhythmia; in 11 of the 26, the arrhythmia occurred ≤30 days after prescription of the drug, whereas this information was unknown in 6 patients.

Treatment. *At 1 and 2 years of follow-up study (Table 2),* all patients were categorized into one of the treatment groups according to the most invasive form of therapy. The number of nonpharmacologic treatments did not increase with time.

At last follow-up evaluation (that is, the last follow-up visit for those who died and at the end of the study period for those still alive), 56 patients had undergone endocardial map-guided antiarrhythmic surgery, 12 had received an automatic internal cardioverter/defibrillator and 6 had been treated by electrical catheter ablation. Fifteen patients underwent coronary artery bypass grafting (in three patients with additional aneurysmectomy); five patients underwent percutaneous transluminal coronary angioplasty and three patients underwent heart transplantation because of concomitant drug-refractory heart failure. The majority of patients (75%) were treated by drugs only.

Mortality (Fig. 1, Table 3). The cumulative mortality rate in the 390 patients at 1 and 2 years was 22% and 34%, respectively. The overall incidence rate was 18 deaths/100 patient-years. Sixty-eight of 161 patients whose arrhythmia developed within 6 weeks after the infarction died, 25 during the hospital phase of infarction. Fifty-six percent of all deaths were related to a recurrent arrhythmic event. Sudden death, recurrent ventricular tachyarrhythmia and pump failure were the three most common causes of death, with cumulative incidences after 2 years of 11%, 8% and 6%, respectively; the corresponding incidence rates were 6, 4 and 3 events/100 patient-years. Recurrent ventricular arrhythmia as a cause of death was frequently observed in patients who died during the hospital phase: of 25 patients who died in the hospital, 13 (57%) died because of recurrent ventricular arrhythmia. In addition, of 31 patients who died of recurrent ventricular tachyarrhythmia, 13 (42%) died during the hospital phase of the infarction.

Table 1. Baseline Characteristics of the 390 Patients in Relation to the Risk of Death

	No. (%)	Mortality per 100 Pt-Years	RR	95% CI
Gender				
Female	44 (11)	21§	—	
Male	346 (89)	18	0.9	0.5–1.5
Age (yr)				
<50	55 (14)	11		
50–60	118 (30)	11	§ —	
60–70	154 (39)	22		
>70	63 (16)	34	2.1	1.4–3.0*
Referral status				
Referred	201 (52)	19§	—	
Nonreferred	189 (48)	17	0.9	0.6–1.3
Multiple previous MIs				
No	298 (76)	17§	—	
Yes	92 (24)	24	1.4	1.0–2.1
Location of MI				
Inferior/posterior	129 (33)	15	§ —	
Undetermined	12 (3)	24		
Anterior	249 (64)	20	1.3	0.9–1.9
Type of MI				
Non-Q wave	25 (6)	12	§ —	
Undetermined	20 (5)	17		
Q wave	345 (89)	19	1.3	0.7–2.3
Clinical condition†				
Unknown	40 (10)	11	§ —	
Killip class I or II	301 (77)	16		
Killip class III or IV	49 (13)	45	2.6	1.7–4.0*
Postinfarction angina				
Unknown	30 (8)	15	§ —	
No	313 (80)	19		
Yes	47 (12)	17	1.0	0.6–1.6
Primary sustained VT/VF†				
Unknown	34 (9)	18	§ —	
No	290 (74)	14		
Yes	66 (17)	14	0.7	0.5–1.2
Second degree AV block‡				
Unknown	38 (10)	18	§ —	
No	312 (80)	18		
Yes	42 (11)	17	1.0	0.5–1.7
RBBB‡				
Unknown	36 (9)	15	§ —	
No	307 (79)	18		
Yes	47 (12)	22	1.2	0.8–2.0
LBBB‡				
Unknown	36 (9)	15	§ —	
No	340 (87)	19		
Yes	15 (4)	18	1.0	0.4–2.4
Complete heart block‡				
Unknown	36 (9)	15	§ —	
No	335 (86)	18		
Yes	19 (5)	37	2.0	1.1–3.9*
Index arrhythmia				
Sust VT	268 (69)	15§	—	
VF	122 (31)	25	1.6	1.1–2.3*
Maximal rate of index VT (n = 268) (beats/min)				
Unknown	11 (3)	29		
100–150	39 (10)	15	§ —	
150–200	127 (33)	14		
200–250	76 (19)	16		
250–300	14 (4)	22		0.6–1.3
300–350	1 (0)	0	0.9	
Signs or symptoms during index arrhythmia				
Syncope	32 (8)	14		
Other	160 (41)	14	§ —	
Palpitation	42 (11)	13		
Cardiac arrest	156 (40)	27	1.9	1.4–2.7
First VT/VF after MI under arrhythmic drugs				
No	77 (20)	16§	—	
Yes	313 (80)	19	1.1	0.7–1.8
First episode of VT/VF after MI				
Unknown	23 (6)	16		
>1 year	107 (27)	16	§ —	
6 weeks–1 year	98 (25)	12		
<6 weeks	162 (42)	26	1.8	1.3–2.5*

*Significant risk ratio; †within semiacute phase of the infarction; ‡during the acute phase of infarction; §reference group. AV = atrioventricular; CI = confidence interval of risk ratio; LBBB = left bundle branch block; MI = myocardial infarction; Pt-Years = patient-years; RBBB = right bundle branch block; RR = risk ratio; Sust = sustained; VF = ventricular fibrillation; VT = ventricular tachycardia.

Table 2. Treatment at 1 and 2 Years of Follow-Up

	Follow-Up	
	1 Year	2 Years
No. patients alive	309	169
Treatment		
Antiarrhythmic surgery	37 (12%)	22 (13%)
AICD	7 (2%)	3 (2%)
ECA	5 (1%)	2 (1%)
Other	14 (5%)	11 (7%)
Drugs only	246 (80%)	131 (78%)

AICD = automatic implantable cardioverter/defibrillator; ECA = electrical catheter ablation.

Prediction of total mortality by univariate analysis. Eleven factors were identified as having an increased risk for total mortality (Table 1). However, the lower limit of the 95% confidence interval was >1 for only six factors. The referral status of patients was not related to mortality.

Prediction of total mortality by multivariate analysis (Tables 4 to 6). Multivariate analysis was performed separately for patients developing the first arrhythmia within 6 weeks after infarction and for those developing the arrhythmia after a longer period. For the former patients, the Cox regression model identified 5 of the 11 baseline characteristics that were potentially relevant to prognosis as independently predictive of total mortality: age >70 years, Killip class III or IV in the first 6 weeks after infarction, anterior infarction, cardiac arrest during the index arrhythmia and history of multiple previous infarctions (Table 4A). For the latter patients, the model selected four variables as independently predictive of total mortality: Q wave infarction, cardiac arrest, Killip class III or IV in the first 6 weeks after infarction and history of multiple previous infarctions (Table 4B).

Table 5 documents the predicted mortality rate for each of the possible combinations of risk factors (that is, patient profiles) based on the results of the two multivariate models. For example, a patient developing the arrhythmia >6 weeks after the infarction and without any risk factor, has a 5% predicted risk of death after 1 year. For a 60 year old patient whose arrhythmia developed within 6 weeks after the infarction and who has cardiac arrest and anterior infarction as risk factors, the predicted mortality risk is 33%.

The relation between the observed and predicted mortality rate according to multivariate analysis (that is, the goodness of fit) is shown in Table 6. Sixty-two percent of patients were grouped at low, 24% at intermediate and 14%

Figure 1. Kaplan-Meier survival curve for all 390 patients with total mortality as the outcome. Vertical lines represent the standard error of the mean. The number of patients at risk is indicated above the horizontal axis.

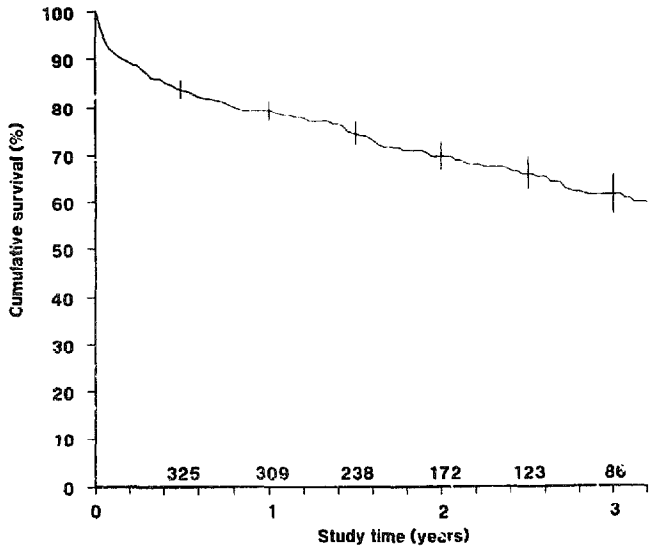

Table 3. Causes of Death With Corresponding Cumulative 2 Year Incidences

	No. (2 year incidence)*
Total mortality	133 (34%)
Cardiac causes	109 (28%)
Arrhythmic death	
Sudden death	41 (11%)
Documented recurrent VT/VF	31 (8%)
Other cardiac causes	
Pump failure without recurrent MI	23 (6%)
Recurrent MI	2 (1%)
Pump failure and recurrent VT/VF	8 (2%)
Other cardiac causes	4 (1%)
Noncardiac causes	13 (3%)
Unknown	11

*Obtained from the Kaplan-Meier survival curve. Abbreviations as in Table 1.

Table 4. Results of Cox Survival Analysis

Variable	Risk Ratio*	95% CI	p Value
A: First VT/VF <6 Weeks After Infarction			
Age >70 years†	4.5	2.6–7.7	0.0000
Cardiac arrest†	1.7	1.0–2.8	0.0025
Killip class III or IV‡	3.5	1.5–4.4	0.0031
Anterior MI	2.2	1.2–3.9	0.0158
Multiple previous MIs	1.6	0.9–2.7	0.1057
B: First VT/VF >6 Weeks After Infarction			
Q wave MI	2.1	0.8–5.9	0.0734
Cardiac arrest†	1.7	1.1–2.9	0.0455
Killip class III or IV‡	1.7	0.8–3.4	0.1861
Multiple previous MIs	1.4	0.8–2.4	0.2559

*The risk ratio was obtained as the exponent of the regression coefficient of the Cox model; †during index arrhythmia; ‡during the semiacute phase of infarction. Abbreviations as in Table 1.

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Table 5. Predicted 1 Year Mortality (%) on the Basis of the Presence or Absence of Determinants of Death

Killip class III or IV*	+	+	+	+	−	−	−	−
Cardiac arrest†	+	+	−	−	+	+	−	−
Multiple MI	+	−	+	−	+	−	+	−
First VT/VF <6 weeks after MI								
Age ≥70 yr†								
Anterior MI	100	99	99	94	94	83	81	66
Nonanterior MI	96	88	86	72	72	56	54	39
Age <70 yr†								
Anterior MI	80	64	62	46	46	33	31	21
Nonanterior MI	52	38	36	25	25	17	16	10
First VT/VF >6 weeks after MI								
Q wave MI	38	29	24	26	18	19	16	12
Non-Q wave MI	18	13	11	12	8	9	7	5

*Within the semiacute phase of infarction; †during the index arrhythmia. According to the patient profile, a related column and row can be determined. The numbers in the crossing of the columns and rows represent the predicted mortality rate (in percent) after 1 year. See text for further explanation and examples. + = determinant present; − = determinant absent; other abbreviations as in Table 1.

at high risk of death; the observed rates were 12%, 28% and 54%, respectively. The observed mortality rate for each category accurately corresponded with the predicted rates in the low and intermediate risk groups. The model slightly overestimated the mortality rate in the high risk group.

Recurrence of arrhythmic events (Fig. 2). At least one recurrent arrhythmic event was documented in 192 patients (49%). These first recurrences were nonfatal in 164 (85%) of the 192 patients. The cumulative rate for all (both fatal and nonfatal) recurrent arrhythmic events after 6 months and 1 and 2 years was 39%, 43% and 49%, respectively, corresponding with an overall incidence rate of 38 events/100 patient-years. These findings illustrate that recurrent arrhythmic events occur early after the first episode of the arrhythmia. The cumulative rate for arrhythmic deaths after 1 and 2 years was 11% and 18%, respectively, which corresponds to an incidence rate of 10 events/100 patient-years. All patients who eventually received a cardioverter/defibrillator had a (nonfatal) recurrent arrhythmic event after entry into the study but before implantation of the device.

Table 6. Observed and Predicted 1 Year Mortality Rates in 390 Patients

Risk	No. of Patients	No. of Deaths	Observed Mortality (%)	Predicted Mortality (%)
Low	243	28	12	13
Intermediate	92	26	28	27
High	55	30	54	64
Total	390	84	22	24

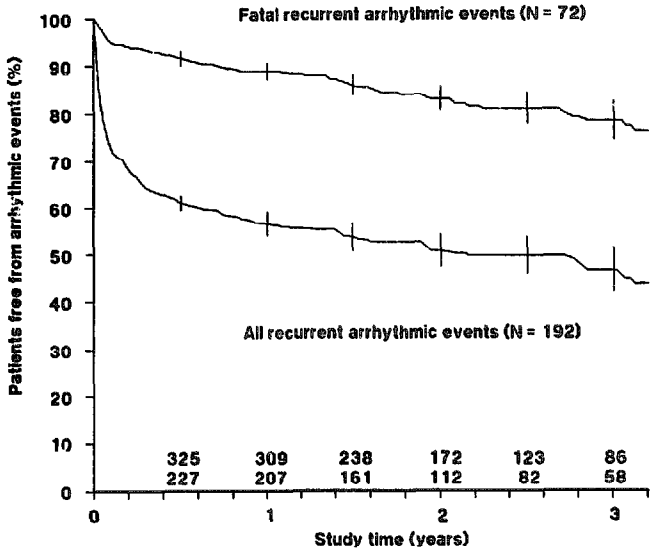

Figure 2. Kaplan-Meier curves for 72 patients with fatal recurrent arrhythmic events (**upper curve**) and all (fatal and nonfatal) arrhythmic events (n = 192) (**lower curve**) as the outcome. **Vertical lines** represent the standard error of the mean. The number of patients at risk of fatal events (**upper row**) and of all arrhythmic events (**lower row**) are indicated above the horizontal axis.

Nonfatal recurrences after implantation of the device, even if possible to assess, could not be taken into account.

Prediction of recurrence of arrhythmic events. In contrast to total mortality, no strong predictors of recurrent arrhythmic events could be identified. All that can be said is that 19 (21%) of 92 patients with multiple infarctions died suddenly compared with 22 (7%) of 298 patients with only one previous acute myocardial infarction. In addition, 2 (3%) of 66 patients with primary sustained ventricular tachycardia or ventricular fibrillation in the acute phase of infarction died suddenly compared with 32 (11%) of 290 patients without primary sustained ventricular tachycardia or ventricular fibrillation. Also, 33 (67%) of 49 patients who were in Killip class III or IV during the first 6 weeks after infarction developed a new arrhythmic event compared with 140 (46%) of 301 patients who were in a better clinical condition. However, none of these univariate predictors was sufficiently strong to warrant multivariate analysis.

Discussion

The natural history of sustained ventricular tachycardia or ventricular fibrillation occurring late after myocardial infarction is unknown. Studies (7,13,23) reporting a poor prognosis are based on relatively small numbers of patients who were treated with drugs, thereby changing the natural history of the disease to an unnatural history. The present study is no exception with respect to the problem of describing the natural history of the disease because all patients

received treatment. It is, however, the first study that prospectively followed up a large group of patients with these malignant ventricular arrhythmias. It outlines the clinical course of patients with symptomatic ventricular tachycardia or ventricular fibrillation late after myocardial infarction who were given the standard antiarrhythmic treatment in The Netherlands during the period from April 1, 1984 to April 1, 1988. In addition, we were able to relate baseline characteristics present at the time of the first episode of the arrhythmia to total mortality.

Profile of the patient developing symptomatic ventricular tachycardia or ventricular fibrillation after myocardial infarction. Entry criteria were selected such that only patients whose ventricular tachyarrhythmia resulted in specific antiarrhythmic therapy were considered. We did not select patients with ventricular tachyarrhythmias attributed to pump failure, ischemia or imbalance of serum electrolytes because treatment of these patients should focus on improving pump function, oxygen supply and homeostasis of electrolytes rather than on treatment of the arrhythmia. Asymptomatic patients were not included because the diagnosis is dependent on the performance of an investigation. In patients with ventricular fibrillation or fast (>250 beats/min) ventricular tachycardia during antiarrhythmic drug treatment, proarrhythmic effects were always considered. According to the definition of proarrhythmia proposed by Morganroth (16) in 1987, however, we determined that the likelihood of the arrhythmia being induced by an antiarrhythmic drug was small (only 9 of 26 patients were receiving the drug for >30 days before the arrhythmia occurred). To exclude proarrhythmic effects of drugs completely, however, is impossible, but the maximal number of patients concerned (17 patients) is small.

The profile of patients developing malignant symptomatic ventricular tachyarrhythmias after infarction can be of value in understanding pathophysiologic mechanisms. In this respect, several findings are noteworthy and suggest that we indeed studied patients with electrical instability as the main problem and not patients with other underlying cardiac abnormalities (such as pump failure) causing secondary ventricular arrhythmias. First, only a relatively small group of patients (13%) had signs or symptoms of a poor clinical condition during the first 6 weeks after myocardial infarction. Second, we observed a high rate (17%) of primary sustained ventricular tachycardia or ventricular fibrillation during the first 48 h of acute myocardial infarction. Other investigators (24–26) reported rates of 1% to 10% in "average" patients with infarction. We also found that patients with these primary sustained ventricular arrhythmias had a lower risk of sudden death than did those without. These results are in contrast to the observations of Schwartz et al. (27), who found both a high total mortality rate and a high incidence of sudden death in patients with acute anterior myocardial infarction and primary ventricular fibrillation. However, they defined primary ventricular fibrillation as documented ventricular fibrillation during the stay in the coronary care unit, without mentioning the time elapsed from the onset of infarction. Hence, some of their cases with "primary" ventricular fibrillation, we would consider "late."

We found a high percent of second degree AV block (10%) and right bundle branch block (12%) during the acute phase of the infarction, whereas others have reported rates ranging from 2% to 10% (mean 5%) for second degree AV block (26,28,29) and 2% to 4% for right bundle branch block (30,31) in the "average" patient with infarction. The high percent of right bundle branch block noted in our study agrees with earlier observations made by Lie et al. (32), who found a high incidence of late ventricular fibrillation in patients with extensive anteroseptal infarction complicated by right bundle branch block.

Treatment. The prognosis described in the present study is conditional on the patient being given standard antiarrhythmic treatment. Two hundred ninety-three patients (75%) were treated with drugs only. The remaining patients eventually received invasive therapy, of which specific antiarrhythmic surgery was the major alternative.

Total mortality. The incidence rate of total mortality was 18 deaths/100 patient-years, with 22% and 31% of patients having died after 1 and 2 years of follow-up study, respectively. In other studies (1,6,33,34), higher mortality rates (29% to 52%) were reported. These studies, however, involved relatively small numbers of patients; the high mortality rates could therefore be at least in part due to chance. Another factor explaining the difference in mortality rates is that in most of the cited studies the arrhythmia occurred early (within 2 to 6 weeks) after infarction. In our study, we observed a 30% and 40% mortality rate after 1 and 2 years, respectively, in 162 patients developing the ventricular arrhythmia within 6 weeks of infarction, whereas the rate was 14% and 23%, respectively, in patients who had these arrhythmias after 6 weeks. Graboys et al. (13) reported an annual mortality rate of 11%, but the underlying heart disease was myocardial infarction in only 50%.

Thus, different study designs, inclusion criteria and definitions of the tachyarrhythmia led to different study groups and contributed to differences in mortality rates. In addition, application of new or improved forms of treatment (35,36) could have played a role in the different mortality rates.

Predictors of outcome events. Multivariate analysis was separately performed for those patients developing the arrhythmia within 6 weeks after the infarction and those developing the arrhythmia after a longer period. The rationale of two separate analyses is based on the difference in the pathologic substrate (the myocardial infarction). The statistically significant difference in the mortality rate between the two groups (Table 1) illustrates the clinical relevance of two separate analyses.

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Five baseline characteristics were independently predictive of total mortality if the analysis was undertaken for patients developing their first arrhythmia within 6 weeks after infarction. Age >70 years (risk ratio 4.5) is the strongest predictor of death. Cardiac arrest during the index arrhythmia was the second most important determinant (risk ratio 1.7). This characteristic was also identified as a risk factor by Brugada et al. (37). The third factor found to be predictive of death is a poor clinical condition (not during the arrhythmia) according to the Killip classification <6 weeks after acute myocardial infarction (risk ratio 3.5). Although this classification is determined by more than left ventricular function alone, patients in Killip class III or IV probably have poor residual left ventricular function. This is in accordance with the fact that poor left ventricular function after myocardial infarction is considered an independent determinant of death (2,3,38). The last two determinants, anterior location of infarction (risk ratio 2.2) and multiple infarctions (risk ratio 1.6), also seem to be important in patients with decreased left ventricular function. Both factors, however, had an additional predictive value over the Killip classification. It is not surprising that multiple previous infarctions and anterior infarction are determinants of death because both are associated with increased myocardial damage (39).

In patients developing the arrhythmia >6 weeks after infarction, cardiac arrest, poor clinical condition during the first 6 weeks after infarction and multiple previous infarctions were also independent determinants of death. In addition, Q wave infarction also emerged as a risk factor. This is remarkable because patients with non-Q wave infarction are considered to have a similar or even higher incidence of postinfarction angina (40), recurrent infarction (41–43) and sudden death (40) in comparison with patients with Q wave infarction. In general, it seems that death in patients with sustained (symptomatic) ventricular tachyarrhythmias after myocardial infarction and that in the "average" patient with infarction is determined by the same variables, especially old age and poor left ventricular function.

Multivariate analysis not only allows identification of determinants of total mortality, but quantification of risk given a particular risk profile. Most patients (62%) were grouped as being at low risk; the observed risk of death was 12%. Ninety-two patients (24%) identified as being at intermediate risk showed an observed risk of 28%, whereas 55 high risk patients (14%) had an observed risk of 54%. The risk profile described in Table 5 applies to patients with symptomatic ventricular tachycardia or ventricular fibrillation after infarction, provided that a similar therapeutic strategy is followed. When the predictive function was derived, we included all patients (and subsequently all deaths) irrespective of the treatments given. Therefore, the predictive function applies prospectively from the moment of ventricular arrhythmia onward. Exclusions based on subsequent clinical decisions (such as performing surgery or other invasive therapies) would have hampered the applicability of the risk function.

No satisfactory model could be derived to predict arrhythmic events. Apparently, more specific characteristics (for example, those derived from angiographic and electrophysiologic studies) must be used to predict new arrhythmic events. In this study, however, details of these investigations were not available in most patients at the time of the occurrence of the index arrhythmia. Using results of investigations performed during the study would lead to an undesirable selection of patients. Moreover, the possible influence of time and treatment on the results of these investigations cannot be established. Hence, in the present analysis, these results were not taken into account.

Limitations of the study. We only enrolled patients who were symptomatic during the arrhythmia. Thus, all results apply only to patients with at least one of the symptoms during the arrhythmia, as previously defined. In addition, patients were not registered if the attending physician thought the ventricular arrhythmia attributable to ischemia or pump failure. However, totally excluding ischemia or pump failure as the trigger initiating the arrhythmia is impossible. Finally, we cannot exclude patient selection due to referral, although we can show that the referral status of patients in this study did not influence their prognosis.

Conclusions and clinical implications. We assessed the clinical course of patients with symptomatic ventricular tachycardia or ventricular fibrillation late after myocardial infarction who were given standard antiarrhythmic treatment. At the time of the occurrence of the arrhythmia, the risk of total mortality within 1 year can be estimated from seven simple and generally available clinical and ECG characteristics. In this way, patients can be identified as being at high, intermediate and low risk. This information can be helpful in establishing the optimal diagnostic and treatment strategy in the individual patient. If predicted risk is high, invasive diagnostic procedures (for example, electrophysiologic studies) and therapeutic interventions may be considered at an earlier stage. In addition, invasive therapy may become acceptable for high risk patients who otherwise would not have seemed to be good candidates for such treatment. Conversely, if predicted risk is low, a conservative attitude seems justified and therapy should probably remain restricted to drug treatment of symptomatic episodes.

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Appendix

The Scientific Board of Interuniversity Cardiology Institute of The Netherlands (F. L. Meijler, MD, Chairman) was responsible for the final scientific conduct of the study.

The Dutch Ventricular Tachycardia Study Group of the Interuniversity Cardiology Institute of The Netherlands is formed by

Study chairmen: M. J. Janse, MD, H. J. J. Wellens, MD.

Steering committee: P. Brugada, MD, F. J. L. van Capelle, PhD, R. N. W. Hauer, MD, D. C. A. van Hoogenhuyze, MD, M. J. Janse, MD, (Chairman), J. H. Kingma, MD, J. G. P. Tijssen, PhD, F. E. E. Vermeulen, MD.

Coordinating center: F. J. L. van Capelle, PhD, A. Heidenrijk, M. J. Janse, MD, M. van Tongeren, A. R. Willems, MD (Coordinator), M. de Zwart.

Participating centers: The Cardiology and Cardiosurgical Departments of the following hospitals: Academic Medical Center, Amsterdam (J. M. T. de Bakker, PhD, J. I. Darmanata, MD, A. C. Moulijn, MD, J. C. J. Res, MD, A. Sippens Groenewegen, MD); Free University Hospital, Amsterdam (W. Jaarsma, MD, J. H. C. Panis, MD); Diakonessenhuis, Groningen (J. H. Bennekers, MD); Diakonessenhuis, Utrecht (A. C. Bredero, MD); Onze Lieve Vrouwe Gasthuis, Amsterdam (R. M. Schuilenburg, MD); Sint Antonius Hospital, Nieuwegein (J. J. Defauw, MD, N. M. van Hemel, MD, J. H. Kingma, MD, F. E. E. Vermeulen, MD); Sint Radboud Hospital, Nijmegen (T. S. Bos, MD); Thoraxcenter, University Hospital, Groningen (H. J. G. M. Crijns, MD, T. Ebels, MD, I. van Gelder, MD, K. I. Lie, MD, J. W. Viersma, MD, L. M. van Wijk, MD); University Hospital, Leiden (H. A. Bosker, MD, H. A. Huijsmans, MD); University Hospital, Maastricht (P. Brugada, MD, O. C. K. M. Penn, MD, F. Simonis, J. P. Smeets, MD, H. J. J. Wellens, MD); University Hospital, Utrecht (P. F. A. Bakker, MD, R. N. W. Hauer, MD, J. F. Hitchcock, MD, E. O. Robles de Medina, MD); Thoraxcenter, University Hospital, Rotterdam (E. Bos, MD, R. Geuskens, MD, B. Mochtar, MD, J. R. T. C. Roelandt, MD); Zuiderziekenhuis, Rotterdam (D. C. A. van Hoogenhuyze, MD).

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