Original articles

Incidence and predictors of sudden cardiac death during long-term follow-up in patients with dilated cardiomyopathy on optimal medical therapy

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Dilated cardiomyopathy; Prognosis; Sudden death.

Background. **In spite of a total mortality reduction in recent years, sudden cardiac death (SD) remains a major problem in patients with idiopathic dilated cardiomyopathy (IDC) and its occurrence is often unpredictable. Furthermore, the risk of SD may change during follow-up because of the natural history of the disease and the effects of therapeutic interventions. In our study, we evaluated the modifications of the risk of SD during follow-up in a cohort of patients with IDC and analyzed the variables predicting SD not only at enrolment but also at the last examination during optimal medical treatment.**

Methods. **Since 1978, 343 consecutive patients with IDC were enrolled in the Heart Muscle Disease Registry of Trieste (Italy) and submitted to complete invasive and non-invasive study. Patients were re-evaluated usually at intervals of 12 months.**

Results. **After a mean of 68 ± 45 months, 125 events (death, heart transplantation or aborted SD) had occurred. The cumulative risk after 5 years was 30%, while after 10 years it almost doubled (54%). During the first 3 months after enrolment, the incidence of SD was high (3%). A plateau, lasting about 3.5 years, followed. A slow but progressive rise in the risk of mortality then occurred (6% at 5 years, 18% at 10 years). No variables evaluated at enrolment were associated with SD at multivariate analysis. On the other hand, the end-diastolic left ventricular diameter (≥ 38 mm/m^2) and ejection fraction (≤ 0.30) were predictive of SD if evaluated within 1 year before the event. Beta-blocker treatment was associated with a non-significant reduction of risk.**

Conclusions. **In patients with IDC the incidence of SD progressively increased during long-term follow-up, especially in those with persistent severe left ventricular dilation and dysfunction who were not on beta-blocker treatment. Serial clinical evaluation may help to select patients at higher risk for SD.**

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Introduction

In spite of a reduction in total mortality and death due to progressive heart failure, in the last two decades the incidence of sudden cardiac death (SD) in patients with idiopathic dilated cardiomyopathy (IDC) has not been significantly modified[1]. Class I antiarrhythmic drugs[2], digoxin[3] and ACE-inhibitors[4,5] do not reduce the incidence of SD, while treatment with beta-blockers[6-8], and perhaps with amiodarone (especially in patients with non-ischemic heart failure)[9,10] has recently been shown to be potentially effective.

In addition, it is very difficult to individualize the risk. In fact, although SD is, in absolute terms, more frequent in the advanced stages of the disease[11], it represents the first cause of death among patients with less severe cardiomyopathy[4,5,12]. Besides, the natural history of the disease and treatment can remarkably modify, in one way or another, the parameters traditionally considered "markers" of severity and the related risk of SD. In most of the studies where a prognostic stratification was attempted, patients were evaluated only at the time of diagnosis or, in any case, before starting an effective therapy and sometimes many years before the final event.

Furthermore, in most studies the sample population was rather heterogeneous (cardiac decompensation of various etiology) or limited in the number of patients.

In this study we evaluated 343 consecutive patients with IDC enrolled in the Heart Muscle Disease Registry of Trieste (Italy). At enrolment all patients were submitted to invasive and non-invasive work-up. Follow-up lasted many years and consisted of serial clinical and instrumental evaluation. We retrospectively analyzed the incidence of progressive heart failure and SD during long-term follow-up and tried to identify the parameters predicting SD at the time of diagnosis and at the last evaluation before the fatal events.

Methods

Patient selection. From January 1, 1978 to June 30, 1997, 343 patients with IDC were prospectively studied and enlisted in the Heart Muscle Disease Registry of Trieste (Italy). All these patients underwent complete physical examination, electrocardiography (12-lead electrocardiography, Holter monitoring since 1980, and since 1991 signal-averaged electrocardiography), echocardiography (two-dimensional, M-mode since 1982 and Doppler since 1989), chest X-ray, an exercise stress test and hemodynamic evaluation comprehensive of coronary angiography. For the patients with an inadequate echocardiogram, the left ventricular ejection fraction was quantified at radionuclide ventriculography. IDC was diagnosed if the left ventricular ejection fraction was < 50% in the absence of any other known cardiac disease[13]. According to this definition, patients with moderate to severe hypertension (> 170/100 mmHg), significant coronary artery disease (> 50% stenosis in an epicardial vessel), right ventricular arrhythmogenic cardiomyopathy, severe valvulopathies, high alcohol assumption (> 100 g/die), tachycardia-induced cardiomyopathies, systemic diseases potentially causing left ventricular dysfunction, severe pericardial and congenital diseases, cor pulmonale and patients with suspected cardiotoxicity were excluded from the study.

At diagnosis most patients underwent endomyocardial biopsy to exclude active myocarditis (according to the Dallas criteria)[14]; in 15 cases (diagnosed since 1995) with a history of heart failure lasting > 24 months and a low clinical probability of active myocarditis, this procedure was not performed.

During the first decade of enlistment, patients were treated since diagnosis with digoxin and diuretics. In this period amiodarone was administered in the presence of frequent and/or repetitive ventricular arrhythmias even when asymptomatic.

ACE-inhibitors were introduced since the mid '80s, initially in patients with more severe heart failure according to the data published in the literature[15].

Since the end of the '80s all patients had been treated, if tolerated and in the absence of contraindications, with digoxin, ACE-inhibitors, beta-blockers and diuretics (as required). Since the mid '90s, an automatic cardioverter-defibrillator (AICD) was implanted in patients with sustained and poorly tolerated ventricular tachycardia, with a history of cardiac arrest due to ventricular tachyarrhythmias or with syncope of unknown origin. In this period amiodarone was administered in the presence of non-sustained but particularly frequent, complex or symptomatic ventricular or supraventricular arrhythmias.

Since 1988, all patients were offered the possibility of participating in a follow-up program, including serial evaluation according to clinical requirements, at the Heart Failure Outpatient Clinic of the Division of Cardiology of Trieste (Italy). A schedule requiring information regarding the possible occurrence of events, subjective conditions, therapeutic regimens currently underway and the physician in charge was annually sent to all patients who were no longer followed at our Outpatient Clinic.

Endpoint definition. All causes of death, aborted SD and heart transplantation were considered primary endpoints. Death was classified as due to progressive heart failure (including death due to refractory heart failure and "expected" SD, i.e. preceded by significant worsening of heart failure), "unexpected" SD (occurring within 1 hour of the development of new symptoms or during sleep in stable NYHA class I-III patients), other cardiovascular deaths, undetermined causes (whenever it was not possible to determine the reason with certainty) and extracardiac causes.

Indications for heart transplantation included frequent hospitalization due to refractory heart failure or refractory life-threatening arrhythmias, or a peak oxygen consumption < 10 ml/kg/min at the exercise test.

Patients submitted to heart transplantation were included in the group of pump failure deaths, since in our population refractory heart failure was the only indication for this procedure. Three patients who were resuscitated from cardiac arrest due to ventricular fibrillation and then treated with an AICD were classified as aborted SD and included in the SD group.

Follow-up was terminated on September 30, 1999 or when the patient died or was submitted to heart transplant. Endpoint information was obtained either directly from the patient during evaluation at follow-up or by telephone interview to the patients, their relatives or to the referring physicians. With regard to the patients lost to follow-up, data were obtained from the birth registry of the place of residence.

Statistical analysis. First of all we analyzed the survivor functions from the time of initial evaluation using the Kaplan-Meier method and the incidence of progressive heart failure and of SD during long-term follow-up.

The clinical findings at enrolment of patients without subsequent fatal events during follow-up (group 1) were compared with those of patients who later died of heart failure (group 2) or SD (group 3). Then, the non-

invasive variables obtained at the last evaluation in patients who survived at least 1 year thereafter (group A) were compared with those of patients who died of progressive heart failure (group B) or SD (group C) within 1 year. Differences among group means were compared by one-way analysis of variance using the Sheffè test for paired comparison. Differences among proportions were compared using the χ^2 test applying the Yates correction. The Cox proportional hazards model was used to analyze the relation between SD and prognostic indices both at enrolment and at the last evaluation.

All clinical data of our patients were recorded in a computerized database (Heart Muscle Disease Registry) at the Heart Failure Outpatient Clinic (DBMS Oracle 8.4 on localnet Windows NT). For our statistical analysis the SPSS version 6.0 for Windows was used. Data are expressed as mean ± SD or as percentages. A p value of < 0.05 was considered as statistically significant.

Results

From January 1, 1978 to June 30, 1997, 343 patients with IDC with an average follow-up of 68 ± 45 months were enrolled in the Heart Muscle Disease Registry.

Among these, 125 primary events occurred: 48 patients (38%) died of refractory heart failure and 29 underwent heart transplantation; 33 (26%) experienced an unexpected (in 3 cases aborted) SD; 15 (12 %) died of other cardiovascular diseases, non-cardiac or unknown causes (Table I).

Analyzing the event-free survival curve, the slope seemed to remain constant during long-term follow-up (Fig. 1) with an average annual event rate of 6.43 events/100 patients-year. The cumulative risk of primary events after 5 years was 30%, while after 10 years this percentage almost doubled (54%).

Even the heart failure rate tended to increase progressively reaching 22% at 5 years, but showed a slower rise during the following years (32% at 10 years).

The slope of the "unexpected" SD curve sharply increased during the first months following enrolment (mortality risk 3% at 3 months), was followed by a plateau lasting about 3.5 years and then rose slowly but progressively (mortality risk 6% at 5 years, 18% at 10 years).

Figure 2 shows the annual event rate according to the different causes of death in two consecutive 5-year periods during follow-up. During the first 5 years, the incidence of "unexpected" SD (1.44/100 patients-year) was lower compared to that of progressive heart failure (4.93/100 patients-year). On the other hand, during the following 5-year period, the incidence of SD slightly increased (2.38/100 patients-year; p = NS vs SD incidence in the first 5 years) and was higher than that of progressive heart failure (1.58/100 patients-year, p = 0.006 vs incidence of progressive heart failure in the first 5 years).

The incidence of SD was particularly high during the first 3 months (9.6/100 patients-year up to the third month vs 0.9/100 patients-year from the third to the sixtieth month). In the first period of follow-up, SD occurred in 8 patients with mild symptoms of heart failure but with severe left ventricular dilation, biventricular dysfunction

Table I. Heart Muscle Disease database: follow-up results.

No. patients	343
Follow-up (months)	68 ± 45
No. primary events	125
Deaths	93
Deaths for pump failure/heart transplantations	77 (62% of events)
Heart transplantations	29 (23% of events)
Refractory heart failure	37 (30% of events)
Expected SD	11 (8% of events)
Unexpected (including aborted) SD	33 (26% of events)
Aborted SD/sustained ventricular tachycardia	3
Pulmonary embolism	1 (1% of events)
Non-cardiac causes	8 (6% of events)
Unknown causes	6 (5% of events)

SD = sudden death.

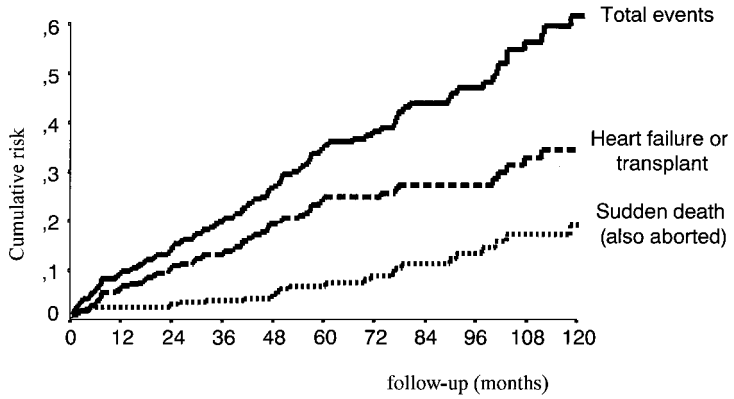

Figure 1. *Risk of death or heart transplantation in 343 patients with idiopathic dilated cardiomyopathy enrolled in the Heart Muscle Disease Registry from 1978 to 1997.*

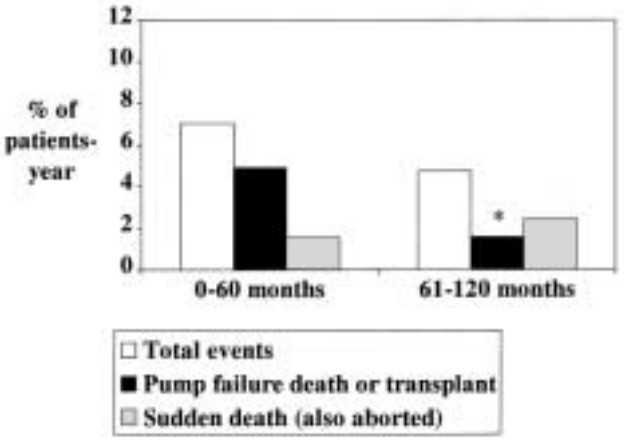

Figure 2. *Cause of death during follow-up in 343 patients with idiopathic dilated cardiomyopathy enrolled in the Heart Muscle Disease Registry from 1978 to 1997. * p = 0.006 compared to incidence of progressive heart failure in the first 60 months.*

and often with a left ventricular restrictive filling pattern. All these patients were on ACE-inhibitor treatment, while only 4 were on beta-blockers (1 on sotalol, 3 on metoprolol, 2 of them on low dosages) (Table II).

At enrolment, a history of syncope was present in 15 patients: 9 patients of group 1 (4%), 5 of group 2 (6%), and 1 of group 3 (3%) (p = NS); during follow-up, a syncopal episode occurred in 10 more patients (5 treated afterwards with an AICD) who were still alive at the end of enrolment (in 1 patient a spontaneous sustained ventricular tachycardia was documented) and in 2 patients who later died of heart failure. During follow-up, no syncopal episodes were observed in patients in whom SD occurred.

Table III shows the parameters evaluated at enrolment in patients still alive at the end of follow-up (group 1), in patients who died of heart failure (group 2) and in patients in whom SD occurred (group 3). The NYHA functional class was lower in patients of group 1, but was similar in patients of groups 2 and 3. At echocardiographic evaluation, the left ventricular end-diastolic diameter, volume and ejection fraction and the right ventricular shortening fraction of areas were significantly less compromised in patients of group 1 compared to those of group 2, but not to those of group 3. Similar results were obtained comparing hemodynamic data.

Table II. Characteristics of patients who died suddenly within 3 months of enlistment (n = 8).

NYHA class	2 ± 0.8
Interval between symptom onset and diagnosis (months)	21 ± 19
Systemic arterial pressure (mmHg)	126 ± 18
Heart rate (b/min)	83 ± 12
Ventricular extrasystoles/24 hours	78 ± 124
Ventricular couplets/24 hours	2.6 ± 4.3
Non-sustained VT/24 hours	0.2 ± 0.2
LVEDDI (mm/m^2)	37 ± 6 (> 33 mm/m^2: 87%)
LVEDVI (ml/m^2)	133 ± 40
LVEF	0.26 ± 0.08 (< 0.40: 100%)
E deceleration time (ms)	140 ± 50 (restrictive filling pattern: 50%)
Right ventricular dysfunction	75%
ACE-inhibitor therapy	87%
Beta-blocker therapy	50% (1 sotalol, 3 metoprolol)

LVEDDI = left ventricular end-diastolic diameter index; LVEDVI = left ventricular end-diastolic volume index; LVEF = left ventricular ejection fraction; VT = ventricular tachycardia; Restrictive filling pattern = E deceleration time < 120 ms.

With regard to the therapy administered at enrolment, a higher percentage of patients of group 1 were on ACE-inhibitors and beta-blockers while the opposite was true for digoxin, diuretics and antiarrhythmics. Group 2 and 3 treatments were very similar.

None of the variables evaluated at enrolment were predictive of SD at multivariate Cox analysis.

Table IV compares the data collected more than 12 (but less than 24) months before the end of the study in patients still alive (group A), with those evaluated within the last year before death for progressive heart failure (group B) or SD (group C). At the last evaluation, patients of group B showed more severe symptoms and exercise limitations. Similarly, the mean heart rate was higher in this group and the frequency of patients in sinus rhythm was lower. No significant differences among groups were shown on ventricular arrhythmias.

At echocardiographic evaluation, in group C the left ventricular systolic function and dimensions, although significantly better than in group B, were significantly more compromised than in group A. Group B patients were less frequently treated with ACE-inhibitors and beta-blockers, while more frequently treated with antiarrhythmics (mainly amiodarone). In this group, amiodarone treatment was interrupted in a lower (although not significantly different) proportion of patients owing to side effects, while similar withdrawal rates characterized groups A and C (group A 35% after 875 ± 820 days; group B 6% after 569 ± 718 days, group C 33% after 1159 ± 837 days; p = NS).

On multivariate analysis, the left ventricular ejection fraction (10 unit increase: odds ratio-OR 0.79, 95% confidence interval-CI 0.69-0.90, p = 0.010) was an independent predictor of SD; a strong trend of significance resulted for beta-blocker treatment (OR 0.84, 95% CI 0.70-1.01, p = 0.068) and left ventricular end-diastolic diameter (10 mm/m^2 increase: OR 1.25, 95% CI 0.95-1.64, p = 0.079). Using an arbitrary cut-off, the association between a left ventricular ejection fraction ≤ 0.30 and an end-diastolic diameter ≥ 38 mm/m^2 at the last evaluation was significantly correlated with an 88% higher risk of SD (95% CI 1.21-2.93, p = 0.005) during the following year (Table V).

Discussion

Incidence of sudden death during follow-up in dilated cardiomyopathy. In the last years, a significant mortality reduction in patients with heart failure and IDC was re-

Table III. Data at enlistment (patients with non-cardiac causes, pulmonary embolism and unknown causes are excluded).

	Group 1 (n=218)	Group 2 (n=77)	Group 3 (n=33)	p
Follow-up (months)	82 ± 43	40 ± 36	49 ± 39	
Gender (males)	75	78	87	NS
Age (years)	48 ± 13	46 ± 18	42 ± 16	NS
NYHA class (I-IV)	1.9 ± 0.8*	2.5 ± 0.9	2.3 ± 0.6**	< 0.0001
Symptom duration (months)	24 ± 40	39 ± 49	26 ± 38	NS
Heart rate (b/min)	79 ± 13	79 ± 13	78 ± 12	NS
Left bundle branch block (% pts)	30	39	50	NS
Sinus rhythm (% pts)	90	89	83	NS
Ventricular ectopic beats/hour	110 ± 225	91 ± 188	73 ± 134	NS
Couplets/hour	2.7 ± 8.3	2.5 ± 6.9	2.8 ± 8.5	NS
Non-sustained VT/hour	0.02 ± 1.5	0.1 ± 0.4	0.2 ± 0.3	NS
LVEDD (mm/m^2)	37 ± 5*	41 ± 6	38 ± 6	< 0.0001
LVEDV (ml/m^2)	110 ± 41*	133 ± 49	115 ± 48	0.008
LVEF (%)	30 ± 9*	27 ± 10	28 ± 9	0.042
RVSFA (%)	45 ± 16*	34 ± 19	36 ± 18	0.0005
E deceleration time (ms)	165 ± 71*	104 ± 51	134 ± 48	< 0.0001
Bicycle exercise time (s)	635 ± 242*	510 ± 273	640 ± 213	0.001
Mean PAP (mmHg)	18 ± 9*	25 ± 13	20 ± 7	< 0.0001
Mean AoP (mmHg)	87 ± 12	83 ± 15	85 ± 11	0.045
RAP (mmHg)	4 ± 3	4 ± 3	4 ± 2	NS
Cardiac output (l/min)	7.1 ± 2*	5.1 ± 1.8§	7.3 ± 2.3	< 0.0001
PAWP (mmHg)	11 ± 7*	16 ± 10	12 ± 7	0.0003
ACE-inhibitors (% pts)	82*	56	74	< 0.0001
Beta-blockers (% pts)	69*	38	39**	< 0.0001
Digitalis (% pts)	81*	96	97	0.001
Diuretics (% pts)	63*	86	77	0.0005
Antiarrhythmics (% pts)	36*	49	58**	0.019
Amiodarone (% pts)	18	26	27	NS

AoP = aortic pressure; LVEDD = left ventricular end-diastolic diameter; LVEDV = left ventricular end-diastolic volume; PAP = pulmonary arterial pressure; PAWP = pulmonary arterial wedge pressure; RAP = right atrial pressure; RVSFA = right ventricular shortening fraction of areas. Other abbreviations as in table II. * $p < 0.05$ group 1 vs group 2; ** $p < 0.05$ group 1 vs group 3; § $p < 0.05$ group 2 vs group 3.

ported by several authors[1,16] and a great proportion of patients can significantly improve with close follow-up and optimization of medical treatment[17]. However, the long-term outcome and cause of death are not clearly known.

In our retrospective analysis of a wide population of patients with IDC enrolled in the last two decades, at enrolment all patients satisfied the criteria of diagnosis[13], underwent the same invasive and non-invasive initial evaluation and were followed with regular non-invasive examinations according to the clinical requirements. Nevertheless some patients were evaluated for the first time many years ago. This caused some heterogeneity in clinical status and treatment and may be a limitation of our analysis.

We observed a significant reduction in mortality due to heart failure after 5 years of follow-up (from 4.93/100 to 1.58/100 patients-year; p = 0.006), while even the SD incidence rose (from 1.44 to 2.38/100 patients-year; p = NS), becoming the first cause of death in the long term. A possible explanation of the increasing rate of SD during follow-up in our population was the competitive risk between heart failure and arrhythmic events. The high probability of long-term clinical improvement or stabilization[17], the consequent significant reduction in progressive heart failure achieved with ACE-inhibitors and beta-blockers and rigorous follow-up in specialized centers could have determined an increase in the number of patients with stable left ventricular dysfunction exposed, in the long term, to the risk of SD. The trend towards a late increase in SD rate together with the reduction in the incidence of progressive heart failure after the first 5 years of follow-up seemed in accordance with this hypothesis.

In the V-HeFT experience[18], SD was more frequent in the first year of follow-up (both in ischemic and non-ischemic patients). Even in our experience, there was a particularly high incidence of SD during the first 3 months after enrolment in our Registry (9.6/100 patients-year). Despite the fact that in these patients a specific clinical pattern was not apparent, some of them had been referred to our center because of worsening conditions after some years of disease (mean duration of symptoms 21 ± 19 months) or because of an inadequate response to initial therapy. Furthermore, beta-blocker treatment was not yet started or the target dosage had still not been achieved in most of the patients who died suddenly during the first months after enrollment.

Table IV. Data at the last evaluation.

	Group A (n=202)	Group B (n=57)	Group C (n=24)	p
Follow-up§§ (months)	18 ± 7	4 ± 4	6 ± 5	NS
Gender (males)	75	77	83	NS
Age (years)	48 ± 13	49 ± 19	50 ± 16	NS
NYHA class (I-IV)	1.5 ± 0.7*	3.2 ± 0.8§	1.9 ± 0.8	< 0.0001
Symptom duration (months)	75 ± 50	68 ± 58	80 ± 63	NS
Heart rate (b/min)	67 ± 12*	80 ± 20§	67 ± 16	< 0.0001
Left bundle branch block (% pts)	35	46	50	NS
Sinus rhythm (% pts)	89*	57§	90	< 0.0001
Ventricular ectopic beats/hour	52 ± 141	76 ± 145	71 ± 97	NS
Couplets/hour	0.8 ± 4.3	2.2 ± 5	1.8 ± 3.4	NS
Non-sustained VT/hour	0.02 ± 0.08*	0.8 ± 4.1	0.07 ± 0.13	NS
LVEDD (mm/m^2)	34 ± 6*	41 ± 8§	36 ± 6	< 0.0001
LVEDV (ml/m^2)	91 ± 37*	138 ± 53	116 ± 53**	< 0.0001
LVEF (%)	41 ± 12*	22 ± 9§	31 ± 12**	< 0.0001
RVSFA (%)	50 ± 12*	28 ± 15§	48 ± 18	< 0.0001
E deceleration time (ms)	202 ± 64	106 ± 47	214 ± 102	NS
Bicycle exercise time (s)	674 ± 224*	341 ± 234§	711 ± 213	< 0.0001
ACE-inhibitors (% pts)	92*	73§	96	0.0002
Beta-blockers (% pts)	86*	38§	63**	< 0.0001
Digitalis (% pts)	69*	93	96**	0.0001
Diuretics (% pts)	49*	84	71	< 0.0001
Antiarrhythmics (% pts)	30*	59	33	0.0004
Amiodarone (% pts)	25*	59	33	0.0003

Abbreviations as in tables II and III. * $p < 0.05$ group 1 vs group 2; ** $p < 0.05$ group 1 vs group 3; § $p < 0.05$ group 2 vs group 3; §§ interval between the last visit and the end of follow-up (group A) or the fatal event (groups B and C).

Table V. Independent predictors of sudden death at last evaluation.

	Beta	SE	OR	95% CI	p
Beta-blocker treatment	-0.18	0.09	0.84	0.70-1.01	0.068
LVEF (10 unit increase)	-0.24	0.07	0.79	0.69-0.90	0.010
LVEDDI (10 mm/m^2 increase)	0.22	0.14	1.25	0.95-1.64	0.079
Beta-blocker treatment	-0.39	0.23	0.68	0.43-1.06	0.091
LVEF ≤ 0.30 + LVEDDI ≥ 38 mm/m^2	0.63	0.23	1.88	1.21-2.93	0.005

CI = confidence interval; OR = odds ratio; SE = standard error. Other abbreviations as in table I.

Mechanism and clinical predictors of sudden death. It is difficult to identify the parameters predicting arrhythmic events, even because the mechanisms underlying SD in patients with IDC are not yet well known. In heart failure of ischemic origin, it is deemed that SD due to hyperkinetic arrhythmias prevails, whereas hypokinetic deaths (total atrioventricular block, pulmonary embolism, cerebral emboli, electromechanical dissociation) are responsible for less than 5% of cases[19]. In dilated cardiomyopathy, the mechanisms underlying the hyperkinetic arrhythmias may not be the same as those observed in ischemic heart disease[20,21] and, especially in more advanced stages, the cause of SD may not necessarily be a hyperkinetic arrhythmia[22].

In most papers, the interval between clinical-instrumental evaluation and the fatal event was considerable, with the possibility that the therapeutic agents and the natural history of the disease could have modified, even substantially, the clinical patterns; thus, the risk of cardiac death in general and that of SD and pump failure could not necessarily be the same during long-term follow-up. For these reasons it is likely that, in view of several suggested variables predicting SD[23], the results of the various papers are not univocal and the evaluation of the risk for the single patient turns out to be difficult.

The event is particularly dramatic for those patients who had no or only mild symptoms until then. Our analysis confirms that the NYHA functional class in patients who died suddenly was, even close to the event, comparable with the functional class of patients with a favorable outcome.

The severity of left ventricular dysfunction is certainly indicated by many studies as one of the major pre-

dictors of SD and total mortality. Analyzing the ESVEM study[24], left ventricular dysfunction (rather than non-sustained arrhythmias) was predictive of major arrhythmic events, and it was observed that a 5% reduction in left ventricular ejection fraction raised the risk of arrhythmic death by 15%. In the V-HeFT II trial[25] only the ejection fraction was predictive of both progressive heart failure ($p = 0.0004$) and SD ($p = 0.0002$). Moreover, in the same trial, the presence of ventricular couplets or tachycardia was predictive of total ($p = 0.0002$) and pump failure death ($p = 0.02$), but not of SD ($p = 0.06$). Even in the paper by Brouwer et al.[26], ventricular arrhythmias were correlated with total death but not with SD. In our population the left ventricular ejection fraction evaluated shortly before the event was significantly worse in patients who died suddenly compared to that observed in patients with a favorable outcome.

Even left ventricular dilation seemed to identify a subgroup at higher risk of SD. It is well known that "myocardial stretch" can cause membrane-potential instability, thus creating the premises for the occurrence of early post-potentials and triggered activity[27] that, according to some[28], is the main mechanism underlying arrhythmias in patients with heart failure. Lee et al.[29] observed that, among patients with advanced heart failure, those with a left ventricular diameter > 4 cm/m^2, even with similar hemodynamic parameters and independently of etiology, had a worse prognosis and a significantly higher risk of SD (27 vs 14% after 1 year; $p = 0.04$). Among patients with IDC, Grimm et al.[30] identified those with an end-diastolic diameter > 70 mm (and non-sustained ventricular tachycardias) as a group with a particularly high risk of major arrhythmic events. In our population the left ventricular end-diastolic diameter was a significant and independent predictor of SD only within 1 year of the event.

Our data confirm that the parameters evaluated at the time of diagnosis may often be poor predictors of outcome[31]; in fact, while in patients who died suddenly there were little modifications in terms of left ventricular dimensions and function during follow-up (Tables II and III), patients who survived, despite similar clinical findings at enrolment, had a much greater left ventricular ejection fraction and smaller left ventricular dimensions at the last visit. According to our data, the persistence, during long-term follow-up, of a particularly poor left ventricular function (ejection fraction ≤ 0.30) together with severe dilation (end-diastolic diameter ≥ 38 mm/m^2) could identify patients (even asymptomatic) at a higher risk of SD.

Sudden death prevention. The role of drugs in reducing SD in patients with IDC is still uncertain. Our work did not include a randomized and controlled evaluation of the effects of therapy on mortality and on the cause of death; nevertheless, data analysis allows some considerations. Table IV shows that patients who died suddenly were, compared to survivors, more frequently treated (in the year preceding the event) with digoxin (96 vs 69%, $p < 0.05$) and less frequently with beta-blockers (63 vs 86%, $p < 0.05$).

It is reasonable to assume a certain negative effect of digoxin on arrhythmic mortality. In support of this hypothesis, it is opportune to recall that, in the DIG trial[3], a small but statistically significant increase in cardiac mortality not due to heart failure (therefore at least partly arrhythmic) was observed in the group treated with digoxin vs placebo (15 vs 13%, $p = 0.04$). On the other hand, the possibility that beta-blockers can reduce SD is, now, a fact confirmed by the large trials recently published[6-8]. The incidence of SD in our population (mostly treated with beta-blockers since the second half of the '80s) after 1 year of follow-up (3.3%) was comparable to that of the US Carvedilol (1.7% at 6 months in the carvedilol group)[6], the CIBIS II (3.6% at 1.3 years in the bisoprolol group)[7] and the MERIT-HF (3.5% at 1 year in the metoprolol group)[8] trials. Even though our study was not conceived to evaluate the effects of beta-blockers, on multivariate analysis the absence of such treatment was of borderline significance in predicting SD.

In accordance with the literature data[4,5,15], there were no evident effects of ACE-inhibitor therapy on SD in our population.

The role of amiodarone in preventing SD is not well defined, but a possible beneficial effect cannot be excluded, especially in patients with non-ischemic IDC[9,10]. In our population a low withdrawal rate (6%) and the frequent use of amiodarone (59%) at the last evaluation characterized group B. On the other hand, in groups A and C a higher interruption rate (35 and 33% respectively) and a lower proportion of patients treated (25 and 33% respectively) were evident. Thus, it cannot be excluded that interruption of amiodarone therapy during follow-up could have a certain role in modifying the cause of death or increasing the SD rate in patients with persistent severe left ventricular dysfunction and dilation.

The debate about the need of an AICD for primary prevention in selected patients with IDC is still unsolved. Its favorable effect in protecting patients from hyperkinetic arrhythmia is certain; nevertheless it is still difficult to select those patients who can really benefit from this therapy. In our population, the long-term SD rate, although increasing during follow-up, was probably too low to justify the extensive use of AICDs. Besides, with regard to the groups at particularly high risk such as those with a history of aborted SD or poorly tolerated ventricular tachycardias[32,33] and probably even those with IDC and syncope of unknown origin[34], there are not yet sufficient data about the real efficacy of the automatic defibrillator as a measure of primary prevention in IDC. For this reason, it is important to make an effort to select patients with a relatively higher risk of SD and a lower risk of death due to pump failure who could really benefit from implantation of an AICD.

It is to be hoped that the results of the Sudden Cardiac Death in Heart Failure Trial[35] on prophylactic amiodarone vs implantable defibrillator and those of the DEFINITE trial[36] will be able to give operatively useful answers.

In the meantime, it is necessary to find the best tailored treatment of heart failure for the single patient, possibly including beta-blockers. Nevertheless, serial evaluation of some parameters (such as for example left ventricular dilation and function) also in clinically stable patients with a long-term follow up, can be useful, keeping in mind that, in most patients, the efficacy of drugs and the right timing in selecting alternative therapeutic strategies to prevent SD are still uncertain.

In conclusion, although medical treatment reduced death due to pump failure in patients with IDC, the risk of SD was not substantially modified in population studies. Only recently have beta-blockers and, to a much lower extent, amiodarone, shown a significant benefit in reducing the incidence of SD.

In our paper we retrospectively analyzed a large population of patients with IDC and submitted to long-term follow-up including serial examinations.

In our population, pump failure was the first cause of death in the first 5 years, but then its incidence dropped dramatically. On the other hand, the incidence of SD was particularly high during the first months after diagnosis and tended to rise only after 5 years of follow-up, to become the first cause of death.

In our study, we did not find, at first evaluation, any parameter capable of predicting SD. However, mildly symptomatic patients with persistent severe left ventricular dilation and dysfunction and on optimal medical treatment during long-term follow-up were at higher risk of dying suddenly in the following year, especially if not taking beta-blockers.

Although stratification of the risk in the single patient remains difficult, serial non-invasive controls during follow-up can help to select patients with a higher risk of SD. Whether this could have any operative consequence remains to be proved.

References

1. Di Lenarda A, Hlede S, Sabbadini G, et al. Improvement of prognosis in idiopathic dilated cardiomyopathy: role of early diagnosis and optimized medical treatment. Study Group on Heart Muscle Diseases. G Ital Cardiol 1999; 29: 1452-62.
2. The Cardiac Arrhythmia Suppression Trial (CAST) Investigators. Preliminary report: effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. N Engl J Med 1989; 321: 406-12.
3. The Digitalis Investigative Group. The effect of digoxin on mortality and morbidity in patients with heart failure. N Engl J Med 1997; 336: 525-33.
4. The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med 1991; 325: 293-302.
5. The SOLVD Investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. N Engl J Med 1992; 327: 685-91.
6. Packer M, Bristow MR, Cohn JN, et al. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. US Carvedilol Heart Failure Study Group. N Engl J Med 1996; 334: 1349-55.
7. The Cardiac Insufficiency Bisoprolol Study II (CIBIS II): a randomised trial. Lancet 1999; 353: 9-13.
8. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). Lancet 1999; 353: 2001-7.
9. Doval HC. Class III antiarrhythmic agents in cardiac failure: lessons from clinical trials with a focus on the Grupo de Estudio de la Sobrevida en la Insuficiencia Cardiaca en Argentina (GESICA). Am J Cardiol 1999; 84: 109R-114R.
10. Singh SN, Fletcher RD, Fisher SG, et al, for the Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure. Amiodarone in patients with congestive heart failure and asymptomatic ventricular arrhythmia. N Engl J Med 1995; 333: 77-82.
11. Saxon LA, Stevenson WG, Middlekauff HR, et al. Predicting death from progressive heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. Am J Cardiol 1993; 72: 62-5.
12. Grandam A, Deedwania P, Cody R, et al. Predictors of total mortality and sudden death in mild to moderate heart failure. J Am Coll Cardiol 1989; 14: 564-70.
13. Report of the 1995 WHO/ISFC Task Force on the definition and classification of cardiomyopathies. Circulation 1996; 93: 841-2.
14. Aretz HT, Billingham ME, Edwards WD, et al. Myocarditis. A histopathologic definition and classification. Am J Cardiovasc Pathol 1987; 1: 3-14.
15. The CONSENSUS Trial Study Group. Effect of enalapril on mortality in severe congestive heart failure: results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). N Engl J Med 1987; 316: 1429-35.
16. Stevenson WG, Stevenson LW, Middlekauff HR, et al. Improving survival for patients with advanced heart failure: a study of 737 consecutive patients. J Am Coll Cardiol 1995; 26: 1417-23.
17. Di Lenarda A, Gregori D, Lardieri G, et al. Metoprolol in dilated cardiomyopathy: is it possible to identify factors predictive of improvement? J Card Fail 1996; 2: 87-102.
18. Goldman S, Johnson G, Cohn JN, et al. Mechanisms of death in heart failure. The Vasodilator-Heart Failure Trials. Circulation 1993; 87 (Suppl VI): VI24-VI31.
19. Uretsky BF, Sheahan RG. Primary prevention of sudden cardiac death in heart failure: will the solution be shocking? J Am Coll Cardiol 1997; 30: 1589-97.
20. Pogwizd SM, McKenzie JP, Cain ME. Mechanisms underlying spontaneous and induced ventricular arrhythmias in patients with idiopathic dilated cardiomyopathy. Circulation 1998; 98: 2404-14.
21. Pogwizd SM. Nonreentrant mechanisms underlying spontaneous ventricular arrhythmias in a model of nonischemic heart failure in rabbits. Circulation 1995; 92: 1034-48.
22. Luu M, Stevenson LW, Brunken RC, et al. Diverse mechanisms of unexpected cardiac arrest in advanced heart failure. Circulation 1989; 80: 1675-80.
23. Ansalone G, Giannantoni P, Santini M. The stratification and prevention of the arrhythmia risk in nonischemic dilated cardiomyopathy. G Ital Cardiol 1998; 28: 1288-302.
24. Caruso AC, Marcus FI, Hahn EA, et al. Predictors of arrhythmic death and cardiac arrest in the ESVEM trial. Circulation 1997; 96: 1888-92.

25. The Vasodilator-Heart Failure Veterans Affairs Cooperative Study Group. A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. N Engl J Med 1991; 325: 303-10.
26. Brouwer J, Van Veldhuisen DJ, Man in't Veld AJ, et al. Prognostic value of heart rate variability during long-term follow-up in patients with mild to moderate heart failure. J Am Coll Cardiol 1996; 28: 1183-9.
27. Campbell RWF. Electrophysiological disturbances in heart failure. Br Heart J 1994; 72 (Suppl): S31-S35.
28. Aronson RS, Ming Z. Cellular mechanisms of arrhythmias in hypertrophied and failing myocardium. Circulation 1993; 87 (Suppl VII): VII76-VII83.
29. Lee TH, Hamilton MA, Stevenson LW, et al. Impact of left ventricular cavity size on survival in advanced heart failure. Am J Cardiol 1993; 72: 672-6.
30. Grimm W, Hoffmann J, Menz V, et al. Arrhythmia risk stratification in idiopathic dilated cardiomyopathy based on echocardiography, ECG, signal-averaged ECG and 24-hour Holter ECG. (abstr) Eur Heart J 1999; 20 (Suppl): 8.
31. Pinamonti B, Zecchin M, Di Lenarda A, Gregori D, Sinagra G, Camerini F. Persistence of restrictive left ventricular filling pattern in dilated cardiomyopathy: an ominous prognostic sign. J Am Coll Cardiol 1997; 29: 604-12.
32. The Antiarrhythmics Versus Implantable Defibrillators (AVID) Investigators. A comparison of antiarrhythmic drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. N Engl J Med 1997; 337: 1576-83.
33. Siebels J, Cappato R, Ruppel R, Schneider MA, Kuck KH. Preliminary results of the Cardiac Arrest Study Hamburg (CASH). CASH Investigators. Am J Cardiol 1993; 72: 109F-113F.
34. Knight BP, Goyal R, Pelosi F, et al. Outcome of patients with nonischemic dilated cardiomyopathy and unexplained syncope treated with an implantable defibrillator. J Am Coll Cardiol 1999; 33: 1964-70.
35. Bardy GH, Lee KL, Marc DB, and the SCD-HeFT Pilot Investigators. The Sudden Cardiac Death in Heart Failure Trial: a pilot study. (abstr) Pacing Clin Electrophysiol 1997; 20: 1148.
36. Kadish A, Quigg R, Schaecter A, Anderson KP, Estes M, Levine J. Defibrillators in nonischemic cardiomyopathy treatment evaluation. Pacing Clin Electrophysiol 2000; 23: 338-43.