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Natural History and Prognostic Factors in Alcoholic Cardiomyopathy

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ABSTRACT

OBJECTIVES This study sought to determine the natural history of contemporary alcoholic cardiomyopathy (ACM), to compare it with that of idiopathic dilated cardiomyopathy (IDCM), and to identify risk factors for poor outcome.

BACKGROUND ACM is a common cause of dilated cardiomyopathy (DCM), but little is known about its natural history or the effect of reducing alcohol intake on disease progression.

METHODS We studied the clinical characteristics and outcomes of 94 consecutive patients with ACM and 188 with IDCM, evaluated over the period between 1993 and 2011.

RESULTS After a median follow-up of 59 months (interquartile range: 25 to 107 months), 14 ACM patients (15%) had died from cardiovascular causes (6 from heart failure and 8 from sudden cardiac death), 14 (15%) underwent heart transplantation, 35 (37%) experienced recovery in left ventricular function, and 31 (33%) remained clinically stable without improvement in systolic function. Transplantation-free survival was higher in ACM patients than in IDCM patients ($p = 0.002$), and ACM was associated with a favorable outcome on multiple analysis of the entire cohort (odds ratio [OR]: 0.4; 95% confidence interval [CI]: 0.2 to 0.8; $p = 0.01$). Independent predictors of death or heart transplantation in ACM identified by multiple logistic regression analysis were atrial fibrillation (OR: 9.7; 95% CI: 2.56 to 36.79; $p = 0.001$); QRS duration >120 ms (OR: 7.2; 95% CI: 2.02 to 26; $p = 0.002$), and lack of beta-blocker therapy (OR: 4.4; 95% CI: 1.35 to 14.49; $p = 0.014$). ACM patients who reduced their alcohol intake to moderate levels exhibited similar survival ($p = 0.22$) and cardiac function recovery ($p = 0.8$) as abstainers.

CONCLUSIONS ACM has a better prognosis than IDCM. Atrial fibrillation, QRS width >120 ms, and the absence of beta-blocker therapy identify patients with a poor outcome. Alcohol abstainers and those who reduce intake to a moderate degree show similar clinical outcomes. (J Am Coll Cardiol HF 2015;3:78–86) © 2015 by the American College of Cardiology Foundation.

Excessive alcohol intake is a major health problem in developed countries. Although light to moderate alcohol intake has been related to a reduction in the risk for coronary heart disease and heart failure (1-4) heavy alcohol consumption is associated with development of left ventricular dysfunction (5-7).

Excess alcohol consumption has been implicated in up to 40% of cases of dilated cardiomyopathy (DCM) (8-11). Similar to other causes of DCM, alcoholic cardiomyopathy (ACM) is characterized by a dilated left ventricle (LV), increased LV mass and a reduced LV ejection fraction (LVEF) (7), but the diagnosis is usually one of exclusion in a patient with a long history of heavy alcohol abuse, as no specific clinical or histological features have been identified (7-10). Very few studies have investigated the natural history of ACM (8-10,12), and all of those were conducted in the era before modern pharmacotherapy (8-12). Moreover, data derived from those studies are

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contradictory, with some showing a better prognosis in ACM than in IDCM (10), and others the reverse (8,9). Similarly, data on the beneficial effects of abstinence from alcohol are inconsistent (8-10,13).

The aims of present study were to define the long-term outcome of ACM in the current era, to compare it with that of idiopathic DCM, and to determine prognostic markers.

METHODS

From January 1993 to December 2011, we collected data from all consecutive ACM patients referred for evaluation to the Heart Failure and Heart Transplant Section of the Hospital Universitario Puerta de Hierro (Madrid, Spain). The study was approved by our institution's local review board and conformed to the principles of the Helsinki declaration.

IDCM was defined according to the World Health Organization criteria (14). Heavy alcohol consumption was defined as a self-reported history of alcohol intake of >80 g per day (8 standard drinks) over a period of at least 5 years (8-10). Alcohol abuse must have been maintained until <3 months before the diagnosis of DCM.

Although a specific and structured program for alcohol discontinuation was not provided, complete abstinence from alcohol was recommended to all ACM patients. During follow-up, patients were classified as abstainers if they reported complete discontinuation of alcohol consumption and as nonabstainers if they reported continued

TABLE 1 Clinical, Electrocardiographic, and Echocardiographic Characteristics at First Evaluation and Follow-Up Findings in Patients With ACM and IDCM

Characteristic	ACM (n = 94)	IDCM (n = 188)	p Value
Mean age, yrs	49.6 ± 10.0	49.9 ± 14.0	0.843
Mean age at start of heart failure symptoms, yrs	47 ± 10	47 ± 15	1.000
Duration of heart failure symptoms, yrs	2.6 ± 4.0	3 ± 4	0.040
Sex			<0.001
Male	99	74	
Female	1	26	
NYHA functional class			0.048
I	7	9	
II	26	40	
III	37	33	
IV	30	18	
Comorbidities			
Hypertension	36	33	0.658
Dyslipidemia	30	30	1.000
Diabetes	23	16	0.128
Smoking	50	16	<0.001
Body mass index, kg/m^2	28.3 ± 5.0	26.3 ± 5.0	0.015
Chronic obstructive pulmonary disease	31	13	<0.001
Liver disease	20	2	<0.001
Nephropathy	7	5	0.363
Blood test results			
Hemoglobin, g/dl	14.3 ± 1.0	14.0 ± 2.0	0.028
Creatinine, mg/dl	1.2 ± 0.3	1.2 ± 0.6	0.356
Bilirubin, mg/dl	1.9 ± 3.3	1.1 ± 1.2	0.074
ALAT, U/l	88 ± 229	32 ± 25	0.053
ASAT, U/l	88 ± 98	30 ± 25	0.038
Patients treated with			
Digoxin	48	43	0.454
Loop diuretics	76	80	0.478
Spironolactone or eplerenone	49	47	0.805
Beta-blockers	60	65	0.383
ACEI or ARB	90	85	0.083
Amiodarone	20	18	0.682
Implantable cardiac defibrillator	32	31	0.588
Cardiac resynchronization therapy	18	12	0.143

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TABLE 1 Continued

Characteristic	ACM (n = 94)	IDCM (n = 188)	p Value
ECG test results			
Sinus rhythm, %	66	76	0.082
Atrial fibrillation, %	34	24	0.082
QRS >120 ms, %	37	46	0.177
QRS duration, ms	111 ± 29	111 ± 32	0.986
Left bundle branch block, %	34	33	0.929
Echocardiography results			
Left ventricular ejection fraction	26 ± 9	27 ± 8	0.277
Left ventricular end-diastolic diameter, mm	68 ± 9	67 ± 9	0.373
Exercise test results			
6-min test, m*	367 ± 74	361 ± 83	0.705
Peak oxygen uptake, l/kg/min†	15 ± 6	20 ± 15	0.162
Evolution			
Death or heart transplantation, %	33	48	0.017
Heart transplantation, %	15	35	<0.001
Death, %	18	13	0.287
Heart failure death, %	6	7	0.934
SCD, %	9	3	0.027
Other death, %	3	3	0.719

*Values are mean ± SD or %. 31 ACM patients (33%) and 101 IDCM patients (54%) underwent a 6-min walking test. †27 ACM patients (29%) and 100 IDCM patients (53%) underwent an exercise test with O_2 consumption.

ACM = alcoholic cardiomyopathy; ACEI = angiotensin-converting enzyme inhibitors; ALAT = alanine transaminase; ARB = angiotensin II receptor blockers; ASAT = aspartate transaminase; ECG = electrocardiography; IDCM = idiopathic dilated cardiomyopathy; SCD = sudden cardiac death.

ABBREVIATIONS AND ACRONYMS

ACEI = angiotensin-converting enzyme inhibitors

ACM = alcoholic cardiomyopathy

ARB = angiotensin II receptor blockers

CG = electrocardiogram

COPD = chronic obstructive pulmonary disease

CPHM = Cox proportional hazards model

DCM = dilated cardiomyopathy

IDCM = idiopathic dilated cardiomyopathy

IQR = interquartile range

LV = left ventricle

LVEF = left ventricular ejection fraction

NYHA = New York Heart Association

SCD = sudden cardiac death

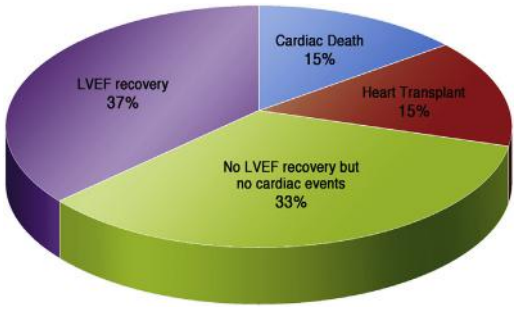

FIGURE 1 Long-Term Cardiovascular Evolution of ACM (n = 94)

Cardiac events are defined as cardiovascular death or heart transplantation. ACM = alcoholic cardiomyopathy.

TABLE 2 Clinical, Electrocardiographic, Echocardiographic, and Hemodynamic Characteristics of ACM Patients With and Without Major Cardiac Events

Characteristic	Cardiac Death or Heart Transplant (n = 28)	No Cardiac Death/ Heart Transplant (n = 66)	p Value
Mean age, yrs	52 ± 8	49 ± 11	0.186
Sex			0.123
Males	97	100	
Females	3	0	
Baseline NYHA functional class			0.853
I	7	6	
II	21	28	
III	43	35	
IV	29	31	
Comorbidities			
Hypertension	25	41	0.142
Dyslipidemia	21	33	0.248
Diabetes	25	23	0.812
Smoking	50	50	0.431
Body mass index, kg/m^2	27 ± 4	29 ± 5	0.241
Chronic obstructive pulmonary disease	39	27	0.229
Nephropathy	11	6	0.432
Blood test results			
Hemoglobin, g/dl	14.0 ± 1.3	15.0 ± 1.5	0.465
Creatinine, mg/dl	1.3 ± 0.3	1.2 ± 0.4	0.150
Sodium, mg/dl	137 ± 3	137 ± 5	0.933
Bilirubin, mg/dl	1.6 ± 1	2.1 ± 4	0.575
ALAT,U/l	122 ± 392	73 ± 108	0.430
ASAT, U/l	34 ± 30	63 ± 112	0.291
GGT, U/l	137 ± 140	162 ± 289	0.722
Treated with			
Digoxin	70	38	0.005
Loop diuretics	89	71	0.064
Spironolactone/eplerenone	48	49	0.925
Beta-blockers	35	70	0.002
ACEI or ARB	82	94	0.075
Amiodarone	30	15	0.117
Implantable cardiac-defibrillator	25	38	0.228
Cardiac resynchronization therapy	14	20	0.533

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alcohol consumption. Nonabstainers were subsequently classified as moderate drinkers if they had reduced consumption to <80 g/day of alcohol, and as heavy-persistent drinkers if they continued abusing alcohol (>80 g/day).

In order to have a reliable and contemporary control IDCM group for comparison, for each case of ACM, we selected the next 2 consecutive new patients with IDCM evaluated at our unit during the following 30 days and at the same setting (hospitalization or outpatient clinic) as the index ACM subject.

Initial assessment of all patients included physical examination, blood tests, and 12-lead electrocardiography (ECG). Additional studies including 24-h ECG monitoring, a 6-min walk test, upright exercise testing, right-heart catheterization, electrophysiological study, cardiac magnetic resonance imaging, and endomyocardial biopsy and were performed as ordered by the treating physician. Successive tests were performed as required. Coronary angiography to rule out coronary heart disease was performed in all but 3 patients. Of these 3 cases, 2 patients had normal coronary computed tomography (CT) scans, and the other was a 30-year-old male without coronary risk factors who completed an exercise test with normal results.

The study began after completion of baseline evaluation and was terminated at the latest available follow-up or at the patient's death or transplantation. Most patients were regularly followed at our center at least once per year. Follow-up data from patients under surveillance at other institutions were also collected. Information on each patient's final status in December 2011 was obtained from their medical records or by telephone calls to the patient or the referring physician. Cause of death was classified as: 1) progressive heart failure; 2) sudden cardiac death (SCD); or 3) noncardiac. Recovery in cardiac function was defined as an absolute increase in LVEF ≥10% to a final value of ≥40% at the end of follow-up.

STATISTICAL ANALYSIS. Categorical data were expressed as percentages and compared using the chi-square test or Fisher's exact test. Normally distributed variables were expressed as means and standard deviations whereas non-normally distributed variables were given as medians and interquartile ranges (IQR). For statistical analysis, Student's *t* test and Mann-Whitney *U* nonparametric test were used in 2-group comparisons.

To predict "cardiac death or heart transplantation" from baseline variables, initially a univariate screening of all parameters at enrollment was made.

In order to identify independent predictors of poor prognosis, all variables that differed between groups with $p < 0.10$ at univariate analysis and also other variables with a p value of >0.10 that were relevant to this study (age, baseline LVEF, alcoholic cause, and alcohol abstinence), were entered into a backward stepwise selection procedure with removal based on the probability of the likelihood-ratio statistic on the maximum partial likelihood estimated.

Peak oxygen uptake, 6-min test results, and right heart hemodynamic parameters were not included in the multiple logistic regression analyses because these tests were performed in <50% of patients. Receiver operating characteristics (ROC) analysis was carried out to assess the performance of selected variables to predict "cardiac death or heart transplantation" in ACM. Area under the ROC curve was calculated for the combination of the independent predictors of "cardiac death or heart transplantation" in this setting.

Transplant-free survival hazards ratios (HRs) and the 95% confidence interval (CI) of the significant predictor factors were also quantified with a Cox proportional hazards model (CPHM). Based on the CPHM results, a scoring system was developed. The score for each factor was 1 point, and the total score for each patient represented the sum of the scores for each factor. Scores ranged from 0 to 3, and ACM patients were divided into 4 groups (0-3).

Finally, transplantation-free survival curves were calculated according to the Kaplan-Meier method, and the log-rank test was used for the comparison between the curves. The level of statistical significance was $p < 0.05$. All hypothesis tests were 2-sided. The entire analysis was performed using SPSS version 14.0 software (IBM, Armonk, New York).

RESULTS

A total of 282 patients with DCM (94 ACM patients and 188 with IDCM) participated in the study (Table 1). Of the patients, 39% (37 in the ACM group and 74 in the IDCM group) were first evaluated during hospitalization, whereas 61% were first seen at our outpatient clinic (57 ACM and 114 IDCM patients). The baseline clinical, ECG and echocardiographic characteristics of patients with ACM and IDCM are shown in Table 1.

ACM PATIENTS. Mean alcohol consumption in ACM patients was 136 ± 64 g/day for 23 ± 12 years. Forty-three patients (46%) consumed 80 to 120 g/day of alcohol, 19 (20%) consumed 120 to 160 g/day, and 32 (34%) consumed >160 g/day. During follow-up, 63% reported remaining abstinent, 32% continued alcohol consumption but had reduced intake to <80 g/day, and only 5% were persistent or heavy alcohol drinkers (>80 g/day). Alcohol abuse was due to distilled spirits (76%), beer (67%), and wine (43%).

TABLE 2 Continued

Characteristic	Cardiac Death or Heart Transplant (n = 28)	No Cardiac Death/ Heart Transplant (n = 66)	p Value
ECG results			
Sinus rhythm	43	74	0.004
Atrial fibrillation	57	26	0.004
QRS, ms	124 ± 25	106 ± 30	0.007
QRS >120 ms	61	27	0.002
Left bundle branch block	48	27	0.040
Echocardiography results			
LVEDD, mm	71 ± 12	67 ± 8	0.059
LVESD, mm	60 ± 12	56 ± 9	0.118
LVEF, %	25 ± 9	27 ± 9	0.256
Right heart catheterization*			
Systolic pulmonary artery pressure, mm Hg	48 ± 20	46 ± 16	0.690
Diastolic pulmonary artery pressure, mm Hg	24 ± 10	24 ± 11	0.882
Mean pulmonary artery pressure, mm Hg	34 ± 15	32 ± 13	0.717
Pulmonary capillary wedge, mm Hg	25 ± 13	23 ± 11	0.664
Cardiac output, l/min	3.8 ± 1.0	4.4 ± 1.4	0.181
Cardiac index, l/min/m^2	2.2 ± 0.4	2.3 ± 0.6	0.653
Exercise test results			
6-min test, m†	338 ± 81	386 ± 65	0.077
Peak oxygen uptake, l/kg/min‡	12 ± 3	17 ± 7	0.079
Alcohol consumption			
Duration of alcohol abuse, yrs	22 ± 10	24 ± 13	0.361
Mean alcohol consumption, g/day	124 ± 47	141 ± 70	0.278
Alcohol intake			0.889
<120 g/day	54	49	
120-160 g/day	19	23	
>160 g/day	27	29	
Type of alcohol consumed			
Spirits	76	80	0.652
Only spirits	20	14	0.651
Only wine and/or beer	24	32	0.652
Wine or beer	56	54	0.651
Wine and beer	24	20	0.651
Alcohol consumption during follow-up			0.789
Alcohol abstinence	61	64	
Persistent alcohol intake	39	36	
Evolution			
Final LVEF >40%	0	61	<0.001
Substantial cardiac recovery	0	53	<0.001
Final NYHA functional class I-II	7	85	<0.001

Values are mean ± SD or %. *19 ACM patients with major cardiac events (61%) and 20 ACM patients without major cardiac events (32%) underwent right heart catheterization. †13 ACM patients with major cardiac events (42%) and 18 ACM patients without major cardiac events (28%) underwent a 6-min walking test. ‡10 ACM patients with major cardiac events (32%) and 17 ACM patients without major cardiac events (27%) underwent an exercise test with O_2 consumption.

GGT = gamma-glutamyl-transferase; other abbreviations are as shown in Table 1.

During a median follow-up of 59 months (IQR: 25 to 107), 17 ACM patients (18%) died: 6 from progressive heart failure, 8 due to SCD, and 3 from noncardiac causes (all from malignancies). Fourteen ACM patients (15%) underwent heart transplantation, and 4 patients (5%) were resuscitated from documented ventricular fibrillation. Among the 32 patients who received an implantable cardioverter-defibrillator (ICD), 9 had appropriate ICD therapies. **Figure 1** shows the long-term cardiovascular outcome of the ACM patients.

Factors associated with the occurrence of major cardiac events (cardiovascular death or heart transplantation) in ACM patients were absence of treatment with beta-blockers, atrial fibrillation, QRS width ≥120 ms, a shorter distance in the 6-minute walking test and the use of digoxin (**Table 2**). Previous mean alcohol consumption, duration of alcohol abuse, and type of alcoholic beverage consumed were not associated with outcome.

Independent predictors of cardiac events in the multiple logistic regression analysis were atrial fibrillation (OR: 9.7; 95% CI: 2.5 to 36.8), QRS width >120 ms (OR: 7.2; 95% CI: 2.0 to 26.0) and absence of beta-blocker therapy (OR: 4.4; 95% CI: 1.35 to 14.5) (**Table 3**). Their HR were 2.84 (95% CI: 1.37 to 5.89), 2.64 (95% CI: 1.24 to 5.58) and 2.25 (95% CI: 1.04 to 4.88), respectively.

Of note, the chance of suffering a major cardiac event on follow-up in our ACM cohort according to the 3 above-mentioned prognostic factors was 0%, 25%, 54%, and 100% for the presence of 0, 1, 2, and 3 risk factors, respectively (**Figure 2**). The AUC obtained with these 3 prognostic factors was 0.82 (95% CI: 0.73 to 0.91) (**Table 3**).

Follow-up LVEF data were available for 92 patients (98%). At the latest follow-up, 39 patients (41%) showed LVEF of ≥40%. Thirty-five patients had substantial cardiac recovery (LVEF absolute improvement of ≥10% with a final LVEF of ≥40%). Rates of antifailure medications at last follow-up among patients who had a substantial cardiac recovery in comparison with patients without LVEF recovery were 97% vs. 86% for angiotensin-converting enzyme inhibitors (ACEI)/angiotensin II receptor blockers (ARB) ($p = 0.9$), 74% vs. 51% for beta-blockers ($p = 0.025$), and 54% vs. 46% for aldosterone antagonists ($p = 0.4$).

Finally, we found no differences in transplantation-free survival between ACM patients who reduced alcohol intake to <80 g/day and abstainers ($p = 0.2$) (**Figure 3**). Both groups exhibited similar clinical status and received similar therapies at baseline.

The mean LVEF improved both among abstainers (26 ± 8% to 37 ± 15%; $p < 0.001$) and moderate drinkers (26 ± 10% to 34 ± 15%, $p = 0.008$). Differences between both groups were not significant (**Figure 4**). In contrast, LVEF decreased in the 5 patients who continued with alcohol consumption >80 g/day, although the difference was not significant (27 ± 11% to 21 ± 4%, $p = 0.3$).

OVERALL STUDY COHORT. Among the overall study cohort (ACM and IDCM) and during a median follow-up of 38 months (IQR: 12 to 77 months), 42 (15%) patients died (9 from noncardiac causes) and 79 (28%) underwent heart transplantation. Independent predictors of death or heart transplantation were atrial fibrillation (OR: 4.88; 95% CI: 2.27 to 10.46), QRS width >120ms (OR: 2.65; 95% CI: 2.27 to 10.46), absence of beta-blocker therapy (OR: 4.76; 95% CI: 2.32 to 9.09) and a higher LV end-diastolic diameter (OR: 1.05; 95% CI: 1.01 to 1.09). History of hypertension (OR: 0.28; 95% CI: 0.13 to 0.59) and alcoholic etiology (OR: 0.4; 95% CI: 0.20 to 0.80) were associated with a better outcome (**Table 4**).

No differences between ACM and IDCM patients were observed at baseline in terms of age, ejection fraction, ECG rhythm, and heart failure treatment (**Table 1**). Among ACM patients, there was a higher prevalence of men, smokers, liver disease, and chronic obstructive pulmonary disease (COPD). ACM patients exhibited worse New York Heart Association (NYHA) functional class and higher body mass index (BMI).

The transplantation-free survival curves of ACM and IDCM cohorts are shown in **Figure 3**. The transplantation-free survival rates at 1, 3, 5, and 10 years were 88 ± 3%, 80 ± 4%, 75 ± 5%, and 65 ± 6% in the ACM cohort and 74 ± 3%, 61 ± 4%, 58 ± 4%, and 46 ± 5% in the IDCM group ($p < 0.01$ in all cases).

DISCUSSION

This study is the largest cohort of ACM patients described to date and is the first in the modern era of heart failure therapy. It shows that approximately one-third of ACM patients have poor prognosis, whereas two-thirds of them remain clinically stable, with one-half of those recovering systolic function. Furthermore, this study shows that presently ACM has a better prognosis than IDCM and identifies several factors associated with poor outcome in ACM. Finally, our study did not find differences in clinical outcomes between ACM patients who abstain completely from alcohol and those who reduce intake to a moderate degree.

NATURAL HISTORY OF ALCOHOLIC CARDIOMYOPATHY. Excessive and prolonged alcohol intake leads to

systolic dysfunction in some alcohol abusers (15-19), most likely due to a genetic susceptibility (20). Given the high incidence of alcohol intake in industrialized nations, alcohol has been proposed as the major contributor to nonischemic DCM in Western countries (8,9,11). Therefore, a better understanding of the natural history of ACM is essential for caregivers and policymakers in order to design care for this group of patients.

In this study, approximately one-third of patients with ACM died or underwent heart transplantation, a third remained clinically stable without improvement in cardiac function, and a third experienced a substantial LVEF recovery. Overall, transplantation-free survival of our ACM cohort was better than that described previously, despite a more severe clinical presentation at baseline and a more prolonged disease (Online Table 1) (8-10,12).

The most likely explanation is the greater use of antifailure therapies such as ACE inhibitors, beta-blockers, and aldosterone antagonists, but it is also possible that the low proportion of persistent-heavy drinkers in our study was also relevant.

As shown in Online Table 1, previous studies of the natural history of ACM were performed before current heart failure drugs were available (8-10,12). In fact, beta-blockers were used only in 0% to 9% of patients, and information about treatment with aldosterone antagonists was not provided (most likely, only a few of those patients received these drugs) (8-10,12). Moreover, due to the era of previous studies, we could assume that both ICD and CRT devices were rarely implanted. In contrast, ACM patients in our series received modern heart failure therapies (**Table 1**). At the initial evaluation, 90% of ACM patients were receiving ACEI/ARBs, 60% beta-blockers and 49% aldosterone antagonists. At the latest follow-up, 84%, 76% and 57% of patients were treated with each medication, respectively.

The natural history of ACM compared with IDCM has been a highly controversial issue. While some studies have reported better prognosis in ACM compared to IDCM (10,13,21), others found the opposite (8,9). In this study, ACM was identified as a protective factor on multivariate analysis (**Table 4**), and transplantation-free survival in ACM was better than in IDCM (**Figure 3**). Similar to previous studies, we found a higher proportion of men, smokers, and liver disease and a greater BMI among alcohol drinkers (8,9). Perhaps for these reasons, COPD was also more frequent in ACM than in IDCM. Despite these differences, IDCM and ACM cohorts were comparable. Age, atrial fibrillation prevalence, QRS duration, and LVEF and hemodynamic parameters, which are strong predictors of cardiac events in DCM, were similar in both groups (**Table 1**).

TABLE 3 Multiple Logistic Regression Analysis Showing the Independent Predictors of Cardiac Death or Transplantation in ACM

Predictor	OR	95% CI	p Value	AUC	95% CI	p Value
Absence of beta-blocker therapy	4.4	1.35–14.49	0.014			
QRS width >120 ms	7.2	2.02–26.00	0.002	0.82	0.73–0.91	<0.001
Atrial fibrillation	9.7	2.56–36.79	0.001			

Variables entered into multiple regression analysis included age (p = 0.186; per 5-year increase); left ventricular ejection fraction (LVEF; p = 0.256; per 5-U decrease); left end-diastolic diameter (p = 0.059; per 5-mm increase); alcohol abstinence (p = 0.789); atrial fibrillation (p = 0.004); QRS >120 ms (p = 0.003); beta-blocker therapy (p = 0.001); ACEI/ARB therapy (p = 0.075); digoxin (p = 0.005); and loop diuretic agent therapy (p = 0.064).
AUC = area under the curve; CI = confidence interval; OR = odds ratio; other abbreviations as in Table 1.

PREDICTORS OF PROGNOSIS IN ACM. Different factors associated with a poor prognosis have been proposed in previous ACM studies; however, those studies are hampered by a small numbers of patients and by the absence of treatment with current standard heart failure therapies (Online Table 1). Prazak et al. (10) found that NYHA functional class III to IV, hepatojugular reflux, and use of diuretics were markers of fatal outcome, whereas Fauchier et al. (8) found that lack of abstinence and an increased LV end-systolic diameter were the only independent

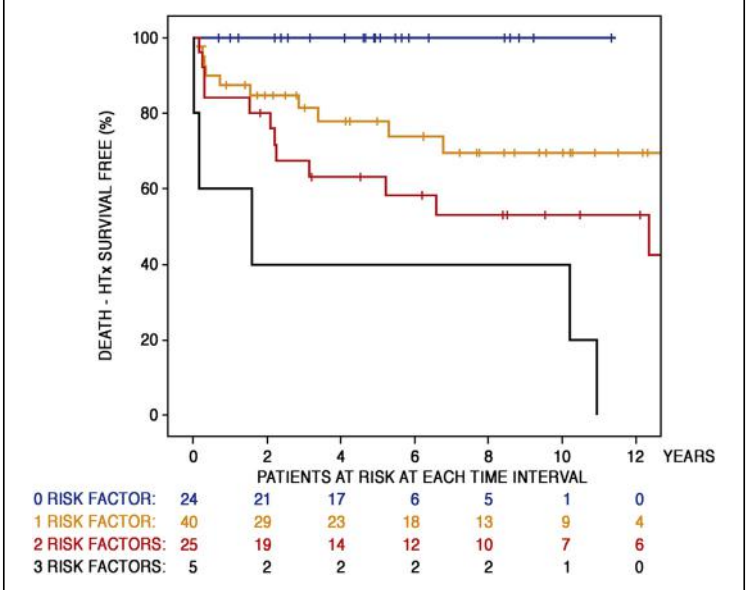

FIGURE 2 Kaplan-Meier Transplantation-Free Survival Stratified by Risk Factors

Kaplan-Meier transplantation-free survival rates are shown stratified by three independent risk factors: atrial fibrillation, QRS width of >120 ms, and lack of beta-blocker therapy at baseline evaluation.

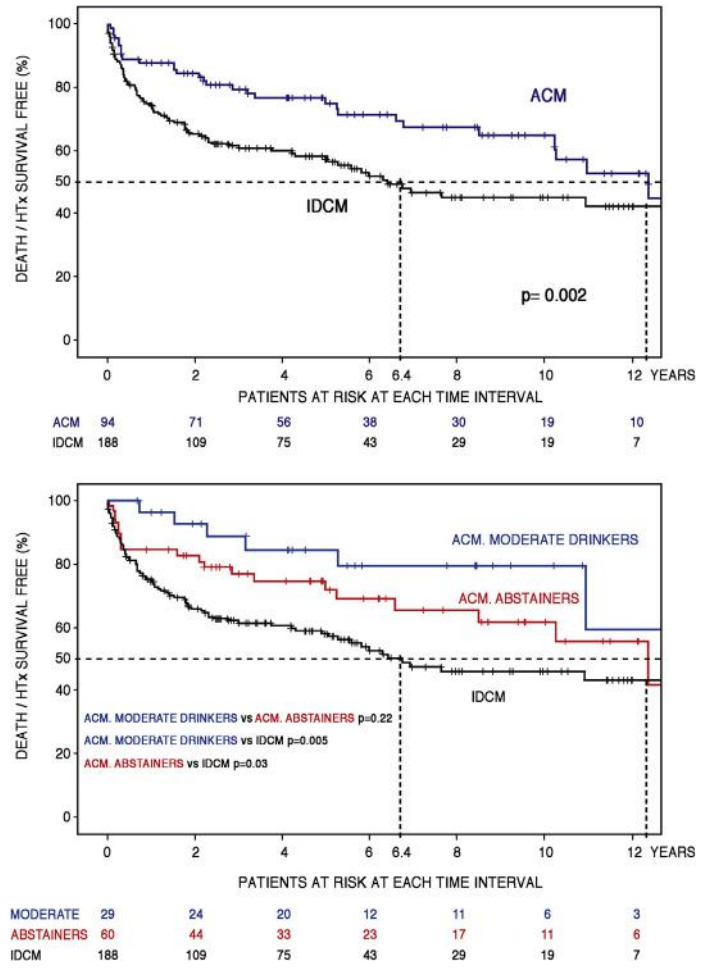

FIGURE 3 Transplantation-Free Survival in IDCM and ACM Cohorts According to Alcohol Consumption

(A) Survival curves of major cardiac events (cardiac death, heart transplantation) in patients with ACM **(blue)** and IDCM **(black)**. **(B)** Survival curves of cardiac events in patients with IDCM **(black)**, ACM with persistent moderate alcohol intake (<80 g/day) **(blue)** and abstainers **(red)**. The number below the x-axis indicates patients at risk at each time interval. ACM = alcoholic cardiomyopathy; IDCM = idiopathic dilated cardiomyopathy.

predictors of cardiac death and cardiac events, respectively. Other authors have also reported that transplantation-free survival and mortality were improved among ACM patients who became abstinent, but did not mention other predictors (9,12).

In our study, we identified atrial fibrillation, QRS width >120 ms, and lack of beta-blockers as independent predictors of cardiac death or heart transplantation. These factors are well-known prognostic factors already identified in other DCM studies and registries (22–25) and, consistently, were also identified in multivariate analysis of the entire cohort. In light of our results, identification of these factors in ACM patients should lead to close follow-up and prompt referral to a transplantation center.

Unlike ACEI, beta-blockers were not proved to be beneficial in heart failure patients at the start of the study cohort and therefore were not uniformly prescribed during the initial years of our study. Although 76% of ACM patients included in our study were receiving beta-blockers at last follow-up, among the 32 patients evaluated before the year 2000 (CIBIS [Cardiac Insufficiency Bisoprolol Study II] study was published in 1999) (22), only 3 patients (9%) received beta-blockers at their initial evaluation, and 19 patients (59%) died or underwent heart transplantation. The use of current heart failure therapies clearly increased in ACM patients evaluated after 2000 in comparison with patients evaluated before this year: ACEI/ARB (97% vs. 78%, $p = 0.01$), beta-blockers (76% vs. 9%, $p < 0.001$), and aldosterone antagonists (61% vs. 48%, $p = 0.27$). In fact, the 1-, 3-, 5-, and 10-year transplantation-free survival rates also improved among patients evaluated after year 2000 (93 ± 3%, 85 ± 5%, 83 ± 5%, and 83 ± 5% vs. 78 ± 7%, 69 ± 8%, 65 ± 8%, and 49 ± 9%, respectively; $p = 0.006$).

Finally, and irrespective of time period analyzed, it is noteworthy that none of the ACM patients who reached an LVEF >40% during follow-up suffered any major cardiac event (cardiac death or heart transplantation).

EFFECT OF ALCOHOL ABSTINENCE ON CLINICAL COURSE. Complete abstinence from ethanol is advocated in all ACM patients (7,9,12,21,26). However, the need for complete alcohol abstinence in advanced ACM is a controversial issue (27). Although several studies have suggested that the clinical outcome of ACM could be improved if patients abstain from alcohol (8,9,21,26), other studies have shown that complete alcohol abstinence may not be necessary to improve LVEF (13). Moreover, some of the previous ACM studies that advocated complete abstinence included light to moderate drinkers in the abstainers group (8,9) or reported good improvement in moderate drinkers (21).

We have found that ACM patients who decreased their alcohol intake to moderate levels had better outcomes than IDCM patients and outcomes similar to those of ACM patients who abandoned alcohol completely (**Figure 3**). Moreover, LVEF during follow-up increased significantly to a similar extent as in abstainers among ACM patients who reduced their alcohol intake to moderate levels (**Figure 4**). Of note, although all patients who reduced alcohol intake to <80 g/day were classified as moderate drinkers, the vast majority of these patients reduced alcohol intake

to <20 to 30 g/day (2 to 3 standard drinks). This amount of alcohol is similar to the amount described in studies which reported that low to moderate alcohol consumption is associated with lower mortality and incidence of nonischemic heart failure (2–4).

Our findings are consistent with prior echocardiographic studies (13). Nicolas et al. (13) found that after 1 year, LVEF increased in a cohort of ACM patients who reduced their alcohol intake to <60 g/day, whereas it decreased in those who maintained an alcohol intake of >80 g/day. In our study, the 5 patients who continued drinking >80 g/day exhibited a clear deterioration of their LVEF, although the difference was not statistically significant, most likely due to the small sample size.

Finally, we could not find any differences in any of the endpoints studied in relation to the type of beverage, amount or duration of self-reported alcohol abuse, perhaps due to the high amount of alcohol necessary to qualify for the study.

STUDY LIMITATIONS. Similar to previous studies of ACM, the allocation of patients to the ACM group and into abstinent or persistent drinkers subgroups was based on patients' self-reported alcohol consumption, which may lead to underestimation. Although we used analytical markers of alcohol consumption, such as average erythrocyte volume and serum gamma-glutamyl transferase levels as an aid to establish abstinence or persistence of alcohol intake in all patients, the quantity of alcohol intake depended solely on the patients' report.

In our study, the group of patients who continued their heavy drinking after medical advice to abstain is very small (5% of cases of ACM) and does not allow for statistically sound comparison with the other groups. Conclusions regarding this group must be drawn with caution.

The definition of ACM used in this study is widely accepted and was used in several previous studies, but may lead to an underrepresentation of women with ACM. The accepted definition of ACM does not differentiate based on sex or BMI. Alcohol affects the heart through a toxic effect that depends on the quantity of alcohol that reaches the heart. As women typically have a lower BMI than men, similar alcohol concentrations in the heart may be achieved in women with lower alcohol intake.

The multiple logistic regression analyses presented in this work were based on a stepwise selection procedure from a larger set of candidate predictor variables. Hence, there is some risk of identifying a false positive predictor due to this multiplicity problem.

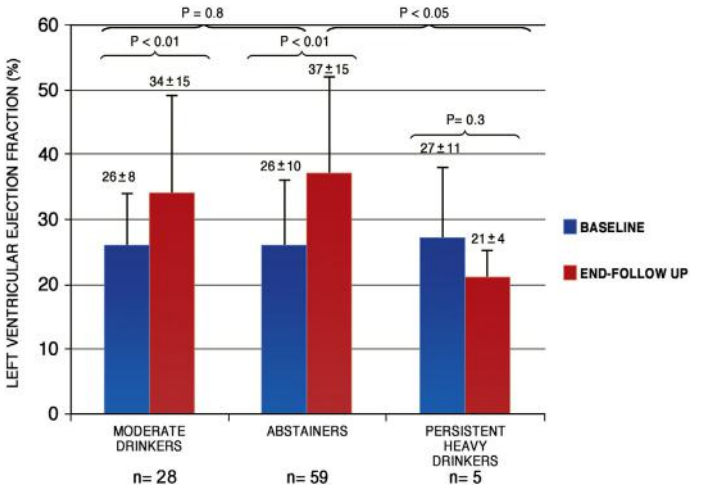

FIGURE 4 Changes in Left Ventricular Ejection Fraction in ACM

Comparison between left ventricular ejection fraction at baseline and at last follow-up according to alcohol consumption in patients with alcoholic cardiomyopathy (ACM).

Finally, our study is strongly influenced by the fact that this cohort of patients was referred to a single Heart Transplant Center from a Mediterranean country.

CONCLUSIONS

This study shows that currently the prognosis for ACM is better than that for IDCM. In our ACM cohort, approximately one-third of the ACM patients died or underwent heart transplantation, whereas another third experienced substantial cardiac recovery, and the remaining third remained clinically stable despite impaired heart function. Atrial fibrillation, QRS width

TABLE 4 Multiple Logistic Regression Analysis Showing the Independent Predictors of Death or Transplantation in the Entire Study Cohort (n = 282)

Predictor	OR	95% CI	p Value
Beta-blocker therapy	0.21	0.11–0.43	<0.001
Hypertension	0.28	0.13–0.59	0.001
Alcoholic etiology	0.39	0.19–0.80	0.010
Left ventricular end-diastolic diameter	1.05	1.01–1.09	0.007
QRS width >120 ms	2.65	1.34–5.24	<0.005
Atrial fibrillation	4.88	2.27–0.46	0.001

Variables entered into multiple regression analysis included hypertension ($p < 0.001$); left end-diastolic diameter ($p = 0.023$; per 5-mm increase); alcoholic causes ($p = 0.06$); atrial fibrillation ($p = 0.012$); QRS >120 ms ($p = 0.002$); beta-blocker therapy ($p < 0.001$); ACEI/ARB therapy ($p = 0.028$); digoxin therapy ($p<0.001$); and loop diuretic therapy ($p < 0.001$).

CI = confidence interval; OR = odds ratio; other abbreviations as in Table 1.

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>120 ms, and absence of beta-blocker treatment were identified as independent prognostic factors associated with poor outcome. Finally, the prognosis of ACM patients who reduce alcohol consumption to moderate levels is similar to abstainers.

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KEY WORDS alcohol, cardiomyopathy, heart failure, prognosis

APPENDIX For a supplemental table, please see the online version of this article.