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Adherence to Mediterranean Diet and All-Cause Mortality After an Episode of Acute Heart Failure

Results of the MEDIT-AHF Study

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ABSTRACT

OBJECTIVES The authors sought to evaluate clinical outcomes of patients after an episode of acute heart failure (AHF) according to their adherence to the Mediterranean diet (MedDiet).

BACKGROUND It has been proved that MedDiet is a useful tool in primary prevention of cardiovascular diseases. However, it is unknown whether adherence to MedDiet is associated with better outcomes in patients who have already experienced an episode of AHF.

METHODS We designed a prospective study that included consecutive patients diagnosed with AHF in 7 Spanish emergency departments (EDs). Patients were included if they or their relatives were able to answer a 14-point score of adherence to the MedDiet, which classified patients as adherents (≥9 points) or nonadherents (≤8 points). The primary endpoint was all-cause mortality at the end of follow-up, and secondary endpoints were 1-year ED revisit without hospitalization, rehospitalization, death, and a combined endpoint of all these variables for patients discharged after the index episode. Unadjusted and adjusted hazard ratios (HRs) were calculated.

RESULTS We included 991 patients (mean age of 80 ± 10 years, 57.8% women); 523 (52.9%) of whom were adherent to the MedDiet. After a mean follow-up period of 2.1 ± 1.3 years, no differences were observed in survival between adherent and nonadherent patients (HR of adherents [HR_{adh}] = 0.86; 95% confidence interval [CI]: 0.73 to 1.02). The 1-year cumulative ED revisit for the whole cohort was 24.5% (HR_{adh} = 1.10; 95% CI: 0.84 to 1.42), hospitalization 43.7% (HR_{adh} = 0.74; 95% CI: 0.61 to 0.90), death 22.7% (HR_{adh} = 1.05; 95% CI: 0.8 to 1.38), and combined endpoint 66.8% (HR_{adh} = 0.89; 95% CI: 0.76 to 1.04). Adjustment by age, hypertension, peripheral arterial disease, previous episodes of AHF, treatment with statins, air-room pulsioxymetry, and need for ventilation support in the ED rendered similar results, with no statistically significant differences in mortality (HR_{adh} = 0.94; 95% CI: 0.80 to 1.13) and persistence of lower 1-year hospitalization for adherents (HR_{adh} = 0.76; 95% CI: 0.62 to 0.93).

CONCLUSIONS Adherence to the MedDiet did not influence long-term mortality after an episode of AHF, but it was associated with decreased rates of rehospitalization during the next year. (J Am Coll Cardiol HF 2017;■:■–■)

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ABBREVIATIONS AND ACRONYMS

AHF = acute heart failure
CI = confidence interval
CVD = cardiovascular disease
ED = emergency department
HF = heart failure
HR = hazard ratio
MedDiet = Mediterranean diet

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality worldwide, and its incidence is especially high in elderly people (1). In this setting, coronary heart disease leading to heart failure (HF) is one of the most common downstream pathways by which CVD influences survival. In fact, the prevalence of HF has increased in recent decades (2), and currently, recurrent episodes of acute HF (AHF) constitute the main cause of hospitalization in older adults (3–5). In Western countries with aging populations, this emerging epidemic is threatening health care system sustainability, and consequently, policymakers are urged to take clear, potent, and general actions against this devastating public health problem (2,4).

Although primary prevention of CVD is the keystone to facing this challenge in the long-term, secondary prevention once a CVD is established has similar importance. In this sense, changes in diet and other lifestyle factors are the most common non-pharmacologic interventions recommended to modify the natural course of CVD. Thus, in recent decades, scientific evidence has shown that changes in overall dietary patterns and, specifically interventions using the traditional Mediterranean diet (MedDiet), constitute a useful tool in CVD primary prevention (6,7). With respect to HF, 2 cohort studies concluded that lower HF risk was associated with better adherence to the MedDiet (8,9), whereas a protocol-specified secondary analysis of the Prevención con Dieta Mediterránea (PREDIMED) randomized controlled trial, which aimed to show the benefits of the MedDiet in primary prevention of CVD in participants at high risk, failed in showing a lower incidence of HF for participants who followed a traditional MedDiet supplemented with either extra-virgin olive oil or nuts, compared with those who followed a control low-fat diet (10).

Nonetheless, in patients who have already suffered an episode of AHF, it is not known whether adherence to the MedDiet is associated with a better prognosis in terms of need of readmission to the emergency department (ED), rehospitalization, or death. In this setting, we began a study on the relationship between adherence to the traditional MedDiet and incidence of different clinical outcomes in patients with coronary heart disease or other cardiomyopathies who had had an episode of AHF. Our hypothesis was that adherence to the MedDiet could be a significant factor influencing mortality.

PATIENTS AND METHODS

MEDIT-AHF (Mediterranean DieT in Acute Heart Failure) was a prospective cohort study imbedded into the Epidemiology of Acute Heart Failure in Emergency departments (EAHFE) Registry phase 4, which included between February 1, 2014, and March, 31, 2014 (2 months). Complete details of patient inclusion into the EAHFE Registry have been reported in previous papers (11–13). For the MEDIT-AHF study, patients were included if they or their relatives were able to answer questions about their regular diet. At first instance, patients were asked to answer the questionnaire. When patients were not available or unable to respond, we accepted a relative as respondent if such relative lived or took care of the patient daily and was aware of the patient's dietary characteristics. We asked about the dietary habits followed by patients during the year before the index episode. Adherence to the traditional MedDiet was estimated by using the 14-point questionnaire of adhesion to the MedDiet used and validated in the PREDIMED trial (14), which investigated 14 different items, including 12 questions related to frequency of consumption of key foods, and 2 questions related to dietary habits characteristic of the MedDiet. Each question scores 0 or 1 point, and the final score ranges between 0 and 14 points indicating null (0 points) or complete (14 points) adherence to the MedDiet. This PREDIMED questionnaire has proved to be very useful in a large Spanish cohort for rapid estimation of adherence to the traditional MedDiet (14). As proposed in other studies (15,16), patients were divided into 2 groups depending on whether they were adherent (9 or more points) or not adherent (8 or fewer points) to the MedDiet, and this was considered the classificatory variable. In addition, there were 55 independent variables that could potentially affect different clinical outcomes (Online Table 1). The entire EAHFE registry protocol was approved by a unique central Ethical

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*For a list of the other investigators of the ICA-SEMES Research Group, please see the online version of this paper.

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Committee at the Hospital Universitario Central de Asturias (Oviedo, Spain), with the reference numbers 49/2010, 69/2011, 166/13, and 160/15, and all patients participating in the MEDIT-AHF gave informed consent to be included in the study.

The primary endpoint was all-cause mortality at the end of follow-up, which was scheduled for July 15, 2017. Vital status was ascertained at least thrice, after 3, 12, and 36 months from the index episode, by means of phone calls and/or review of primary care and hospital medical records. Medical history is regionally connected and allows registering other interactions between the patient and the public health system, as well as patient death, usually within a few days after death. As secondary endpoints, we collected 3 different short-term outcomes during the first year after the index episode (and a forth consisting of a combined endpoint if any of them was present): ED revisits due to HF (without need of hospitalization), need for rehospitalization due to HF, and all-cause death. For these secondary outcomes, only patients discharged alive after the index episode were included.

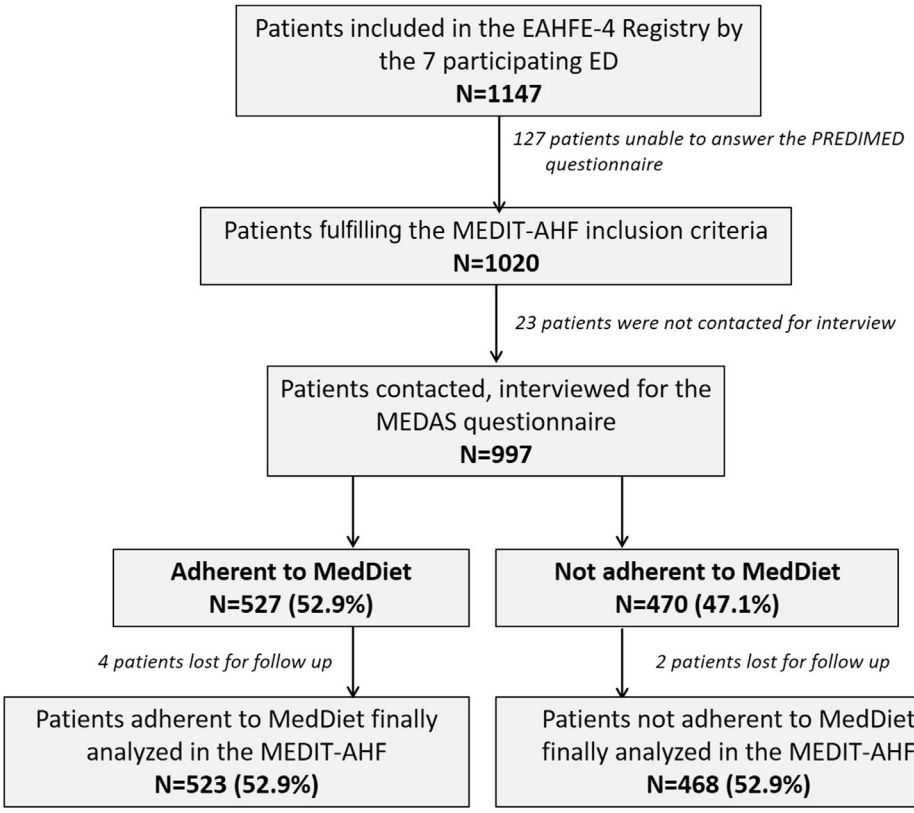
The sample size was calculated based on a bilateral hypothesis of the existence of a relative difference of 20% in the primary endpoint between patients adherent and not adherent to the MedDiet. One-year mortality, based on our previous published data from the EAHFE registry, was estimated to be 28%; alpha error was set at 0.05, and beta error at 0.20. Under these assumptions, the sample size needed for analysis was 943 patients, and, considering a potential loss of 15% of patients (unable to answer the 14-point PREDIMED questionnaire, denying consent to be contacted, loss at follow-up, or others), the final size was established at 1,109 patients. According to our previous experience, a mean of 60 to 100 patients per month are recruited at every ED (depending on the hospital size and ED census). Accordingly, we selected 7 Spanish EDs (from the Hospital Clínico, and Hospital Gregorio Marañón, Madrid; Hospital Universitario Central de Asturias, Oviedo; Hospital de Bellvitge, Hospital del Mar, Hospital de Sant Pau, and Hospital Clínic, Barcelona) to participate in the MEDIT-AHF study during the 2-month period of the EAHFE-4 recruitment to cover the required sample size. They were asked to assess adherence to the MedDiet through the PREDIMED questionnaire to all of the 1,120 consecutive patients who we expected they would include in their EAHFE-4 phase. The survey was performed using the phone by a single professional interviewer with skills acquired in previous studies on HF and diet assessment (16,17). The phone contact with the patient or a relative living with her or him was performed within the first month of the index episode. We used this strategy because, on one hand, we preferred to use the same interviewer for all patients, and on the other hand, we assumed that changes in diet would be minimal in this narrow interval of time (maximum: 1 month) between admission at ED and diet recording. No diet instructions (except salt intake) were given to the patients included during their stay in the ED. We tried to contact the patients who were alive at the end of the follow-up to investigate if there had been changes in their diet in relation to that reported at the beginning of the MEDIT-AHF study.

STATISTICAL ANALYSIS. Quantitative variables are expressed as mean ± SD or as median (25th to 75th percentiles) if not normally distributed. Dichotomous variables are expressed as absolute values and percentages. Comparison was performed using 1-way analysis of variance for quantitative variables (or the Mann-Whitney nonparametric test when needed) and with the chi-square test (with Yate's correction when needed) for qualitative variables. Survival tables were obtained by the Kaplan Meier method, and comparisons of primary and secondary outcomes were performed following the Cox model. We first obtained the unadjusted curves for both groups of patients (adherent and not adherent) and crude hazard ratios (HRs) with 95% confidence intervals (CIs) for adherent compared with nonadherent patients were calculated. Afterwards, we adjusted the survival curves by all independent variables obtaining a p value of <0.10 in the univariable comparisons, forcing the entrance of all these variables in a multivariable Cox model. As a sensitivity analysis, we repeated the adjustment after replacing the missed values of the independent variables included in the model by the mode (qualitative variables) or the median (quantitative variables). In addition, we investigated if an interaction was present depending on whether the PREDIMED questionnaire had been answered by the patient or relatives, as well as depending on whether there had been dietary changes throughout the study period for those patients contacted at the end of the study. Finally, the individual influence of every 1 of the 14 dietary components of the PREDIMED questionnaire on the primary endpoint was studied. Statistical significance was accepted if 95% CI of HRs excluded the value 1 or the p value was <0.05. All calculations were performed using the IBM SPSS Statistics package, version 24 (IBM, North Castle, New York).

RESULTS

The 7 participating EDs recruited 1,148 consecutive patients diagnosed with AHF for the EAHFE-4

FIGURE 1 Flow Diagram of Patient Inclusion



EAHFE-4 = Epidemiology of Acute Heart Failure in Emergency departments, recruitment phase 4; ED = emergency department; MEDAS = Mediterranean Diet Adherence Screener; MedDiet = Mediterranean diet; MEDIT-AHF = Mediterranean Diet in Acute Heart Failure; PREDIMED = Prevención con Dieta Mediterránea.

registry, and 991 were finally included in the MEDIT-AHF study (Figure 1), with a mean age of 80 ± 10 years and 57.8% being women. The PREDIMED questionnaire was answered by patients in 566 cases (57.1%) and by relatives in 425 cases (42.9%). Other characteristics are reported in Table 1. Patients included in the MEDIT-AHF study had a high number of comorbidities and had been administered many drugs, and most of them had functional limitations (Barthel Index was less than 100 points in 58.6% of patients). Only 5 of 55 variables had missing values for more than 10% of the patients: body mass index, Barthel Index, left ventricular ejection fraction, systolic dysfunction, and troponin level at ED. On the basis of the results of the PREDIMED questionnaire, 52.9% of patients were classified as adherent to the MedDiet. These patients were significantly younger, had more frequent hypertension, less frequent peripheral arterial disease as comorbidities, and showed higher pulsioxymetry values at ED arrival compared to patients with low adherence to the MedDiet (all $p < 0.05$).

A total of 569 patients (57.4%) died during a mean follow up of 2.1 ± 1.3 years (median: 2.6 years; 25th to 75th percentile: 0.9 to 3.3) with no differences between both groups in the follow up time ($p = 0.41$). The cumulative mortality at the end of the study was lower in patients adherent to the MedDiet than in those who were not adherent, although the difference did not reach statistical significance (HR: 0.86; 95% CI: 0.73 to 1.02; $p = 0.08$) (Figure 2). A total of 934 patients (94.2%) were discharged alive from the hospital after the index episode. The incidence of the secondary endpoints at 1 year for these patients was as follows: new visits to the ED not causing hospital admission, 24.5%; need for hospitalization, 43.7%; death, 22.7%; and combined events, 66.8%. There were no statistically significant differences between adherent and nonadherent patients for incidence of new visits to the ED, all-cause

TABLE 1 Baseline Characteristics of Patients Included in the Study and Comparison According to Their Adherence to the Mediterranean Diet

	Total (N = 991)	Missing Values	Adherent (n = 523)	Not Adherent (n = 468)	p Value
Demographic data					
Age (yrs)*	80 ± 10	0	80 ± 10	81 ± 10	0.03
Female	579 (57.8)	4 (0.4)	302 (58.0)	268 (57.5)	0.94
Comorbidities					
Arterial hypertension*	846 (85.5)	1 (0.1)	461 (88.1)	385 (82.4)	0.01
Diabetes mellitus	387 (39.1)	1 (0.1)	202 (38.6)	185 (39.6)	0.80
Dyslipidemia	531 (53.6)	1 (0.1)	289 (55.3)	242 (51.8)	0.31
Ischemic heart disease	299 (30.2)	1 (0.1)	157 (30.0)	142 (30.4)	0.95
Chronic kidney failure	268 (27.1)	1 (0.1)	147 (28.1)	121 (25.9)	0.48
Cerebrovascular disease	137 (13.8)	1 (0.1)	66 (12.6)	71 (15.2)	0.28
Arial fibrillation	483 (48.8)	1 (0.1)	264 (50.5)	219 (46.9)	0.29
Peripheral arterial disease*	108 (10.9)	2 (0.2)	46 (8,8)	62 (13.3)	0.03
Heart valve disease	295 (29.8)	1 (0.1)	146 (27.9)	149 (31.9)	0.19
Chronic obstructive pulmonary disease	237 (23.9)	1 (0.1)	118 (22.6)	119 (25.5)	0.32
Active cancer	144 (14.5)	1 (0.1)	74 (14.1)	70 (15.0)	0.78
Dementia	119 (12.0)	1 (0.1)	64 (12.2)	55 (11.8)	0.90
Prior episode of heart failure†	535 (54.4)	7 (0.7)	298 (57.3)	237 (51.1)	0.06
Baseline status					
Body mass index (kg/m^2)	27.8 ± 5.0	458 ± 46.2	27.7 ± 4.7	28.0 ± 5.4	0.55
Barthel Index (points)	83 ± 23	121 ± 12.2	84 ± 22	82 ± 23	0.15
Advanced cardiorespiratory class (NYHA functional class III-IV)	210 (22.6)	61 (6.2)	115 (23.4)	95 (21.7)	0.59
Left ventricular ejection fraction (%)	51 ± 14	401 ± 40.5	51 ± 14	52 ± 14	0.68
Systolic dysfunction by echocardiography	275 (46.6)	401 (40.5)	149 (47.0)	126 (46.2)	0.90
Chronic treatments					
Diuretics	709 (72.1)	8 (0.8)	375 (72.1)	334 (72.1)	0.99
ACE inhibitor or ARB	570 (58.0)	9 (0.9)	308 (59.3)	262 (56.6)	0.42
Beta-blocker	434 (44.2)	9 (0.9)	241 (46.3)	193 (41.8)	0.17
Aldosterone antagonist	177 (18.0)	9 (0.9)	91 (17.5)	86 (18.6)	0.73
Nitrates	172 (17.5)	9 (0.9)	95 (18.3)	77 (16.6)	0.54
Statins†	495 (50.4)	8 (0.8)	276 (53.1)	219 (47.3)	0.08
Anti aggregators	389 (39.6)	8 (0.8)	201 (38.7)	188 (40.6)	0.58
Anticoagulation	385 (39.2)	9 (0.9)	211 (490.7)	174 (37.6)	0.36
Amiodarone	60 (6.1)	8 (0.8)	38 (7.3)	22 (4.8)	0.12
Digoxin	134 (13.6)	9 (0.9)	76 (14.6)	58 (12.5)	0.38
Beta-agonist bronchodilators	183 (18.6)	8 (0.8)	90 (17.3)	93 (20.1)	0.30
Anticholinergic bronchodilators	213 (21.7)	9 (0.9)	115 (22.1)	98 (21.2)	0.79
Pacemaker or defibrillator	92 (9.4)	9 (0.9)	52 (10.0)	40 (8.6)	0.53
Vitals at ED during acute episode					
Systolic blood pressure (mm Hg)	141 ± 26	11 ± 1.1	142 ± 25	140 ± 26	0.17
Heart rate (beats/min)	88 ± 24	15 ± 1.5	88 ± 24	87 ± 24	0.82
Temperature (°C)	36.2 ± 0.7	86 ± 8.7	36.2 ± 0.7	36.3 ± 0.3	0.65
Air-room pulsioxymetry (%)*	93 ± 6	42 ± 4.2	93 ± 5	92 ± 7	0.04
ECG abnormalities at ED during acute episode					
Atrial fibrillation	455 (46.7)	17 (1.7)	242 (47.5)	213 (45.9)	0.67
Left bundle-branch block	97 (10.0)	17 (1.7)	51 (10.0)	46 (9.9)	0.99
Pacemaker rhythm	88 (9.0)	17 (1.7)	48 (9.4)	40 (8.6)	0.75

Continued on the next page

mortality, and the combined variable (p = 0.49, p = 0.71, and p = 0.13, respectively); however, patients adherent to the MedDiet showed a significantly lower hospitalization rate than nonadherent patients (HR: 0.74; 95% CI: 0.61 to 0.90; p = 0.003) (Figure 2).

We adjusted the primary and secondary endpoints for the 7 variables having a $p < 0.10$ in the univariate analysis: age, hypertension, peripheral arterial disease, previous episodes of HF, treatment with statins, air-room pulsioxymetry, and use of ventilation support at ED. After such adjustments, the only

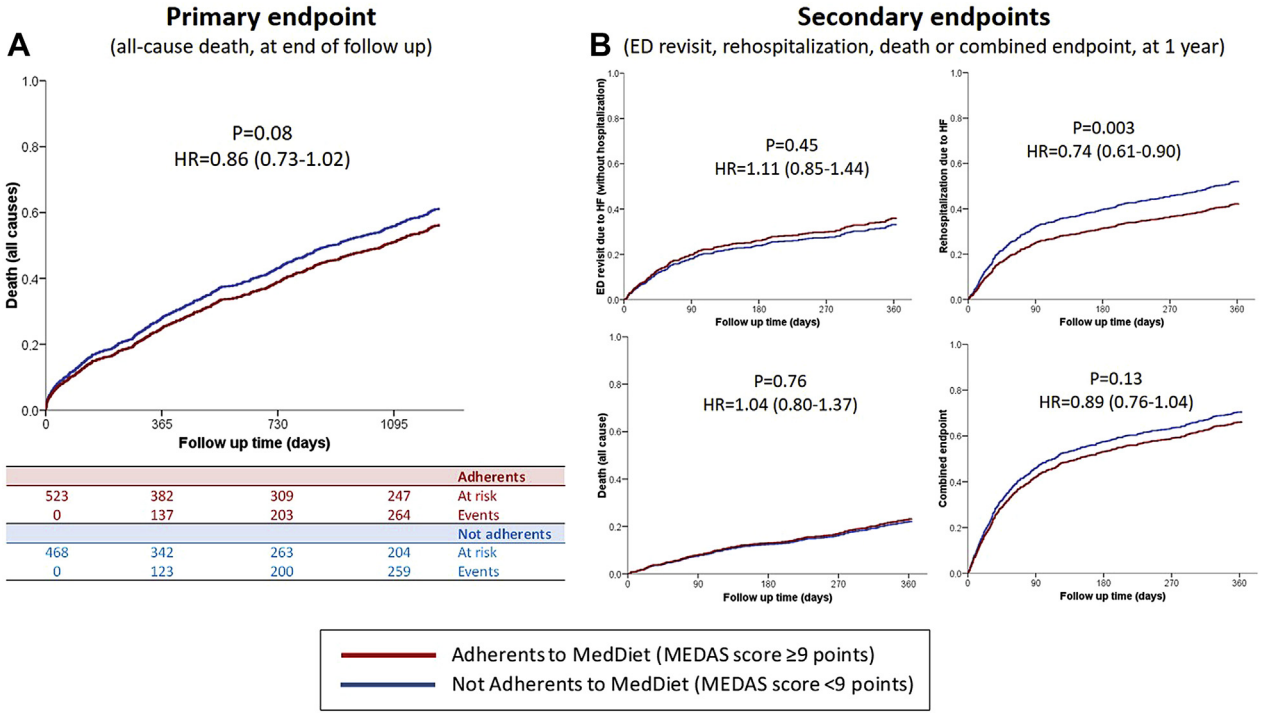
TABLE 1 Continued

	Total (N = 991)	Missing Values	Adherent (n = 523)	Not Adherent (n = 468)	p Value
Analytical data at ED during acute episode					
Glycemia (mg/dl)	126 (103-165)	21 (2.1)	126 (102-162)	126 (104-167)	0.62
Creatinin (mg/dl)	1.16 (0.91-1.57)	11 (1.1)	1.16 (0.91-1.54)	1.15 (0.90-1.59)	0.97
eGFR (ml/min/m^2)	54 (39-73)	15 (1.5)	55 (40-73)	54 (38-72)	0.64
Hemoglobin (g/l)	119 (21)	21 (2.1)	120 (21)	119 (21)	0.59
Potassium <3.5 or >5 (mmol/l)	160 (17.0)	49 (4.9)	78 (15.8)	82 (18.3)	0.35
Hyponatremia (<135 mmol/l)	178 (18.3)	16 (1.6)	99 (19.2)	79 (17.2)	0.46
Troponin positive	182 (36.5)	493 (497)	92 (36.5)	90 (36.6)	0.99
Management at ED					
Need of intravenous morphine	58 (5.9)	8 (0.8)	31 (6.0)	27 (5.8)	0.99
Need of intravenous nitrates	197 (20.0)	8 (0.8)	114 (22.1)	83 (17.8)	0.11
Need of inotropics/vasopressors	7 (0.7)	9 (0.9)	3 (0.6)	4 (0.9)	0.90
Need of non invasive ventilation	48 (4.9)	8 (0.8)	20 (3.9)	28 (6.0)	0.16
Need of mechanical ventilation	8 (0.8)	8 (0.8)	3 (0.6)	5 (1.1)	0.62
Need of any ventilation support†	55 (5.6)	8 (0.8)	22 (4.3)	33 (7.1)	0.08
Admission at hospital	745 (75.2)	0 (0)	384 (73.4)	361 (77.1)	0.20
Admission at intensive care unit	8 (0.8)	0 (0)	2 (0.4)	6 (1.3)	0.16

Values are mean ± SD, n (%), or median (25th to 75th percentile). *Statistical significance ($p < 0.05$). †Included in multivariate adjustment ($p < 0.10$) in addition to variables with statistical significance ($p < 0.05$).

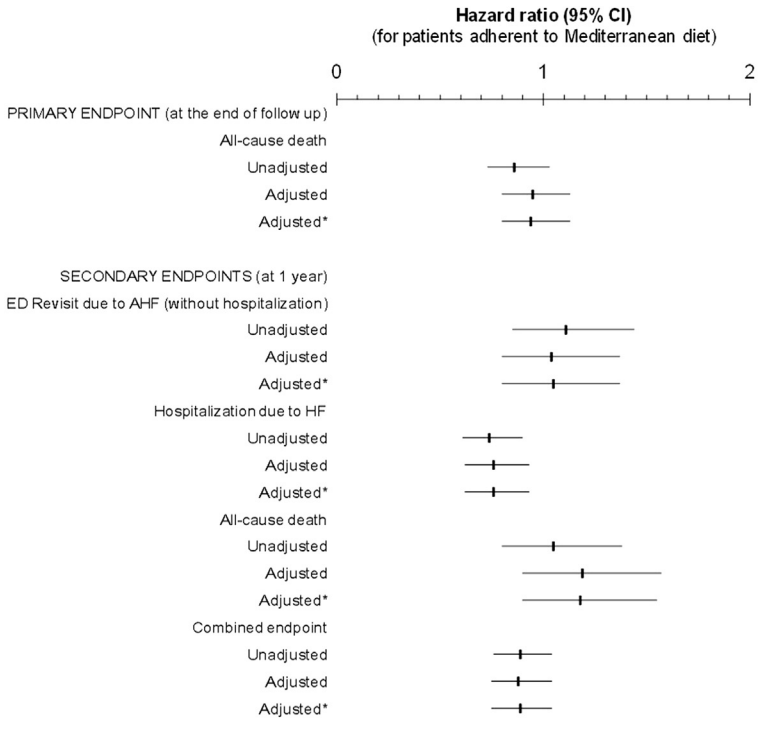
ACE = angiotensin-converter enzyme; ARB = angiotensin receptor blocker; ED = emergency department; eGFR = estimated glomerular filtration rate.

FIGURE 2 Unadjusted Proportional Risks of Developing the Primary Endpoint and the Secondary Endpoints



(A) All-cause mortality at the end of follow-up. **(B)** The secondary endpoints (1-year emergency department revisit without hospitalization, hospitalization, death, and combined) according to whether patients with acute heart failure were adherent or not adherent to the Mediterranean diet (MedDiet). ED = emergency department; HF = heart failure; HR = hazard ratio.

FIGURE 3 Unadjusted and Adjusted Hazard Ratios for Primary and Secondary Endpoints



	Hazard Ratio	95% CI lower limit	95% CI upper limit	P value
PRIMARY ENDPOINT (at the end of follow up)				
All-cause death				
Unadjusted	0.86	0.73	1.03	0.08
Adjusted	0.95	0.80	1.13	0.50
Adjusted*	0.94	0.80	1.13	0.50
SECONDARY ENDPOINTS (at 1 year)				
ED Revisit due to AHF (without hospitalization)				
Unadjusted	1.10	0.84	1.42	0.49
Adjusted	1.03	0.78	1.35	0.85
Adjusted*	1.07	0.82	1.39	0.61
Hospitalization due to HF				
Unadjusted	0.74	0.61	0.90	**0.003**
Adjusted	0.76	0.62	0.93	**0.008**
Adjusted*	0.76	0.62	0.93	**0.007**
All-cause death				
Unadjusted	1.05	0.80	1.38	0.71
Adjusted	1.19	0.90	1.57	0.22
Adjusted*	1.18	0.90	1.55	0.23
Combined endpoint				
Unadjusted	0.89	0.76	1.04	0.13
Adjusted	0.88	0.75	1.04	0.14
Adjusted*	0.89	0.75	1.04	0.14

Adjustment was performed using the 7 independent variables found to be differently distributed (with a $p < 0.10$) among adherent and nonadherent patients in the univariate analysis: age, arterial hypertension, peripheral artery disease, previous episodes of acute heart failure, chronic treatment with statins, air-room pulsioxymetry at emergency department arrival, and need for any ventilation support at emergency department. *Adjustment was performed using the same 7 independent variables mentioned above, but with imputation of missing values (replacing missing values by mode for qualitative variables and by median for quantitative variables). AHF = acute heart failure; CI = confidence interval; ED = emergency department; HF = heart failure.

endpoint that remained statistically significant was again the need of rehospitalization 1 year after being discharged for the index event, which was lower in patients adherent to the MedDiet. The same results were found when the adjustment was repeated after the imputation of missing values (68 of 6,937 values [0.98%] were missed) (Figure 3). The trend towards statistically significant differences in the primary endpoint found in the raw analysis ($HR_{adh} = 0.86$; 95% CI: 0.73 to 1.02) tended to disappear after adjustment.

Interaction analysis showed that there was no influence depending on whether the PREDIMED questionnaire was answered by patients or relatives on long-term mortality and on 1-year ED revisit, rehospitalization, death, or combined event (p for interaction for the adjusted models of 0.99, 0.90, 0.14, 0.89, and 0.45, respectively). At the end of the study, 199 of 422 survivors (47.1%) were reinterviewed; only 30 (15.2%) had changed their diet: 17 allocated into the nonadherent group (increasing the PREDIMED score from 7.3 ± 1.1 to 8.5 ± 2.4 points; $p = 0.03$) and 13 into the adherent group (decreasing the PREDIMED score from 10.1 ± 0.8 to 8.2 ± 1.9 points; $p = 0.002$). The few patients in each group precluded any comparison with respect to primary or secondary endpoints. However, we did not find any interaction between the presence or absence of changes in dietary habits throughout the period and ED revisit, rehospitalization, and combined events, with p values of 0.46, 0.73, and 0.86, respectively (as all surveyed patients were alive, interaction for long-term and 1-year post-discharge mortality could not be assessed). Finally, adherence to 10 of 14 MedDiet items contained in the PREDIMED score had HRs below 1 with respect to nonadherent patients for the primary endpoint (with items 7 and 13 being statistically significant in unadjusted and adjusted analysis), and 4 of 14 having HRs above 1 (none of them statistically significant) (Table 2).

TABLE 2 Analysis of the Impact of Each Individual Element of the Mediterranean Diet Included in the PREDIMED Score on Survival at the End of Follow-Up (Primary Endpoint)

Dietary Element of the Mediterranean Diet Evaluated by the 14 Items of the MEDES Questionnaire	Unadjusted HR (95% CI)	p Value	Adjusted HR (95% CI)	p Value	Adjusted* HR (95% CI)	p Value
Item 7: To drink <1 sweet or carbonated beverage per day	0.53 (0.37-0.75)	<0.001	0.63 (0.44-0.90)	0.011	0.62 (0.43-0.89)	0.009
Item 5: To consume <1 serving of red meat, hamburger, or meat products (ham, sausage, etc.) per day (1 serving: 100 to 150 g)	0.56 (0.30-1.04)	0.07	0.63 (0.32-1.23)	0.17	0.59 (0.31-1.10)	0.10
Item 13: To preferentially consume chicken, turkey, or rabbit meat instead of veal, pork, hamburger, or sausage	0.70 (0.56-0.88)	0.002	0.71 (0.58-0.89)	0.003	0.71 (0.57-0.89)	0.003
Item 6: To consume <1 serving of butter, margarine, or cream per day (1 serving: 12 g)	0.78 (0.51-1.19)	0.24	–		–	
Item 4: To consume 3 or more fruit units (including natural fruit juices) per day	0.90 (0.76-1.08)	0.26	–		–	
Item 3: To consume 2 or more vegetable servings (or 1 or more portion if raw or as a salad) per day (1 serving: 200 g [consider side dishes as half a serving])	0.91 (0.77-1.09)	0.31	–		–	
Item 14: To consume 2 or more times per week vegetables, pasta, rice, or other dishes seasoned with sofrito (sauce made with tomato and onion, leek, or garlic and simmered with olive oil)	0.94 (0.78-1.14)	0.56	–		–	
Item 11: To consume <3 times per week commercial sweets or pastries (not homemade), such as cakes, cookies, biscuits, or custard	0.94 (0.76-1.17)	0.59	–		–	
Item 2: To consume 4 or more tablespoons of olive oil in a given day (including oil used for frying, salads, out-of-house meals, etc.)	0.96 (0.80-1.14)	0.61	–		–	
Item 9: To consume 3 or more servings of legumes per week (1 serving: 150 g)	0.96 (0.81-1.15)	0.70	–		–	
Item 12: To consume 3 or more servings of nuts (including peanuts) per week (1 serving: 30 g)	1.02 (0.80-1.30)	0.85	–		–	
Item 10: To consume 3 or more servings of fish or shellfish per week (1 serving: 100 to 150 g of fish or 4 to 5 U or 200 g of shellfish)	1.09 (0.89-1.33)	0.43	–		–	
Item 1: To use olive oil as main culinary fat	1.16 (0.67-2.01)	0.60	–		–	
Item 8: To drink 7 or more glasses of wine per week	1.26 (0.99-1.60)	0.06	1.25 (0.97-1.62)	0.08	1.27 (0.99-1.62)	0.06

The components are ordered according to the magnitude of unadjusted HRs for the adherent patients respect to the not adherent patients, and after adjustment for those variables with a p value < 0.10 in the crude analysis. Adjustment was performed using the 7 independent variables found to be differently distributed (with a p < 0.10) among adherent and nonadherent patients in the univariate analysis: age, arterial hypertension, peripheral artery disease, previous episodes of acute heart failure, chronic treatment with statins, air-room pulsioxymetry at emergency department arrival, and need of any ventilation support at emergency department. *Adjustment was performed using the same 7 independent variables mentioned above but with imputation of missing values (replacing missing values by mode for qualitative variables and by median by quantitative variables).

CI = confidence interval; HR = hazard ratio; MEDES = Mediterranean diet adherence screener PREDIMED = Prevención con Dieta Mediterránea.

DISCUSSION

The MEDIT-AHF study did not show any association of the MedDiet with mortality of patients who had had an episode of AHF and were followed up a median of 2.6 years. Although the follow-up time was relatively limited from the perspective of the usual length that diet intervention studies require, it does not seem that a longer follow-up time could result in any evidence of beneficial effects of the MedDiet with respect to all-cause death, especially because the unadjusted apparent benefit tended to disappear after adjustment. Similar results were obtained in the PREDIMED trial (7), despite the fact that the design of both studies is different. The current study is a prospective cohort study of patients admitted to an ED because of an episode of AHF, whereas the PREDIMED trial was a primary prevention randomized intervention trial aimed to analyze the efficacy of a MedDiet on primary prevention of CVD (7). However, both studies reached the same conclusion: the MedDiet was not useful in the primary (PREDIMED trial) (10) or secondary (MEDIT-AHF study) reduction of mortality. Perhaps reduction in intake of some key nutrients, such as salt (sodium) (18), is more important than following a healthy dietary pattern such as the MedDiet in prevention of all-cause mortality. In fact, in the PREDIMED trial, decreasing sodium intake to <2,300 mg/day was associated with a reduced risk of all-cause mortality, whereas increasing intake to >2,300 mg/day was associated with a higher risk of CVD (19). In addition, the MEDIT-AHF study included a cohort of patients with a very high number of comorbidities and, in a group with such poor health status, effects on long-term outcomes may be beyond the influence of the adherence to the MedDiet pattern. On the other hand, 2 other prospective cohort studies with up to 10 years of follow-up observed an inverse association between adherence to the MedDiet and HF incidence and mortality. In these studies, the number of events was high (1,648 in men and 1,269 in women). Perhaps low sodium

intake may enhance beneficial effects of the MedDiet on CVD and its main clinical features, such as HF. However, salt intake, as well as dietary energy intake, was not recorded in the MEDIT-AHF study; therefore, our comments in this regard are speculative. Conversely, we analyzed the effect on mortality of each individual MedDiet component investigated in the PREDIMED questionnaire and found that to drink less than 1 carbonated beverage per day (item 7) and to preferentially consume chicken, turkey, or rabbit meat instead of veal, pork, hamburger, or sausage (item 13) were the 2 components of the MedDiet that could have the greatest benefit to improving survival in our cohort. Nonetheless, this was not the primary aim of our study, and these results must be confirmed in further studies.

When analyzing the secondary endpoints, there were no significant differences in 1-year new visits to the ED, death, or combined events during the next year after being discharged from the index episode of AHF between adherent and nonadherent participants, but higher adherence to the MedDiet was significantly associated with lower hospitalizations rates ($p = 0.003$, $p = 0.008$, and $p = 0.007$ after adjustments, respectively). At this point, we should consider the mechanisms by which the MedDiet would reduce the incidence of hospitalization rate due to new episodes of AHF. In the PREDIMED study, intervention with the MedDiet reduced plasma concentrations of several HF biomarkers such as nonterminal pro-B-type natriuretic peptide, oxidized low-density lipoprotein cholesterol and lipoprotein (a) (20). The MedDiet is also a useful tool to prevent HF because of its beneficial effects on CVD (7), hypertension (21), diabetes (22), and obesity (23). These beneficial effects of the MedDiet and its main components may be explained by the increase of plasma nitric oxide concentration (24) and/or its antioxidant and anti-inflammatory actions (24,25). Previous studies have observed that consumption of some key foods such as walnuts or red wine increase plasma nitric oxide and consequently reduce blood pressure. In addition, early studies performed in the frame of the PREDIMED trial have shown that the MedDiet supplemented with extra virgin olive oil or nuts reduces plasma concentration of oxidized low-density lipoprotein cholesterol particles, a measurement of oxidative status (24), and several inflammatory biomarkers related to the onset and progression of atherosclerosis (25), suggesting that this dietary pattern has antioxidant and anti-inflammatory effects. We believe that all these protective mechanistic effects could account for the reduced incidence of episodes of AHF needing hospitalization in adherent patients observed in the present study. We speculate that the discrepancy between these results and those coming from the secondary analysis of the PREDIMED (10) (in which no reduction in incidence of HF episodes was found) could rely on salt intake because in the MEDIT-AHF population (which is 13 years older than the PREDIMED population), it was probably lower, although as already noted, we did not measure salt intake in our patients; therefore, this remains to be confirmed. Nonetheless, as salt intake emerges again as a potential key factor and one of the most prognostic factors in development of CVD (18,19), we believe that the dietary recommendations should include following the MedDiet with reduction of salt intake.

One of the strengths of the MEDIT-AHF study is that it was performed in a real-world cohort of unselected patients, as only patients or relatives unable to provide dietary habits were excluded. We believe that our cohort very closely represents the scenario of AHF because the majority of patients with AHF will go to an ED for care. Therefore, our results provide information useful for clinicians involved in HF management and health care. On the other hand, the percentage of patients with higher adherence to the MedDiet is in the range of previously reported figures for the Spanish populations within this age range, such as high cardiovascular risk subjects (7). Finally, we have ascertained that dietary habits remained unchanged for 85% of our patients for the duration of our study, which was not unexpected considering the advanced age of many of them. Unfortunately, because only a few patients changed from one group to the other, we could not explore the effects of such spontaneous changes in diet.

STUDY LIMITATIONS. First, because the MEDIT-AHF is a real-world observational study, diagnosis of patients was based on Framingham's clinical criteria; we preferred this pragmatic approach that would reproduce what happens in many EDs worldwide. This fact may imply that we have erroneously included some misdiagnosed patients. However, we tried to minimize this limitation by ascertaining the diagnosis, when possible, using echocardiographic data or plasma natriuretic peptide determinations when obtained in the ED or during hospitalization in conventional wards. Second, the sample size was calculated for the primary endpoint. For this reason, when we could commit a type-II error when evaluating secondary endpoints. Third, this is a very elderly cohort, with some patients having been diagnosed with CVD a long time ago and many who have had previous AHF episodes that required admission to an ED. In this

setting, the potential impact of dietary habits on survival tends to be minimized, and any demonstration would require a very long follow-up period. Our results may not apply to younger populations or those with a recent diagnosis of a CVD. Fourth, as this is a noninterventional study, the potential benefit of increasing adherence to the MedDiet has not been evaluated. Fifth, as sodium and energy intake were not measured, the influence of these dietary components were not evaluated in the MEDIT-AHF study.

CONCLUSIONS

The results of the MEDIT-AHF study do not show that high adherence to the MedDiet reduces mortality in patients who had already had an episode of AHF. However, the number of hospitalizations due to AHF was lower in participants with high adherence to the MedDiet, suggesting lesser severity of AHF in these participants compared with those with lower adherence to this diet. Further randomized controlled studies with HF as a primary endpoint are needed to better assess the specific effect of the traditional MedDiet on HF risk.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Changes in diet and other lifestyle factors are one of the most common nonpharmacologic interventions recommended to modify the natural course of CVD. It is unclear that changes in overall dietary patterns (using the MedDiet) decrease the risk of HF.

TRANSLATIONAL OUTLOOK: The MEDIT-AHF study did not show any effect of the MedDiet in mortality of patients who had had an episode of AHF. On the contrary, the number of hospitalizations due to AHF was significantly lower in participants with high adherence to the MedDiet, suggesting a lower severity of AHF in these participants compared to those with lower adherence.

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KEY WORDS acute heart failure, cardiovascular disease, diet, heart failure, Mediterranean diet, outcome

APPENDIX For the other investigators of the ICA-SEMES Research Group as well as a supplemental table, please see the online version of this paper.