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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SUMMARY (word count 250)

Objective: To evaluate clinical outcomes of patients after an episode of acute heart failure (AHF) according to their adherence to Mediterranean diet (MedDiet).

Methods: We designed a prospective study that included consecutive patients diagnosed with AHF in 7 Spanish Emergency Departments (EDs) during a two-month period. Patients were included if they or their relatives were able to answer a 14-points score of adherence to Mediterranean Diet (PREDIMED score), which classified patients as adherent (>8 points) or not adherent (<9 points) to MedDiet. Fifty-five variables that could potentially affect different clinical outcomes were collected. The primary endpoint was 1-year all-cause mortality, and secondary endpoints were 3-month admissions to ED without hospitalization, rehospitalisation, death, and a combined endpoint of all these variables. Unadjusted and adjusted hazard ratios (HR) were calculated using the Cox model.

Results: We included 991 patients (age 80 (10), 57.8% women); 523 (52.9%) adherent to MedDiet. The 1-year cumulative mortality for the entire cohort was 24.7%, with a HR for adherents (HR_{adh}) of 1.10 (0.86-1.42). The 90-day cumulative admissions to ED were 22.4% (HR_{adh}=1.02 (0.75-1.40)), hospitalization was 21.9% (HR_{adh}=0.73 (0.53-1.02)), death was 6.0% (HR_{adh}=1.06 (0.60-1.90)), and the combined endpoint was 40.7% (HR_{adh}=0.89 (0.72-1.11)). In addition, no differences were observed between these groups after adjustment by age, gender, previous diagnosis of hypertension or peripheral arterial disease, previous episodes of AHF, treatment with statins, and air-room pulsioxymetry, plasma troponin concentration, and need of ventilation support to ED.

Conclusion: Adherence to MedDiet did not influence 1-year mortality after an episode of AHF.

Key words: heart failure, acute heart failure, diet, cardiovascular disease, Mediterranean diet, outcome.

INTRODUCTION

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 impacts on the people survival. In fact, the prevalence of heart failure (HF) has been increasing during the last decades (2) and, currently, the recurrent episodes of acute HF (AHF) constitute the main cause of hospitalization in older adults (3-5). In Western countries, whose populations show progressive aging, this emerging epidemic is threatening the health care system sustainability and, consequently, policy-makers 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 face this challenge in long-term, secondary prevention once a CVD is already established has similar importance. In this sense, changes in diet and other lifestyle factors are one of the most common non-pharmacologic interventions recommended to modify the natural course of CVD. Thus, during the last decades, scientific evidences have 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). In respect to HF, two cohort studies concluded that lower HF risk was associated with better adherence to MedDiet (8,9) , while one protocol-specified secondary analysis of the PREDIMED randomized controlled trial, which was aimed to demonstrate the benefits of MedDiet in primary prevention of CVD in participants at high risk, failed in demonstrating a lower incidence of HF for participants who followed up a traditional MedDiet supplemented with either extra-virgin olive oil or nuts, compared to those who followed a control low-fat diet (10).

Nonetheless, in patients that have already suffered an episode of AHF, it is not known if adherence to MedDiet, considered as secondary prophylaxis, is associated with a better prognosis in terms of need of re-admission in ED, rehospitalisation or death. In this setting, we embarked in a study on the relationship between adherence to traditional MedDiet and incidence of different clinical outcomes in patients with coronary heart disease or other cardiopathies who had had an episode of AHF. Our hypothesis was that MedDiet could be a significant factor influencing in mortality.

Patients and Methods

The MEDIT-AHF (Mediterranean DieT in Acute Heart Failure) was a prospectively cohort study imbedded into the EAHFE Registry phase 4, which accounted between February 1st and 31st March 2014 (2 months). The EAHFE Registry started at 2007 and every 2-3 years it recruits during 1-2 months all consecutive patients diagnosed with AHF in the Spanish Emergency Departments (EDs) that participate in the project. To date, 5 recruitment phases (at 2007, 2009, 2011, 2014, and 2016) have been performed in 42 EDs of community and university hospitals across Spain, and 13,793 single episodes of AHF were recorded. Details of patient inclusion have been reported in previous papers (11-13). Shortly, patient identification was done by any attending emergency physician of the participating EDs, which are given specific instructions about the study protocol during a meeting held in every ED the week before starting the recruitment period. All identified cases were double-checked by the principal investigator of each centre prior to inclusion into the database in order to ascertain whether patients fulfilled the clinical diagnostic criteria of ADHF based on the Framingham clinical criteria (14). In addition, when possible, the diagnosis is confirmed by measurement of plasma natriuretic peptide and/or echocardiography findings during their ED or hospitalization stay in accordance with the European Society of Cardiology criteria in force (15,16) (performed in 92% of the cases). However, patients with clinical diagnostic criteria but without echocardiographic or natriuretic peptide were accepted in the analysis in order to obtain a cohort as close as possible to what is observed in the routine emergency medicine practice. The principal investigator of each centre was the responsible of the final diagnostic adjudication of the cases. All principal investigators were provided with a dictionary of terms in order to have common definitions at all centres (available as **Supplementary Table 1**). The only exclusion criterion to EAHFE Registry was patients having a primary diagnosis of ST-elevation myocardial infarction (STEMI) while concurrently developing AHF (which occurred in 3% of AHF cases).

For the MEDIT-AHF Study, patients were included if they or their relatives were able to answer questions on their regular diet. The adherence to the traditional MedDiet was estimated using the 14-point questionnaire of adhesion to MedDiet used and validated in the PREDIMED trial (17), which investigates 14 different items related to MedDiet: 12 questions refer to consumption frequency of key foods and 2 questions to food intake habits characteristic of the MeDiet. Each question scores 0 or 1 point, and the final score ranges between 0 and 14 indicating null (0 points) or complete (14 points) adherence to MedDiet. The PREDIMED questionnaire has proved to be very useful in a large Spanish cohort for rapid estimation of adherence to the MedDiet (17). As proposed in other studies (18,19), patients were divided into two groups depending on whether they were adherent (9 or more points) or not adherent (8 or less points) to MedDiet, and this was considered the classificatory variable. In addition, 55 independent variables that could potentially affect different clinical outcomes were recorded at ED, including demographic data (2 variables), comorbidities (13 variables), baseline status (5 variables), chronic treatments (13 variables), relevant examination measurements at ED arrival (4 variables), electrocardiogram (ECG) abnormalities (3 variables) and analytical data (7 variables); as well as, 8 variables related to management at ED during the acute episode were also recorded (**Supplemental Table 1**).

The primary endpoint was 1-year all-cause mortality, which was ascertained at least twice, after 3 and 12 months of the index episode, by means of phone call and review of primary care and hospital medical records. As secondary endpoints, we collected three different short-term outcomes during the 3 months after the index episode (and a forth one consisting in a combined endpoint if any of them was present): re-admissions to ED due to HF (without need of hospitalization), need of rehospitalisation 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 (1-year mortality) between patients adherent and not adherent to MedDiet. One-year mortality, based on our previous published data of the EAHFE Registry, was estimated in 28%; and 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, taking into account 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 in 1109 patients. According to our previous experience, a mean of 60-100 patients per month are recruited at every ED (depending on the hospital size and ED census). Accordingly, we selected 7 EDs centres to participate in the MEDIT-AHF Study during the 2-month period of the EAHFE-4 recruitment to cover the required sample size (the result of 80 patients per ED and month multiplied by 2 months and multiplied by 7 EDs, totalizing 1120 patients), and they were asked to assess adherence to MedDiet through the PREDIMED questionnaire to all the 1120 consecutive patients that we expected they would include in such EAHFE-4 phase. Participating hospitals were the following: Hospital Clínico San Carlos (Madrid), Hospital General Universitario Gregorio Marañón (Madrid), Hospital Universitario Central de Asturias (Oviedo), Hospital Universitari de Bellvitge (Barcelona), Hospital del Mar (Barcelona), Hospital de la Santa Creu i Sant Pau (Barcelona) and Hospital Clínic (Barcelona). The survey was performed by phone and was done by a single professional interviewer with skills acquired in previous studies on HF and diet assessment (19-21). The phone contact with the patient or a relative living with her/him was done within the first month of 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. It is important to remark that no diet instructions (except salt intake) were given to the patients included during the stay in the ED. The EAHFE Registry whole protocol was approved by a unique central Ethical Committee at the Hospital Universitario Central de Asturias (Oviedo, Spain), with the **reference numbers 49/2010, 69/2011, 166/13, and 160/15**. Due to the non-interventional design of the study, the Spanish legislation allows the rest of centres participating in a multicenter study to include patients with such a central Ethical Committee approval, just informing their local Ethical Committees about their participation. All patients participating in the MEDIT-AHF gave informed consent to be included in the study.

Statistical analysis

Quantitative variables are expressed as mean and standard deviation (SD) if they were normally distributed according to the Kolmogorov-Smirnov test; otherwise, they are expressed as median and percentiles 25-75

(p25-75). Qualitative variables are expressed as absolute values and percentages. Comparison between patients adherent and not adherent to MedDiet was carried out through one-way ANOVA for quantitative variables (or through the Mann-Whitney non-parametric test if not normally distributed) and through chi square test (with Yate's correction) for qualitative variables. Comparisons of primary and secondary outcomes were performed using survival curves following the Cox model. We first obtained the unadjusted curves for both groups of patients (adherents and not adherents) and crude hazard ratios (HR) with 95% confidence interval (95% CI) for adherent patients respect to not adherents were calculated. We also planned the adjustment of the survival curves by all independent variables obtaining a p value of less than 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). Statistical significance was accepted if 95% of HR excluded the value 1 or the p value was less than 0.05.

Results

The seven participating ED recruited 1148 consecutive patients diagnosed with AHF for the EAHFE-4 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 other characteristics are reported in **Table 1**. It is remarkable that patients included in the MEDIT-AHF Study had much co-morbidities, received many drugs, and most of them had some functional limitation (Barthel index was less than 100 points in 58.6% of patients). Only 5 out 55 variables had missing values for more than 10% of the patients: body mass index (BMI), Barthel index, left ventricular ejection fraction, systolic dysfunction, and troponin at ED. Based on the results of the PREDIMED questionnaire, 52.9% of patients were classified as adherent to MedDiet. These patients were significantly younger, had more frequently hypertension and peripheral arterial disease as comorbidities, and showed high pulsioxymetry values at ED arrival compared to patients with low adherence to MedDiet ($P < 0.05$; all).

A total of 238 patients died during the study follow up. The cumulative 1-year mortality, the primary endpoint of the MEDIT-AHF Study, for the entire cohort was 24.7%, and we did not find statistically significant differences between adherent and not adherent patients (p=0.45, **Figure 2**). A total of 934 patients (94.2%) were discharged alive from the hospital after the index episode. The cumulative events for the secondary endpoints at 90 days for these patients were as follow: new visits to ED not causing hospital admission 22.4%; need of hospitalization 21.9%; death 6.0%; and the combined endpoint 40.7%. There were no statistically significant differences between adherent and not adherent patients for incidence of new visits to the ED, all-cause mortality at 3 months and the combined variable (p=0.88, p=0.83, and p=0.32, respectively; **Figure 3**). However, those patients who reported a high adherence to MedDiet tended to a low hospitalization rate due to AHF than those with low adherence, although the differences did no attain statistical significance (P=0.06).

We adjusted the primary and secondary endpoints by the seven variables having a $p<0.10$ in the univariate analysis: age, hypertension, peripheral arterial disease, previous episodes of HF, chronic treatment with statins, air-room pulsioxymetry, raised troponin and use of ventilation support at ED. After such adjustments, we failed in demonstrating any difference between patients adherent and not adherent to MedDiet for any endpoint (**Figure 4**). When we repeated the adjustment after the imputation of missing values (68 out of 6937 values, 0.98%, were missed), we failed again in demonstrating any statistically significant difference in primary and secondary endpoints (**Figure 4**). Again, after both type of adjustments, patients adherent to MedDiet showed a trend to get less hospitalizations during the 3 months following patient discharge for the episode of AHF (p=0.08 and 0.09, respectively).

Discussion

The MEDIT-AHF Study failed in demonstrating any effect of the MedDiet in 1-year mortality of patients who had had an episode of AHF. Although the follow up was limited to only one year, it does not seem that a longer follow up could result in any evidence of beneficial effects of MedDiet in respect of all-cause death. In fact, the curve of events for patients with higher adherence to MedDiet is even slightly over the curve for patients with lower adherence. Similar results were obtained in the PREDIMED trial (7), despite the design of both studies is absolutely 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 analyse the efficacy of a MedDiet on primary prevention of cardiovascular disease (7). However, both studies reached the same conclusion; MedDiet was no useful in the primary (PREDIMED trial) (10) or secondary (MEDIT-AHF Study) prevention of HF. Perhaps reduction in intake of some key nutrients, like salt (sodium) (22) is more important than to follow-up a healthy dietary pattern such as the MedDiet in prevention of all-cause mortality. In fact, in the PREDIMED trial, decreasing sodium intake to <2300 mg/d was associated with a reduced risk of all-cause mortality, whereas increasing the intake to >2300 mg/d was associated with a higher risk of CVD (23). On the other hand, two other prospective cohort studies with up to 10 years of follow-up observed inverse association between adherence to MedDiet and HF incidence and mortality. In these studies the number of events was high (1648 in men and 1269 in women). Perhaps, low sodium intake may enhance beneficial effects of the MedDiet on CVD and its main clinical features, as HF.

When analysing the secondary endpoints, there were no significant differences in new visits to ED between adherent and non-adherent participants, but those with higher adherence to MedDiet tended to show lower hospitalizations rate during the next 3 months after being discharged from the index episode of AHF that allowed the entrance to the study (p=0.06; p=0.08 and 0.09 after adjustments). Again, we wonder whether a longer follow-up would allow the differences among groups to reach statistical significance.

At that point, we should consider the mechanisms by which the MedDiet would reduce the incidence of AHF and hospitalizations by this cause. In the PREDIMED, intervention with MedDiet reduced plasma concentrations of several HF biomarkers such as NT-proBNP, oxidized-LDL cholesterol and lipoprotein (a) (24). MedDiet is also a useful tool to prevent HF because of its beneficial effects on cardiovascular disease (7), hypertension (25), diabetes (26), and obesity (27). These beneficial effects of MedDiet and its main components may be explained by the reduction on plasma oxide nitrite concentration (25) and/or its anti-oxidant and anti-inflammatory actions (28,29). Early studies performed in the frame of the PREDIMED trial have demonstrated that MedDiet supplemented with extra virgin olive oil or nuts reduces plasma concentration of oxidized LDL-cholesterol particles, a measurement of oxidative status (28), and several inflammatory biomarkers related to the onset and progression of atherosclerosis (29), suggesting that this dietary pattern have anti-oxidant and anti-inflammatory effects.

One of the strengths of the MEDIT-AHF Study is that it was carried out in a real-world cohort of unselected patients, as only patients/relatives unable to provide dietetic habits were excluded. We believe that our cohort very closely represents the scenario of AHF, since the majority of patients with AHF will attend to an

ED. 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 MedDiet is into the range of previously reported figures for the Spanish populations within this age range, such as high cardiovascular risk subjects (7).

However, there are some limitations for the MEDIT-AHF Study that need to be highlighted. First, being a real-world observational study, diagnosis of patients was initially based on Framingham's criteria, but this pragmatic approach that may not reproduce what is happening in many EDs worldwide. 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 awards. Second, the sample size was pre-fixed for the primary endpoint. For this reason, when we could to commit a type-II error when evaluating secondary endpoints, and specially the need of hospitalization, for which p values were close to statistical significance. Third, this is a very elderly cohort, with some patients diagnosed with CVD long time ago and many have had previous HF that needed admission to an ED. Then, our results could not apply to younger populations or those with recent diagnosis of a CVD. Forth, as this is a non-interventional study, the potential benefit of increasing adherence to MedDiet has not been evaluated. Fifth, the time of follow-up for secondary outcomes was too short (3 months). Perhaps a longer period would allow reaching statistical significances between both groups at least in the hospitalization rate after the episode of AHF.

In conclusion, the results of the current study does not show that high adherence to MedDiet reduces the risk of new clinical cases of AHF in patients who had already had an episode of AHF. On the contrary, the number of hospitalizations due to AHF was lower in participants with high adherence to MedDiet, very close to achieve statistical significance, suggesting a lower severity of AHF in these participants compared to those with lower adherence. This pre-specified secondary analysis of the MEDIT-AHF Study may have been underpowered to provide valid conclusions. 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.

Competency in medical Knowledge

Changes in diet and other lifestyle factors are one of the most common non-pharmacologic interventions recommended to modify the natural course of CVD. It's unclear that changes in overall dietary patterns (using MedDiet) decrease the risk of HF.

Translational outlook

The MEDIT-AHF Study failed in demonstrating any effect of the MedDiet in 1-year mortality of patients who had had an episode of AHF. On the contrary, the number of hospitalizations due to AHF was lower in participants with high adherence to MedDiet, very close to achieve statistical significance, suggesting a lower severity of AHF in these participants compared to those with lower adherence.

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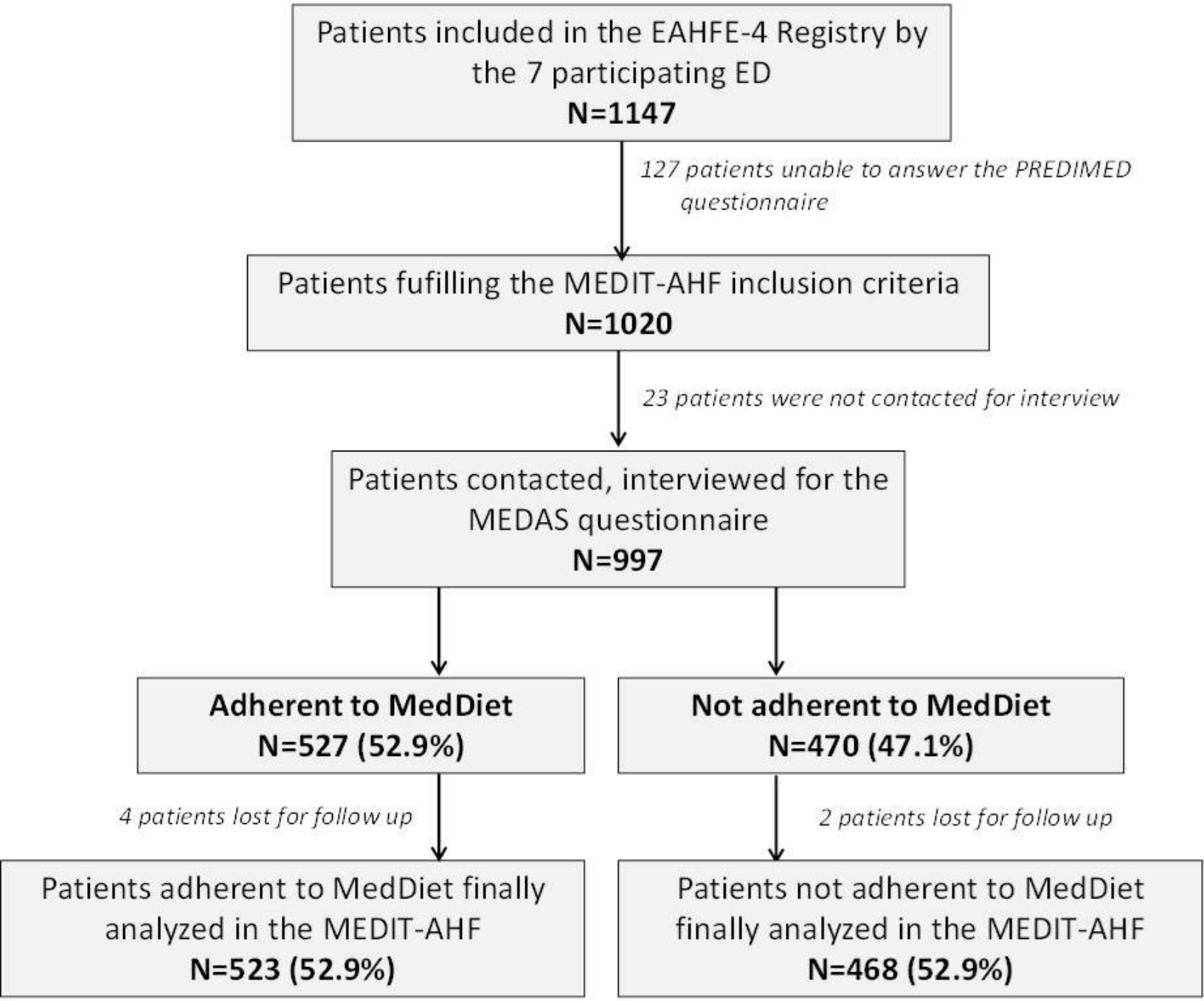
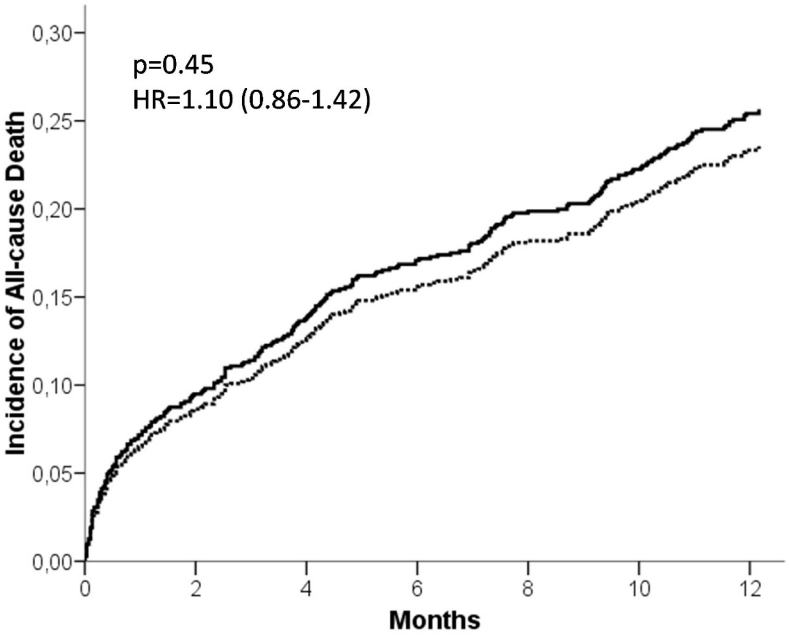
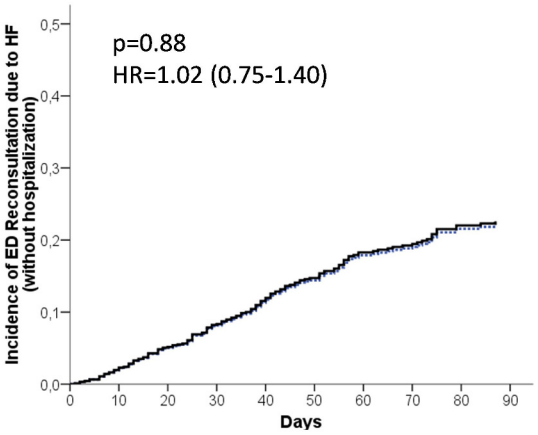

Patients included in the EAHFE-4 Registry by the 7 participating ED
N=1147
127 patients unable to answer the PREDIMED questionnaire
Patients fufilling the MEDIT-AHF inclusion criteria
N=1020
23 patients were not contacted for interview
Patients contacted, interviewed for the MEDAS questionnaire
N=997
Adherent to MedDiet
N=527 (52.9%)
Not adherent to MedDiet
N=470 (47.1%)
4 patients lost for follow up
2 patients lost for follow up
Patients adherent to MedDiet finally analyzed in the MEDIT-AHF
N=523 (52.9%)
Patients not adherent to MedDiet finally analyzed in the MEDIT-AHF
N=468 (52.9%)

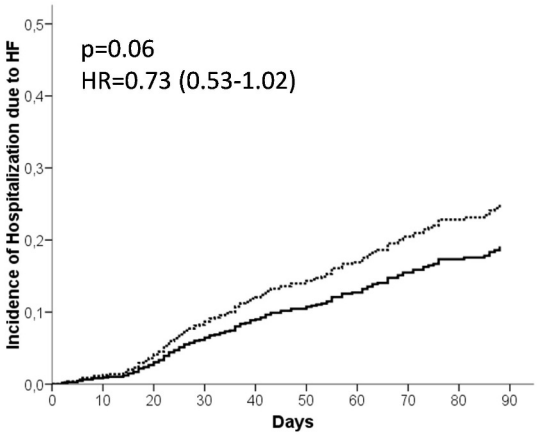
Primary endpoint (1 year)

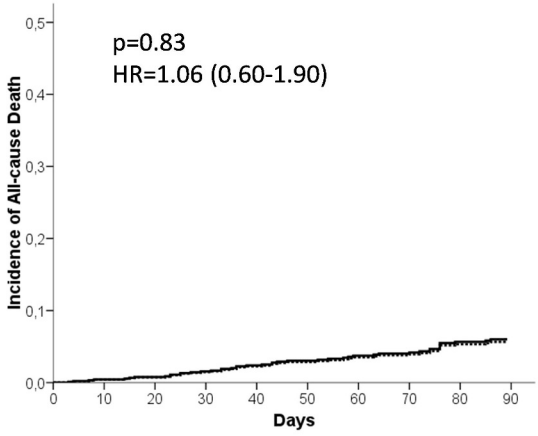


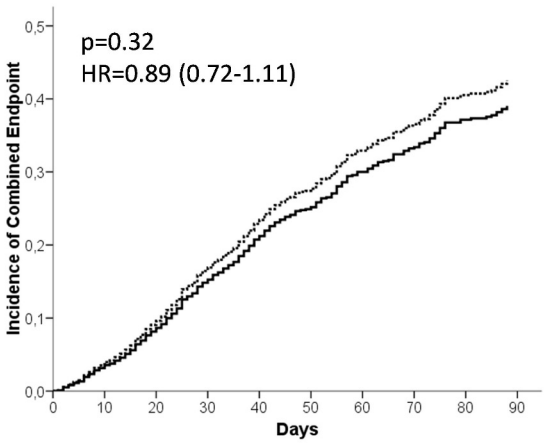
Adherents							
Patients at risk	523	469	444	422	408	397	345
Events	0	51	70	88	102	113	130
Not adherents							
Patients at risk	468	427	399	383	372	359	321
Events	0	39	60	73	84	96	108

Secondary endpoints (90 days)

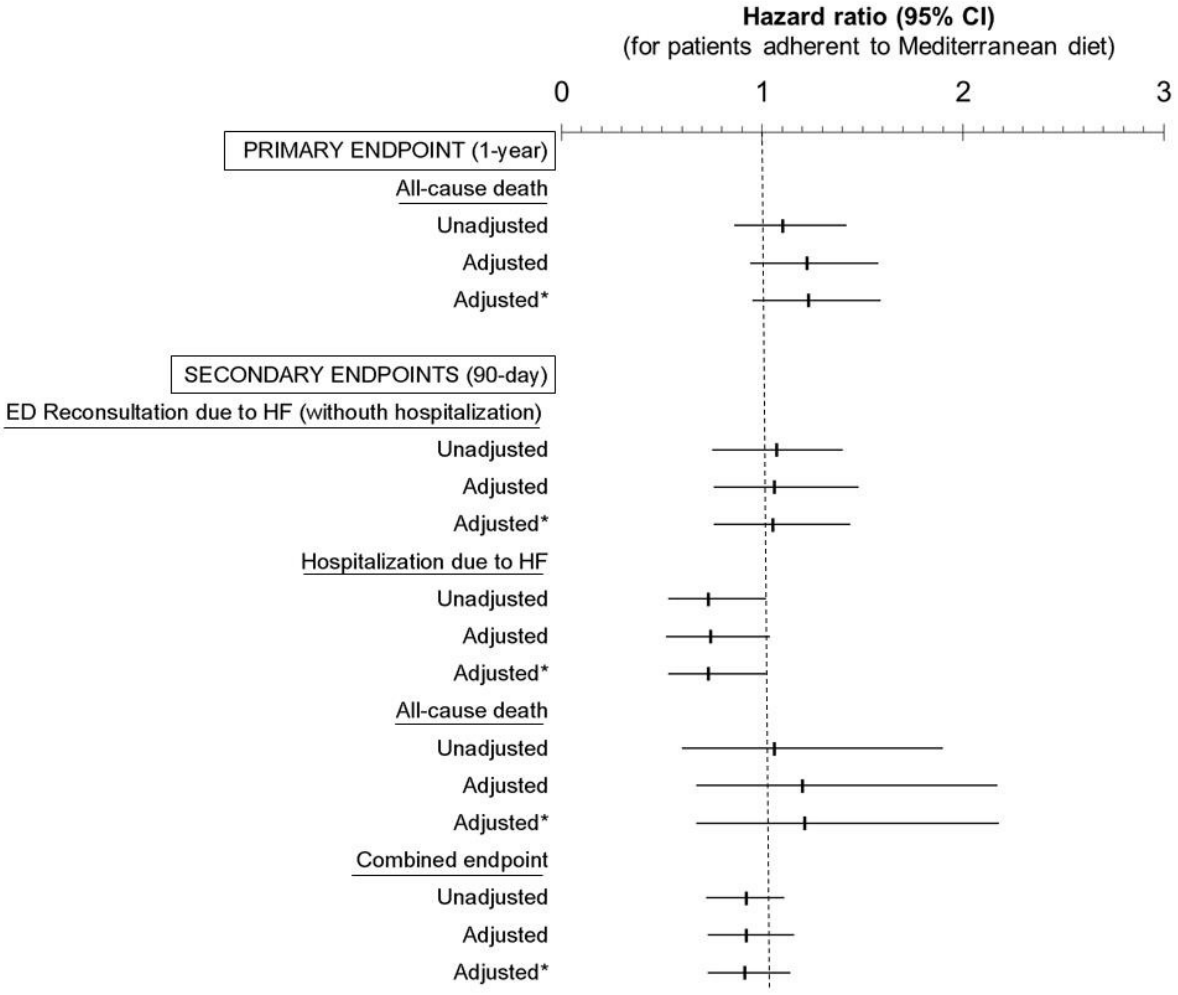








Adherents to MedDiet (MEDAS score ≥9 points)
Not adherents to MedDiet (MEDAS score <9 points)



	Hazard Ratio	95% CI lower limit	95% CI upper limit	P value
PRIMARY ENDPOINT (1-year)				
All-cause death				
Unadjusted	1.10	0.86	1.42	0.45
Adjusted	1.22	0.94	1.58	0.14
Adjusted*	1.23	0.95	1.59	0.12
SECONDARY ENDPOINTS (90-day)				
ED Reconsultation due to HF (withouth hospitalization)				
Unadjusted	1.07	0.75	1.40	0.88
Adjusted	1.06	0.76	1.48	0.72
Adjusted*	1.05	0.76	1.44	0.76
Hospitalization due to HF				
Unadjusted	0.73	0.53	1.02	0.06
Adjusted	0.74	0.52	1.04	0.08
Adjusted*	0.73	0.53	1.02	0.09
All-cause death				
Unadjusted	1.06	0.60	1.90	0.83
Adjusted	1.20	0.67	2.17	0.54
Adjusted*	1.21	0.67	2.18	0.53
Combined endpoint				
Unadjusted	0.92	0.72	1.11	0.32
Adjusted	0.92	0.73	1.16	0.47
Adjusted*	0.91	0.73	1.14	0.40

Table 1: Characteristics of patients included in the study and comparison according their adherence to Mediterranean diet (MedDiet).

	Total N=991 (n[%])	**Missing values** (n[%])	**Adherent** N=523 (n[%])	**Not adherent** N=468 (n[%])	**p value**
Demographic data					
Age (years) (mean (SD))	***80 (10)***	***0 (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) (mean (SD))	27.8 (5.0)	458 (46.2)	27.7 (4.7)	28.0 (5.4)	0.55
Barthel Index (points) (mean (SD))	83 (23)	121 (12.2)	84 (22)	82 (23)	0.15
Advanced cardiorespiratory class (NYHA III-IV)	210 (22.6)	61 (6.2)	115 (23.4)	95 (21.7)	0.59
Left ventricular ejection fraction (%) (mean (SD))	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 (mmHg) (mean (SD))	141 (26)	11 (1.1)	142 (25)	140 (26)	0.17
Heart rate (bpm) (mean (SD))	88 (24)	15 (1.5)	88 (24)	87 (24)	0.82
Temperature (ºC) (mean (SD))	36.2 (0.7)	86 (8.7)	36.2 (0.7)	36.3 (0.3)	0.65
Air-room pulsioxymetry (%)(mean (SD))	***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
Analytical data at ED during acute episode					
Glycaemia (mg/dL) (median (p25-75))	126 (103-165)	21 (2,1)	126 (102-162)	126 (104-167)	0.62
Creatinin (mg/dL) (median (p25-75))	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) (median (p25-75))	54 (39-73)	15 (1.5)	55 (40-73)	54 (38-72)	0.64
Hemoglobin (g/L) (median (p25-75))	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 (< 135mmol/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

ACE: angiotensin-converter enzyme; ARA: angiotensin-II receptor antagonist; eGFR: estimated glomerular filtration rate; ED: emergency department. Variables in bold letter denote those achieving statistical significance (p<0.05), and variables in italics denote those included in the multivariate adjustment (p<0.10)