Mediterranean diet and risk of heart failure: results from the PREDIMED randomized controlled trial

Introduction

The prevalence of heart failure (HF) is increasing during the last decades.[1] HF is also the leading cause of hospitalisation in older adults and it is associated with an enormous burden of disability and healthcare costs.[2] This emerging epidemic represents an insurmountable public health challenge that can compromise the sustainability of national health systems.[1,2]

Primary prevention of HF should be a priority.[3] Hypertension, obesity and type 2 diabetes (T2D)[4] are strong risk factors not only for HF, but also stroke, myocardial infarction (MI), atrial fibrillation (AF)[5] and peripheral arterial disease (PAD).[6] Multi-morbidity is common in HF and higher cardiovascular (CVD) mortality is observed when several of these CVD manifestations coexist.[7] Therefore, effective preventive interventions against MI or stroke seem also likely to reduce HF.

In this context, there is increasing evidence that changes in overall dietary patterns, and, specifically, interventions using the traditional Mediterranean diet (MedDiet) are a useful tool in CVD prevention.[8,9] Two cohort studies reported a lower HF risk associated with better adherence to MedDiet.[10,11] However, no randomised controlled trial to date has examined the effect of the MedDiet on the primary prevention of HF. One-year results from the PREvención con DIeta MEDiterránea (PREDIMED) randomised controlled trial showed that the MedDiet favourably affected HF biomarkers compared to a low-fat diet.[12] In PREDIMED, the MedDiet also favourably influenced major HF risk factors, such as T2D,[13] obesity[14] and hypertension.[15] The aim of this study was to investigate with a randomised design the

effect of the MedDiet on HF incidence, a protocol-specified secondary outcome of the PREDIMED trial.[16] We hypothesised that the MedDiet would result in lower HF incidence, compared to a control, low-fat, diet.

Methods

Study design

The detailed methods of this trial (www.predimed.es) have been described.[9,16] In brief, PREDIMED was a large, parallel-group, randomised controlled trial conducted in 11 centres in Spain, designed to examine the effect of the MedDiet on primary CVD prevention. The trial was registered (ISRCTN35739639) and conformed with the principles outlined in the Declaration of Helsinki. The protocol was approved by the Institutional Review Boards of participating centres and all participants provided written informed consent to take part in the study. Participants were recruited between 10/2003 and 03/2009 from Spanish primary care centres. The study was planned for 6 years, but was stopped at 4.8 years of median follow-up (12/2010), because of evidence of early benefit.[9] Yearly follow-up measurements continued until 10/2012.

Participants and randomisation

Participants were men (55-80 years) and women (60-80 years) who were free of CVD at enrollment but who were at high-CVD-risk, as defined by the presence of T2D and/or ≥3 CVD risk factors, namely smoking, hypertension, elevated low-density lipoprotein (LDL) cholesterol, low high-density lipoprotein (HDL) cholesterol, overweight/obesity (body mass index, BMI≥25kg/m^2), or family history of premature coronary heart disease (CHD). Detailed inclusion and exclusion criteria are provided elsewhere.[9,16]

Participants were randomly assigned to one of three dietary intervention groups (1:1:1 ratio): (i) MedDiet supplemented with extra-virgin olive oil (EVOO), (ii) MedDiet supplemented with mixed nuts or (iii) low-fat control diet. Randomisation was conducted centrally using a computer-generated random-number sequence. All clinical investigators, laboratory technicians and members of Committees assessing clinical events were blinded to intervention allocation.

Intervention description

The PREDIMED dietary intervention has been detailed elsewhere.[9,16] Briefly, all participants received repeated and continuous advice from trained dietitians to follow their allocated diets (during both individual and group sessions, separately for each group) on a quarterly basis.[9,16] The diets were *ad libitum* regarding total energy intake. Physical activity was assessed but not promoted.

Participants assigned to the MedDiet+EVOO group were provided with 1 litre of EVOO/week (including family needs), whereas those in the MedDiet+nuts group received 30 grams/day of mixed nuts. These supplementary foods were given for free in order to facilitate adherence. Participants in the control group received small non-food gifts.

Measurements

All measurements were carried out at baseline and yearly and comprised a 47-item questionnaire assessing sociodemographic characteristics, medical conditions, medication use and lifestyle habits, a 14-item questionnaire assessing MedDiet adherence,[17] an 137-item FFQ, used to assess nutrient and energy intake,[18] and the Spanish version of the Minnesota Leisure-Time Physical Activity questionnaire.[9,16]

Trained nurses collected fasting blood samples and measured blood pressure, body weight, height and waist circumference to calculate waist-to-height ratio (WtHR).

Clinical endpoints

The primary outcome for the present study was HF incidence, a protocol-specified secondary outcome of the PREDIMED trial.[16] All HF events were evaluated according to the 2005 (time of study design) guidelines on the diagnosis and treatment of acute and chronic HF of the European Society of Cardiology.[19,20] The diagnostic criteria for ascertaining HF events are presented in Supplementary Appendix 1.

All endpoints of the PREDIMED trial, including HF, were identified prospectively through contacts with participants and family physicians, annual reviews of all participants' outpatient and inpatient medical records and linkage to the National Death Index and were analysed by events. If an HF diagnosis was an explicit medical diagnosis, all relevant documentation, including clinical records of hospital discharge, outpatient clinics and family physicians' records, was sent to the Clinical Adjudication Committee. This documentation was independently reviewed and blindly evaluated by two cardiologists. If there was disagreement regarding the acceptance or rejection of an event, a third cardiologist (the Committee's Chair) intervened until agreement was reached (in some cases, more information was requested to complete the ascertainment). All members of the Clinical Adjudication Committee and the adjudication process were blinded to group allocation. This paper reports on HF events that occurred during the trial's active intervention (10/2003-07/2010).

Statistical analyses

Cox regression models with robust variance estimators were fitted to estimate Hazard Ratios (HR) and 95% confidence intervals (CIs) for the incidence of HF by group assignment (using the control group as reference).

The assumption of proportional hazards was tested using time-dependent covariates. We stratified all models by centre and baseline T2D. A crude model was followed by an age- and sex-adjusted model. We further adjusted for pre-randomisation values of education, smoking, WtHR, physical activity, dyspnea and non-AF arrhythmias (model 1), and, additionally for history of hypertension, history of dyslipidaemia, family history of premature CHD and baseline prevalence of AF (model 2), and additionally for total energy intake (model 3). We evaluated potential effect modification by sex, age, CVD risk factors, WtHR, and baseline MedDiet adherence.

Follow-up time was the interval between randomisation and diagnosis, death or the last visit, whichever occurred first. We defined event rates as the number of participants diagnosed with an event over the follow-up time in each group. All analyses were performed on an intention-to-treat basis.

Results

After excluding 44 participants with prevalent HF at baseline, 7403 were included in the present analyses (Supplementary Appendix 2). The three groups were well balanced regarding baseline characteristics (Table 1).

Ninety-four participants developed HF during the trial period with active intervention (Table 2). Of these, 19 (20.2%) had preceding ischemic heart disease and 58 (61.7%) were hospitalised. Data on receipt of treatment following HF diagnosis were available for 79 participants, who received ACE inhibitors/ARA II (74.7%),

diuretics (65.8%), beta-blockers (26.6%), calcium channel blockers (20%), antiplatelet therapy (29.1%) and oral anticoagulants (25%). Ventricular function information after HF diagnosis (assessed via echocardiography) was available for 80 participants, who presented with preserved ejection fraction (>45-50%) (60%) and reduced ejection fraction (40%). Twenty-one (out of 94) participants (22.3%) died by 2012 (end of extended follow-up).

The baseline characteristics of participants who developed HF during the active intervention period and those who did not are shown in Supplementary Appendix 3. Those who developed HF were generally older and had higher WtHR and B-type natriuretic peptide levels. The unadjusted HR indicated non-significant associations for the MedDiet+EVOO (HR=0.68; 95% CI, 0.41-1.13) and MedDiet+nuts (HR=0.92; 95% CI, 0.56-1.49), compared with the control group. Multivariate analyses did not alter these results (Table 2, Figure 1). There was no evidence of a significant association for the two MedDiets combined, compared with the control group, in the unadjusted (HR=0.79; 95% CI, 0.51-1.22) and multivariable-adjusted models (Supplementary Appendix 4).

In subgroup analyses (Supplementary Appendix 5), the effect of the MedDiet on reducing HF, though statistically non-significant, was stronger among participants without T2D (P for interaction=0.010). A higher baseline WtHR was associated with a risk reduction related to the MedDiet+nuts and higher baseline MedDiet adherence was associated with an inverse association of MedDiet+EVOO with HF. In both cases the P for interaction was significant, but the effect within subgroups was not.

Overall, 141 HF events occurred during the trial period with active intervention and extended follow-up (Supplementary Appendix 6). The unadjusted HRs were 0.71 (95% CI, 0.47-1.07) for the MedDiet+EVOO and 0.99 (95% CI, 0.67-

1.48) for the MedDiet+nuts, compared with the control diet. Adjusting for different covariates (Supplementary Appendix 6) and examining the combined effect of the two MedDiet groups, compared with the control group (Supplementary Appendix 4), did not alter these findings.

Discussion

This secondary analysis of a pre-specified outcome of the PREDIMED trial showed no evidence of a significant effect on HF incidence for the intervention using a MedDiet+EVOO or a MedDiet with nuts, compared to the control diet. Our hypothesis of a beneficial effect of the MedDiet on HF incidence in this sample of high-CVD-risk individuals was therefore not confirmed for this secondary endpoint of the trial. However, the explanation for the non-significant results for HF might stem from the relatively small number of observed HF events (n=94) and it should be given the interpretation that our findings are inconclusive.

To our knowledge, PREDIMED is the first randomised controlled trial in which the potential effect of an intervention with the traditional MedDiet on primary HF prevention could be explored (as HF was a secondary, and not a primary outcome of PREDIMED). An earlier report of the PREDIMED trial showed that the intervention with the MedDiet reduced the levels of HF biomarkers, including N-terminal pro-brain natriuretic peptide, oxidised LDL-cholesterol and lipoprotein(a).[12] Despite this beneficial effect on HF biomarkers,[12] as well as on HF risk factors such as hypertension,[15] T2D[13] and obesity,[14] we may have had here limited statistical power to demonstrate an effect on the incidence of newly-onset clinical cases of HF considered alone. Nevertheless, the finding that HF incidence was consistently lower in the point estimates during the trial for the MedDiet+EVOO, regardless of the

176 factors we adjusted for (risk reduction range, 22-32%), generates a hypothesis for
177 future randomised controlled trials to examine the potential effect of the traditional
178 MedDiet on HF as a primary outcome, in a sufficiently powered study.

179 Two recent prospective cohorts with up to 10 years of follow-up reported
180 inverse associations of the MedDiet with HF incidence and mortality (1648 events) in
181 men[11] and HF incidence (1269 events) in women.[10] An exploratory meta-analysis of
182 prospective cohort studies[21,22] conducted for the purposes of the current paper
183 suggested that, according to previous evidence, for each 2 additional points of
184 MedDiet adherence (0 to 9 score), the relative risk of HF decreased by 8% (95% CI,
185 0.90-0.95, without evidence of heterogeneity, I^2=0%) (Supplementary Appendix 7).
186 The difference in the number of observed events and the length of follow-up between
187 these studies and the PREDIMED randomised trial might explain why our study was
188 probably not sufficiently powered as to confirm these previous observational findings.
189 Although the findings of the current study are inconclusive, when they are considered
190 together with the results from other prospective studies, they may suggest a potential
191 beneficial role of the MedDiet in HF prevention. The advantage and novelty of
192 PREDIMED is that our results come from a randomised intervention. Additionally,
193 the PREDIMED trial started on the basis of a relatively high baseline adherence to the
194 MedDiet in the three arms of the trial, which might have attenuated the findings. In an
195 exploratory secondary analysis of the association between participant baseline
196 characteristics and HF, we found that older age at baseline and T2D history were
197 significantly associated with higher HF rates, whereas higher baseline MedDiet
198 adherence (assessed in an observational approach) might have been associated with a
199 37% (HR=0.63; 95% CI, 0.40-0.98) lower HF rate (Supplementary Appendix 8). It
200 might be, however, that this high baseline adherence reflected better compliance with

other lifestyle factors that may have an influence on HF, and residual confounding cannot be excluded in this observational approach.

Several mechanisms might explain a potential beneficial role of the MedDiet for HF prevention, as suggested by our exploratory meta-analysis, including the MedDiet's anti-inflammatory[23] and antioxidant[24] properties. Oxidative stress[25] and inflammation[26] accompany HF and olive oil, in particular, has been associated with reduced HF risk.[27] Earlier PREDIMED reports showed that biomarkers of inflammation[28] and oxidation[12] were reduced with the MedDiet+EVOO compared to the other two groups. In the current analyses, the difference in the size of the association with HF incidence between the MedDiet+EVOO and MedDiet+nuts groups (although both non-significant) might have resulted from the fact that participants in the MedDiet+EVOO group were provided (at no cost) with EVOO with highly constant content of polyphenols. In contrast, that was not the case for participants in the MedDiet+nuts group who bought their own oils, with potentially varied polyphenol content. The anti-inflammatory and antioxidant properties of EVOO, attributed to its polyphenol content, have been well documented[29] and add biological plausibility to the hypothesis of a protection against HF by a MedDiet high in EVOO. As results from the current study were inconclusive, this hypothesis should be studied further by future randomised controlled trials with longer follow-up periods and sufficient statistical power to examine whether this protective effect exists.

HF shares common risk factors with other cardiovascular conditions and earlier studies have included HF as part of a composite CVD endpoint. For example, the Lyon Heart Study showed that a MedDiet reduced the risk of a composite endpoint that included HF by 67% (RR 0.33; 95% CI, 0.21-0.52).[8] A recent

226 randomised controlled trial, Look AHEAD,[30] also included HF in its composite CVD
227 endpoint. An exploratory secondary analysis of our data that examined the effect of
228 the MedDiet on a composite outcome of 634 observed total CVD events (i.e. MI,
229 stroke, CVD death, HF, AF or PAD) showed that the unadjusted HRs were 0.62 (95%
230 CI, 0.51-0.75) for the MedDiet+EVOO and 0.77 (95% CI, 0.63-0.93) for the
231 MedDiet+nuts, compared to the control diet (Supplementary Appendix 9;
232 Supplementary Appendix 10). Although this specific exploratory analysis might be
233 prone to bias, as it was not a pre-specified outcome of the PREDIMED trial, it might
234 allow useful comparisons with existing or future studies examining the effect of the
235 MedDiet on composite CVD outcomes that include HF.
236 Our study also has limitations. HF was a pre-specified secondary endpoint of
237 the PREDIMED trial, and the trial was probably underpowered, taking into account
238 the small number of observed HF events. Further, HF is a syndrome with various
239 clinical etiologies and symptoms, as well as definitions,[19,20,31] and the effect of dietary
240 patterns might differ according to the type, severity and pathogenesis of the
241 condition.[1,2] We could not determine HF etiology or severity in PREDIMED and the
242 possibility of some degree of HF misclassification may exist. In addition, we used the
243 2005 HF guidelines to adjudicate HF events, concomitant with the time of the
244 PREDIMED trial's design.[16] Nevertheless, our HF diagnostic criteria are in agreement
245 with the recently published American College of Cardiology/American Heart
246 Association clinical data standards, where 'HF can be diagnosed when a patient
247 demonstrates or there is objective evidence of new or worsening HF symptoms and
248 receives HF-specific treatment, with objective evidence results from at least two
249 physical examination findings'.[31] In any case, the use of specific criteria to adjudicate
250 events and the adjudication by an independent Committee in the context of a large and

well-known randomised trial reduce the potential for misclassification. Finally, our results are not generalisable to other populations (e.g. non-Mediterranean countries, younger adults or adults without CVD risk).

In conclusion, we were not able to show that an intervention with MedDiet reduced the risk of clinical cases of HF. However, this pre-specified secondary analysis of the PREDIMED trial may have been underpowered to provide valid conclusions. Further randomised 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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Supplementary Information

Additional Supporting Information may be found in the online version of this article:

Supplementary Appendix S1: Diagnostic criteria for trial endpoint.

Supplementary Appendix S2: Flow chart of participants.

Supplementary Appendix S3: Baseline characteristics of participants who developed heart failure during the trial period with active intervention (2003-2010) and those who did not.

Supplementary Appendix S4: Incidence of heart failure during the trial period with active intervention (2003-2010) and trial period with active intervention and extended follow-up (2003-2012): combined Mediterranean diets compared with control diet

Supplementary Appendix S5: Subgroup analyses of the incidence of heart failure during the trial period with active intervention (2003-2010) by intervention group

Supplementary Appendix S6: Incidence of heart failure during the trial period including both the active intervention period and the extended follow-up (2003-2012) by intervention group

Supplementary Appendix S7: Exploratory meta-analysis of observational cohort studies examining the association between Mediterranean diet adherence and heart failure incidence

Supplementary Appendix S8: Factors independently associated with heart failure

Supplementary Appendix S9: Incidence of total cardiovascular events (stroke, myocardial infarction, cardiovascular death, heart failure, atrial fibrillation or peripheral arterial disease) during the trial period with active intervention (2003-2010) by intervention group

Supplementary Appendix S10: Kaplan–Meier estimates of total cardiovascular events (stroke, myocardial infarction, cardiovascular death, heart failure, atrial fibrillation or peripheral arterial disease) in the total study population (trial intervention period, 2003-2010)

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Conflict of interest

Dr Ros is a consultant for the California Walnut Commission and Dr Salas-Salvadó is a consultant for the International Nut Council. Dr Papadaki reports travel reimbursement from the California Walnut Commission. Dr Ros reports grants from the California Walnut Commission and Dr Salas-Salvadó reports grants from the International Nut Council. The other authors report no conflicts of interest.

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Legends

Figure 1 Kaplan–Meier estimates of the incidence of heart failure in the total study population (trial intervention period, 2003-2010)

Footnote to Figure 1:

Hazard ratios were stratified by centre and history of diabetes (Cox model with robust variance estimators).