Evidence-Based Medicine: Mediterranean Diet vs Low-Fat Diet in Secondary Prevention of Cardiovascular Disease

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Feb 6, 2025



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Our patient . . .



Jerry M. Wallace School of Osteopathic Medicine You are seeing a 58-year-old man who was hospitalized about six months ago for an MI. He underwent PCI and is doing well. He asks you about the diet you would recommend in the long term to decrease his risk of worsening CAD.



Clinical Question:

Among patients with established CAD, what is the impact of a Mediterranean diet compared to a low-fat diet on cardiovascular morbidity and mortality?



Source:

Delgado-Lista J, et al. Long-term secondary prevention of cardiovascular disease with a Mediterranean diet and low-fat diet (CORDIOPREV): a randomized trial. Lancet 2022; vol 399, May 14th, 1876-1885.



Critical Appraisal of a Single Therapeutic Trial: Is the Trial Valid?

Sackett, Richardson, Rosenberg and Haynes: Evidence-Based Medicine; How to Practice and Teach EBM, London: Churchill Livingstone, 1997

1. Was the assignment of patients to treatment randomized? And was the randomization list concealed?

2. Were all patients who entered the trial accounted for at its conclusion? And were they analyzed in the groups to which they were randomized?



Critical Appraisal of a Single Therapeutic Trial: Is the Trial Valid?

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- 1. Were the patients and clinicians kept "blind" to which treatment was being received?
- 2. Aside from the experimental treatment, were the groups treated equally?
- 3. Were the groups similar at the start of the trial?

If the study satisfies these criteria, then it has *internal validity*.



Critical Appraisal of a Single Therapeutic Trial: Can you apply the evidence in this trial to your patient?

Sackett, Richardson, Rosenberg and Haynes: Evidence-Based Medicine; How to Practice and Teach EBM, London: Churchill Livingstone, 1997

Do these results apply to your patient?

(ie. Do the results have *external validity*?)

- Is the patient so different from those in the trial that its results cannot help you?
- How great would the potential benefit of therapy actually be for your individual patient?



Critical Appraisal of a Single Therapeutic Trial: Can you apply the evidence in this trial to your patient?

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- Are your patient's values and preferences satisfied by the regimen and its consequences?
 - Do your patient and you have a clear assessment of their values and preferences?
 - Are they met by this regimen and its consequences?



Mediterranean vs Low-Fat Diet in Secondary Prevention of Cardiovascular Events

Design: Single center, randomized, dietary intervention trial. Patients and dieticians were not blinded to patient diet assignment . All other study team members were blinded to patient assignment.

Setting: Reina Sofia University Hospital, Cordoba, Spain

Was the assignment of patients treatment randomized? And was the randomization list concealed?

Were the patients and clinicians kept "blind" to which treatment was being received?

Jerry M. Wallace School of Osteopathic Medicine You can't blind patients to what they are eating for seven years!







Jerry M. Wallace School of Osteopathic Medicine Mediterranean vs Low-Fat Diet in Secondary Prevention of Cardiovascular Events : Patients included



Mediterranean vs Low-Fat Diet in Secondary Prevention of Cardiovascular Events : Patients included

- Men and women ages 20 to 75 years
- Free of clinical events related to CAD for previous six months

- Established CAD
 - Acute MI
 - Hospitalization for unstable angina
 - Chronic high-risk ischemic heart disease

• Able to follow long-term dietary intervention



Mediterranean vs Low-Fat Diet in Secondary Prevention of Cardiovascular Events : Patients included

• No severe illnesses

• Written informed consent

• No life expectancy shorter than length of study



Mediterranean vs Low-Fat Diet in Secondary Prevention of Cardiovascular Events: Interventions



Mediterranean vs Low-Fat Diet in Secondary Prevention of Cardiovascular Events: Interventions

- Patients were randomized in 1:1 fashion to a Mediterranean diet or a Low-fat diet. Randomization stratified by
 - Age
 - Sex
 - Previous MI
- Patients were followed a median of seven years.



Mediterranean vs Low-Fat Diet in Secondary Prevention of Cardiovascular Events: Interventions

Mediterranean diet:

- At least 35% of calories as fat
 22% monounsaturated
 6% poly unsaturated
 < 10% saturated
- 15% protein
- Maximum 50% carbohydrates

Low-fat Diet:

- Less than 30% of total fat

 < 10% saturated
 12-14% monounsaturated
 < 6-8% polyunsaturated
- 15% protein
- Minimum of 55% carbohydrates

In both diets, total cholesterol < 300 mg per day



Component	Mediterranean Diet	Low fat Diet
Oil for cooking, dressings	Extra virgin olive oil	Vegetable oil
and meals outside the	Four or more	Less than two
home	tablespoons per day	tablespoons per day
Fruit	Three or more servings	Three or more servings
Vogotabloc	Two or more cervings (at	Two or more cervings
vegelanies	least one raw) per day	per day



Component	Mediterranean Diet	Low fat Diet
Grains and potatoes	Six servings, preferably whole grains per day	Six to 11 servings of grains (preferably whole) per day
Legumes (Lentils, peas,broad beans, chickpeas, soybeans, beans, lima,peanuts)	Three or more servings per week	Six to 11 servings of grains (preferably whole) or legumes per day
Dairy	Two servings per day	Two to three servings per day, low-fat

Component	Mediterranean Diet	Low fat Diet
Tree nuts (almonds, Brazil nuts, cashew nuts, hazelnuts, walnuts, pecans, pistachios and macadamia nuts)	Three or more servings raw, non-roasted or fried per week	One serving or less, raw, non-roasted or fried per week
Fish and seafood	Three or more servings per week, fatty fish (salmon, lake trout, sardines, and albacore tuna)	One or fewer serving per week of lean fish (flounder, sole, cod, red snapper, bass, perch, halibut and pike)



Component	Mediterranean Diet	Low fat Diet
White meat	Chicken, turkey, rabbit; remove skin and visible fat	Poultry and lean cuts of beef
Red or processed meats	Less than one serving per week	One or fewer servings per week
Eggs	Two to four per week	Two or fewer egg <i>yolks</i> per week



Component	Mediterranean Diet	Low fat Diet
Commercial bakery products, sweets and pastries	One serving or fewer per week	One serving or fewer per week
Butter and margarine	Not allowed	One serving or fewer per week



Component	Mediterranean Diet	Low fat Diet
Wine	Optional. One glass per day for women and two glasses per day for men	Not allowed
Sweet or carbonated beverages	Less than one drink per day	Less than one drink per day



Component	Mediterranean Diet	Low fat Diet
Culinary techniques	Slow cooked in olive oil	Use low-fat cooking methods (broiling, grilling, roasting, baking, microwaving, and poaching)



Mediterranean vs Low-Fat Diet in Secondary Prevention of Cardiovascular Events: Interventions

Contact between patients and dieticians:

- Telephone calls every two months
- Group sessions every three months
- Face-to-face visits every six months



Mediterranean vs Low-Fat Diet in Secondary Prevention of Cardiovascular Events: Interventions

• Intention-to-treat analysis: every subject included in data analysis once randomization has occurred.

Were all patients who entered the trial accounted for at its conclusion? And were they analyzed in the groups to which they were randomized?



Mediterranean vs Low-Fat Diet in Secondary Prevention of Cardiovascular Events: Outcomes



Mediterranean vs Low-Fat Diet in Secondary Prevention of Cardiovascular Events: Primary Outcome

- Composite of major cardiovascular events:
 - MI
 - Revascularization
 - Ischemic stroke
 - Documented peripheral arterial disease
 - Cardiovascular death



Mediterranean vs Low-Fat Diet in Secondary Prevention of Cardiovascular Events: Study Power



Mediterranean vs Low-Fat Diet in Secondary Prevention of Cardiovascular Events: Study Power

- Assuming 24.9% incidence of composite endpoint at seven years among patients on low-fat diet
- A 30% difference in composite endpoint between Mediterranean Diet and Low Fat Diet
- AND if study has 80% power to detect these differences between groups

- With a 5% risk of concluding a true difference exists between groups when the difference is really due to chance alone (Risk of *type 1 error* of 5% or p< 0.05)
- THEN the study would need:
 - At least 491 patients on Mediterranean diet
 - At least 491 patients on low fat diet



Mediterranean vs Low-Fat Diet in Secondary Prevention of Cardiovascular Events: Main Results



Mediterranean vs Low-Fat Diet in Secondary Prevention of Cardiovascular Events: Study Design

At least 491 patients needed in each group

Study was adequately powered





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Characteristic	Mediterranean diet (N= 502)	Low fat diet (N=500)
Age (years)	59.7	59.5
Male (%)	82.5	82.6
Female (%)	17.5	17.4



Characteristic	Mediterranean diet (N= 502)	Low fat diet (N=500)
BMI (kg/m2)	31.0	31.2
LDL (mg/dl)	88.9	88.2



Characteristic (%)	Mediterranean diet (N= 502)	Low fat diet (N=500)
Family hx of premature CAD	14.9	14.8
Diabetes	51.0	56.8
HTN	68.9	67.4



Characteristic (%)	Mediterranean diet (N= 502)	Low fat diet (N=500)
Hx CABG	3.8	2.6
Hx PCI	90.8	91.6
Current smoker	8.7	10.7
Former smoker	63.8	65.4



- NO significant difference between groups regarding medical therapy:
 - Antiplatelets or anticoagulants
 - Statins
 - Other lipid-lowering drugs
 - ACE-I or ARB
 - Beta blockers
 - Calcium channel blockers
 - Diuretics
 - Insulin
 - Oral diabetes medications



Characteristic (%)	Mediterranean diet (N= 502)	Low fat diet (N=500)
LVEF > 50%	94.3	95.6
Hx MI	62.2	61.6
Hx TIA or ischemic stroke	5.2	5.0

Aside from the experimental treatment, were the groups treated equally?

Were the groups similar at the start of the trial?



Mediterranean vs Low-Fat Diet in Secondary Prevention of Cardiovascular Events: Primary Outcome



Mediterranean vs Low-Fat Diet in Secondary Prevention of Cardiovascular Events: Primary Outcome

Primary composite end point:

- MI
- Revascularization
- Ischemic stroke
- Peripheral arterial disease
- Cardiovascular death





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Mediterranean vs Low-Fat Diet in Secondary Prevention of Cardiovascular Events: Primary Outcome

Primary composite end point:

- MI
- Revascularization
- Ischemic stroke
- Peripheral arterial disease
- Cardiovascular death





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Mediterranean diet (N-502)	Low fat diet (N=500)	ARR (absolute risk reduction)	
(14-302)		(CER-EER)	
(EER)	(CER)		
17.3%	22.2%	4.9%	
EER= experiment	al event rate	CER= control event rate	

Mediterranean diet (N=502)	Low fat diet (N=500)	HR (95%CI)
(EER)	(CER)	(EER/CER)
17.3%	22.2%	0.779 Unadjusted 0.745 (0.563 to 0.986)

EER= experimental event rate

CER= control event rate



HR (95%CI)

(EER/CER)

0.779

Unadjusted HR 0.745 (0.563 to 0.986) Adjusted HR 0.719 (0.541 to 0.957) Adjusted for:

- Age
- Sex
- Family hx early CAD
- Smoking
- BMI
- LDL
- DM
- HTN
- Statin use
- Changes in weight and physical activity on follow up
- Randomization order



Mediterranean diet (N=502)	Low fat diet (N=500)	ARR (absolute risk reduction) (CER-EER)	Number needed to treat (NNT)
(EER)	(CER)		(,
17.3%	22.2%	4.9%	1/ARR = 21



Mediterranean vs Low-Fat diet and secondary prevention of cardiovascular events : Main Conclusions



Mediterranean vs Low-Fat diet and secondary prevention of cardiovascular events: Main conclusions

- Among patients with established CAD, a Mediterranean diet was superior to a low-fat diet in the prevention of major cardiovascular events over a follow up of seven years.
- The magnitude of the decrease in major cardiovascular events expressed as a Hazard Ratio is about 0.75 or about a 25% reduction.
- The number needed to treat is 21



Mediterranean vs Low-Fat diet and secondary prevention of cardiovascular events: Study strengths

- Clearly defined dietary interventions
- Close follow up of patients by expert dieticians
- Clinically important outcomes



Mediterranean vs Low-Fat diet and secondary prevention of cardiovascular events: Study limitations

- Single-center study in a single geographic region
- Sample was over 80% men, so conclusions about women are not clear
- Follow up was intense and long-term



Back to our patient. . .

Is the patient similar enough tothose in the trial that its results can help you?

YES



Jerry M. Wallace School of Osteopathic Medicine You are seeing a 58-year-old man who was hospitalized about six months ago for an MI. He underwent PCI and is doing well. He asks you about the diet you would recommend in the long term to decrease his risk of worsening CAD.



You recommend a Mediterranean diet to your patient and refer him to a dietician to discuss the details of a plan.



Questions?



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Thank you!



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