CRNH
CENTRE DE RECHERCHE EN NUTRITION HUMAINE OUEST

La médecine basée sur les preuves : quelle place dans la Nutrition ?

M.Krempf

Nantes

Liens d'intérêt: Danone, Nestlé, Unilever, Sanofi, Triballat, Pierre Fabre

Bases du raisonnement médicale

- L'expérience …
- La physiopathologie
- L'épidémiologie
- Les preuves scientifiques (EBM)
- …

Les grades de recommandations

Niveau de preuve scientifique	Grade
Niveau 1: Essai(s) comparatif(s) randomisé(s); Méta-analyse(s)	A
Niveau 2 : Essai(s) randomisé(s) faible(s); Essai(s) non randomisé(s), études de cohorte	B
Niveau 3 : Etudes cas-témoins	C
Niveau 4 : Séries de cas, études rétrospectives, essais avec biais importants	

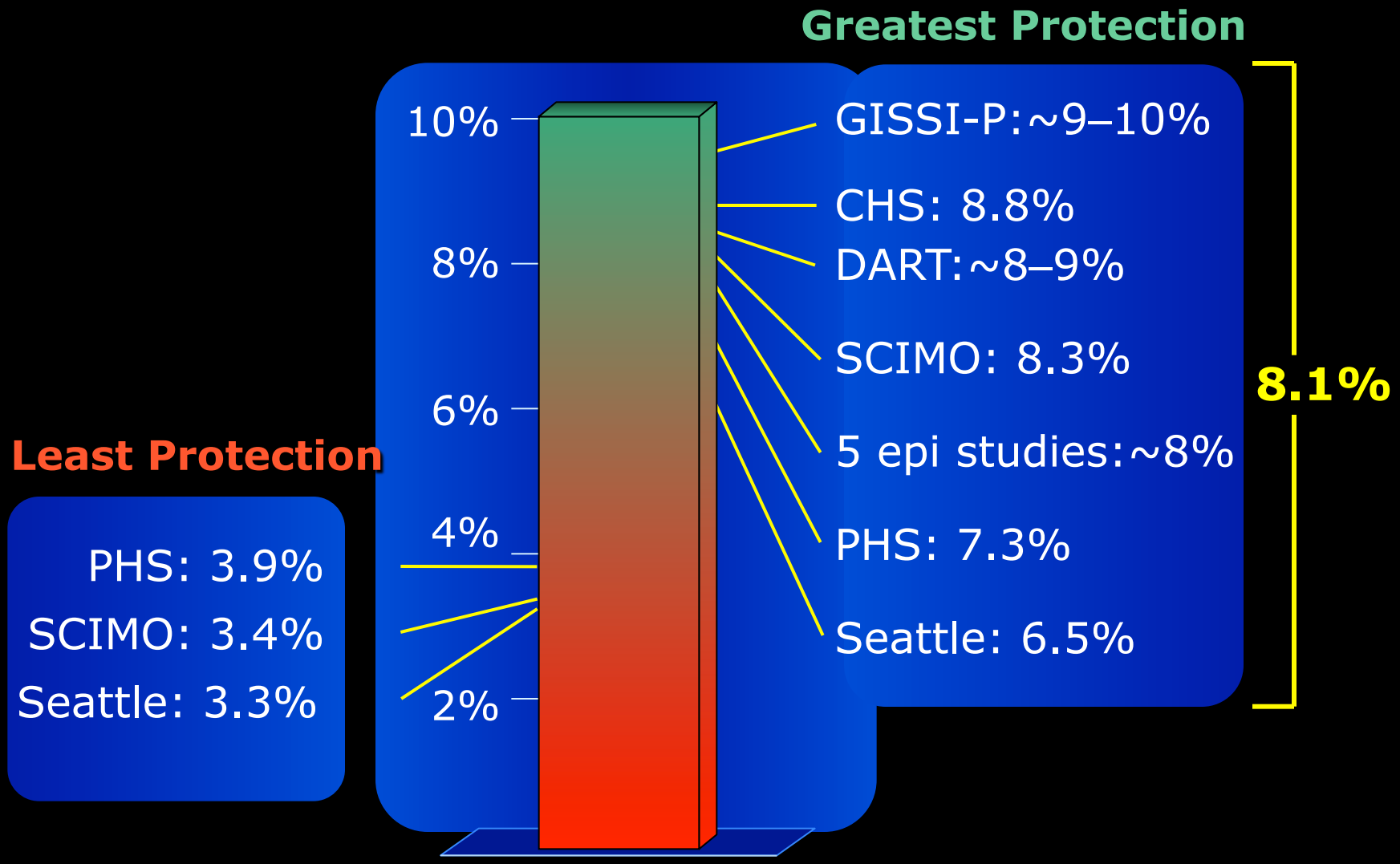
Risks of CHD & fish intake

	Average Frequency of Fish Intake					
	<1 per mo	1-3 Times per mo	Once per wk	2-4 Times per wk	≥5 Times per wk	*P* for Trend
Total CHD						
Cases, No.	117	386	752	182	76	
Person-years	67 537	337 393	690 479	157 711	54 525	
Age-adjusted	1.00	0.64 (0.52-0.79)	0.54 (0.45-0.66)	0.55 (0.44-0.69)	0.64 (0.48-0.86)	<.001
Multivariate 1†	1.00	0.79 (0.64-0.97)	0.71 (0.58-0.87)	0.69 (0.55-0.88)	0.66 (0.50-0.89)	.001
Multivariate 2‡	1.00	0.79 (0.64-0.97)	0.72 (0.59-0.88)	0.72 (0.57-0.91)	0.69 (0.52-0.93)	.007
Fatal CHD						
Cases, No.	41	126	231	61	25	
Age-adjusted	1.00	0.58 (0.41-0.83)	0.46 (0.33-0.64)	0.52 (0.35-0.77)	0.59 (0.36-0.97)	.01
Multivariate 1†	1.00	0.81 (0.57-1.15)	0.66 (0.47-0.92)	0.73 (0.49-1.08)	0.55 (0.33-0.90)	.01
Multivariate 2‡	1.00	0.80 (0.56-1.15)	0.65 (0.46-0.91)	0.72 (0.48-1.09)	0.55 (0.33-0.91)	.01
Nonfatal MI						
Cases, No.	76	260	521	121	51	
Age-adjusted	1.00	0.68 (0.52-0.87)	0.59 (0.46-0.75)	0.57 (0.43-0.76)	0.67 (0.47-0.96)	.003
Multivariate 1†	1.00	0.78 (0.60-1.00)	0.74 (0.58-0.94)	0.68 (0.51-0.90)	0.73 (0.51-1.04)	.03
Multivariate 2‡	1.00	0.78 (0.60-1.01)	0.75 (0.59-0.96)	0.71 (0.53-0.96)	0.77 (0.54-1.11)	.10

*Data are presented as relative risk (95% confidence interval) unless otherwise indicated. The χ^2 test was used for *P* values.
†Relative risk was adjusted for age (continuous), time periods, smoking status (never, past, current [1-14, 15-24, ≥25 cigarettes/d]), body mass index (<22, 22-22.9, 23-24.9, 25-28.9, ≥29 kg/m^2), alcohol intake (0, <5, 5-14, ≥15 g/d), menopausal status and postmenopausal hormone use, vigorous to moderate activity (<1, 1-1.9, 2-3.9, 4-6.9, ≥7 h/wk), number of times aspirin was used per week (<1, 1-2, 3-6, 7-14, and ≥15), multivitamin use (yes vs no), vitamin E supplement use (yes vs no) and history of hypertension (yes vs no), hypercholesterolemia (yes vs no), diabetes (yes vs no).
‡Also adjusted for intake of *trans*-fat, the ratio of polyunsaturated fat to saturated fat, and dietary fiber (all in quintiles).

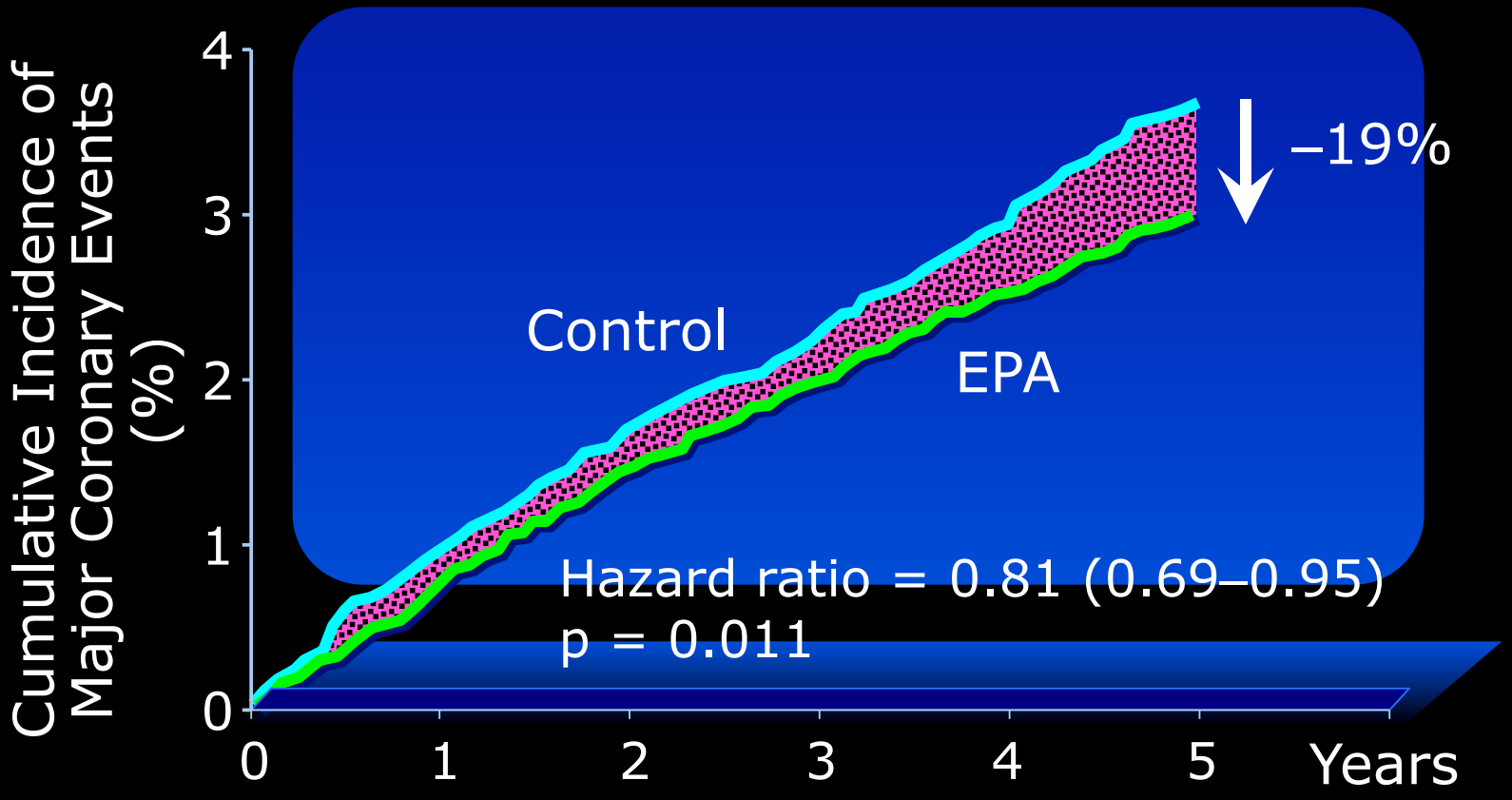
(Hu, 2002)

Omega-3 Index: *Study Estimates*



Harris WS et al. *Prev Med* 2004;39:212-220.

Japan EPA Lipid Intervention Study (JELIS)



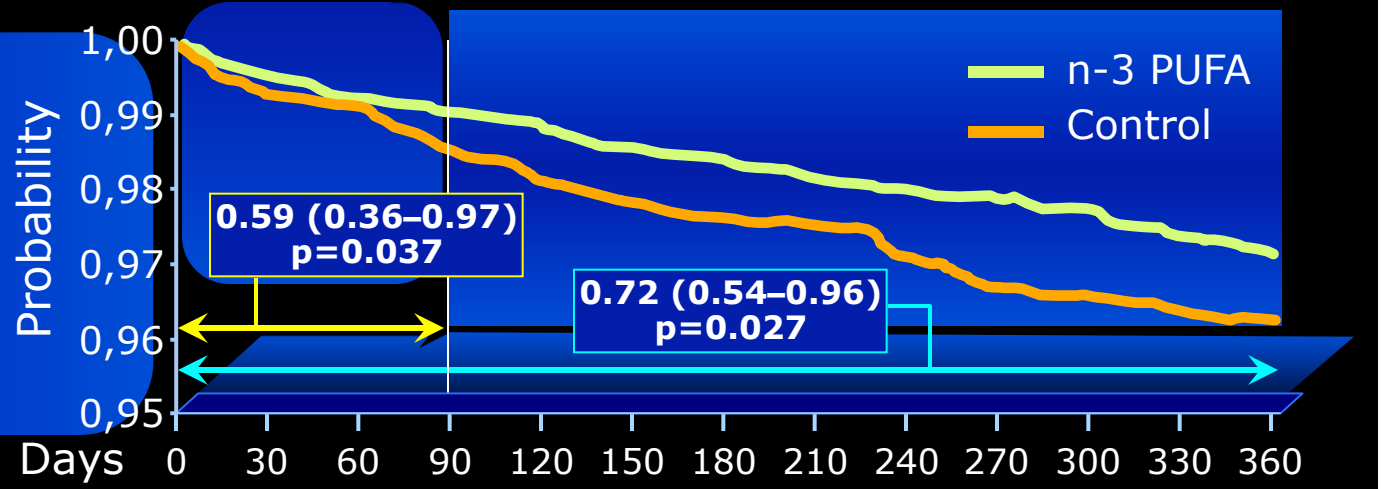
18,645 Japanese (70% women, mean age 61 years) randomized to statin alone or statin + EPA (1.8 g/d) and followed for 5 years

Yokoyama M. Presented at American Heart Association Scientific Sessions, Dallas, Texas, 14 November 2005.

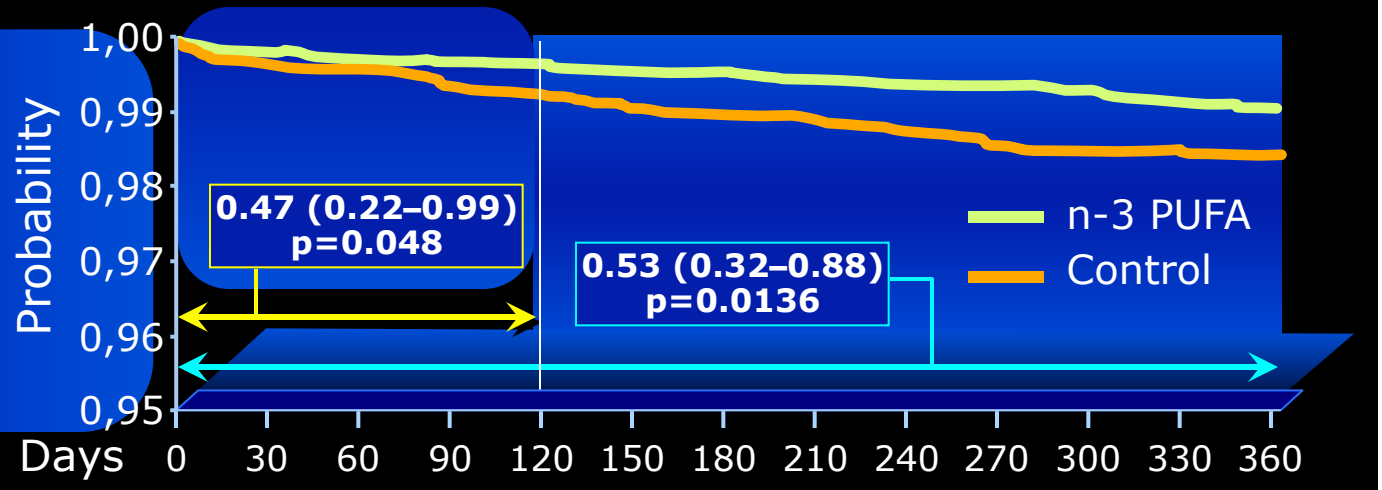
GISSI-Prevenzione: *Time Course of Clinical Events*

>11,300 post-MI patients were given usual care with or without **850** mg EPA+DHA for 3.5 years

Total mortality reduced by 28% (p=0.027)

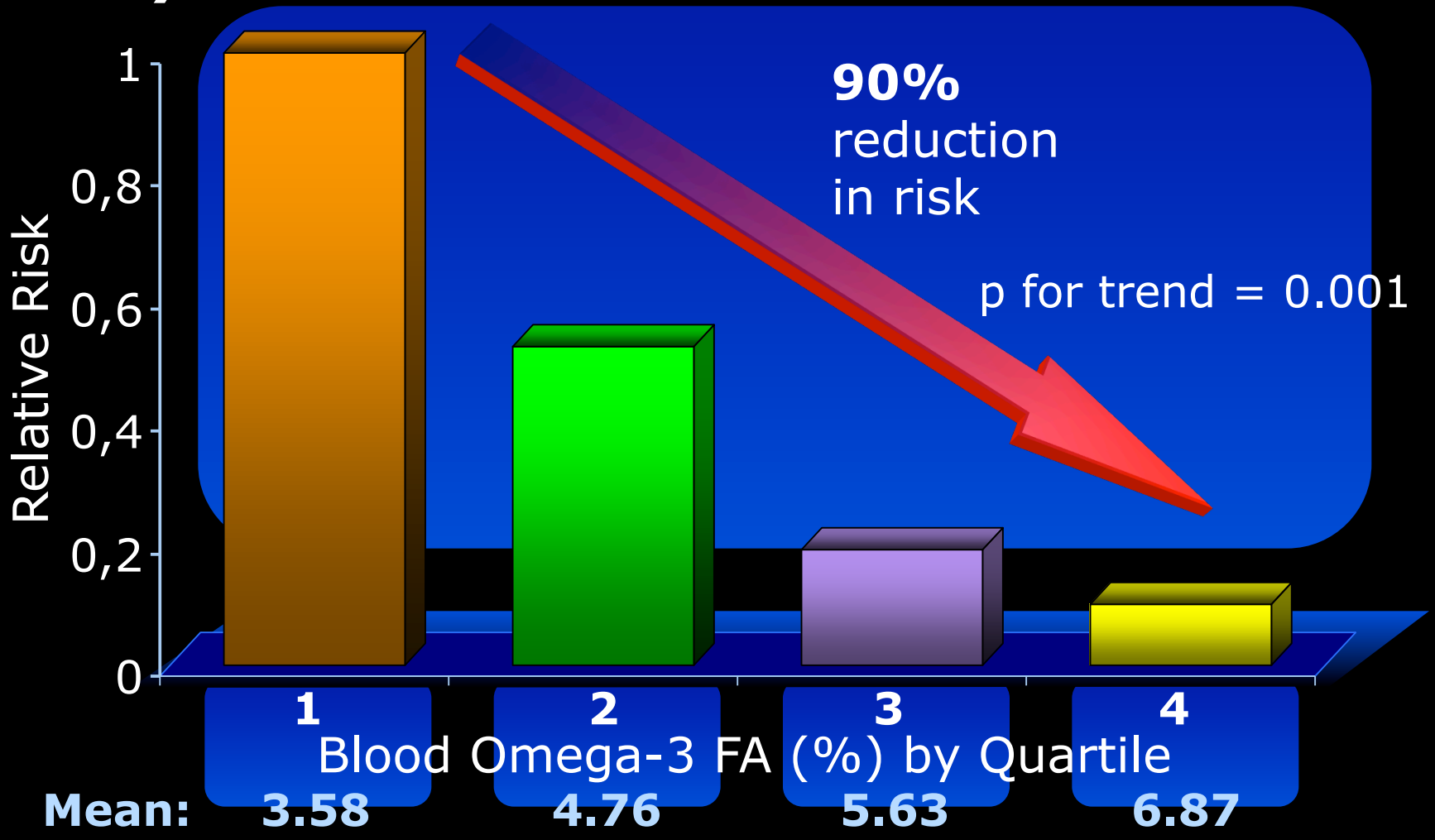


Sudden death reduced by 47% (p=0.0136)



Marchioli R et al. *Circulation* 2002;105:1897-1903.

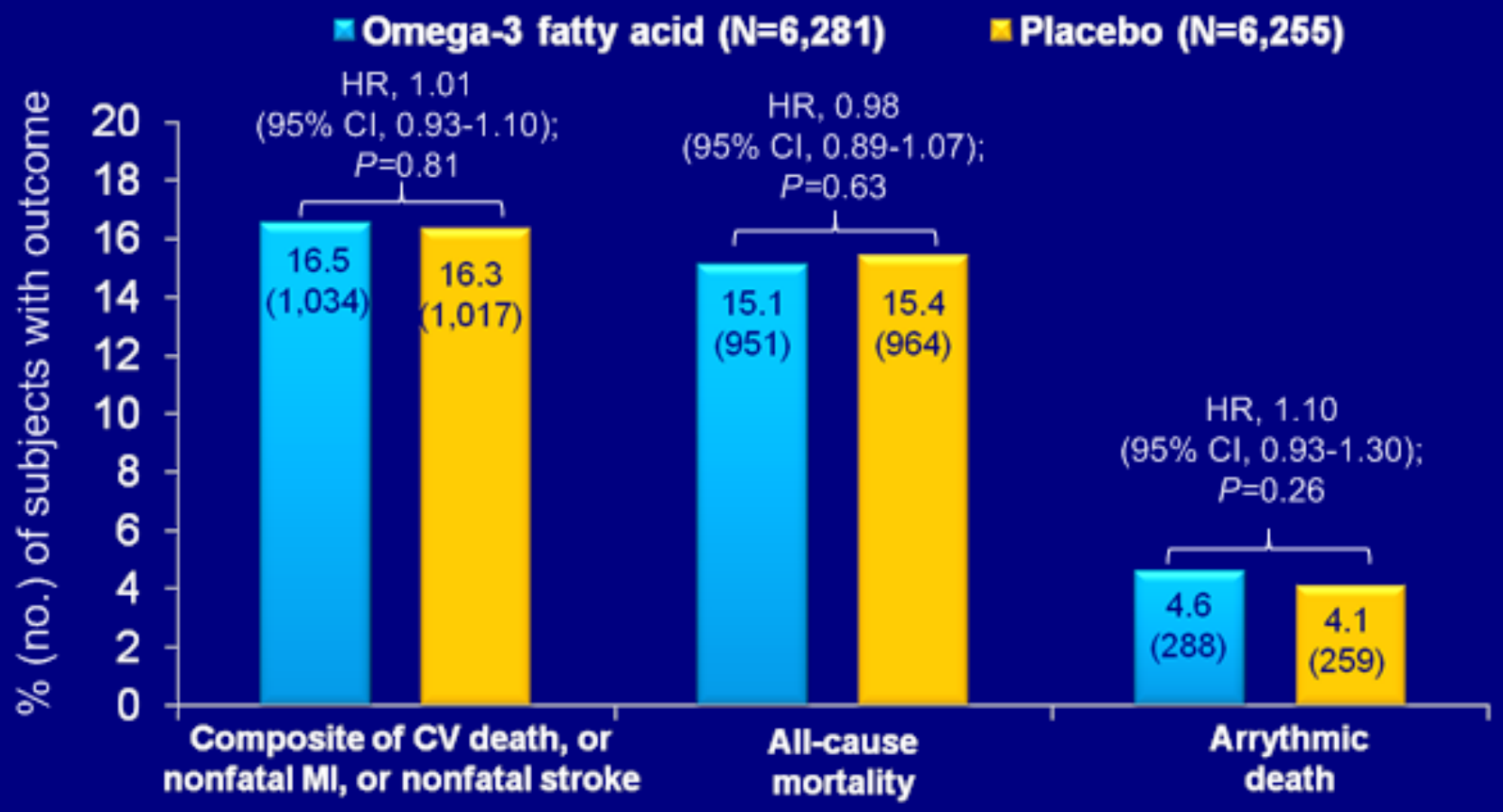
Relative Risk of Sudden Cardiac Death and Blood Omega-3 Levels: *Physicians' Health Study*



Albert CM et al. *N Engl J Med* 2002:346:1113-1118.

ORIGIN
Omega-3 Fatty Acid Trial: Secondary Outcomes

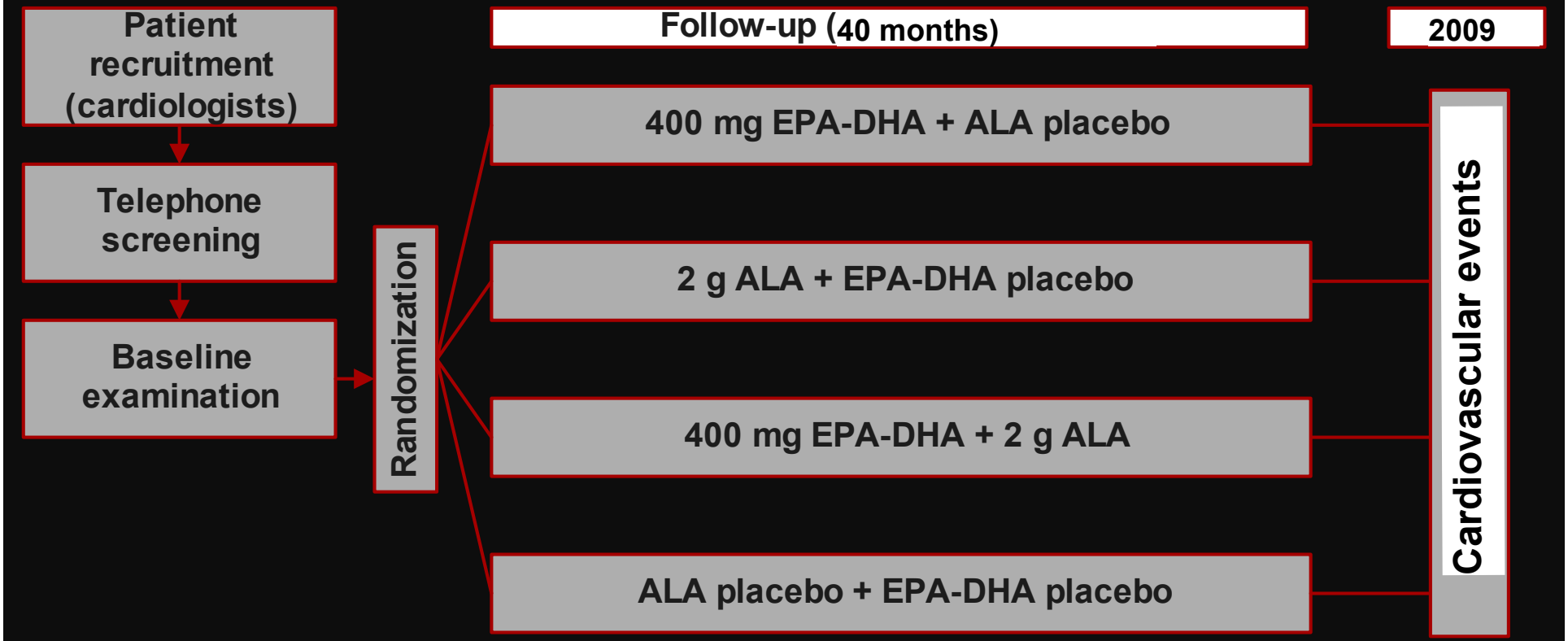
Continuous coverage of the American Diabetes Association 72nd Scientific Sessions



ORIGIN=Outcome Reduction with Initial Glargine Intervention

The ORIGIN Trial Investigators. *N Engl J Med*. 2012; Jun 11. Epub ahead of print.

DESIGN ALPHA OMEGA TRIAL



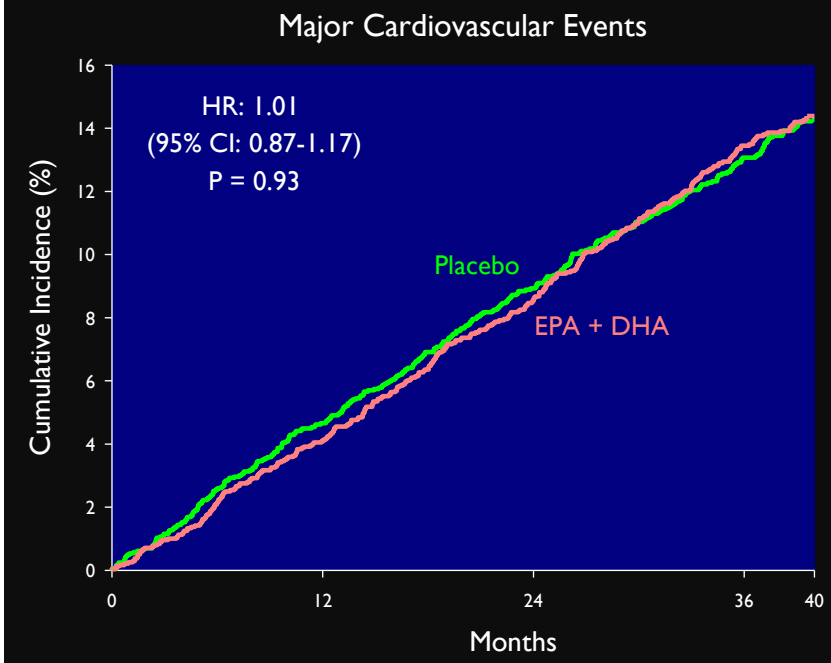
N Engl J Med 2010: 2015

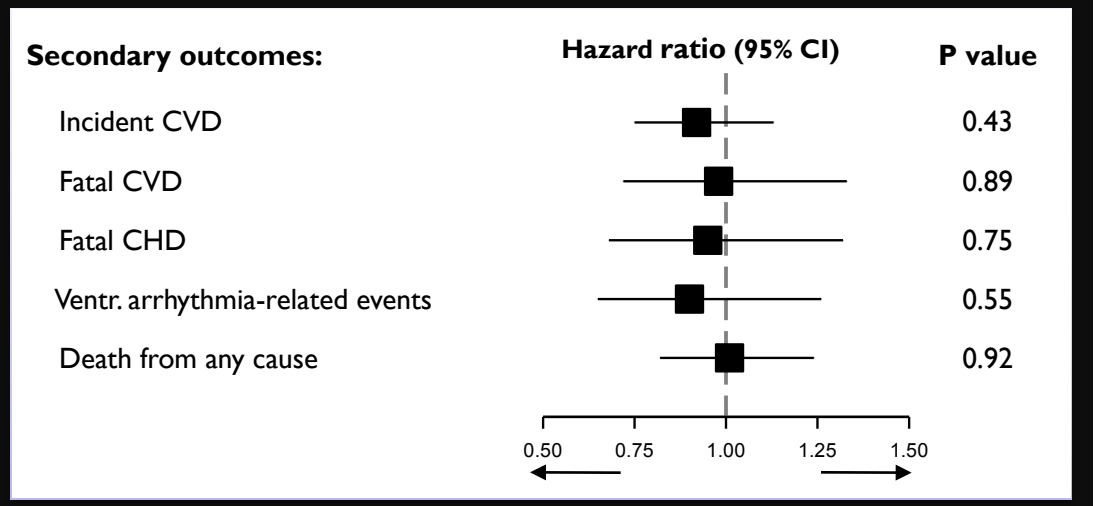
PATIENT CHARACTERISTICS

	EPA+DHA and ALA n=1212	EPA+DHA n=1192	ALA n=1197	Placebo n=1236
Age, y	69 ± 6	69 ± 6	69 ± 6	69 ± 6
Men, %	78	78	78	79
Time since MI, y	4.2 ± 3.1	4.3 ± 3.2	4.4 ± 3.3	4.3 ± 3.3
Diabetes mellitus, %	20	22	22	20
Cardiovascular medication, %				
Antithrombotic agents	96	98	98	98
BP lowering drugs	90	91	88	89
Lipid lowering drugs	87	85	86	85
Antiarrhythmic drugs	3	3	3	3
Systolic blood pressure, mmHg	141 ± 22	142 ± 22	141 ± 21	142 ± 22
Serum total cholesterol, mmol/l	4.7 ± 1.0	4.8 ± 1.0	4.7 ± 1.0	4.8 ± 1.0
Body mass index, kg/m^2	27.8 ± 4.0	27.7 ± 3.7	27.8 ± 3.8	27.8 ± 3.9
Current smoker, %	15	17	17	18

N Engl J Med 2010: 2015

EPA+DHA AND ENDPOINTS

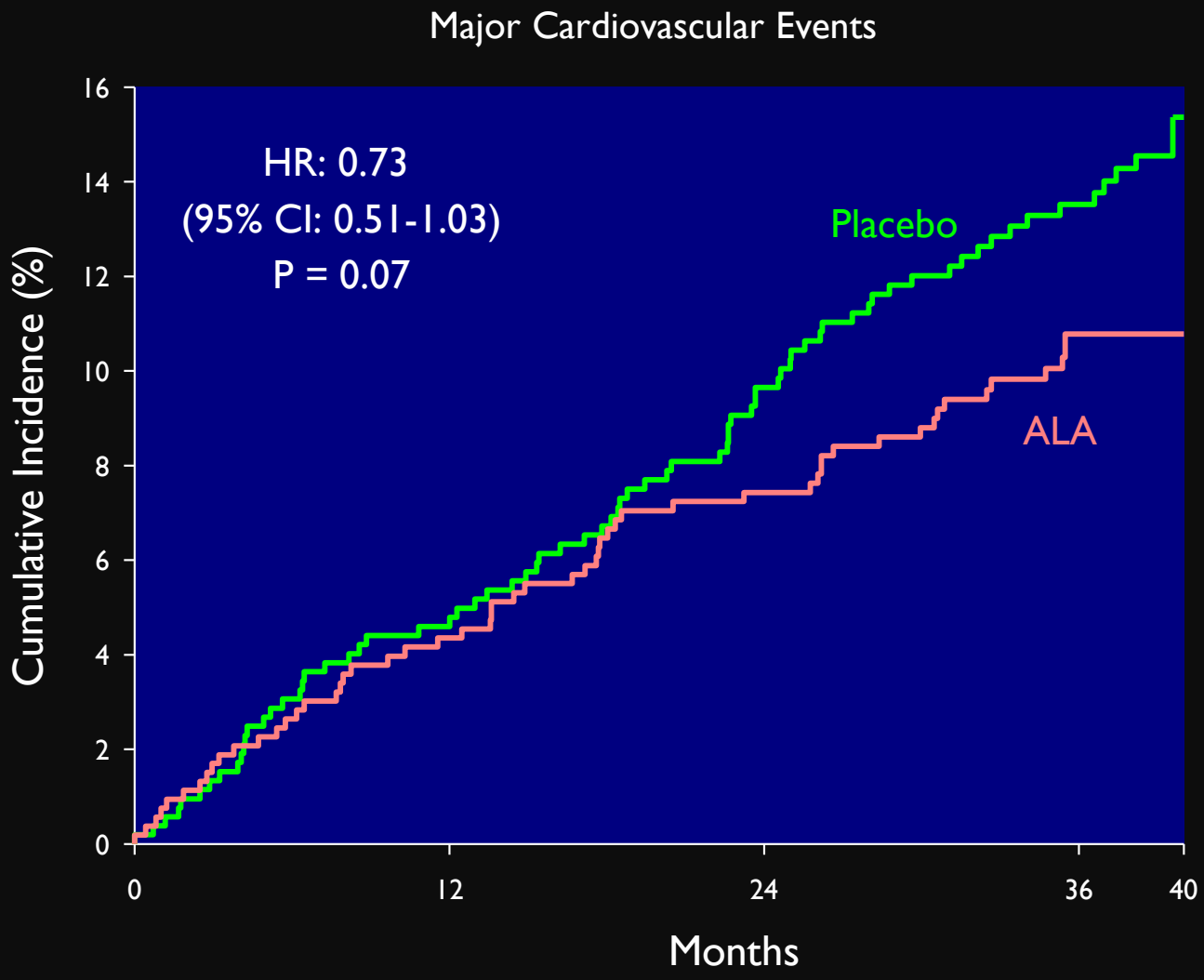




Findings were similar in men and women

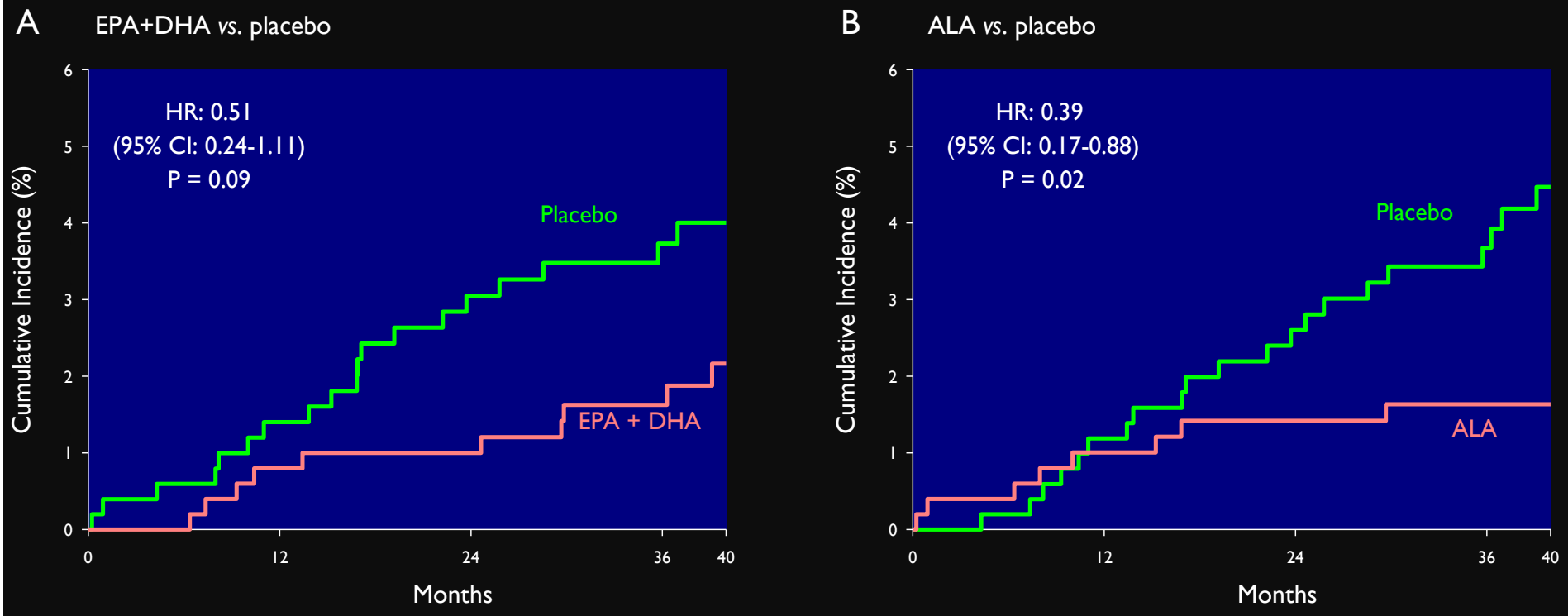
N Engl J Med 2010: 2015

RESULTS IN WOMEN



N Engl J Med 2010: 2015

VENTRICULAR ARRHYTHMIA-RELATED EVENTS IN DIABETIC PATIENTS



Ventricular arrhythmia-related events:
defined as sudden death, cardiac arrest, and implantable cardioverter-defibrillator placement

N Engl J Med 2010: 2015

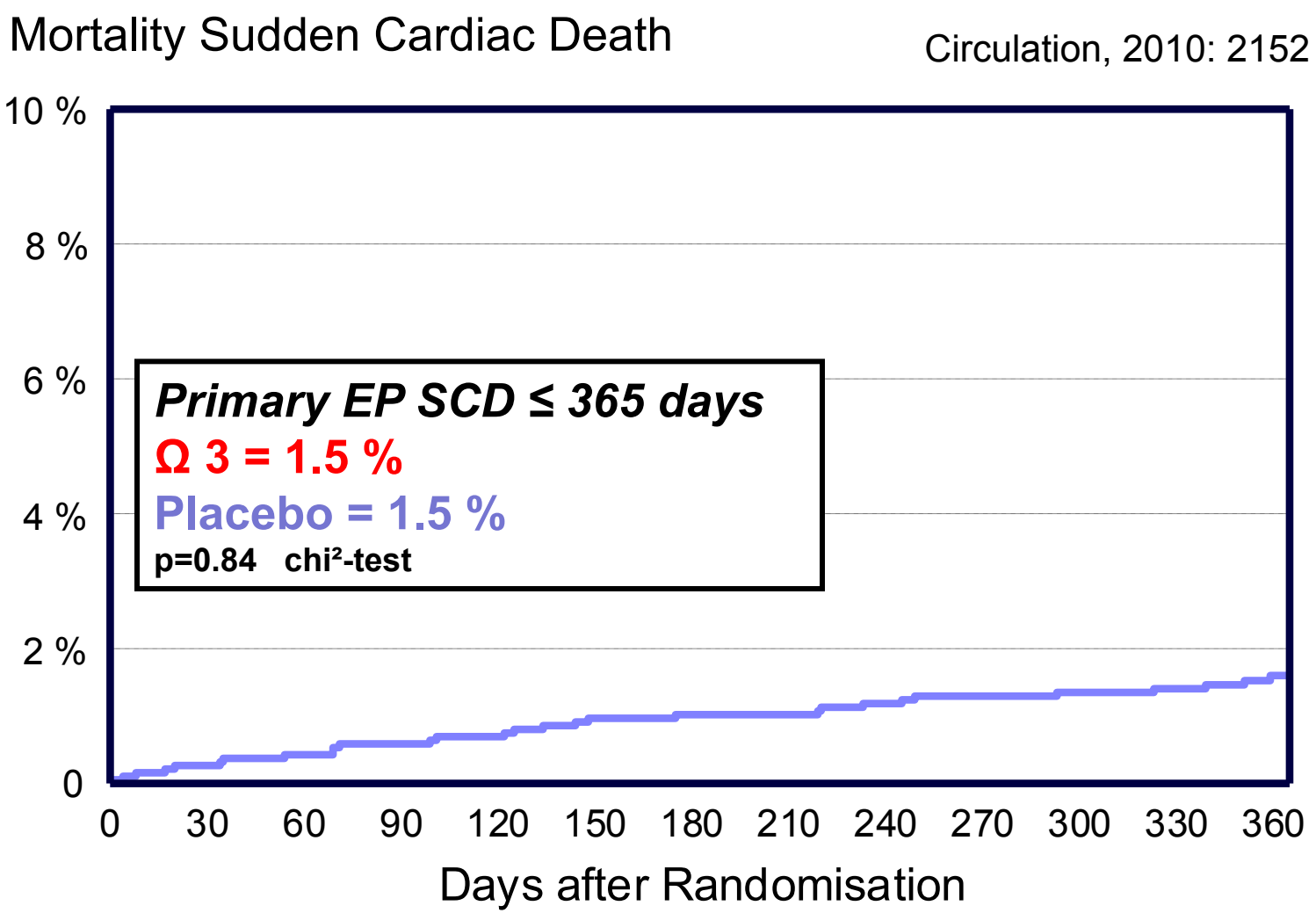
Randomized Trial of Omega – 3 Fatty Acids on Top of Modern Therapy after Acute Myocardial Infarction: The OMEGA-Trial

Circulation, 2010: 2152

Annual Scientific Session of the American College of Cardiology 2009

Primary Endpoint Sudden Cardiac Death

Institut für Herzinfarktforschung Ludwigshafen an der Universität Heidelberg



Secondary Endpoints (1) ≤ 365 days

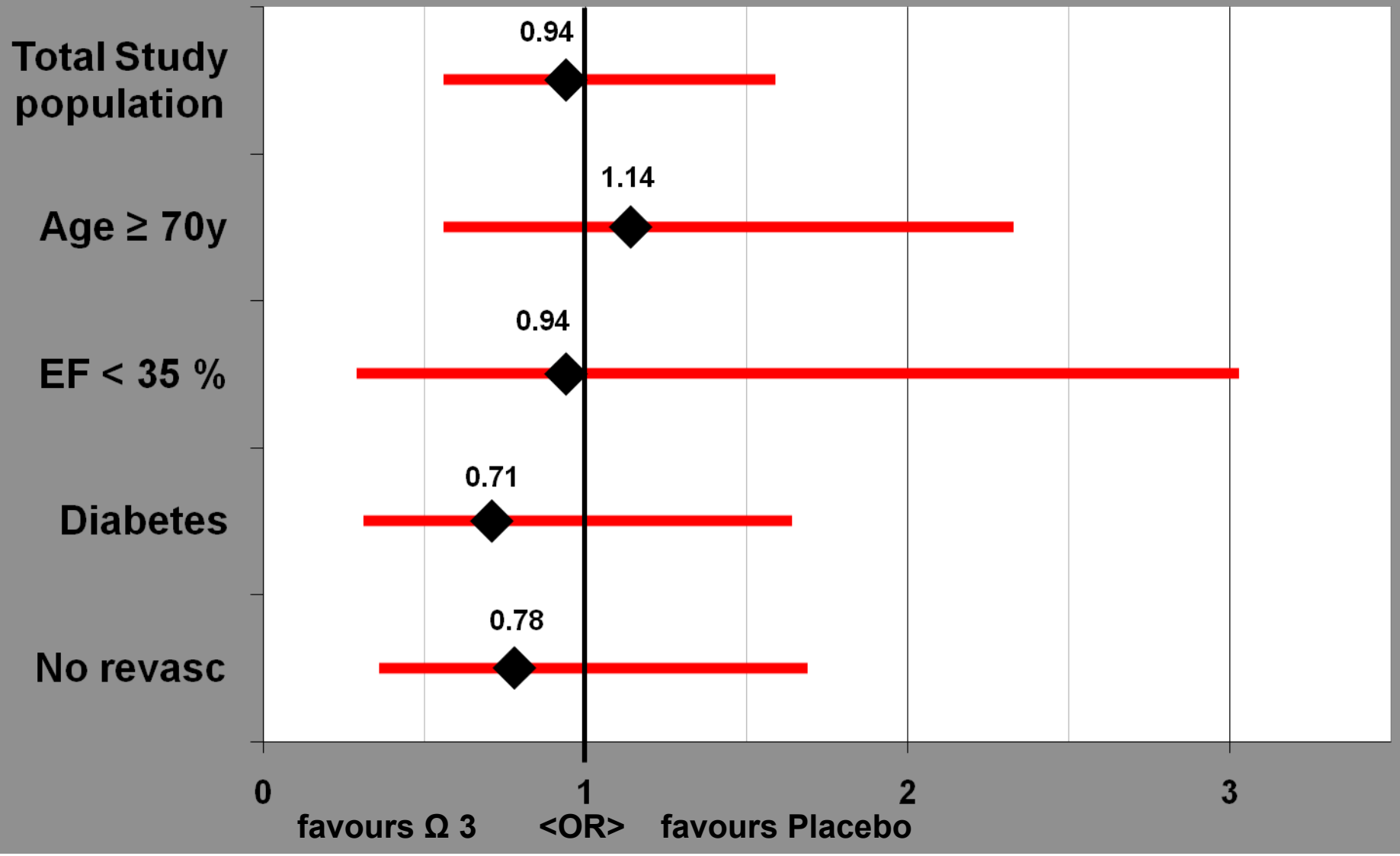
Institut für Herzinfarktforschung Ludwigshafen
an der Universität Heidelberg

	Total	Ω 3	Placebo	P-Value
Total death	4.2 %	4.6 %	3.7 %	0.18
Re-infarction	4.3 %	4.5 %	4.1 %	0.63
Stroke	1.1 %	1.4 %	0.7 %	0.07
MACCE (Total death, Re-MI, Stroke)	9.6 %	10.4 %	8.8 %	0.10
Arrhythmic events				
Total events	0.9 %	1.1 %	0.7 %	0.22
Resuscitation or DC-shock	0.6 %	0.6 %	0.6 %	0.98
ICD-terminated VT/VF	0.3 %	0.5 %	0.1 %	0.07

Circulation, 2010: 2152

SCD in predefined high risk Subgroups

Institut für Herzinfarktforschung Ludwigshafen
an der Universität Heidelberg



SU-FO-LOM 3

BMJ, 2010:c6273

Endpoint	Events (%)		Relative Risk	95% CI
	Studied treat.	Control treat.		
Major cardiovascular events	75 / 1242 (6,0%)	82 / 1259 (6,5%)	0,93	[0,68;1,26]
Non-fatal myocardial infarction	28 / 1242 (2,3%)	32 / 1259 (2,5%)	0,89	[0,54;1,46]
All coronary events	49 / 1242 (3,9%)	55 / 1259 (4,4%)	0,90	[0,62;1,32]
Stroke	21 / 1242 (1,7%)	36 / 1259 (2,9%)	0,59	[0,35;1,01]
All cerebrovascular events	35 / 1242 (2,8%)	48 / 1259 (3,8%)	0,74	[0,48;1,13]
All revascularisations	155 / 1242 (12,5%)	153 / 1259 (12,2%)	1,03	[0,83;1,27]
Other cardiovascular events	224 / 1242 (18,0%)	212 / 1259 (16,8%)	1,07	[0,90;1,27]
All deaths	72 / 1242 (5,8%)	45 / 1259 (3,6%)	1,62	[1,13;2,33]

n–3 Fatty Acids in Patients with Multiple Cardiovascular Risk Factors

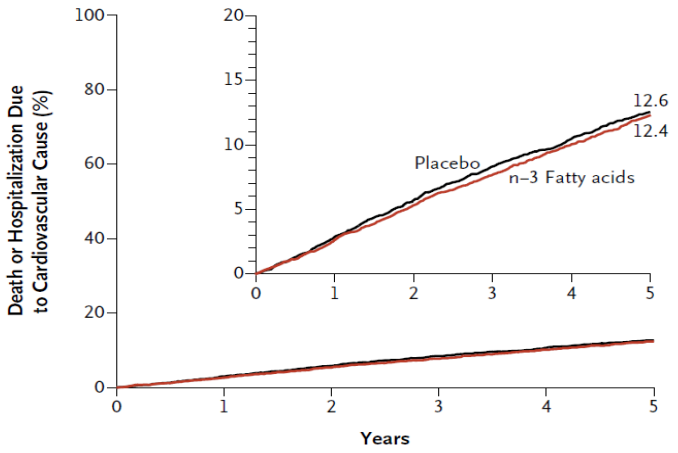
The Risk and Prevention Study Collaborative Group*

Characteristic	n–3 Fatty Acids (N = 6239)	Placebo (N = 6266)	P Value
Age — yr	63.9±9.3	64.0±9.6	0.54
Male sex — no. (%)	3890 (62.3)	3797 (60.6)	0.04
History of cardiovascular disease or risk factors — no. (%)			
Angina	778 (12.5)	730 (11.7)	0.16
Revascularization intervention	555 (8.9)	551 (8.8)	0.84
Stroke	296 (4.7)	298 (4.8)	0.98
Transient ischemic attack	521 (8.4)	501 (8.0)	0.47
Peripheral artery disease	499 (8.0)	487 (7.8)	0.63
Heart failure	180 (2.9)	219 (3.5)	0.05
Hypertension	5280 (84.6)	5297 (84.5)	0.87
Hypercholesterolemia	4402 (70.6)	4486 (71.6)	0.21
Diabetes mellitus	3721 (59.6)	3773 (60.2)	0.53
Obesity	3046 (48.8)	3036 (48.5)	0.69
Family history of premature cardiovascular disease	1964 (31.5)	1922 (30.7)	0.33
Current smoking	1377 (22.1)	1339 (21.4)	0.16
Medical treatment — no. (%)			
ACE inhibitor	2831 (45.4)	2807 (44.8)	0.52
ARB	1366 (21.9)	1371 (21.9)	0.98
Diuretic agent	2608 (41.8)	2576 (41.1)	0.43
Calcium-channel blocker	1812 (29.0)	1710 (27.3)	0.03
Beta-blocker	1316 (21.1)	1258 (20.1)	0.16
Oral hypoglycemic drug	2745 (44.0)	2771 (44.2)	0.80
Insulin	419 (6.7)	403 (6.4)	0.52
Statin	2544 (40.8)	2594 (41.4)	0.48
Antiplatelet agent	2569 (41.2)	2601 (41.5)	0.71
Fish consumption — no./total no. (%)			0.76
Never or very seldom	1444/6066 (23.8)	1467/6092 (24.1)	
1 time/wk	2625/6066 (43.3)	2620/6092 (43.0)	
2 times/wk	1635/6066 (27.0)	1666/6092 (27.3)	
≥3 times/wk	362/6066 (6.0)	339/6092 (5.6)	

N Engl J Med 2013;368:1800-8.

n–3 Fatty Acids in Patients with Multiple Cardiovascular Risk Factors

The Risk and Prevention Study Collaborative Group*



Outcome	n–3 Fatty Acids (N=6281)		Placebo (N=6255)		Adjusted Hazard Ratio (95% CI)	P Value
	no. (%)	*rate/100 patient-yr*	*no. (%)*	*rate/100 patient-yr*		
Primary outcome: death from cardiovascular causes	574 (9.1)	1.55	581 (9.3)	1.58	0.98 (0.87–1.10)	0.72
Secondary outcomes						
Myocardial infarction, stroke, or death from cardiovascular causes	1034 (16.5)	2.92	1017 (16.3)	2.88	1.01 (0.93–1.10)	0.81
Death from any cause	951 (15.1)	2.57	964 (15.4)	2.62	0.98 (0.89–1.07)	0.63
Death from arrhythmia*	288 (4.6)	0.78	259 (4.1)	0.70	1.10 (0.93–1.30)	0.26
Other outcomes						
Fatal and nonfatal myocardial infarction	344 (5.5)	0.95	316 (5.1)	0.88	1.09 (0.93–1.27)	0.28
Fatal and nonfatal stroke	314 (5.0)	0.86	336 (5.4)	0.93	0.92 (0.79–1.08)	0.32
Hospitalization for heart failure	331 (5.3)	0.91	320 (5.1)	0.88	1.02 (0.88–1.19)	0.76
Revascularization procedure	866 (13.8)	2.54	896 (14.3)	2.65	0.96 (0.87–1.05)	0.39
Angina†	724 (11.5)	2.11	725 (11.6)	2.12	1.00 (0.90–1.10)	0.94
Limb or digit amputation for ischemia	52 (0.8)	0.14	47 (0.8)	0.13	1.09 (0.74–1.62)	0.67
Hospitalization for any cardiovascular cause	2055 (32.7)	6.87	2087 (33.4)	7.00	0.98 (0.92–1.04)	0.50

N Engl J Med 2013;368:1800-8.

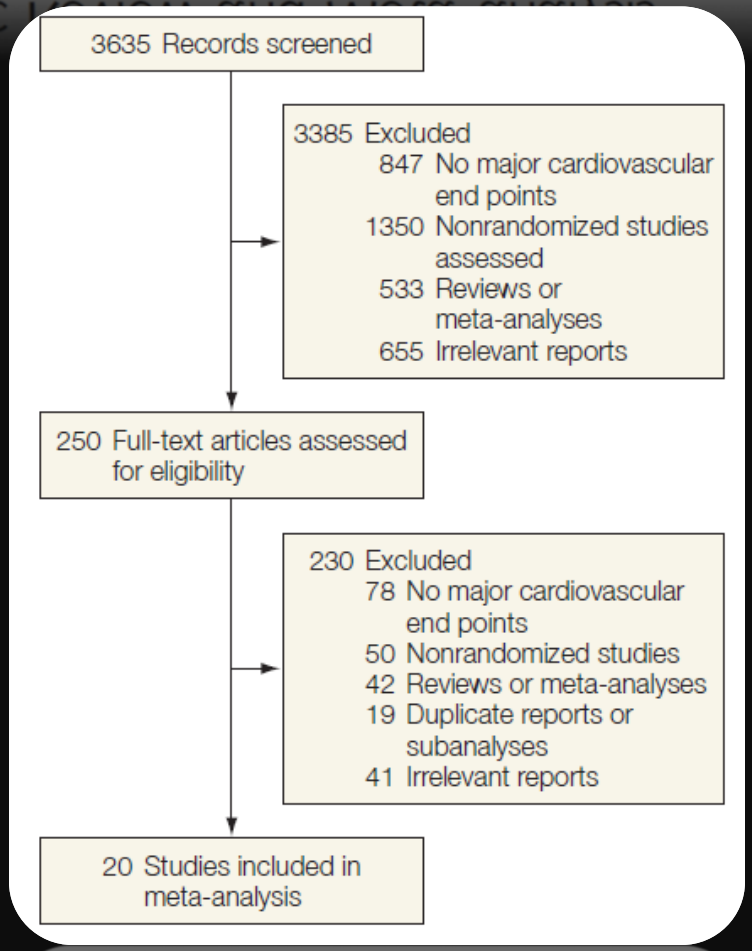
Les études n-3 les plus récentes…

- ✓ 5 études contrôlées randomisées avec une méthodologie moderne sont négatives !

- ✓ Discussion:
  - ✓ Dose
  - ✓ Durée
  - ✓ Population (Prévention 2, trop bien traitée…)

Association Between Omega-3 Fatty Acid Supplementation and Risk of Major Cardiovascular Disease Events

A Systematic Review and Meta-analysis

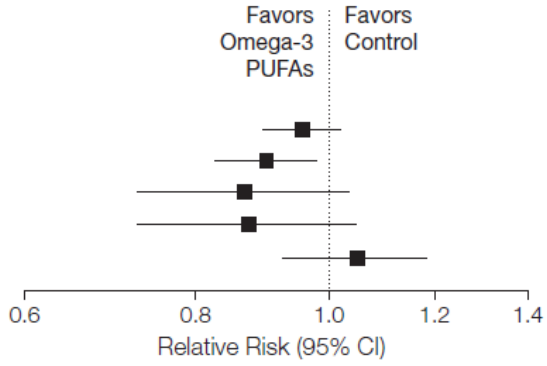


JAMA. 2012;308(10):1024-1033

Association Between Omega-3 Fatty Acid Supplementation and Risk of Major Cardiovascular Disease Events

A Systematic Review and Meta-analysis

Outcome	No. Studies	No. Events	No. Participants	RR (95% CI)
All-cause mortality	17	6295	63 279	0.96 (0.91-1.02)
Cardiac death	13	3480	56 407	0.91 (0.85-0.98)
Sudden death	7	1030	41 751	0.87 (0.75-1.01)
Myocardial infarction	13	1755	53 875	0.89 (0.76-1.04)
Stroke	9	1490	52 589	1.05 (0.93-1.18)



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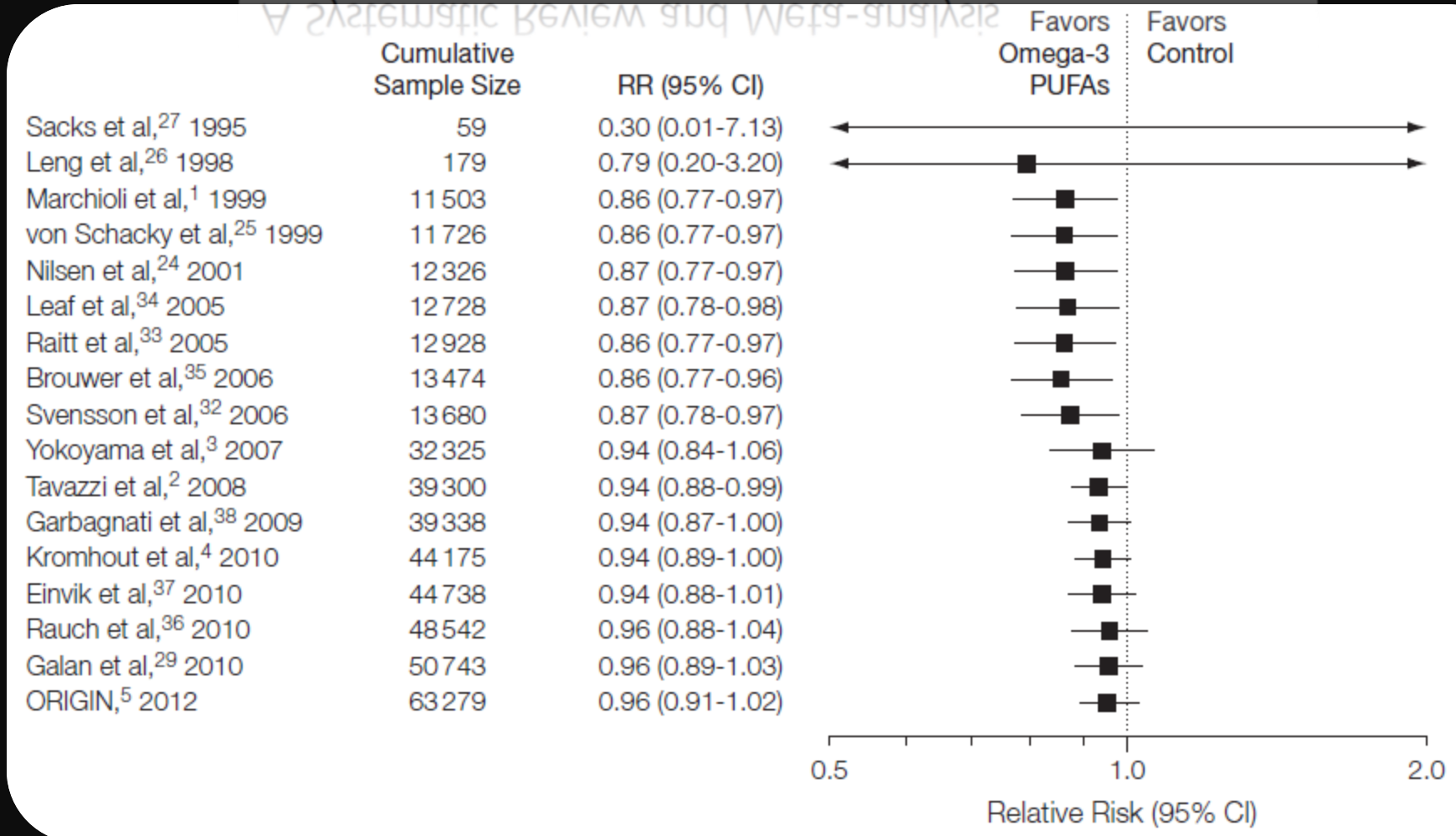


JAMA. 2012;308(10):1024-1033

Welcome to the ASCEND Trial Website

Recruitment is now Complete - 15,480 participants randomised. Follow-up to continue until 2017.

Diabetes is common, and increases the risks of suffering heart attacks or strokes. Aspirin is known to reduce the risk of these complications in people with circulatory problems, whether or not they have diabetes. However, there is no evidence that aspirin is beneficial in individuals with diabetes who do not have vascular disease, and few use it routinely.

The ASCEND randomised trial should provide the first reliable evidence about the effects of aspirin and of omega-3 fatty acids in diabetes. ASCEND has recruited 15,000 people with diabetes (either type 1 or type 2) who were not known to have vascular disease. ASCEND volunteers are randomly allocated to take either 100mg aspirin daily or placebo (dummy) and 1 gram capsules containing naturally occurring omega-3 fatty acids ("fish-oils") or placebo capsules containing olive oil. If favourable results emerge, this could lead to the widespread use of these treatments in diabetes, and avoidance of many thousands of heart attacks and strokes.

Funding for the study is being provided by the British Heart Foundation, packaged aspirin and matching placebo is being provided by Bayer AG and packaged omega-3 fatty acid supplements and matching placebo capsules by Abbott Products Operations AG (formerly Solvay Pharmaceuticals).

The trial is coordinated by the University of Oxford Clinical Trial Service Unit and started during 2004, and is scheduled to continue until 2017.

This website is intended for participants in ASCEND and people with diabetes interested in taking part in ASCEND, and their doctors and other healthcare professionals.

http://www.ctsu.ox.ac.uk/ascend/

Descriptive Information	
Brief Title ICMJE	Vitamin D and Omega-3 Trial (VITAL)
Official Title ICMJE	Vitamin D and Omega-3 Trial (VITAL)
Brief Summary	The VITamin D and OmegA-3 TriaL (VITAL) is a randomized clinical trial in 20,000 U.S. men and women investigating whether taking daily dietary supplements of vitamin D3 (2000 IU) or omega-3 fatty acids (Omacor® fish oil, 1 gram) reduces the risk of developing cancer, heart disease, and stroke in people who do not have a prior history of these illnesses.
Detailed Description	The VITamin D and OmegA-3 TriaL (VITAL) is a randomized clinical trial of vitamin D (in the form of vitamin D3 [cholecalciferol]) and marine omega-3 fatty acid (eicosapentaenoic acid [EPA] + docosahexaenoic acid [DHA]) supplements in the primary prevention of cancer and cardiovascular disease. Existing data from laboratory studies, epidemiologic research, small primary prevention trials, and/or large secondary prevention trials strongly suggest that these nutritional agents may reduce risk for cancer or cardiovascular disease, but large primary prevention trials with adequate dosing in general populations are lacking. Eligible participants will be assigned by chance (like a coin toss) to one of four groups: (1) daily vitamin D3 and omega-3; (2) daily vitamin D3 and omega-3 placebo; (3) daily vitamin D placebo and omega-3; or (4) daily vitamin D placebo and omega-3 placebo. Participants have an equal chance of being assigned to any of these four groups and a 3 out of 4 chance of getting at least one active agent. Participants in all groups will take two pills each day -- one softgel that contains either vitamin D3 or vitamin D placebo and one capsule that contains either omega-3 or omega-3 placebo. Participants will receive their study pills in convenient calendar packages via U.S. mail. Participants will also fill out a short (15-20 minute) questionnaire each year. The questionnaire asks about health; lifestyle habits such as physical exercise, diet, and smoking; use of medications and dietary supplements; family history of illness, and new medical diagnoses. Occasionally, participants may receive a phone call from study staff to collect information or to clarify responses on the questionnaire.
Study Type ICMJE	Interventional
Study Phase	Phase 3
Study Design ICMJE	Allocation: Randomized Endpoint Classification: Efficacy Study Intervention Model: Factorial Assignment Masking: Double Blind (Subject, Investigator, Outcomes Assessor) Primary Purpose: Prevention
Condition ICMJE	•Cancer •Cardiovascular Disease

Trial.gouv

2000 Consensus Statement - London

International Task Force for Prevention of Coronary Heart Disease

Characteristics of the Traditional Mediterranean Diet

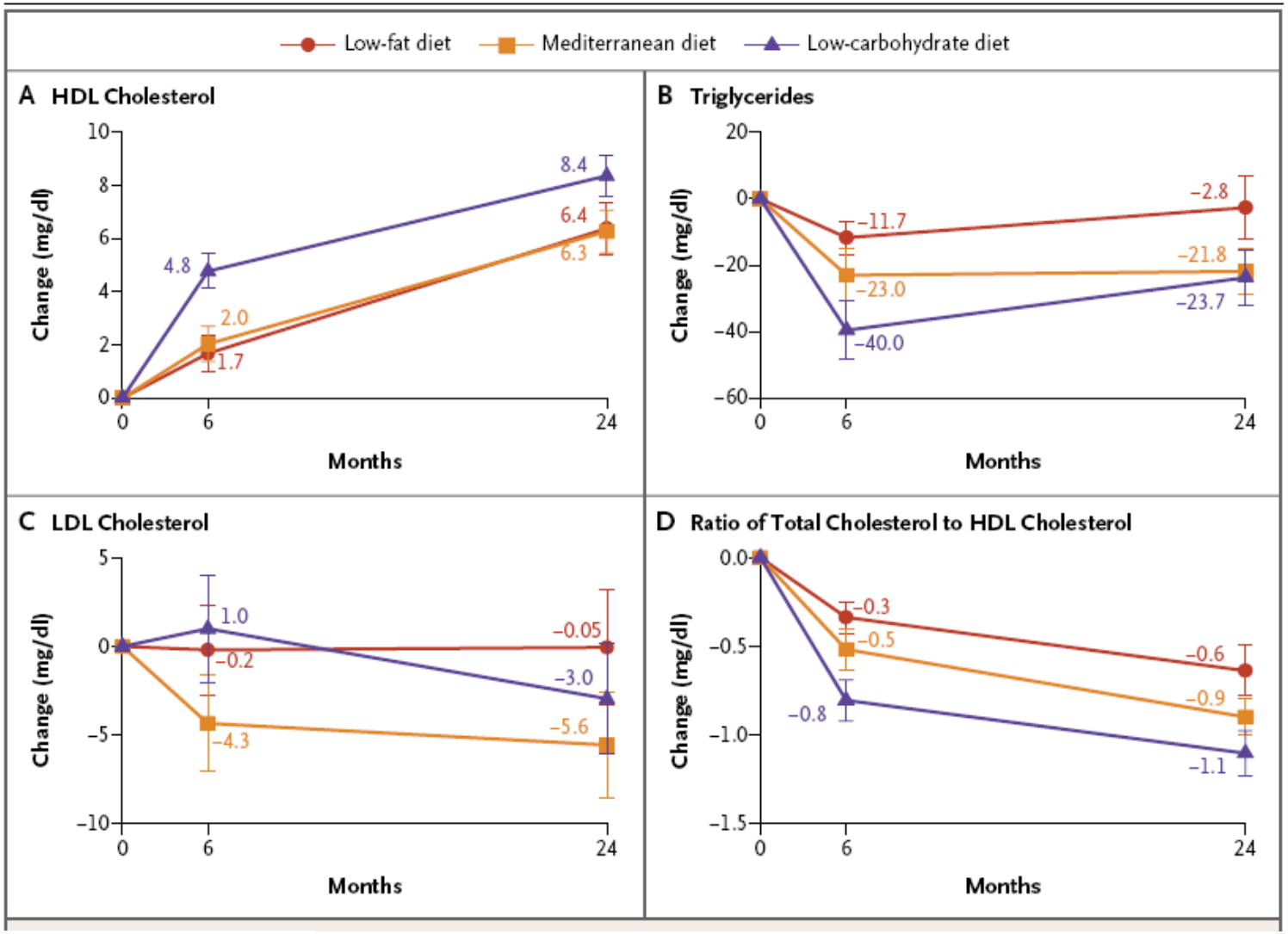
- Aliments d'origine végétale +++
  - fruit, legumes, pain, ceréales, pomme de terre, noix
  - Peu transformés, de saison, et locaux
- Huile d'olive comme matière grasse principale
- Produits laitiers (yaourt et fromage) en quantité faible à modérée
- Poissons et volailles en quantité modérée
- Viande rouge en faible quantité
- Vin avec modération et aux repas

Weight Loss with a Low-Carbohydrate, Mediterranean, or Low-Fat Diet

- **Two-year trial**
- **322 obese patients (BMI = 31kg/m², 52 yrs old, 86 % men)**
- **Randomly assigned to :1) low fat diet, restricted-calorie – 2) Mediterranean restricted-calorie or 3) low fat-non-restricted-calorie**

N Engl J Med 2008;359:229-41.

Weight Loss with a Low-Carbohydrate, Mediterranean, or Low-Fat Diet



N Engl J Med 2008;359:229-41.

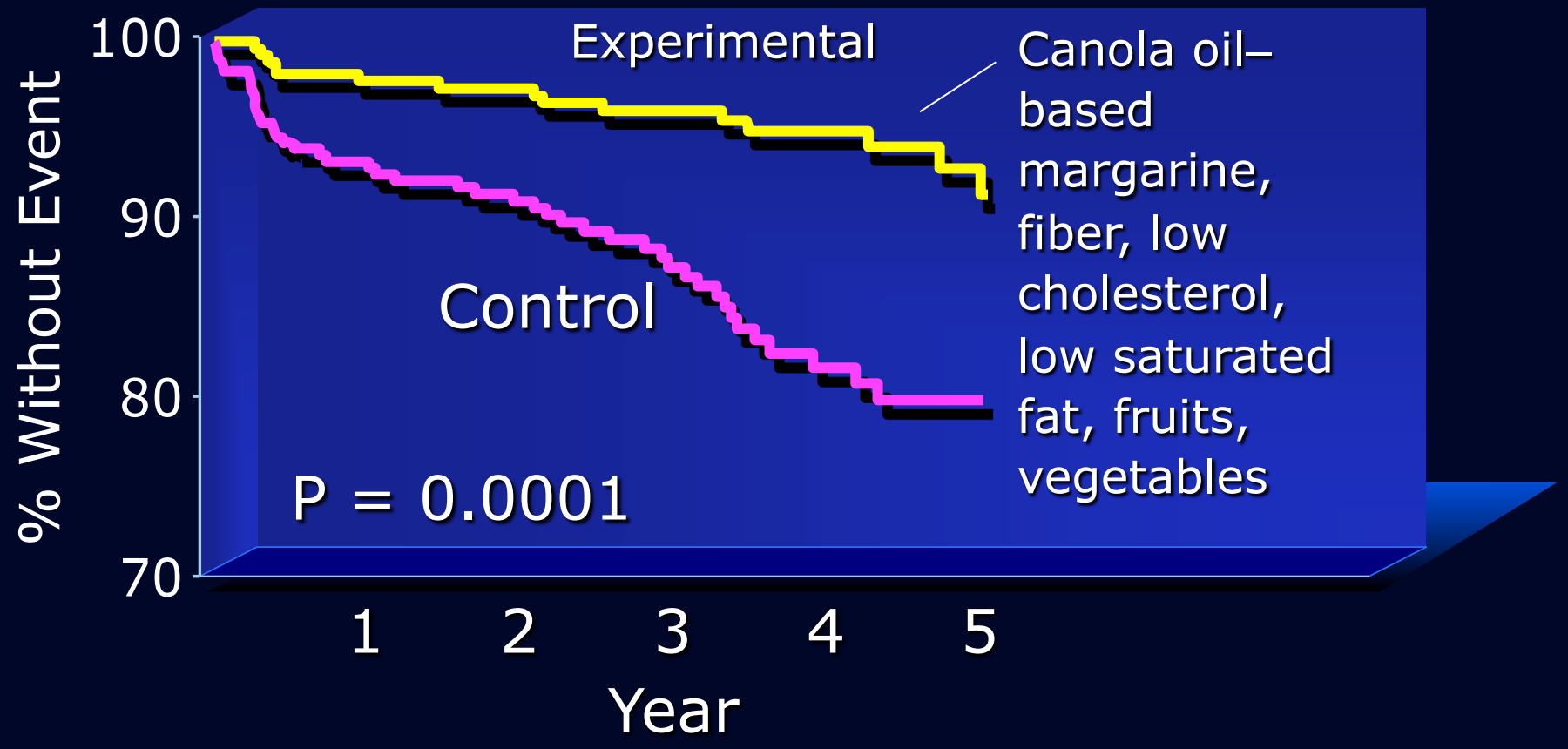
Lyon Diet Heart study :Comparison of the Diets

Item	Experimental	Control
Total calories	1947	2088*
Total fat	30.4%	33.6%*
Saturated fat	8%	11.7%
Dietary cholesterol	203 mg/dl	312 mg/dl*
Alcohol	Same	Same
Olive oil	None	None
MUFA n-9	Increased*	
PUFA	Increased*	
n-3/n-6 fatty acids	Increased*	
Fiber	18.6	

*Significantly different

de Lorgeril M, et al. *Circulation*. 1999;99:779-785.

Lyon Diet Heart Study: *Cumulative Survival without Cardiac Death and Nonfatal MI*



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Primary Prevention of Cardiovascular Disease with a Mediterranean Diet

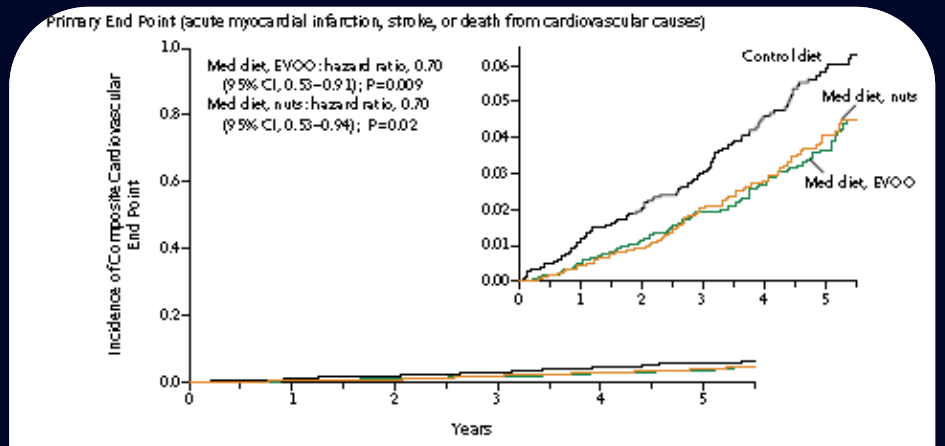
Table 2. Baseline Characteristics of the Participants According to Study Group.*

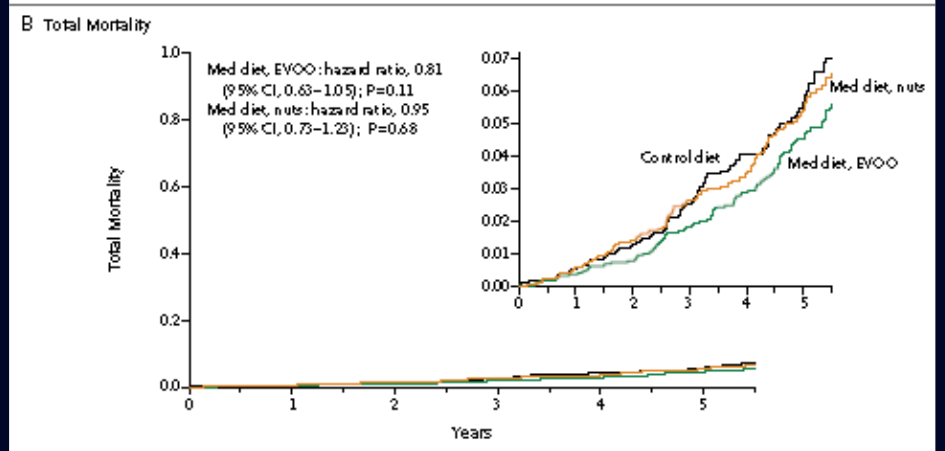
Characteristic	Mediterranean Diet with EVOO (N=2543)	Mediterranean Diet with Nuts (N=2454)	Control Diet (N=2450)
Female sex — no. (%)†	1493 (58.7)	1326 (54.0)	1463 (59.7)
Age — yr†	67.0±6.2	66.7±6.1	67.3±6.3
Race or ethnic group — no. (%)			
White, from Europe	2470 (97.1)	2390 (97.4)	2375 (96.9)
Hispanic, from Central or South America	35 (1.4)	29 (1.2)	38 (1.6)
Other	38 (1.5)	35 (1.4)	37 (1.5)
Smoking status — no. (%)			
Never smoked	1572 (61.8)	1465 (59.7)	1527 (62.3)
Former smoker	618 (24.3)	634 (25.8)	584 (23.8)
Current smoker	353 (13.9)	355 (14.5)	339 (13.8)
Body-mass index†‡			
Mean	29.9±3.7	29.7±3.8	30.2±4.0
<25 — no. (%)	195 (7.7)	204 (8.3)	164 (6.7)
25–30 — no. (%)	1153 (45.3)	1163 (47.4)	1085 (44.3)
>30 — no. (%)	1195 (47.0)	1087 (44.3)	1201 (49.0)
Waist circumference — cm	100±10	100±11	101±11
Waist-to-height ratio†§	0.63±0.06	0.63±0.06	0.63±0.07
Hypertension — no. (%)¶	2088 (82.1)	2024 (82.5)	2050 (83.7)
Type 2 diabetes — no. (%)†‖	1282 (50.4)	1143 (46.6)	1189 (48.5)
Dyslipidemia — no. (%)**	1821 (71.6)	1799 (73.3)	1763 (72.0)
Family history of premature CHD — no. (%)††	576 (22.7)	532 (21.7)	560 (22.9)

Table 1. Summary of Dietary Recommendations to Participants in the Mediterranean-Diet Groups and the Control-Diet Group.

Food	Goal
Mediterranean diet	
Recommended	
Olive oil*	≥4 tbsp/day
Tree nuts and peanuts†	≥3 servings/wk
Fresh fruits	≥3 servings/day
Vegetables	≥2 servings/day
Fish (especially fatty fish), seafood	≥3 servings/wk
Legumes	≥3 servings/wk
Sofrito‡	≥2 servings/wk
White meat	Instead of red meat
Wine with meals (optionally, only for habitual drinkers)	≥7 glasses/wk
Discouraged	
Soda drinks	<1 drink/day
Commercial bakery goods, sweets, and pastries§	<3 servings/wk
Spread fats	<1 serving/day
Red and processed meats	<1 serving/day
Low-fat diet (control)	
Recommended	
Low-fat dairy products	≥3 servings/day
Bread, potatoes, pasta, rice	≥3 servings/day
Fresh fruits	≥3 servings/day
Vegetables	≥2 servings/wk
Lean fish and seafood	≥3 servings/wk
Discouraged	
Vegetable oils (including olive oil)	≤2 tbsp/day
Commercial bakery goods, sweets, and pastries§	≤1 serving/wk
Nuts and fried snacks	≤1 serving /wk
Red and processed fatty meats	≤1 serving/wk
Visible fat in meats and soups¶	Always remove
Fatty fish, seafood canned in oil	≤1 serving/wk
Spread fats	≤1 serving/wk
Sofrito‡	≤2 servings/wk

Primary Prevention of Cardiovascular Disease with a Mediterranean Diet





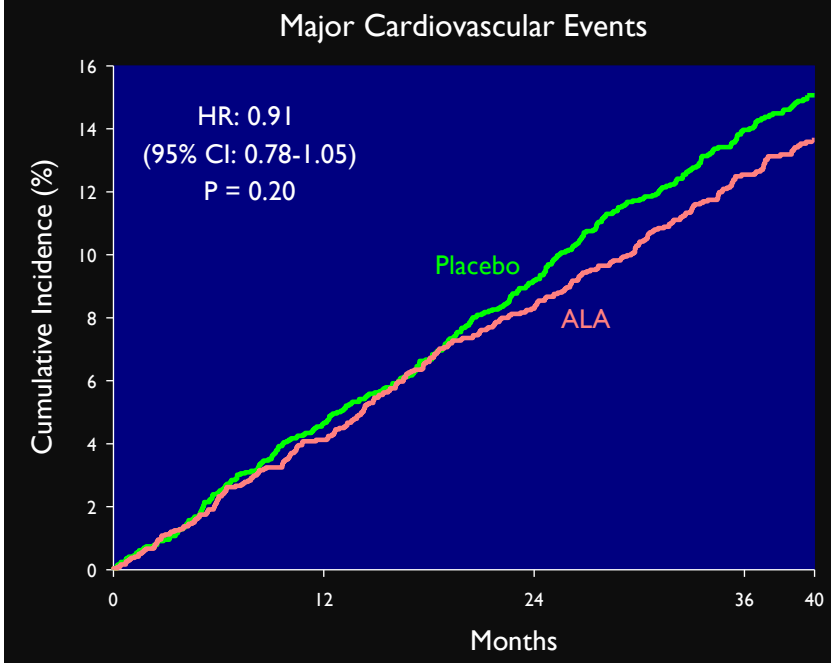
Primary Prevention of Cardiovascular Disease with a Mediterranean Diet

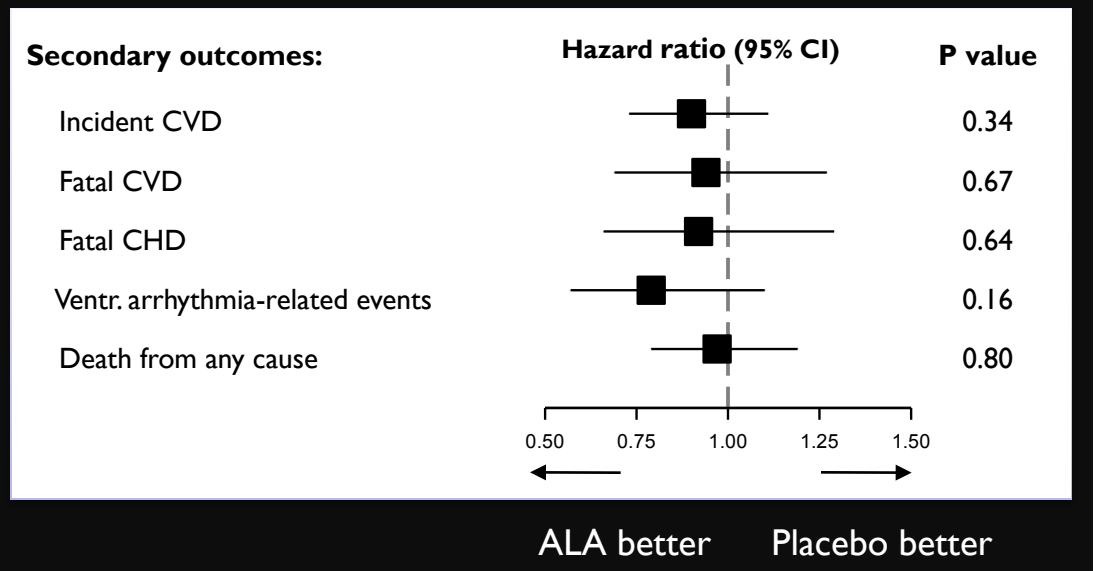
End Point	Mediterranean Diet with EVOO (N=2543)	Mediterranean Diet with Nuts (N=2454)	Control Diet (N=2450)	P Value*	
				Mediterranean Diet with EVOO vs. Control Diet	Mediterranean Diet with Nuts vs. Control Diet
Person-yr of follow-up	11,852	10,365	9763		
Primary end point†					
No. of events	96	83	109		
Crude rate/1000 person-yr (95% CI)	8.1 (6.6–9.9)	8.0 (6.4–9.9)	11.2 (9.2–13.5)	0.009	0.02
Secondary end points					
Stroke					
No. of events	49	32	58		
Crude rate/1000 person-yr (95% CI)	4.1 (3.1–5.5)	3.1 (2.1–4.4)	5.9 (4.5–7.7)	0.03	0.003
Myocardial infarction					
No. of events	37	31	38		
Crude rate/1000 person-yr (95% CI)	3.1 (2.2–4.3)	3.0 (2.0–4.2)	3.9 (2.8–5.3)	0.31	0.25
Death from cardiovascular causes					
No. of events	26	31	30		
Crude rate/1000 person-yr (95% CI)	2.2 (1.4–3.2)	3.0 (2.0–4.2)	3.1 (2.1–4.4)	0.15	0.85
Death from any cause					
No. of events	118	116	114		
Crude rate/1000 person-yr (95% CI)	10.0 (8.2–11.9)	11.2 (9.3–13.4)	11.7 (9.6–14.0)	0.11	0.68
Hazard ratio for each Mediterranean diet vs. control (95% CI)					
Primary end point					
Unadjusted	0.70 (0.53–0.91)	0.70 (0.53–0.94)	1.00 (ref)	0.009	0.02
Multivariable-adjusted 1§	0.69 (0.53–0.91)	0.72 (0.54–0.97)	1.00 (ref)	0.008	0.03
Multivariable-adjusted 2¶	0.70 (0.54–0.92)	0.72 (0.54–0.96)	1.00 (ref)	0.01	0.03
Secondary end points‖					
Stroke	0.67 (0.46–0.98)	0.54 (0.35–0.84)	1.00 (ref)	0.04	0.006
Myocardial infarction	0.80 (0.51–1.26)	0.74 (0.46–1.19)	1.00 (ref)	0.34	0.22
Death from cardiovascular causes	0.69 (0.41–1.16)	1.01 (0.61–1.66)	1.00 (ref)	0.17	0.98
Death from any cause	0.82 (0.64–1.07)	0.97 (0.74–1.26)	1.00 (ref)	0.15	0.82

Conclusion

- L'essai contrôlé randomisé de grande envergure en Nutrition est possible !
- Avec des limites fortes en lien avec l'amplitude des effets testés, la durée, le nombre de sujets, et le financement …
- La réflexion devrait probablement plus s'orienter sur des interventions combinées (style d'alimentation, mode de vie…) mais suffisamment contrastées plus que sur une intervention ne visant qu'un paramètre.

ALA AND ENDPOINTS





Findings differed between men and women

N Engl J Med 2010: 2015