Mediterranean Diet, Traditional Risk Factors, and the Rate of Cardiovascular Complications After Myocardial Infarction
Final Report of the Lyon Diet Heart Study

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Background—The Lyon Diet Heart Study is a randomized secondary prevention trial aimed at testing whether a Mediterranean-type diet may reduce the rate of recurrence after a first myocardial infarction. An intermediate analysis showed a striking protective effect after 27 months of follow-up. This report presents results of an extended follow-up (with a mean of 46 months per patient) and deals with the relationships of dietary patterns and traditional risk factors with recurrence.

Methods and Results—Three composite outcomes (COs) combining either cardiac death and nonfatal myocardial infarction (CO 1), or the preceding plus major secondary end points (unstable angina, stroke, heart failure, pulmonary or peripheral embolism) (CO 2), or the preceding plus minor events requiring hospital admission (CO 3) were studied. In the Mediterranean diet group, CO 1 was reduced (14 events versus 44 in the prudent Western-type diet group, $P=0.0001$), as were CO 2 (27 events versus 90, $P=0.0001$) and CO 3 (95 events versus 180, $P=0.0002$). Adjusted risk ratios ranged from 0.28 to 0.53. Among the traditional risk factors, total cholesterol (1 mmol/L being associated with an increased risk of 18% to 28%), systolic blood pressure (1 mm Hg being associated with an increased risk of 1% to 2%), leukocyte count (adjusted risk ratios ranging from 1.64 to 2.86 with count $>9\times10^9$/L), female sex (adjusted risk ratios, 0.27 to 0.46), and aspirin use (adjusted risk ratios, 0.59 to 0.82) were each significantly and independently associated with recurrence.

Conclusions—The protective effect of the Mediterranean dietary pattern was maintained up to 4 years after the first infarction, confirming previous intermediate analyses. Major traditional risk factors, such as high blood cholesterol and blood pressure, were shown to be independent and joint predictors of recurrence, indicating that the Mediterranean dietary pattern did not alter, at least qualitatively, the usual relationships between major risk factors and recurrence. Thus, a comprehensive strategy to decrease cardiovascular morbidity and mortality should include primarily a cardioprotective diet. It should be associated with other (pharmacological?) means aimed at reducing modifiable risk factors. Further trials combining the 2 approaches are warranted. (***Circulation***. 1999;99:779-785.)

Key Words: diet ■ trials ■ coronary disease ■ myocardial infarction

R ecent dietary trials in secondary prevention of coronary heart disease (CHD) reported impressive reduction of the recurrence rate by a range of 30% to 70%.[1–3] These were in contrast with previous dietary trials, which were aimed at reducing blood cholesterol by a low-cholesterol, low-saturated-fat, high-polyunsaturated-fat diet and failed to significantly improve the overall clinical prognosis of the dieters.[4] The successful trials tested dietary patterns characterized by a low intake of total and saturated fats[2,3] and/or increased intake of marine[1] or plant ω-3 fatty acids[2,3] and were not intended primarily to reduce blood cholesterol. Two of these trials[2,3] also included a high intake of fresh fruits and vegetables, legumes, and cereals containing large amounts of

fibers, antioxidants, minerals, vegetable proteins, and vitamins of the B group. The credibility of these recent trials was considerably reinforced by a number of recent studies showing major cardioprotective effects of most of these foods and nutrients,[5–14] with a particular emphasis on ω-3 fatty acids[8,9] and on folates for their role in hyperhomocysteinemia and in the arginine–nitric oxide–tetrahydrobiopterin pathway,[10–14] 2 possible major mediators in the development of CHD.

The Lyon Diet Heart Study is a randomized, single-blind secondary prevention trial aimed at testing whether a Mediterranean-type diet, compared with a prudent Western-

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TABLE 1.   End Points in the 2 Groups and Risk Ratios for the 3 Composite Outcomes Calculated With the Cox Proportional-Hazards Model

	Control		Experimental			
	Number	Rate*	Number	Rate	Risk Ratio† (95% CI)	P
Major primary end points						
Cardiac deaths	19	1.37	6	0.41	0.35 (0.15–0.83)	0.01
Nonfatal AMI	25	2.70	8	0.83		
Total primary end points (composite outcome 1)	44	4.07	14	1.24	0.28 (0.15–0.53)	0.0001
Noncardiac deaths	5	0.36	8	0.54		
All-cause deaths	24	1.74	14	0.95	0.44 (0.21–0.94)	0.03
Major secondary end points						
Periprocedural infarction	2		0			
Unstable angina	24		6			
Heart failure	11		6			
Stroke	4		0			
Pulmonary embolism	3		0			
Peripheral embolism	2		1			
Total secondary end points	46	4.96	13	1.35		
Total primary+secondary end points (composite outcome 2)	90	9.03	27	2.59	0.33 (0.21–0.52)	0.0001
Minor secondary end points						
Stable angina	29		21			
Elective myocardial revascularization	45		37			
Post-PTCA restenosis	15		9			
Thrombophlebitis	1		2			
Total minor end points	90	9.71	68	7.04		
Total major and minor end points (composite outcome 3)	180	18.74	95	9.63	0.53 (0.38–0.74)	0.0002

AMI indicates acute myocardial infarction.

*The rates are given per 100 patients per year of follow-up; they were calculated from a follow-up of 1383 and 1467 person-years for mortality in the control and experimental groups, respectively, and 927 and 966 person-years for nonfatal events.

†To calculate the risk ratios, only the time of first event (major, primary or minor, secondary end points) was used, adjusted for age, sex, smoking, cholesterol, systolic blood pressure, leukocyte count, and aspirin usage.

type diet, may reduce recurrence after a first myocardial infarction.[3] We previously reported a significant reduction of the rates of cardiovascular complications,[3,15] and no major bias was detected in the trial.[16] However, despite confluent epidemiological and clinical data supporting the results,[5–14] certain commentators put forth the relatively small number of events, the wide CIs of the risk ratios at the intermediate analysis, and hence the uncertainty regarding the true reduction of risk. In this report, we present data resulting from an extended follow-up, providing a total of 275 events over a mean follow-up of 46 months per patient. We also examined the relationships between traditional risk factors, dietary patterns, and the occurrence of complications.

Methods

The design, methods, and results of an intermediate analysis of the Lyon Diet Heart Study have been reported.[3,15,16] Briefly, consecutive patients who survived a first myocardial infarction were randomized between March 1988 and March 1992. Eligible patients were <70 years old, were clinically stable, and had no medical or social

conditions that would limit their ability to participate in a dietary trial.

Inclusion of patients was based on a modified Zelen design.[17] Briefly, during their stay in hospital, patients were asked to participate in a cohort study with a follow-up of 5 years. They were not fully informed about the design of the study, especially regarding the comparison of 2 diets. Patients assigned to the experimental group were asked to comply with a Mediterranean-type diet and had to sign a second consent form. Patients of the control group received no dietary advice from the investigators but nonetheless were advised to follow a prudent diet by their attending physicians.[3]

An intermediate analysis was proposed by the Scientific Committee to be performed in March 1993, clinical data being frozen after a minimum follow-up of 1 year for each patient. Because of a statistically significant result, the decision was made to stop the trial. The first report was published in June 1994.[3] For ethical, medical, and scientific reasons, all patients were invited to come to the Research Unit for a final visit, during which they were fully informed about the main results of the trial. Hence, given the delay after the clinical status of the 2 groups in March 1993, the decision to invite the patients to a new assessment, and the time needed to see each patient, an additional follow-up of ≈19 months was available in the 2 groups to perform the final analyses. This offered the
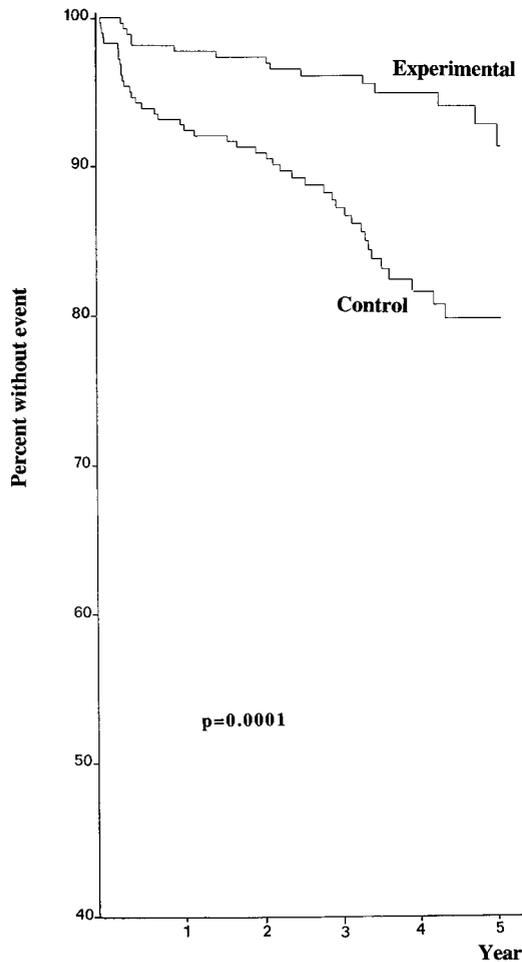
Figure 1. Cumulative survival without nonfatal myocardial infarction (CO 1) among experimental (Mediterranean group) patients and control subjects.

Figure 2. Cumulative survival without nonfatal infarction and without major secondary end points (CO 2).

opportunity to evaluate the long-term (mean, 4 years) effect of the diet tested in the trial and whether the patients continued to comply with it.

As in the previous analysis, only clinical events requiring hospital admission were considered. The End-Point Committee met for a final and blinded evaluation of the raw data obtained from hospital files and, for patients who had died, from the civil status office of the patient's birthplace. Definitions of the end points were reported previously,[3,15,16] and the basic principles of the experimental diet have been described.[3,15,16] In practical terms, the dietary instructions were detailed and customized to each patient,[16] and a dietary survey at each visit allowed us to check for adhesion and compliance to the experimental diet. In addition, plasma fatty acids were analyzed (gas-liquid chromatography) in the 2 groups as described[3] and used as objective biomarkers.

Analyses were done on the intention-to-treat principle. Event-free survival for myocardial infarction, cardiovascular death, and 3 composite outcomes (COs) were estimated by the Kaplan-Meier method. The censoring date was the date of the earliest event or the end of follow-up. The Cox proportional-hazards model was used to calculate the risk ratios and to quantify the associations between each traditional risk factor and the different COs, namely myocardial infarction plus cardiovascular death (CO 1); myocardial infarction plus cardiovascular death plus major secondary events including episodes of unstable angina, as previously defined,[3,15] episodes of overt heart failure, stroke, or pulmonary or peripheral embolism (CO 2); or the preceding plus minor events requiring hospital admission, including recurrent stable angina, postangioplasty restenosis, surgi-
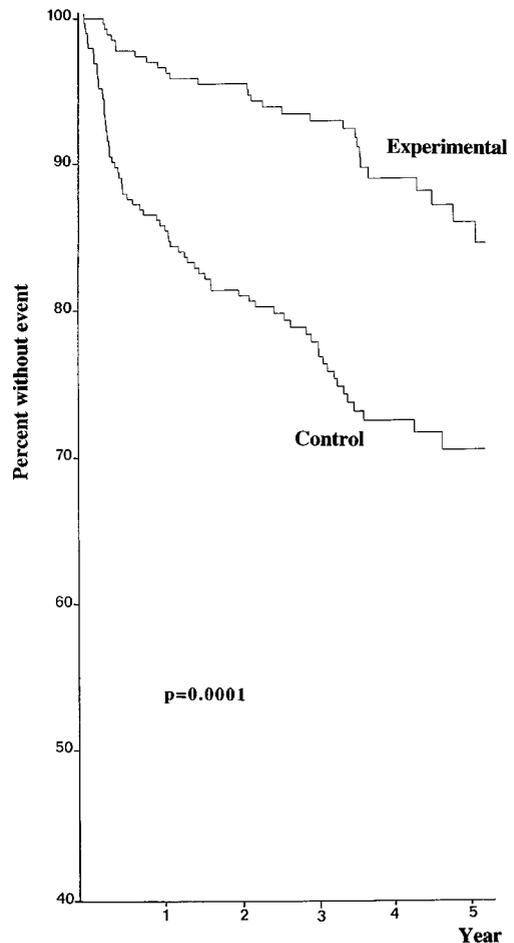
cal or medical myocardial revascularization, and thrombophlebitis (CO 3). Also considered in a separate analysis were the medications recorded 2 months after randomization. Because the use of lipid-lowering drugs varied considerably during the study in France, these drugs were not included in these analyses. This point has been described and analyzed elsewhere.[16]

Results

The great majority (93.4% of control and 92.4% of experimental subjects) of patients still alive and not censored at the time of the final visit in the 2 groups agreed to come to the Research Unit. Among the patients who did not come for a final visit (15 control and 19 experimental), the vital status was unknown for 4 patients (3 control and 1 experimental). Mean follow-up for survival was 44.9 months in the control group and 46.7 months in the experimental group. The numbers and rates of new events are shown in Table 1. All-cause and cardiovascular ($P=0.01$) mortality and the combination of recurrent myocardial infarction and cardiac death (CO 1, $P=0.0001$) were reduced. The combined major primary and secondary end points (CO 2, 90 events versus 27 and CO 3, 180 events versus 95, giving an adjusted risk ratio of 0.53, $P=0.0002$) were also reduced. Event-free survival curves are shown in Figures 1 through 3.

Main cardiovascular risk (or prognosis) factors and the mean daily nutrient intake recorded on the final visit are
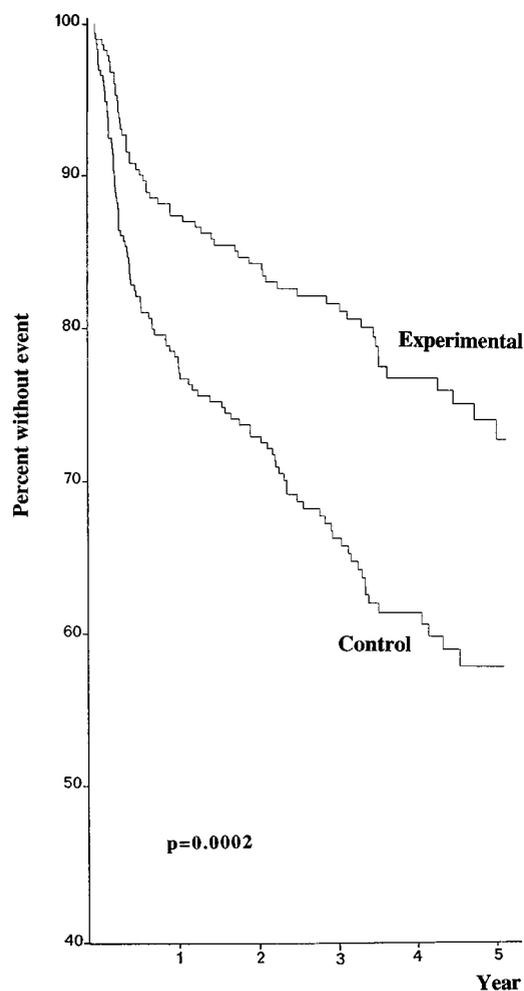
Figure 3. Cumulative survival without nonfatal infarction, without major secondary end points, and without minor secondary end points (CO 3).

given in Tables 2 and 3. Data are quite similar to those recorded at and 2 months after randomization.[3]

Univariate associations between major risk factors recorded 2 months after randomization (data not shown) and the 3 composite outcomes are shown in Table 4. Among the medications used (data not shown), only aspirin was significantly (and inversely) associated with the outcomes and was then included in the multivariate analyses. A threshold effect was observed with leukocyte count (quartile analyses), with a markedly increased risk when the count was $>9\times10^9$/L. Thus, leukocyte count was used as a categorical variable, whereas total cholesterol and blood pressure (no J-shaped curve) were used as continuous variables in further analyses.

With regard to any association between the plasma concentration of major fatty acids and recurrence, only 18:3(ω-3) and 22:6(ω-3) tended to be inversely associated with recurrence ($P=0.11$ and $P=0.16$, respectively, versus CO 1).

Then, the effect of traditional risk factors on recurrence was analyzed with the multivariate Cox proportional-hazards model (Table 5). When the plasma fatty acid concentrations were entered into the model, 18:3(ω-3) was the only fatty acid significantly associated with CO 1 (risk ratio, 0.20; 95% CIs, 0.05 to 0.84 after adjustment for age, sex, smoking, total

TABLE 2. Main Risk Factors and Selected Biological Parameters Recorded on the Final Visit

	Control (n=204)	Experimental (n=219)
Body mass index, kg/m^2	26.9 (3.4)	26.3 (3.7)
Systolic blood pressure, mm Hg	128 (16)	128 (17)
Diastolic blood pressure, mm Hg	79 (10)	78 (11)
Total cholesterol, mmol/L	6.18 (1.04)	6.20 (1.06)
Triglycerides, mmol/L	1.75 (0.83)	1.94 (0.85)
HDL-cholesterol, mmol/L	1.28 (0.34)	1.29 (0.34)
LDL-cholesterol, mmol/L	4.23 (0.98)	4.17 (0.93)
Lipoprotein (a), g/L	0.35 (0.49)	0.33 (0.35)
Albumin, g/L	47.10 (2.88)	47.28 (3.07)
Glycated hemoglobin, %	4.61 (1.23)	4.66 (1.52)
Creatinine, μmol/L	116 (20)	115 (21)
Uric acid, μmol/L	348 (81)	338 (87)
Leukocyte count, $\times10^9$/L	6.00 (1.69)	5.99 (1.68)
Current smokers, %	17.9	18.3
Medication, %		
Anticoagulant agents	16.1	11.4
Antiplatelet agents	69.7	75.8
β-Blocking agents	47.3	47.5
Calcium channel blockers	28.4	25.6
ACE inhibitors	17.4	18.3
Lipid-lowering drugs	34.0	26.5

Values are mean (SD).

cholesterol, blood pressure, leukocyte count, and aspirin use). With regard to the effect of 18:3(ω-3) on CO 2 and CO 3, the associations were borderline nonsignificant ($P=0.08$ and $P=0.12$).

Discussion

Including a total of 275 events recorded during a mean follow-up of 46 months, this report shows that longer

TABLE 3. Daily Nutrient Intake Recorded on the Final Visit in 83 Control and 144 Experimental Nonselected Consecutive Patients

	Control	Experimental	P
Total calories	2088 (490)	1947 (468)	0.033
% calories			
Total lipids	33.6 (7.80)	30.4 (7.00)	0.002
Saturated fats	11.7 (3.90)	8.0 (3.70)	0.0001
Polyunsaturated fats	6.10 (2.90)	4.60 (1.70)	0.0001
18:1(ω-9) (oleic)	10.8 (4.10)	12.9 (3.20)	0.0001
18:2(ω-6) (linoleic)	5.30 (2.80)	3.60 (1.20)	0.0001
18:3(ω-3) (linolenic)	0.29 (0.19)	0.84 (0.46)	0.0001
Alcohol	5.98 (6.90)	5.83 (5.80)	0.80
Proteins, g	16.6 (3.80)	16.2 (3.10)	0.30
Fiber, g	15.5 (6.80)	18.6 (8.10)	0.004
Cholesterol, mg	312 (180)	203 (145)	0.0001

Values are mean (SD).

TABLE 4. Univariate Associations Between Traditional Risk Factors and the 3 COs

	Conditional Risk Ratios and 95% CIs		
Variables	CO 1	CO 2	CO 3
Diet group (Mediterranean vs control)	0.23 (0.11–0.48)*	0.30 (0.18–0.51)*	0.51 (0.35–0.73)*
Age, y	0.98 (0.95–1.02)	1.00 (0.98–1.03)	1.00 (0.98–1.02)
Sex, male vs female		0.60 (0.18–2.01)	0.87 (0.39–1.94)
Smoking, yes or no	1.50 (0.67–3.37)	1.52 (0.81–2.88)	0.98 (0.57–1.69)
Total cholesterol, mmol/L	1.31 (1.05–1.65)*	1.31 (1.10–1.57)*	1.22 (1.06–1.40)*
HDL cholesterol, mmol/L	0.59 (0.17–2.10)	0.42 (0.16–1.12)	0.50 (0.24–1.04)
Systolic blood pressure, mm Hg	1.01 (0.98–1.03)	1.02 (0.99–1.04)	1.00 (0.99–1.01)
Diastolic blood pressure, mm Hg	1.01 (0.97–1.05)	0.99 (0.96–1.02)	1.01 (0.99–1.03)
Blood glucose, mmol/L	1.11 (0.89–1.36)	1.03 (0.89–1.18)	0.96 (0.84–1.09)
Serum albumin, g/L	0.97 (0.89–1.06)	0.97 (0.91–1.04)	1.00 (0.95–1.05)
Leukocyte count, $\times 10^9$/L	1.48 (1.06–2.07)*	1.49 (1.16–1.90)*	1.07 (0.87–1.32)
Neutrophil count, $\times 10^9$/L	0.81 (0.53–1.23)	0.76 (0.55–1.04)	1.05 (0.80–1.38)

See Table 1 for the definitions of the COs. Risk ratios are calculated with the Cox proportional-hazards model.
*Significant associations ($P<0.05$).

follow-up and inclusion of more events in the analyses do not substantially alter the picture in the Lyon Study and confirms the results of the intermediate analysis.[3,15] Also, the influence of the risk factors on prognosis was similar to that reported in other low-risk populations, indicating that a low-fat Mediterranean diet does not qualitatively alter the usual relationships between the risk factors and recurrence rate.

Mediterranean Dietary Pattern and Recurrence

The rate of cardiac death and nonfatal infarction in the experimental group after 46 months (1.24 per hundred patients per year) is similar to that observed after 27 months (1.32). The rate in control subjects was 4.07 after 46 months, whereas it was 5.55 after 27 months.[3] Hence, the data confirm the impressive protective effect of the Mediterranean diet.

It has been argued that it is easier to prescribe drugs than to change the dietary habits of patients, a task often considered to be difficult; and unfortunately, after some attempts, many physicians do give up. This study shows that several years after randomization, most experimental patients were still closely following the Mediterranean diet recommended to them. This suggests, in contrast to the current opinion, that the adoption of and compliance with new dietary habits is not so difficult, provided that the instruction of patients (and of their families) and surveillance are properly (professionally) conducted.[16] Of course, the new dietary habits need to be financially and gastronomically acceptable and practically feasible for patients (and their relatives) who often have to adapt to a difficult working environment and the stressful urban way of life. Finally, it should be emphasized that taking 1 or several drugs prescribed by their attending physician, as most of the patients did in the 2 groups of the present trial, is not incompatible with the adoption of new dietary habits. This trial even supports the view that pharmacological treat-

TABLE 5. Multivariate Proportional-Hazards Analyses Associating Selected Traditional Risk Factors With the 3 COs

	Conditional Risk Ratios and 95% CIs		
Variables	CO 1	CO 2	CO 3
Diet group (Mediterranean vs Western)	0.28 (0.15–0.53)*	0.33 (0.21–0.52)*	0.53 (0.38–0.74)*
Age, y	0.99 (0.96–1.02)	1.00 (0.98–1.02)	0.99 (0.98–1.02)
Sex, male vs female		0.27 (0.09–0.86)*	0.46 (0.22–0.96)*
Smoking, yes or no	1.65 (0.82–3.32)	1.41 (0.81–2.48)	0.96 (0.58–1.57)
Total cholesterol, mmol/L	1.28 (1.03–1.59)*	1.21 (1.02–1.43)*	1.18 (1.04–1.34)*
Systolic blood pressure, mm Hg	1.02 (1.00–1.03)*	1.01 (1.00–1.02)*	1.01 (0.99–1.02)
Leukocyte count, > or $\leq 9 \times 10^9$/L	2.86 (1.58–5.29)*	2.21 (1.36–3.61)*	1.64 (1.08–2.49)*
Aspirin use, yes or no	0.59 (0.35–1.01)	0.63 (0.41–0.94)*	0.82 (0.59–1.14)

*Significant ($P<0.05$) associations.

ment (for instance, with aspirin) and dietary prevention had additional and independent beneficial effects.

Blood Pressure, Smoking, Cardiovascular Medications, and Recurrence

In multivariate analyses, blood pressure, but not smoking, was significantly and independently associated with recurrence. It should be noted, however, that we did not analyze the effect of the true blood pressure of each patient because many of them were taking at least 1 pressure-lowering drug as part of a systematic secondary prevention treatment.

In secondary prevention, it is usually the effect of current (and not past) smoking that is analyzed. In the present cohort, <20% of the patients in the 2 groups were current smokers on the final visit. It is therefore likely that, in this population with a low prevalence of smoking, the number of events was too small and the length of follow-up too short to allow an actual evaluation of the true effect of persistent smoking.

The effects of cardiac medications in this study were quite disappointing, because only aspirin was consistently associated with a protective effect. However, the study was not designed primarily to test these medications, and data should be interpreted cautiously. It is nonetheless noteworthy that, in secondary prevention, the effect of β-blockers was shown to be quite small[18] and that such low efficacy was probably difficult to demonstrate in a low-risk population. The same reasoning can apply to calcium channel blockers, whose effect (either protective or deleterious) is the object of a bitter controversy.[19]

Plasma Fatty Acids and Recurrence

Major difficulties in randomized dietary trials are the prevention of "attending physician bias"[16] and between-group contamination during follow-up. For that purpose, patients were not fully informed that they were participating in a dietary trial with the comparison of 2 diets. The lack of knowledge of that comparison by the patients of both groups (and by their attending physicians) may minimize the physician bias.[16] Thus, in the first part of the study, the dietary habits of the control patients were not investigated and recorded so as not to influence them. Consequently, we cannot include their dietary parameters in the Cox model to prospectively analyze their relationships with recurrence. Instead, we used the plasma fatty acids measured 2 months after randomization as crude estimates of dietary data. Only α-linolenic acid was significantly associated with an improved prognosis, which is in agreement with a recent study reporting a negative correlation between the intake of α-linolenic acid and the risk of myocardial infarction.[20] Conversely, we did not find any correlation between long-chain ω-3 fatty acid and recurrence. Several animal[21] and clinical[1–3,8,9] studies, however, have shown the beneficial effects of these fatty acids on CHD, whereas a few studies were apparently inconsistent, even putting forth the hypothesis that high dosages may be noxious.[22] In moderate amounts, such as are consumed in the traditional Mediterranean diet, the protective effects of ω-3 fatty acids are probably related to their multiple actions on the various factors that modulate the cascade of events leading to acute myocardial ischemia and its acute complications, in

particular sudden death.[23] It is likely that the lack of significant correlations (although a trend toward protection was observed) in this study may be partly explained by the relatively small number of sudden deaths and fatal myocardial infarctions, which are apparently the main types of complications prevented by moderate consumption of these fatty acids.[8,9]

Blood Cholesterol, Leukocyte Count, and Recurrence

As expected, total cholesterol and leukocyte count were major independent and joint predictors of recurrence, along with the dietary pattern. A leukocyte count $>9\times10^9$/L increased the risk by a factor of 1.6 to 2.9, and each increase of 1 mmol/L of total cholesterol increased the risk of recurrence by 20% to 30%. Epidemiological studies have consistently shown a positive correlation between plasma cholesterol levels and the incidence of (and mortality from) CHD in various populations.[24,25] Thus, our population does not appear to be different from other low-risk populations.[25,26] In other words, the data indicate that neither the Mediterranean dietary pattern nor any major bias has altered the usual and expected relationships between the major risk factors of CHD and recurrence.

Leukocyte count also has been shown to be a marker for increased risk of CHD mortality in many studies.[27] In most studies, this effect is partly independent of smoking. A plausible mechanism to explain this relationship is that leukocytes are involved not only in the inflammation and ulceration of the arterial lesion[28] but also in the exacerbation of acute myocardial ischemia. This may ultimately result in an increased infarct size, the major determinant of postinfarction survival. Experimental studies have indeed suggested the implication of leukocytes in acute myocardial ischemia,[29] and human and animal studies have consistently shown that leukocytes play a role in the severity of ventricular arrhythmias during ischemia.[29,30] In this study, high leukocyte count was associated with an increased risk of major acute coronary events, such as cardiac death and acute infarction (risk ratio, $\approx$3), whereas the association was lower (risk ratio, 1.6) when recurrent stable angina and the need for myocardial revascularization were considered, suggesting that leukocytes are more important in acute myocardial complications than in the development of subacute coronary artery lesions.

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