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Effect of a Mediterranean Type of Diet on the Rate of Cardiovascular Complications in Patients With Coronary Artery Disease

Insights Into the Cardioprotective Effect of Certain Nutriments

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Objectives. **We sought to describe the various cardiovascular complications that occurred in the Lyon Diet Heart Study (a secondary prevention trial testing the protective effects of a Mediterranean type of diet), to analyze their relations with the associated drug treatments and to gain insights into the possible mechanisms underlying the beneficial effects of certain nutriments.**

Background. **Dietary habits are implicated in coronary heart disease, and the traditional Mediterranean diet is thought to be cardioprotective. However, the exact mechanisms of this protection are unknown.**

Methods. **A total of 605 patients (303 control subjects and 302 study patients) were studied over a mean period of 27 months. Major primary end points (cardiovascular death and nonfatal acute myocardial infarction), secondary end points (including unstable angina, stroke, heart failure and embolisms) and minor end points (stable angina, need for myocardial revascularization, postangioplasty restenosis and thrombophlebitis) were analyzed separately and in combination.**

Results. **When major primary and secondary end points were combined, there were 59 events in control subjects and 14 events in the study patients, showing a risk reduction of 76% ($p < 0.0001$). When these end points were combined with the minor end points, there were 104 events in control subjects and 68 events in the study patients, giving a risk reduction of 37% ($p < 0.005$). By observational analysis, only aspirin among the medications appeared to be significantly protective (risk ratio after adjustment for prognosis factors 0.45; 95% confidence interval 0.25 to 0.80).**

Conclusions. **These data show a protective effect of the Mediterranean diet. However, the risk reduction varied depending on the type of end point considered. Our hypothesis is that different pathogenetic mechanisms were responsible for the development of the various complications. It is likely that certain nutriments characteristic of the Mediterranean diet (omega-3 fatty acids, oleic acid, antioxidant vitamins) have specific cardioprotective effects.**

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Although dietary habits were thought to be implicated in coronary heart disease and previous dietary trials showed inconsistent results (1), few controlled dietary trials were initiated during the last decade, probably because of the many technical difficulties inherent in such studies. However, previous simplistic hypotheses were finally abandoned and the need for multifactorial intervention was recognized (1–3). In particular, the concept of the traditional ethnic cardioprotective diet recently emerged (1–5).

The Lyon Diet Heart Study, whose primary results have been published (3), is a secondary prevention trial that demonstrated a protective effect of a Mediterranean type of diet in survivors of a first recent myocardial infarction. Because a chance effect could not be totally eliminated although recent dietary trials in Great Britain (2) and India (4), based on similar approaches, showed results comparable to those of the Lyon study, complementary data regarding secondary and minor end points may help to evaluate plausibility of the results. The aims of the present study were therefore to report the various cardiovascular events that occurred in the control and study groups during the Lyon trial, to analyze their relation with the associated drug treatment and to gain insights into the possible mechanism or mechanisms underlying the beneficial effects of the Mediterranean type of diet tested in the trial.

Methods

Study design and participants. The study design, participants and most of the methods of the Lyon Diet Heart Study have been described (3). Briefly, the study is a randomized single-blind trial to test the hypothesis that a Mediterranean type of diet may reduce the risk of cardiovascular complica-

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Abbreviations and Acronyms
ACE = angiotensin-converting enzyme
CI = confidence interval
ECG = electrocardiogram

tions in survivors of a first acute myocardial infarction. A two-step recruitment technique, a modification of the Zelen design (6), was used. Patients who agreed to be followed up for 5 years by the Research Unit (annual visit including clinical examination by a cardiologist, electrocardiogram (ECG) and blood sampling for routine biologic measurements) signed a first consent form and were randomly assigned to a control or a study group. At this stage, patients of both groups were not fully informed about the study and only patients randomized to the study group were invited to sign a second consent form in which they agreed to adopt a Mediterranean type of diet. This design was used 1) to avoid between-group contamination, a major difficulty in dietary trials; and 2) to avoid influencing how physicians would follow up and treat their patients in the event of new symptoms or a heart attack. It was indeed suspected that knowledge of group assignment by physicians in both groups could cause them, consciously or not, to modify their usual practice and consequently influence results of the trial. Thus, control subjects did not receive dietary information from the investigators of the study. They were expected to follow the dietary advice given by their attending physicians, similar to that of step 1 of the prudent diet of the American Heart Association.

After the randomization visit, patients of both groups were scheduled to be seen 2 months later and then annually at the Research Unit. These visits did not replace their regular visits to the attending physicians, who were responsible for all aspects of treatment, including use of medication and of invasive diagnostic and therapeutic procedures.

The main characteristics of the Mediterranean type of diet tested in the study group have been previously reported (3,5). Briefly, this diet was designed to supply 1) <35% of energy as fat; 2) <10% of energy as saturated fat; 3) <4% of energy as linoleic acid [18:2 (n-6)]; 4) >0.6% of energy as alpha-linolenic acid [18:3 (n-3)]. In practical terms, the dietary instructions were personalized and described in detail to each patient. The techniques used to obtain changes derived from those recommended in other contexts by Erickson and Rossi (7) and Watzlawick (8). Briefly, patients were advised to modify their regular diet in two stages. The aim of stage 1 was to prepare patients to accept the detailed instructions given in the second stage. Stage 2 of the intervention was conducted by the dietitian of the study and consisted of helping patients and their family to adapt their usual diet to the Mediterranean type of diet tested in the trial. At this stage the dietitian needed to take into account such factors as the wishes and gastronomic preferences of the patients, the geographic origin of the family (e.g., south or north of France, Spain, Italy, North Africa), the job of the patient, the number of persons at home, financial resources and community where the family lives (e.g., center of city, small village). Instructions had to be detailed, easy to execute, safe, not expensive and compatible with the way of living (e.g., unmarried, couple, large family, retired), race, gender and religion of each patient.

Primary and secondary end points. Whereas cardiovascular death and nonfatal acute myocardial infarction were the primary end points of the trial, secondary end points were also scrupulously documented and recorded provided they required hospital admission. These end points included 1) episodes of unstable angina (defined as spontaneous rest angina, decubitus and nocturnal angina or exercise angina that recently increased in frequency or duration or that was increasingly resistant to antianginal therapy); 2) recurrent stable angina whose severity necessitated in-hospital invasive investigations; 3) episodes of overt heart failure (New York Heart Association functional class III or IV); 4) transient or permanent cerebral stroke; 5) pulmonary embolism; 6) peripheral arterial embolism; 7) thrombophlebitis; 8) need for myocardial revascularization (angioplasty or bypass surgery, or both); 9) postangioplasty restenosis (diagnosis based on the association of recurrent angina and confirming angiography).

Among patients admitted to the hospital with the diagnosis of unstable or stable angina, only those who underwent coronary angiography to document severity and aspects of coronary lesions were included in the analysis. The need for myocardial revascularization (bypass surgery or percutaneous coronary angioplasty) and periprocedural complications (myocardial infarction and clinically significant coronary artery restenosis after angioplasty) were also considered secondary end points.

Detailed information on each end point was collected from hospital records, and raw data were reviewed in blinded manner, validated and classified according to predefined criteria by the two experienced cardiologist members of the Endpoint Committee (3).

Statistical analysis. Analyses were performed according to the intention-to-treat principle and with the use of two-sided tests. In life-table analyses and the Cox model, the time of the first event (either major primary, secondary or minor end point) was used. The log-rank test was used to compare survival curves, and adjusted risk ratios were calculated by the Cox proportional hazards model. In analyses of combined end points, end points were mutually exclusive. We also examined the protective role of the anti-ischemic or major cardiac drugs, including anticoagulant agents, aspirin, beta-adrenergic blocking agents, calcium-channel blocking agents and inhibitors of the angiotensin-converting enzyme (ACE).

To analyze the relation between drug treatment and the occurrence of new complications, we included in the calculations only the major complications: the combination of cardiac death and nonfatal infarction and this combination plus cerebral stroke, unstable angina, heart failure, pulmonary and peripheral embolism.

Table 1. Use of Anti-Ischemic and Major Cardiac Drugs

	Study Group		Control Group	
	Baseline	1st Year	Baseline	1st Year
Oral anticoagulant agents	29.4%	21.8%	26.4%	18.7%
Aspirin	64.8%	65.3%	62.6%	60.9%
Beta-blocking agents	60.2%	47.6%*	63.4%	47.4%*
Calcium channel blockers	20.4%	25.8%	21.7%	29.5%
ACE inhibitors	9.3%	15.2%	6.1%	9.2%

*$p < 0.05$ versus baseline. Similar figures were observed during follow-up beyond the 1st year. Data presented are percent of patients in group. ACE = angiotensin-converting enzyme.

Results

The main data of the Lyon Diet Heart Study regarding patient accrual, baseline characteristics, follow-up and rate of withdrawal have been reported (3). Although recruitment was started in March 1988, an intermediate analysis was proposed by the Scientific Committee after a follow-up period of ≥1 year for each patient. This analysis was performed in March 1993 (3).

A total of 605 patients (303 control subjects and 302 study patients) were randomized and included into the analysis. Patients were primarily male, with a male/female ratio of ~90/10 in both groups. The mean age ± SD was 53.5 ± 10 years in both groups. Other baseline characteristics except for smoking were similar in both groups. The proportion of smokers at randomization was higher in the study group (7.6%) than in the control group (4.9%, $p < 0.05$); after 1 year, the difference (19% vs. 15%) was not significant and continued to be insignificant in subsequent years.

The use of anti-ischemic agents and ACE inhibitors did not differ between groups at randomization or during follow-up (Table 1). Aspirin use was stable during follow-up, indicating that the drug is well tolerated at low dosage (~250 mg/day) in such patients, whereas the use of anticoagulant agents decreased slightly after 1 year, a reduction that is concordant with the current practice of French physicians. Between randomization and the 1-year visit, there was a small but significant ($p < 0.05$) reduction in the use of beta-blocking agents in both groups that suggests either that these agents were not well tolerated or that physicians were not persuaded of their usefulness beyond the 1st year after infarction. For calcium channel blockers and ACE inhibitors, there was a nonsignificant tendency to increased use after 1 year, probably to compensate for the reduced use of beta-blockers.

Taken together, the data regarding medication use show a parallel course in the two groups over the years, which suggests that the participation of patients in the trial did not influence the current practice of the attending physicians in either group. This is a major point to be considered when discussing the question of physician bias in a single-blind trial such as the Lyon study (see later discussion).

Primary and secondary end points. Results for the primary end point (combination of cardiovascular death and nonfatal acute myocardial infarction) have been reported (3). These data are summarized in Table 2, which also summarizes data on major and minor secondary end points. The results are based on a total of 594 person-years in the control group and 606 person-years in the study group.

Table 2. Primary and Major and Minor Secondary End Points in the Two Groups

	Control Group (n = 303)		Study Group (n = 302)	
	Events (no.)	Rate*	Events (no.)	Rate*
Major primary end points				
CV deaths	16	2.69	3	0.50
Nonfatal myocardial infarction	17	2.86	5	0.82
Subtotal	33	5.55	8	1.32
Non-CV deaths	4	0.67	5	0.82
Overall mortality	20	3.37	8	1.32
Major secondary end points				
Periprocedural infarction	2		0	
Unstable angina	21	3.53	4	0.66
Nonfatal heart failure	8	1.35	2	0.33
Stroke	3		0	
Pulmonary embolism	2		0	
Peripheral embolism	1		0	
Subtotal	37	6.23	6	0.99
Minor secondary end points				
Stable angina	27	4.54	17	2.81
Elective myocardial revascularization (angioplasty/bypass surgery)	41	6.90	31	5.11
Postangioplasty restenosis	15	2.53	9	1.49
Thrombophlebitis	1		1	
Subtotal	84	14.14	58	9.57

*Per 100 patients per year of follow-up. CV = cardiovascular.

To be noted is the large difference between groups in the number of new infarctions and episodes of unstable angina. When primary and major secondary end points were combined in the proportional hazards model, there were 59 events in the control group and 14 in the study group. The risk ratio was 0.24 (95% confidence interval [CI] 0.13 to 0.44, $p < 0.0001$) after adjustment for age, gender, smoking status, serum cholesterol, systolic blood pressure and infarct location. Survival curves are shown in Figure 1.

When the preceding major primary and secondary end points were combined with the minor end points in the same way as before, there were 104 events in the control group and 68 in the study group, giving a risk ratio of 0.63 (95% CI 0.46 to 0.87, $p < 0.005$). Survival curves are shown in Figure 2.

Relations between medication use and the various end points. Regarding combined cardiac death and nonfatal acute myocardial infarction (n = 41), the use of aspirin was the sole factor significantly (and inversely) associated with new events (Table 3A). When secondary end points were added to the analysis (n = 73, Table 3B), aspirin use remained significantly and inversely associated with new events. The use of anticoagulant agents and ACE inhibitors became of borderline significance.

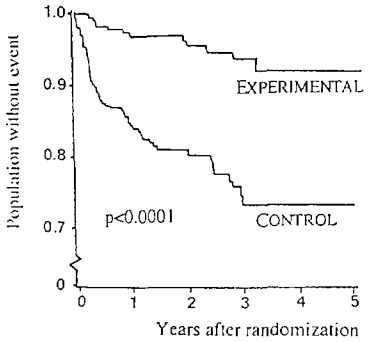

Figure 1. Survival curves for combined cardiac death, nonfatal infarction, unstable angina, heart failure, stroke and thromboembolism. Log-rank test using the time of the first event was used to compare the control and study (EXPERIMENTAL) groups. There was already a striking difference between the two groups within the 1st year ($p < 0.0001$).

Discussion

Summary of results. These data extend the finding that the Mediterranean type of diet tested in the trial was protective in survivors of a first infarction. The absolute number of events is a critical point to be considered when examining the results of any trial. Whereas the combination of cardiovascular death and nonfatal infarction was the primary end point used in the statistical calculations to define sample size and duration of follow-up, secondary and minor end points (provided they were validated and classified by an independent committee) were also considered. Thirty-seven major secondary events, including cerebral stroke, major episodes of cardiac decompensation, episodes of unstable angina and various types of embolism, occurred in the control group in contrast to six in the study group. The ratio was 33:8 for the primary end points, cardiac death and nonfatal infarction (3). This finding shows that the data on primary and secondary end points are concordant, and it adds plausibility to the overall message of the trial. However, when major primary and secondary events were combined with the minor events, the difference between groups was much less impressive. The reduction of risk was 37% in contrast to 76% when only primary and secondary end points were included. This finding suggests that when more events (104 in the control group vs. 68 in the study group) are included, the difference between groups is attenuated and perhaps more realistic. Another hypothesis is that the pathogenetic mechanisms underlying the various events are different and were differently influenced by the nutriments characteristic of the Mediterranean diet.

Figure 2. Survival curves for combined major primary and secondary end points and minor end points including episodes of stable angina necessitating hospital admission, need for elective myocardial revascularization, postangioplasty restenosis and venous thrombophlebitis. Although statistically significant ($p = 0.0018$), the difference between groups shown here was less impressive than that shown (Fig. 1) when fewer events were included in the analysis (see text for details).

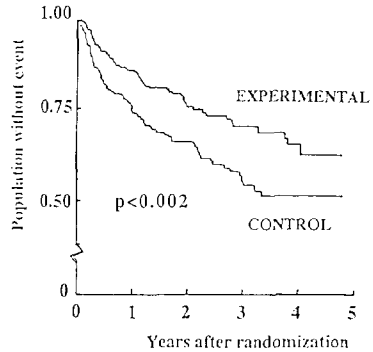

Table 3. Relation Between the Use of Anti-Ischemic and Cardiac Drugs and the Occurrence of New Cardiac Events

	Risk Ratio (95% CI)*
A. Cardiac Death and Nonfatal AMI	
Anticoagulant agents	0.50 (0.22–1.19)
Aspirin	0.46 (0.22–0.99)
Beta-blocking agents	1.05 (0.50–2.22)
Calcium channel blocker	1.82 (0.83–4.02)
ACE inhibitors	2.63 (0.86–8.04)
B. Cardiac Death, Nonfatal AMI and Other Events†	
Anticoagulant agents	0.51 (0.27–0.98)
Aspirin	0.45 (0.25–0.80)
Beta-blocking agents	1.26 (0.72–2.20)
Calcium-channel blocker	1.31 (0.70–2.44)
ACE inhibitors	2.57 (1.17–5.68)

*Risk ratios are given after adjustment for age, gender, diet group assignment, systolic blood pressure, total cholesterol and infarct location (anterior vs. other). †Other events are the major secondary end points described in the Methods section and in Table 2. ACE = angiotensin-converting enzyme; AMI = acute myocardial infarction.

The greatest differences between groups occurred with nonfatal infarction (17 events vs. 5) and unstable angina (21 events vs. 4). This is not surprising because the two complications are related to similar pathogenetic mechanisms (9–11). In both myocardial infarction and unstable angina, localized arterial inflammation, plaque ulceration and acute occlusive or subocclusive thrombosis are thought to be causal mechanisms (9–11). In contrast, recurrent stable angina probably results from the slow progression of the arterial disease, which is probably related to a different mechanism. In addition, the occurrence of certain minor end points such as the need for coronary angiography or revascularization (bypass surgery or angioplasty) depends, at least in part, on the official policy in a given cardiology center or on the beliefs of physicians rather than on objective clinical status alone. Thus, in the present trial, we cannot exclude the possibility of a physician bias; that is, that the physicians of the control group might have managed their subjects more aggressively (using invasive diagnostic and therapeutic procedures more often) than did the physicians of the study patients. However, this possibility is quite unlikely because no difference between the two groups in the use of medication was detectable. Indeed, more intensive drug treatment in the control patients would have been detected if their

physicians had actually intended, consciously or not, to compensate for the difference in diet group assignment by more frequently prescribing anti-ischemic drugs as well as coronary angiography, bypass surgery and angioplasty.

Among the medications used by the patients in the Lyon study, aspirin was significantly and inversely associated with the occurrence of new events. The positive association between ACE inhibitors and the occurrence of new events can probably be explained by the fact that at the time of the study, ACE inhibitors were usually prescribed to patients with a very poor prognosis, with a large anterior infarction or a prior episode of heart failure, or both. Thus, the use of ACE inhibitors in that context should be considered a marker of a major alteration of left ventricular function at the time of randomization rather than a factor implicated in the occurrence of new events.

Which nutriments of the Mediterranean diet were cardioprotective? To evaluate the plausibility of the results of the trial, it is important to try to identify which biologic factors modified by the Mediterranean diet may have been cardioprotective. Two major biologic factors were modified by the intervention: 1) the antioxidant vitamins, alpha-tocopherol and ascorbic acid, which were increased in the plasma of the study patients (3,5); 2) the plasma fatty acid profile, with a noticeable increase in omega-3 fatty acids and a decrease in omega-6 fatty acids in the study group (3,5). Other factors such as the antioxidant flavonoids (12) and minerals, arginine, glutamine and methionine (13–15) and vitamins of the B group including folic acid (16,17) probably played important roles but were not measured in the study.

Favorable effects of omega-3 fatty acids were reported in association with elevation of their plasma levels (18), for instance, antiarrhythmogenic effect (19–21). A low fat diet enriched in monounsaturated fatty acids (22,23) is also characteristic of the Mediterranean diet, and its favorable effects have been extensively discussed (24).

In fact, several lines of evidence indicate that the major mechanisms leading to acute arterial manifestations—in particular, sudden death, unstable angina and myocardial infarction—in various conditions including heart transplantation (25–28) are localized inflammation and immune-mediated processes with macrophage infiltration (29) preceded or followed, or both, by lipid modification (oxidation) and accumulation. These initiating events eventually lead to lesion hemorrhage, plaque ulceration and rupture and, ultimately, occlusive or subocclusive coronary thrombosis (10,11). Some of these processes were apparently prevented in the study patients of the Lyon trial.

The next question therefore should be whether certain nutriments of the Mediterranean diet are able to prevent or reduce plaque inflammation. Recent studies in humans (30,31) have shown a direct influence of dietary fatty acids on the fatty acid composition of arterial lesions. Rapp et al. (30) reported the incorporation of dietary omega-3 fatty acids in obstructive arterial lesions within some days after starting supplementation. The striking feature of their study conducted in humans was the rapidity with which the atherosclerotic lesions were loaded with omega-3 fatty acids. The arterial lesions at risk of rupture are known to be lipid-rich, young and not very fibrotic or very stenotic (25–27). Incorporation of new fatty acids at a rapid rate by means of dietary changes in young and dangerous lesions is thus conceivable in patients who have consumed an alpha-linolenic–rich diet. This possibility may explain why in recent dietary trials, beneficial effects in dieters were apparent within a few weeks after start of the trial (2–4). Omega-3 fatty acids may have an anti-inflammatory and stabilizing effect on the lipid-rich lesions because they have been shown in various animal models (32,33) and in humans (34–37) to interfere with the many secretory and proinflammatory properties of leukocytes. They prevent the development of atherosclerotic lesions in rabbits and mice by modulating macrophage secretory activities (32,33), whereas the activated lesion macrophages seem to be the main determinants of plaque inflammation and rupture in humans (26,29). Thus, loading plaque with omega-3 fatty acids, as occurs in patients with high intake and high plasma levels of omega-3 fatty acids (30,31), can induce local anti-inflammatory activity.

Oxidized lipids are also thought to play a major role in arterial complications by stimulating macrophages, injuring endothelial cells and promoting leukocyte coagulant activity and platelet reactivity (38). The nature of the substrate for lipid peroxidation, mainly the polyunsaturated fatty acids, is a dominant influence in determining the rate of peroxidation, in association with the content of antioxidants (38). The importance of the fatty acid composition of lipids in determining their susceptibility to oxidation was impressively demonstrated by recent studies (39,40) comparing lipoproteins enriched in either linoleate or oleate in both animal models and humans: Lipids enriched in oleate were remarkably resistant to oxidation. The study group in the Lyon study had a plasma fatty acid profile extremely favorable for protecting circulating or tissue lipids against oxidation; oleic acid intake was increased, linoleic acid intake was decreased (3,5) and similar profiles were observed in plasma (3,5). Also, antioxidant defenses were reinforced with higher plasma levels of antioxidant vitamins (3,5). This effect probably protected against uncontrolled lipid oxidation (38), suppressed leukocyte production of reactive oxygen species (41) and inhibited monocyte function (42). In addition, the ratio of arachidonic acid to eicosopentanoic acid in the plasma (see Ref 3) was also extremely favorable for obtaining an antithrombotic effect through an improved balance in the generation of prostacyclin and thromboxane (43,44). This is a major point because lesion ulceration and plaque disruption eventually culminate in thrombotic occlusion, which is thought to determine the acuteness of the clinical presentation (11).

We conclude that the present data support the view that comprehensive dietary modifications can rapidly induce a multitude of significant biologic changes at various cellular and molecular levels. These changes are probably capable of interfering with the pathogenesis of acute coronary events.

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