Food for prevention of coronary heart disease: Beyond the low fat, low cholesterol diet

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The single major cause of death throughout the world is coronary heart disease. Prevalence is stable or decreasing in North America, Australasia and most of Europe, while rapidly increasing in eastern Europe, Asia and Africa. Atherosclerosis is the underlying pathology. This is one of the classic lifestyle diseases on the background of genetic susceptibility. Diet plays a key role in the initiation and progression of coronary heart disease. A low total fat diet is almost universally recommended throughout the world. However, the most successful secondary prevention diet trials have used modification of fat, rather than decrease in total fat per se. Successful diet trials suggest that diet modification is as effective as accepted drug therapy to prevent recurrent coronary events, and importantly is very cost effective. Marine lipid supplementation has been demonstrated beyond reasonable doubt to decrease total mortality and in particular sudden death in patients who have survived their first myocardial infarction. Large-scale diet intervention trials are indicated to improve the scientific basis for dietary recommendations to prevent initial and recurrrent coronary heart disease.

Key words: cholesterol, low-fat diet, coronary heart disease.

Make food thy medicine.
Hippocrates, circ. 400 BC

Introduction

Coronary heart disease (CHD) is almost entirely due to atherosclerosis in the coronary arteries. Rupture of an atheromatous plaque in a coronary artery is the pathological event underlying the acute coronary syndromes of sudden death, acute myocardial infarction or unstable rest angina.[1] Plaques that rupture are generally cholesterol rich and inflammation is present in their shoulder regions. Lifestyle factors and, in particular, diet play a major role in the pathogenesis of coronary atherosclerosis. Diet has significant effects on serum lipids and may also impact on other risk factors, such as blood pressure and haemostatic factors.

In 1961 the American Heart Association (AHA) published the first major dietary recommendations for the prevention of CHD.[2] These were based on epidemiological observations and short-term trials that assessed dietary fat intake and serum lipid changes. There were no published randomized clinical trials that assessed the affect of various diets on clinical end-points. It was recommended to decrease saturated fat (SFA) and that the fat intake should be between 25 and 30% of energy. One of the six authors, Ancel Keys, noted in 1987 ‘a policy of reducing fat intake to 30% or less of dietary energy should apply only to populations such as those in northern Europe and the United States where most of the fat comes from meat and dairy products.[3] The specific cultural relevance of the AHA Guidelines is often not appreciated. This caveat by Ancel Keys needs to be highlighted in multicultural societies and when these guidelines are transferred to different communities for whom they were not designed.

Recent versions of the original AHA recommendations are the AHA and the National Cholesterol Education Program (NCEP) Diets.[4,5] Both are two-stage diets with the common theme that total fat should be less than or equal to 30% of energy (Tables 1,2). At one stage the AHA diet had a third step with fat being 20% of energy.[6] The success of these diets for an individual is assessed only by the achievement of target goals of serum low-density lipoprotein (LDL) cholesterol. For an asymptomatic individual and patient with CHD, target levels for total serum cholesterol are 6 mmol/L and 4 mmol/L, respectively. If these levels are not reached then drug therapy may be needed.

Over the past decade, scientific committees of the AHA have graded recommendations for treatments of CHD according to how well accepted the agreement is amongst committee members and the strength of the evidence of the recommendations. The strongest recommendations are class I in which there is general agreement that a treatment is useful and effective. Evidence based on data obtained from multiple randomized trials involving large numbers of patients was ranked highest (A). Intermediate ranking (B) was given to evidence derived from data obtained from a limited number of randomized trials involving small numbers of patients or alternatively careful analysis of non-randomized studies or observational registries (Tables 3,4). The lowest ranking (C) was assigned when expert consensus was the primary basis for recommendation.[7]

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The latest joint recommendation by the American College/American Society of Internal Medicine of Cardiology, AHA and American College of Physicians regarding risk factor treatment, classified lipid lowering as class I with an evidence level of A (Table 5).[8] There is not a separate classification of dietary management. In the same document it was recommended that all patients with CHD have an AHA Step 2 diet. To justify this ungraded recommendation, the authors reviewed the seven randomized dietary trials in patients with CHD. It was noted that the first four low-fat interventions did not prevent CHD morbidity nor mortality.[9–12] In contrast, the three most recent diet trials reported a 32–66% reduction of coronary events and less all-cause mortality.[13–15] These are the only dietary trials ever to have shown a decrease in cardiac mortality with diet therapy. These trials used the AHA Step 1 diet as the control diet.

In the Diet and Reinfarction Trial (DART), 2033 men with post-infarction were randomized to no fat advice, AHA Step 1 diet, fatty fish or fish oil and, finally, a cereal-type diet. Only the fish or fish oil diet prevented coronary events. There was a 29% reduction in 2 year all-cause mortality. The AHA diet was no more effective than the no fat advice, confirming the results of the first four unsuccessful low-fat trials.

In the Singh Trial 621 patients with post-infarction were randomized to AHA Step 1 diet or a vegetarian diet that was rich in fish, nuts, fruit, vegetables and spices. In the experimental group there was a 45% reduction in 12 month mortality and a 39% reduction in major coronary events.

The Lyon Diet Heart Study enrolled 605 patients 6–8 weeks post-infarction. The mean age of patients was 53.7 years and 91% were males. A Mediterranean-type diet was compared to an AHA Step 1 diet. It was planned that patients be followed for 5 years but the Scientific Committee stopped the trial at 27 months due to the clear benefit of the Mediterranean-type diet. The Lyon diet was based on the intake of food in Crete around 1960. Patients had a 1 hour session with a dietician and dietary prescriptions were tailored to the individual patient and then summarized in practical terms as 'Six Dietary Commandments': (i) more bread; (ii) more vegetables and legumes; (iii) more fish; (iv) less meat, use poultry; (v) no day without fruit; (vi) no butter and cream, use margarine, canola and olive oil for foods.

There was a dramatic decrease in major and minor coronary events and total mortality (Table 6). The Mediterranean diet was associated with a reduction in total mortality of 56% (risk ratio (RR) 0.21–0.94; $P = 0.03$), a reduction in major coronary events of 67% (RR 0.21–0.52; $P = 0.0001$) and in major and minor events of 47% (RR 0.38–0.74; $P = 0.0002$).[16]

Table 1. American Heart Association diets

	Step I	Step II (equivalent to NCEP 2)
Total fat	30%	< 30%
Saturated fatty acids	10%	< 7%
Monounsaturated fatty acids	10%	
Polyunsaturated fatty acids	10%	
Cholesterol	< 300 mg	< 200 mg

NCEP, National Cholesterol Education Program.

Table 2. National Cholesterol Education Program diets*

	Step 1	Step 2
Total fat	≤ 30% energy	—
Saturated fatty acids	8–10% energy	< 7% energy
Cholesterol	< 300 mg	< 200 mg

Source: Grundy *et al.*[4]
*Goal of therapy is to lower low-density lipoprotein (LDL) cholesterol. Target LDL cholesterol is: (i) no coronary heart disease (CHD) < 160 mg/dL and (ii) CHD ≤ 100 mg/dL.

Table 3. American Heart Association recommendations

Class I	General agreement of treatment being useful and effective
Class II	Conflicting evidence and opinion Weight in favour Less well established
Class III	General agreement MAY BE HARMFUL

Source: Gibbons *et al.*[7]

Table 4. American Heart Association recommendations and levels of evidence

Highest	Multiple randomized clinical trials (large numbers)
Intermediate	Limited number of randomized trials (small numbers) Careful analysis of non-randomized studies
Low rank	Observation registries when expert consensus was primary for recommendation

Source: Gibbons *et al.*[7]

Table 5. Risk factor treatment

	Class	Level of evidence
Lipid lowering		
LDL cholesterol ≥ 130 mg/dL target	I	A
Hypertension	I	A
Diabetes	I	C
Folate if elevated homocysteine	IIb	C
Vitamins C and E	IIb	B
Depression	IIb	C
Garlic	III	C

LDL, low-density lipoprotein.
Source: Gibbons *et al.*[16]

Table 6. Lyon Diet Heart Study*

End-points	AHA	Med	RR	*P*
Mortality	24	14	0.44 (0.21–0.94)	0.03
Major	90	27	0.33 (0.21–0.52)	0.0001
Total	180	95	0.53 (0.38–0.74)	0.0002

Source: de Lorgeril *et al.*[24]
AHA, American Heart Association; Med., Mediterranean; RR, risk ratio.
*Note that the Scientific Committee stopped trials at 27 months.

Table 7. Major coronary event reduction

Trial	Risk reduction	*P*
4S*	0.66 (0.59–0.75)	< 0.00001
Lipid†	0.76 (0.65–0.85)	< 0.00002
Lyon‡	0.33 (0.21–0.52)	0.0001

*Source: de Lorgeril *et al.*[14]
†Source: N Engl J Med 1998: 339: 1349–1357.[25]
‡Source: Lancet 1994; 344: 1383–1389.[26]

The benefits were not due to changes in serum cholesterol as no significant difference was observed between low fat and Mediterranean diet groups. The beneficial trend in the Mediterranean diet group began within a few months. An extended follow-up for 4 years has shown continuing sustained benefit.[17] The benefit with diet treatment occurred earlier than in the recent statin trials and is of similar magnitude (Table 7).

The 25 years follow-up of the Seven Countries Study helps to explain at first glance the amazing results of the Lyon trial.[18] The Seven Countries Study demonstrated that risk factors were universal but the force is culturally dependent. Serum cholesterol of 5.4 mmol/L in southern Europe is associated with one-third of the death rate from CHD of northern Europe (Fig. 1). The difference is not explained by high-density lipoprotein (HDL) cholesterol levels, nor other classic biological factors. Similar cardiac protection from mild hypertension was also seen in the Mediterranean region, with a four-fold difference in death from CHD between northern and southern Europe.[19] Lifestyle factors are probably a key to explain the difference, with diet being a major component of lifestyle.

In Crete, the diet was rich in monounsaturated fat (MUFA), almost exclusively from olive oil, was mainly vegetarian and probably also has a high intake of *n*-3 fatty acids. The Mediterranean-type diet was rich in antioxidants, fibre, nuts and wine. Diets rich in these antioxidants inhibit oxidization of LDL, improve endothelial function, decrease adhesion molecule expression and may favourably affect haemostatic factors.[20–23]

In the DART trial, serum cholesterol in the fish group was not different from the control group. In the Lyon trial there was no significant difference in serum cholesterol between the low fat and Mediterranean group. In the Singh trial there was 7% lower serum cholesterol in the active group. These trials provide evidence that diet prevents CHD death by mechanisms that are different from cholesterol lowering, which has been and still is the prime aim and measure of success of a diet for CHD patients.

When these successful diet trials are compared to other treatments for secondary prevention, diet not only is inexpensive but it is one of the most effective treatments to prevent CHD events. Benefit with diet was seen in populations with high or low event rates in placebo groups. This background event rate depends on risk factors and medical therapies (Tables 8–10).

The study of populations suggest that either a very low-fat or a high-fat Mediterranean-type diet is associated with low rates of CHD. However, the clinical trial data so far demonstrates that prescribing a low-fat diet is ineffective in preventing CHD events. The recent successful intervention diet trials have all modified the type of fat as a primary goal, increased the variety of food and have been vegetarian in type. The control diets were either prescribed AHA Step 1 or the assumption was made that with 'usual care' control patients would receive diet advice equivalent to this low-fat diet.

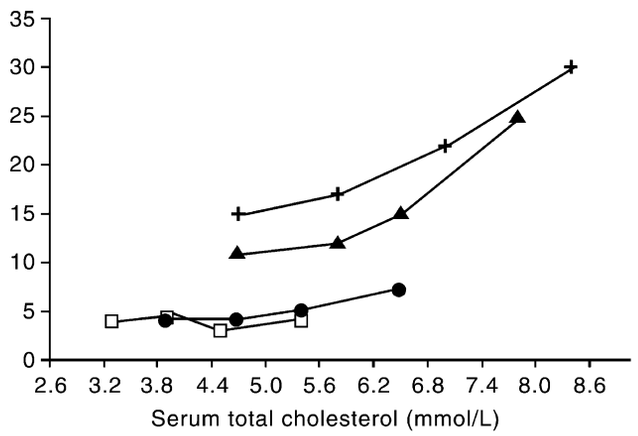

Figure 1. Seven Countries Study: 25 year coronary heart disease mortality rates. (□) Japan; (●) southern Europe, Mediterranean; (▲) United States; (+) northern Europe. Source: Verscharan *et al.*[17]

Table 9. Cost/year life gained (Net £)

Simvastatin	7240
Atenolol	130
Mediterranean diet	180
Fish diet	610

Source: Ebrahim *et al.*[27]

Table 10. Number needed to treat to prevent coronary heart disease (CHD) event over 5 years

Annual risk of CHD	OR	0.5%	3%	6%
Aspirin	0.82	222	37	18
Beta-blocker	0.78	181	30	15
Statins	0.74	154	26	13
Smoking advice	0.68	125	21	10
Fish (± fish oil)	0.65	114	19	9
Mediterranean diet	0.24	52	9	4

Low fat diets odds ratio (OR) = 0.96; 95% confidence interval 0.89–1.04.
Source: Ebrahim *et al.*[27]

Table 8. Event rates in recent randomized diet trials (per 100 patients/year of follow-up)

Trial:	DART			INDIAN			LYON		
No. subjects:	2033			621			605		
Duration:	24 months			12 months			27 months		
	Diet	AHA	RR	Diet	AHA	RR	Diet	AHA	RR
Total mortality	4.7	6.4	0.71	10.3	18.3	0.55	1.3	3.4	0.30
Cardiac death	3.8	5.7		10.2	16.8	0.58	0.5	2.7	0.24
Non-fatal infarction	2.4	1.6		14.7	23.8	0.62	0.8	2.9	0.30
Combined cardiac death and non-fatal infarction	6.2	7.3	0.84	24.5	40.6	0.59	1.3	5.6	0.27

AHA, American Heart Association; RR, risk ratio. Source: de Lorgeril *et al.*[24]

The recent Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarcto mio cardico Prevenzione (GISSI-P) Trial demonstrated beyond any reasonable doubt the cardioprotective effect of marine lipids.[16] In this trial, 11 324 infarct survivors were randomized to one gelatin capsule of 850–882 mg eicosapentaenoic acid (EPA) and docasahexaenoic acid (DHA; average ratio EPA : DHA was 1 : 2 of marine lipid) or placebo and were followed for 3.5 years. There was a 20% reduction in total mortality with marine lipid supplementation. This benefit was independent of use of statins, diet or other medications.

The commonly recommended low fat, low cholesterol diets have not demonstrated prevention of cardiac death nor in most studies prevention of cardiac morbidity. The only three successful randomized diet trials (i.e. the DART trial, the Lyon trial and the Singh trial) were not specifically low fat and did not have target LDL cholesterol levels as measures of success of diet intervention. The time has come to reconsider both what may be the best diet advice and what ought to be the goals of diet therapy. Apart from the GISSI-P trial, these successful diet trials have been small compared to the recent pharmacological trials and there is a need to duplicate these dramatic findings.

The Brisbane OLIVE study is comparing a Mediterranean diet to an NCEP Step 2 diet. This is an angiographic study that will enrol 180 patients. Currently, 75 patients have been randomized. Being planned are a Boston Mediterranean study and a British Mediterranean study. When these trials are completed, a level of evidence for dietary recommendations ought to be Class A.

Until evidence for diet therapy reaches this standard, understandably, clinicians will remain unsure of the extent of benefit of diet therapy and that changes in serum lipid ought not to be a prime measure of success or otherwise of diet therapy. While awaiting the result of the current trials it is reasonable that patients be given a choice of alternatives to a low fat diet and enjoy healthy cardioprotective cuisines from Greece, Spain, southern Italy, southern France, Mediterranean Turkey and Asian cuisines such as those from China, Thailand, Japan and Indonesia.

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