

Symposium on ‘Nutrition interventions in high-risk groups’

Secondary prevention of CHD in UK men: the Diet and Reinfarction Trial and its sequel

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The Diet and Reinfarction Trial (DART) involved 2033 men (mean age 56.5 years) recovering from myocardial infarction. They were randomly allocated to receive advice or to receive no advice on each of three dietary factors: an increase in fatty fish intake; a reduction in fat intake with an increase in polyunsaturated fat:saturated fat; an increased intake of cereal fibre. Compliance was satisfactory with the fish and fibre advice, but less so with the fat advice. The men given fish advice had 29% lower 2-year all-cause mortality; the other forms of advice did not have any significant effects. The Diet and Angina Randomized Trial (DART-2) involved 3114 men (mean age 61.1 years) with stable angina, who were followed up for 3–9 years. Advice to eat oily fish or take fish oil did not affect all-cause mortality, but it was associated with a significant increase in sudden cardiac death ($P = 0.018$), and this effect was largely confined to the subgroup given fish oil capsules. Advice to eat more fruit and vegetables had no effect, probably because of poor compliance. The outcome of DART-2 appears to conflict with that of DART and some other studies; various possible explanations are considered. Nutritional interventions are not equally acceptable and should be tailored to the individuals for whom they are intended. Various distinct groups have a raised risk of CHD, and it cannot be assumed that the same nutritional interventions are appropriate to them all. Nutritional supplements do not necessarily have the same effects as the foods from which they are derived.

Fish: Heart disease: Myocardial infarction

The Diet and Reinfarction Trial

Study design

In 1983 a randomized controlled trial (the Diet and Reinfarction trial; DART) was set up to determine whether mortality and morbidity can be reduced among men (aged <70 years) recovering from myocardial infarction (MI) by giving them simple dietary advice. The trial had a factorial design, i.e. the subjects were randomly allocated to three different interventions independently, so that all combinations occurred.

The factors selected to be tested in this trial were:

1. advice to eat at least two portions of oily fish (mackerel, herring, kipper, pilchard, sardine, salmon and trout, but not tinned tuna) each week, amounting

to 200–400 g weekly. Men who found this unpalatable were given fish oil (up to three ‘Maxepa’ capsules (170 mg EPA and 115 mg DHA per capsule; Seven Seas Limited, Hull, Humberside, UK) daily) as a partial or total replacement;

2. advice to reduce fat intake to 30% total energy and to increase the polyunsaturated fat:saturated fat to 1:0;
3. advice to increase the intake of cereal fibre to 18 g/d.

The advice was given by a dietitian to the subjects and their partners both verbally and as an information sheet. The subjects were revisited after 1, 3 and 6 months, then contacted by telephone every 3 months for ≤ 2 years from entry. At baseline, 6 months and 2 years the men were interviewed and blood was taken for serum cholesterol measurement. Compliance was monitored by means of

Table 1. Diet and Reinfarction Trial*: deaths and myocardial infarctions (MI) in 2033 men grouped according to three types of dietary advice

	No. of subjects	All deaths		IHD deaths		Non-fatal MI	
		<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
Fish advice	1015	94	9.3	78	7.7	49	4.8
No fish advice	1018	130	12.8	116	11.4	33	3.2
Significance of difference: <i>P</i>		<0.05		<0.01		NS	
Fat advice	1018	111	10.9	97	9.5	35	3.4
No fat advice	1015	113	11.1	97	9.6	47	4.6
Significance of difference: <i>P</i>		NS		NS		NS	
Fibre advice	1017	123	12.1	109	10.7	41	4.0
No fibre advice	1016	101	9.9	85	8.4	41	4.0
Significance of difference: <i>P</i>		NS		NS		NS	

*For details of trial, see p. 9.

questionnaires and, in a subset, 7 d weighed dietary intakes. In another subset plasma EPA levels were measured. At 2 years after entering the study it was ascertained whether each man was alive.

Results

Altogether 2033 men (mean age 56.5 years) were recruited. Compliance with the fish advice was good. Dietary questionnaires showed that it produced a substantial difference in oily fish consumption, which was confirmed in a subset of 459 men who recorded 7 d weighed dietary intakes; the mean daily intakes (g) were 32 and 9 for the fish-advice and no-fish-advice groups respectively. In the men whose plasma fatty acids were measured, the geometric mean percentage of EPA in relation to all plasma fatty acids was 0.59 and 0.46 in the fish-advice and no-fish-advice groups respectively (Burr *et al.* 1989a,b).

The advice about dietary fat intake did not achieve the expected differences in intake, partly because of incomplete compliance with the advice and partly because of spontaneous changes in the control group. The weighed dietary intakes showed that total fat (% energy) accounted for 31.4 and 35.2 in the fat-advice and no-fat-advice groups respectively, and the corresponding mean polyunsaturated fat:saturated fat were 0.8 and 0.4. The fat-advice group also showed a small reduction in serum cholesterol. Compliance with fibre advice was good. The mean daily intake of cereal fibre (g) was 15 and 9 for the fibre-advice and no-fibre-advice groups respectively (Burr *et al.* 1989a).

Table 1 shows the deaths and non-fatal reinfarctions that occurred within 2 years of entry to the trial. The men are classified in three different ways according to each dietary factor independently of the others. Men who were given fish advice had a significantly lower mortality from all causes ($P < 0.05$) and particularly from IHD ($P < 0.01$), with no reduction in the incidence of non-fatal MI. Fish advice was associated with a 29% reduction in overall mortality, and this result was unaffected by adjusting for slight differences in certain variables at baseline. The survival

curves diverged after 2 months, but by 12 months they had become virtually parallel and remained so thereafter (Burr *et al.* 1989b). Mortality among the men who were given fish oil was similar to that in those who were advised to eat fish (Burr *et al.* 1994). There were no significant differences in mortality or reinfarction in relation to advice on fat or fibre.

When the analysis was completed in 1989, the surviving men were told the results and were all advised to eat oily fish. A further follow-up was undertaken in 1999–2000, 12–16 years after the men had entered the trial. The reduction in mortality associated with fish advice had not persisted beyond 2 years; no clear evidence emerged about the effects of fat or fibre advice on cardiac mortality, although the risk of stroke death was greater in the fat-advice group (Ness *et al.* 2002).

Implications

The main practical implication of this study is that advice to eat oily fish is acceptable and reduces mortality in men recovering from acute MI. Advice to modify fat intake did not confer any obvious benefit, perhaps partly because it entailed greater changes in dietary habits and was therefore inadequately followed; the difference between the intervention and control groups was further eroded by spontaneous changes among the controls. No benefit could be attributed to advice to eat more cereal fibre despite good compliance; indeed, the fibre-advice group had higher mortality in the first 2 years, of borderline statistical significance (Ness *et al.* 2002). This excess did not persist and was perhaps a chance effect, but it suggests that cereal fibre is unlikely to reduce mortality in the post-MI period.

It therefore seems reasonable to conclude that men recovering from MI should be advised to eat oily fish; if they find this unpalatable, they can be given fish oil capsules instead. Evidence from other studies suggests that modification of fat intake would be helpful (Hooper *et al.* 2001), but more persuasive methods of influencing patients' diets need to be used. Cereal fibre seems to confer no benefit in this connection.

Table 2. Diet and Angina Randomized Trial*: deaths in 3114 men grouped in two according to two types of dietary advice

	No. of subjects	All deaths		Cardiac deaths		Sudden deaths	
		<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
Fish advice	1571	283	18.0	180	11.5	73	4.6
No fish advice	1543	242	15.7	139	9.0	47	3.0
Significance of difference: <i>P</i> =		0.08		0.02		0.02	
Fruit advice	1586	275	17.3	158	10.0	61	3.9
No fruit advice	1528	250	16.4	161	10.5	59	3.8
Significance of difference: <i>P</i> =		0.47		0.60		0.98	

*For details of trial, see p. 11.

What mechanism might explain the effect of fish?

The effect of fish appeared early in the trial (within 2 months), and was related to death but not reinfarction. Experimental studies on rats (McLennan *et al.* 1990) and monkeys (Charnock, 1991) have shown that the *n*-3 fatty acids found in fish oil (EPA and DHA) prevent ventricular fibrillation in acute ischaemia, and *in vitro* studies have also shown an anti-arrhythmic effect (Leaf *et al.* 2003). Such an effect would explain a reduction in mortality during the period following MI when fatal arrhythmia is especially likely to occur. Thus, it seems likely that an anti-arrhythmic action of fish oil would explain the DART findings, especially as it would account for an effect on mortality rather than reinfarction.

Diet and Angina Randomized Trial

Purpose and design of study

A further trial was set up in 1990 (the Diet and Angina Randomized Trial; DART-2) to take the DART findings forward in three ways. First, details would be obtained about the mode of death of subjects in the trial in order to distinguish between sudden and non-sudden death, sudden death being a surrogate for fatal arrhythmia. With this approach it would be possible to test the hypothesis that fish oil protects against arrhythmic death. Second, the study would be conducted in a different high-risk group, men with stable angina, to determine whether fish oil protects at a different stage in the natural history of IHD. Third, a factorial design would again be utilized, but this time to test the effect of advice to eat more fruit, vegetables and oats (Burr *et al.* 2003).

The design of the trial was broadly the same as that for DART. Similar advice was given to the fish-advice group, except that part way through the trial this group was sub-randomized so that one subgroup was initially offered fish oil (and advised to eat oily fish only if they disliked the capsules), while the other subgroup was preferentially advised to eat fish (and given capsules if they disliked fish, as in DART). As the sub-randomization was introduced part way through recruitment to the trial, the fish oil subgroup spent less time on average in the trial than the dietary fish subgroup, and statistical adjustment for this difference was made. Independently of the main

intervention, the men were randomly divided into two groups, one of which was advised to eat more fruit and vegetables (four or five portions daily, apart from potatoes), to drink at least one glass of natural orange juice daily and to increase the intake of oats.

The subjects were seen after 6 months, written to annually thereafter and telephoned if dietary charts were not returned or they showed poor compliance. Compliance was monitored at 6 months by means of questionnaires. At baseline and 6 months samples of plasma were taken from a subset of men for measurement of EPA and β -carotene to provide some objective evidence on compliance. It is recognised that plasma β -carotene is a rather crude index of fruit and vegetable consumption; the intention to also monitor plasma ascorbate was not feasible logistically because of financial constraints.

The end points of the trial were all deaths, cardiac deaths and sudden cardiac deaths occurring up to 31 March 1999. Decisions as to whether a death was cardiac or sudden were made by predetermined criteria and without any knowledge of the men's allocation in the trial.

Results

Men were recruited into the study between 1990 and 1996, so that they spent up to 9 years in the trial. Altogether 3114 men (mean age 61.1 years) were recruited. The sub-randomization of the fish-advice group occurred only after 1993, so that fewer men were preferentially allocated to receive capsules than were advised to eat fish.

Reported compliance with fish advice was good, which was confirmed by measurements of plasma EPA, which rose by 12.3 mg/l in the fish-advice group and fell by 1.6 mg/l in the control group. Reported compliance with advice to eat fruit and vegetables was good, but was not borne out by β -carotene measurements, which remained virtually constant in the groups irrespective of whether they were given this advice.

The main results are shown in Table 2. Contrary to expectations, mortality was higher in the fish-advice group, significantly so for cardiac deaths ($P = 0.02$) and sudden deaths ($P = 0.02$). No differences occurred between the men given advice on fruit and vegetables and those not given this advice. Table 3 shows the fish-advice group subdivided according to whether the men were randomly allocated to dietary fish or fish oil and the mortality

Table 3. Diet and Angina Randomized Trial*: adjusted hazard ratios (HR)† for subjects randomly allocated to dietary fish or fish oil relative to subjects given no fish advice

Randomized group	All deaths	Cardiac deaths	Sudden deaths
Dietary fish (<i>n</i> 1109)			
<i>n</i>	198	121	49
HR	1.13	1.20	1.43
95% CI	0.94, 1.37	0.93, 1.53	0.95, 2.15
<i>P</i> =	0.20	0.16	0.086
Fish oil (<i>n</i> 462)			
<i>n</i>	85	59	24
HR	1.19	1.45	1.84
95% CI	0.92, 1.54	1.05, 1.99	1.11, 3.05
<i>P</i> =	0.19	0.024	0.018

*For details of trial, see p. 11.

†Adjusted for age, smoking, previous myocardial infarction, history of hypertension, diabetes, BMI, serum cholesterol, medication and fruit advice.

expressed as hazard ratios relative to the men who were given no fish advice; these ratios were adjusted for various baseline variables in order to eliminate chance differences between the groups. Although all hazard ratios exceeded 1.0 (implying some excess mortality), the only values to do so significantly were in the fish oil subgroup, i.e. the excess in cardiac and sudden deaths was located in this subgroup rather than in the dietary fish subgroup.

Implications

The main practical implications of these results are that eating more oily fish does not confer any great benefit on men with stable angina, and that taking fish oil may even be harmful to such individuals. Advice to eat more fruit and vegetables did not appear to be of benefit either, despite other evidence of a protective effect (Ness & Powles, 1997). The lack of benefit was probably a result of poor compliance; the reported increase in intake of these foods was not supported by objective measurements, and a follow-up postal questionnaire showed only very slight differences in fruit and vegetable consumption attributable to this advice (Ness *et al.* 2004). Thus, the increase reported at 6 months was presumably either transitory or fallacious.

Other studies relating to fish oil and heart disease

Two other large randomized trials have investigated the cardio-protective effects of the *n*-3 fatty acids associated with fish oil. In the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico Prevenzione trial (Marchioli *et al.* 2002), which involved 11 323 patients recovering from MI, a dose of EPA and DHA corresponding to 100 g oily fish daily was found to reduce total mortality and sudden death, the effect appearing within 4 months (as in DART). In the Japan EPA Lipid Intervention Study (Goyal *et al.* 2006), which involved 18 645 hypercholesterolaemic patients, treatment with EPA was found to reduce the incidence of major (particularly non-fatal) coronary events. A systematic review (Hooper *et al.* 2006)

has found no clear evidence that marine *n*-3 fats reduce mortality or cardiovascular events; this analysis did not include the Japan EPA Lipid Intervention Study, which has been published only in abstract form so far. In addition, the Alpha Omega Trial (see The Royal Netherlands Academy of Arts and Sciences (KNAW), 2006), a multi-centre placebo-controlled double-blind intervention study that started in 2002 and will be completed in 2008, will test the effects of low doses of *n*-3 fatty acids on CHD mortality in Dutch patients with a history of MI.

Differences between various high-risk groups

Are different interventions required in different groups?

There are several ways of identifying individuals who are at above-average risk of death from CHD, and it cannot be assumed that the same interventions are equally appropriate for them all. Examples of high-risk groups include: individuals with a family history of heart disease; patients recovering from acute MI; patients with current angina; other individuals with a past history of MI; patients with peripheral arteriosclerotic disease; individuals who have had coronary artery bypass grafts; diabetic patients; cigarette smokers; asymptomatic individuals with various risk factors such as high serum cholesterol and high blood pressure. When the effects of an intervention are reviewed by means of a meta-analysis evidence from a variety of these groups is amalgamated, and this process may conceal real differences between some of them, both in the acceptability of the intervention and in its biological action.

Differences in acceptability of nutrition interventions

Different high-risk groups have very different perceptions of their need to modify their behaviour. In DART the men were first contacted while they were still in hospital recovering from MI, usually their first attack. They had all just had a very nasty shock. Having been previously (in most cases) apparently healthy, they had passed through a life-threatening experience accompanied by severe symptoms that they were most anxious to avoid in future. They welcomed the offer of dietary advice, and they complied well with the instructions about fish and fibre intake. They found the fat advice more difficult to follow, but part of the problem with the interpretation of the effect of this intervention was a spontaneous change in the group not given this advice, i.e. to some extent the control group altered their fat intake without being given any specific advice to do so.

In DART-2 the men were in a steady-state at recruitment. They all gave a history of treatment for angina, but many of them were virtually asymptomatic, either because their angina was medically controlled or because they avoided any activity that might cause symptoms. They did not perceive any need to change their lifestyle very radically. Advice to eat fish (or to take capsules) was acceptable because it did not greatly alter their usual diet, but advice to eat more fruit and vegetables had very little long-term effect. Middle-aged men may be particularly resistant to advice of this kind (perhaps especially in South

Wales); interventions directed to women might be more effective (Ness *et al.* 2004).

Thus, of the nutritional interventions that might benefit individuals at high risk of CHD, some fail to be effective because of inadequate compliance. Different methods may be needed to help different high-risk groups attain similar diets, with more detailed and sustained advice and support being required for some groups than for others.

Differences in appropriateness of nutrition interventions

Given the wide variety of criteria that define high-risk groups, it would hardly be surprising if the most appropriate nutrition intervention differed from one group to another. In a systematic review of randomized trials designed to reduce or modify fat intake (Hooper *et al.* 2001) only a small reduction in cardiovascular risk was found overall. The subjects were at various initial levels of risk, and perhaps greater effects might be found in particular subgroups. The DART findings suggest that increasing the intake of cereal fibre is unlikely to reduce mortality in the post-infarct period, although it may well be beneficial in other circumstances. The contrasting results of DART and DART-2 in relation to fish oil are a particularly striking instance of a nutritional intervention having different effects in different high-risk groups.

Possible reasons for different effects of fish oil in different groups

Among the possible explanations for the unexpected findings of DART-2, the first to be considered is risk compensation; i.e. a change in behaviour among men given capsules that was a consequence of the belief that fish oil would protect them against heart disease. This effect seems to occur in other situations (e.g. in relation to risks of HIV infection (Richens *et al.* 2000) and skin cancer (Autier *et al.* 1998)), and harmful changes in behaviour could conceivably outweigh the protective effect of fish oil. Follow-up data do not reveal any obvious changes of this kind, although they cannot be wholly ruled out (Ness *et al.* 2004).

The subjects in DART were recruited while recovering from acute MI, whereas those in DART-2 had stable angina. Although both trial groups were at above-average risk of cardiovascular death, they represented different stages in the natural history of IHD, with different myocardial pathology, and it may well be that fish oil has different effects in these two situations.

The findings of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico Prevenzione trial (Marchioli *et al.* 2002) confirm the cardio-protective effects of the *n*-3 fatty acids associated with fish oil during the post-infarct period. As in DART, the survival curves for the intervention and control groups were found to diverge within 4 months but become virtually parallel by 12 months. Thus, both these trials suggest that fish oil reduces mortality during recovery from MI (probably by preventing arrhythmias that often occur then) but is of no comparable benefit subsequently, while DART-2 suggests

that it may even be harmful among men with chronic stable angina.

The causation and prevention of cardiac arrhythmia depend on the balancing of finely-tuned ionic mechanisms in the myocardium. It is an established fact that pharmacological agents that prevent arrhythmias in one clinical situation will cause them in another. The anti-arrhythmic drugs encainide and flecainide have been found to increase the risk of fatal and near-fatal arrhythmias in post-infarct patients with asymptomatic or mildly symptomatic ventricular arrhythmia (The Cardiac Arrhythmia Suppression Trial (CAST) Investigators, 1989). Perhaps it should not be surprising to find that a nutritional agent with anti-arrhythmic properties in some circumstances is pro-arrhythmic in others.

This suggestion is borne out by the results of a randomized trial of fish oil in patients with implantable defibrillators (Raitt *et al.* 2005), which indicate that fish oil increases the risk of recurrent episodes of ventricular tachycardia or fibrillation and the incidence of these arrhythmias in patients with previous ventricular tachycardia. Furthermore, studies in pigs show that a fish oil diet induces changes in ionic sarcolemmal currents that could have pro-arrhythmic or anti-arrhythmic consequences (Verkerk *et al.* 2006). The authors conclude that the impact of a fish oil-enriched diet may depend on the pathophysiological setting. Other *in vitro* work shows that cardiomyocytes enriched with EPA and DHA are more vulnerable to hypoxia but recover more quickly during reoxygenation (Durot *et al.* 1997). Perhaps the different effects of these fatty acids in normoxic and hypoxic conditions explain why they seem to have both anti- and pro-arrhythmic actions, particularly as the cells most vulnerable to anoxia in the patients in DART may have been eliminated by a recent MI.

Another possible mechanism for these contrary effects, proposed by Leaf *et al.* (2003), is that after MI fatal arrhythmias are initiated by hyperexcitable partially-depolarized myocytes at the periphery of the ischaemic zone. Fish oil inactivates these cells and thus prevents arrhythmia. However, patients with advanced chronic IHD may depend on partially-depolarized myocytes for their hearts to function adequately, and inactivating these cells could then cause death. As support of this hypothesis, about half the subjects in DART-2 reported a previous heart attack, so it may be assumed that at least this proportion had chronic myocardial ischaemic damage. Furthermore, among those deaths in DART-2 for which postmortem reports were obtained, in every case chronic myocardial pathology was reported (ventricular hypertrophy, fibrosis or old infarction). Leaf *et al.* (2003) see an analogy with the effects of the Ca-channel blocker diltiazem, which reduces post-MI mortality in patients with well-preserved ventricular function but is harmful to patients with multiple infarcts and left ventricular dysfunction (Boden *et al.* 1991).

A different hypothesis has been put forward by Oliver (2002), who suggests that in an acute coronary syndrome catecholamine-stimulated lipolysis causes a sudden rise in plasma NEFA, which in turn are liable to cause ventricular fibrillation. A high intake of fatty acids taken over several

months in a concentrated form could cause excess storage of adipocyte lipid, increasing the risk of excess plasma NEFA concentration in the event of an episode of acute ischaemia.

The previous dietary habits and nutritional status may also modify the effect of a given nutritional intervention. The Japan EPA Lipid Intervention Study (Goyal *et al.* 2006) was conducted in subjects whose fish intake already exceeded that of most of the UK population, and perhaps they were less likely to be adversely affected by a further rise in fish oil intake than individuals who are unaccustomed to these fatty acids.

Patients at high cardiovascular risk are often taking medication, and the possibility should be considered that nutritional interventions interact with drugs, favourably or unfavourably. In DART-2 the adverse effects of oily fish were found to be increased by treatment with digoxin but eliminated by β -blockers and nifedipine (Burr *et al.* 2005). Other examples of such interactions include grapefruit juice with Ca-channel blockers and green vegetables with warfarin; no doubt there are more interactions that have not been described. It cannot therefore be assumed that a given nutritional intervention will have similar effects in patients receiving different types of medication.

Oily fish or fish oil?

In DART-2 the adverse effect seemed to be attributable to fish oil rather than dietary fish. It cannot be assumed that these two interventions have identical effects. Fish contains many ingredients beside fatty acids, and perhaps some other components contribute to its health benefits. Alternatively, the rate of absorption of fatty acids may be important; taking fish oil on an empty stomach could produce a bolus effect of sudden high concentrations that do not occur when food is gradually digested and that have a different pharmacological action. There are other examples that should warn against assuming that isolated nutrients have the same effects as the foods from which they are derived, e.g. the adverse effects of β -carotene in individuals at high risk of lung cancer (The Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group, 1994; Omenn *et al.* 1996).

Conclusions

The two studies considered here (DART and DART-2) illustrate several issues that are relevant to a variety of nutritional interventions for individuals at high risk of death from CHD.

First, some nutritional interventions are easier to adopt than others, and some high-risk groups find certain dietary changes particularly difficult. It is therefore necessary to tailor the manner in which dietary advice is offered so that it is as helpful as possible to the individuals who need it.

Second, there are several distinct groups of individuals who are at high risk of CHD, and it should not be assumed that the same nutritional interventions are equally appropriate for them all. In order to maximize the likelihood of detecting effects various high-risk groups are often

amalgamated in randomized trials and, in particular, in meta-analyses, but this procedure may obscure important differences and even contrary effects in different groups.

Third, the benefits of a dietary change cannot necessarily be replicated (let alone improved upon) by taking specific nutrients such as vitamins or fatty acids in a purified form. Nutritional supplements have the advantage of convenience, but it cannot be assumed that they always have the same effects as the foods in which they occur naturally.

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