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Reflections on the Diet and Reinfarction Trial (DART)

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The Diet and Reinfarction Trial (DART) was the first randomized controlled trial to test the hypothesis that oily fish confers protection against coronary heart disease. It showed a reduction in mortality during the 2 years after myocardial infarction among men who were advised to eat about 300 g of oily fish per week, or who took fish oil supplements giving an equivalent amount of n-3 fatty acids. These findings have been confirmed by the GISSI–Prevenzione trial, the Lyon Diet Heart Study, and various cohort studies.

Taken together, the evidence suggests that fish oil reduces CHD mortality, the effect being greatest during the period of recovery from acute myocardial infarction. It seems likely that the protection is at least partly attributable to a reduction in the incidence of fatal arrhythmia by n-3 fatty acids. Further research is indicated to investigate this hypothesis.

Randomized controlled trials are particularly important in this connection. Observational studies can supply useful supportive evidence, but they are susceptible to selection bias and can be misleading. There is scope for trials of dietary advice and of nutritional supplements; compliance and indirect effects may well be different, even if the biological mechanisms are the same.

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Key Words: Fish oil, coronary heart disease, n-3 fatty acids.

Background

When the Diet and Reinfarction Trial (DART) was set up in 1983, the hypothesis that oily fish confers protection against coronary heart disease (CHD) was relatively new. Sinclair[1] had suggested in 1956 that the absence of atherosclerotic disease in Eskimos was attributable to their intake of marine fats. Investigations by Bang and Dyerberg[2] drew attention to the likely role of n-3 fatty acids in preventing CHD, and three cohort studies showed an inverse relationship between fish intake and CHD mortality[3–5]. Various studies had been published concerning the effects of n-3 fatty acids on haematological variables, blood pressure and restenosis following coronary angioplasty, but the role of fish oil in reducing mortality had not been addressed by a randomized trial.

The DART study

Design

Testing the fish hypothesis was not the only objective of the DART study. At that time, far more importance was generally given to the role of saturated fatty acids in heart disease, while cereal fibre was seen as a major protective dietary factor. The DART study was therefore set up with a factorial design so as to test three interventions simultaneously and independently: a reduction in fat intake with an increase in the ratio of polyunsaturated to saturated fat; an increase in cereal fibre intake; and an increase in the intake of fatty fish[6].

Subjects for the trial were non-diabetic men under the age of 70 years who had recently recovered from myocardial infarction (MI). After a preliminary interview, the subjects were randomly allocated between eight groups, covering all combinations of the three dietary interventions. Dietary advice was given according to the random allocation and the subjects were followed up for 2 years. During this time the subjects' compliance was monitored by means of dietary questionnaires and (in a subset) plasma fatty acid measurements. Subjects in the fish group were advised to eat at least two portions each week (200–400 g) of fatty fish; those who could not eat this amount of fish were given 'Maxepa' capsules and asked to take up to three every day as a partial or total substitute for fish.

The subjects were all contacted again 2 years after they had entered the trial; for those who had died, causes of death were obtained from the death certificates. Hospital notes were examined for all subjects who had

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Table 1 Deaths and reinfarctions (%) in relation to dietary advice

	Total number	Deaths	CHD deaths	Non-fatal MI	CHD events
Fish advice	1015	94 (9·3)*	78 (7·7)†	49 (4·8)	127 (12·5)
No fish advice	1018	130 (12·8)	116 (11·4)	33 (3·2)	149 (14·6)
Fat advice	1018	111 (10·9)	97 (9·5)	35 (3·4)	132 (13·0)
No fat advice	1015	113 (11·1)	97 (9·6)	47 (4·6)	144 (14·2)
Fibre advice	1017	123 (12·1)	109 (10·7)	41 (4·0)	150 (14·7)
No fibre advice	1016	101 (9·9)	85 (8·4)	41 (4·0)	126 (12·4)

*$P<0·05$, †$P<0·01$ (log rank test).

been admitted to hospital and whose history suggested the possibility of reinfarction. All decisions about reinfarction and causes of death were made without knowledge of the dietary group to which the subjects were allocated.

Results

In total, 2033 men entered the trial, of whom 224 died within 2 years. Table 1 shows the percentages who died, of all causes and of CHD, within the randomized groupings, together with the incidence of non-fatal MI and CHD events (CHD death plus non-fatal MI). No significant differences were attributable to fat or fibre advice, but the subjects who were advised to eat fish had a significantly lower mortality, due to a reduction in CHD deaths. They did not show a similar reduction in non-fatal MI — in fact, the incidence of this was slightly higher in the fish advice group — and there was little difference attributable to fish advice in the incidence of CHD events. Allowing for a variety of potential confounders, the relative risk of death in those given fish advice was 0·71 (95% confidence interval 0·54–0·93) compared with those not given fish advice (i.e. a reduction of 29%). The corresponding relative risks relating to fat and fibre advice were 1·00 and 1·27 respectively; for fibre advice, the difference from unity bordered on statistical significance (95% CI 0·99–1·65)[6].

The dietary intakes of the subjects were calculated from detailed questionnaires obtained when they had been in the trial for 6 months. The intake of eicosapentaenoic acid (EPA), including that derived from capsules, gives some indication of compliance with fish advice (supported by changes in plasma fatty acids in a subset of subjects). Similarly, the ratio of polyunsaturated to saturated fatty acids (P:S ratio) and the intake of cereal fibre indicate compliance with the advice regarding fat and fibre respectively. Table 2 shows the EPA intakes at 6 months in relation to the deaths that occurred between that point and two years later. The numbers are less than in Table 1 because some had died (about half the deaths occurred in the first 6 months) and a few failed to complete the dietary questionnaire. There is some evidence of dose-response among the subjects given fish advice; the relationship between intake and mortality was remarkably consistent between

Table 2 EPA intake at 6 months and subsequent mortality

	EPA intake per week at 6 months			All subjects
	<1 g	1–2 g	>2 g	
Fish advice				
Total number	114	373	460	947
Deaths (%)	7 (6·1)	19 (5·1)	19 (4·1)	45 (4·8)
No fish advice				
Total number	678	216	36	930
Deaths (%)	42 (6·2)	11 (5·1)	4 (11·1)	57 (6·1)

the two randomized groups, except for those taking more than 2 g per week, where the number was small in the group not given fish advice.

In Table 3 the subjects are classified by fat advice and P:S ratio. The two randomized groups had very similar death rates within each band of P:S ratio, and in both groups the death rate fell as the P:S ratio increased.

Table 4 shows similar data in relation to fibre advice and cereal fibre intake, expressed as grams per 1000 kcal. In the group given fibre advice the death rate declined as fibre intake increased, but it tended to be higher than the corresponding rate in the group not given fibre advice, except for those with the highest intake, among whom there were few control group subjects.

Table 5 shows associations between the three dietary variables and subsequent mortality among the whole cohort. When adjustments were made for age, smoking and energy intake, none of the associations were significant; they were of similar magnitude for the three variables, that for cereal fibre being marginally higher than the others.

A subgroup analysis was conducted among subjects who received fish oil capsules rather than dietary fish. Their 2-year mortality tended to be lower than that of matched subjects not given fish advice or capsules, suggesting that the protective effect of fish was attributable to the oil rather than some other ingredient[7].

Implications

The results of this trial show that a modest intake of fatty fish, amounting to about 300 g per week, reduces

Table 3 P:S ratio at 6 months and subsequent mortality

	P:S ratio at 6 months			All subjects
	<0·4	0·4–0·8	>0·8	
Fat advice				
Total number	105	393	439	937
Deaths (%)	7 (6·7)	20 (5·1)	21 (4·8)	48 (5·1)
No fat advice				
Total number	563	320	57	940
Deaths (%)	36 (6·4)	16 (5·0)	2 (3·5)	54 (5·7)

Table 4 Cereal fibre intake at 6 months and subsequent mortality

	Cereal fibre per 1000 kcal at 6 months			All subjects
	<7 g	7–11 g	>11 g	
Fibre advice				
Total number	219	329	378	926
Deaths (%)	20* (9·1)	19 (5·8)	17* (4·5)	56 (6·0)
No fibre advice				
Total number	742	168	43	953
Deaths (%)	37* (5·0)	5 (3·0)	4 (9·3)	46 (4·8)

*$P<0·05$ (χ^2 test).

Table 5 Associations between diet at 6 months and subsequent mortality

Variable	t-Value of dietary association with mortality allowing for:			
	Nothing else	Age	Age, smoking	Age, smoking, energy intake
EPA	− 1·61	− 1·59	− 1·47	− 1·34
P:S ratio	− 1·54	− 1·31	− 1·10	− 1·42
Cereal fibre	− 2·05*	− 2·16*	− 1·97*	− 1·45

*$P<0·05$.

mortality after MI in non-diabetic men, particularly during the first 6 months. There was no corresponding reduction in the incidence of nonfatal MI, which in fact was slightly higher in the fish group.

Advice to modify fat consumption had no clear effect on mortality, probably because of poor compliance: there was only a small decline in serum cholesterol concentration attributable to fat advice[6]. The relationship between fibre intake and mortality was paradoxical: within the group advised to eat more fibre there was an inverse relationship between fibre intake and mortality, yet its overall mortality was higher than that of the group not given this advice. There was a favourable effect of compliance with all three interventions, of roughly equal size — a 'healthy complier effect' that was independent of the efficacy of the intervention. Good compliance seems to be a marker for something else, possibly a tendency to comply with other aspects of management that really do bestow benefit, or perhaps a better state of health: conceivably, people who feel unwell cannot be bothered to follow uncongenial diets. It is very difficult to allow adequately for such confounders.

These findings illustrate the importance of the controlled trial as against observational studies. If the subjects advised to eat fibre are treated as a cohort, they appear to provide evidence of a protective effect of cereal fibre, an impression which the randomized trial shows to be misleading. Several cohort studies have shown an apparently favourable effect of cereal fibre on CHD[8–11], but confirmation by a randomized controlled trial is lacking.

DART and other studies of n-3 fatty acids

The study most closely resembling DART is the GISSI–Prevenzione trial[12]. This showed a reduction in mortality (all-cause and cardiovascular) attributable to n-3 polyunsaturated fatty acids among patients who had recently survived MI. Like DART, the trial had a factorial design, the other factor being vitamin E, which conferred no benefit. The reductions in mortality were less than those in DART, possibly because the patients (being Italians) already ate a Mediterranean diet. As in DART, the benefits occurred in the earlier rather than the later part of the follow-up period. The decrease in mortality was greatest among the sudden deaths.

The Lyon Diet Heart Study was a randomized trial of the Mediterranean diet in survivors of a first MI[13]. The diet involved a high intake of bread, fruit and vegetables, more fish, less meat and the replacement of butter and cream by a special margarine. In consequence, there was an enhanced intake of n-3 polyunsaturated fatty acids, particularly alpha-linolenic acid. Over 4 years of follow-up there was a significant and substantial reduction in several endpoints, including all-cause deaths and cardiac deaths. The results are consistent with those of the DART and GISSI–Prevenzione studies in relation to n-3 fatty acids, although they may have been partly attributable to other dietary factors.

Several cohort studies have examined the relationship between the intake of fish (or n-3 polyunsaturated fatty acids) and CHD. A recent systematic review concluded that fish consumption at 40–60 g daily markedly reduces CHD in high-risk but not in low-risk populations[14]. This confirms the findings of the DART and GISSI–Prevenzione studies, in which high-risk groups obtained protection from a modest intake of fish or fish oil. The evidence from these studies is somewhat inconsistent as to whether the effect is greater for sudden[15] or non-sudden[16] death.

There is a body of evidence, derived largely from animal experiments, pointing to an antiarrhythmic

action of fish oil on the heart. Studies in rats[17], dogs[18] and primates[19] have demonstrated that n-3 fatty acids prevent ventricular fibrillation induced by acute ischaemia or reperfusion. In humans, two randomized controlled trials have shown a beneficial effect of n-3 polyunsaturated fatty acids on heart rate variability, one in survivors of MI[20] and the other in male (but not in female) healthy volunteers[21]. Heart rate variability reflects parasympathetic cardiac tone, which protects the myocardium against ventricular arrhythmias and raises the threshold for ventricular fibrillation. Thus there is evidence from both human and animal work that fish oil can prevent fatal arrhythmias in vulnerable hearts, a mechanism that could explain the DART finding of a reduction in deaths after a recent MI but not in non-fatal MI.

Conclusions

The following conclusions arise from a review of the DART findings in the light of other work:

(1) Fish oil reduces CHD mortality more than incidence of MI, suggesting a reduction in case-fatality.
(2) The effect is greatest in the period immediately after acute MI. Further work should be undertaken among patients during the first few weeks following MI.
(3) These observations, together with experimental evidence, suggest that n-3 fatty acids have an anti-arrhythmic effect. This should be investigated, for example among patients with implantable defibrillators.
(4) There is no substitute for the randomized controlled trial in the investigation of causality. Observational studies supply valuable supportive evidence, but they are susceptible to selection bias, in that people who choose to eat a particular diet (or who comply with dietary advice) may well differ from other people in ways that cannot always be allowed for.
(5) There is a place for trials of foods (such as fish) and of specific nutrients (such as n-3 fatty acids). Even if their direct effects are identical, they may have different indirect effects (e.g. on other aspects of diet, lifestyle and compliance with treatment) that could affect outcome.

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