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Lack of benefit of dietary advice to men with angina: results of a controlled trial

ML Burr[1]*, PAL Ashfield-Watt[1], FDJ Dunstan[1], AM Fehily[2], P Breay[1], T Ashton[1], PC Zotos[1], NAA Haboubi[3] and PC Elwood[1]

[1]*University of Wales College of Medicine, Cardiff, UK;* [2]*Tinuviel Software, Warrington, UK; and* [3]*Carmarthenshire NHS Trust, Carmarthen, UK*

Objective: To see whether mortality among men with angina can be reduced by dietary advice.
Design: A randomized controlled factorial trial.
Setting: Male patients of general practitioners in south Wales.
Subjects: A total of 3114 men under 70 y of age with angina.
Interventions: Subjects were randomly allocated to four groups: (1) advised to eat two portions of oily fish each week, or to take three fish oil capsules daily; (2) advised to eat more fruit, vegetables and oats; (3) given both the above types of advice; and (4) given no specific dietary advice. Mortality was ascertained after 3–9 y.
Results: Compliance was better with the fish advice than with the fruit advice. All-cause mortality was not reduced by either form of advice, and no other effects were attributable to fruit advice. Risk of cardiac death was higher among subjects advised to take oily fish than among those not so advised; the adjusted hazard ratio was 1.26 (95% confidence interval 1.00, 1.58; $P=0.047$), and even greater for sudden cardiac death (1.54; 95% CI 1.06, 2.23; $P=0.025$). The excess risk was largely located among the subgroup given fish oil capsules. There was no evidence that it was due to interactions with medication.
Conclusions: Advice to eat more fruit was poorly complied with and had no detectable effect on mortality. Men advised to eat oily fish, and particularly those supplied with fish oil capsules, had a higher risk of cardiac death. This result is unexplained; it may arise from risk compensation or some other effect on patients' or doctors' behaviour.
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Introduction

Various dietary factors appear to influence the mortality and morbidity of ischaemic heart disease (IHD). The evidence for a protective effect of fish oil is principally derived from two controlled trials (Burr *et al* 1989; GISSI-Prevenzione Investigators, 1999), several cohort studies (Marckmann & Grønbæk, 1999), and a body of animal experiments (McLennan & Charnock, 1988; Charnock 1994; Billman *et al*, 1997). The overall conclusion is that marine n-3 polyunsaturated fatty acids reduce mortality among persons at high risk of death from IHD, particularly patients who have recently recovered from myocardial infarction (MI), and that this effect is probably mediated by a reduction in the incidence of fatal arrhythmia.

Fruit and vegetables also seem to be protective. Here the evidence is largely based on observational studies (Ness & Powles, 1997); no controlled trial has yet been conducted with cardiovascular mortality as an endpoint, although in two trials a reduction in cardiac deaths was attributable to dietary interventions that included an increased intake of fruit and vegetables (Singh *et al*, 1992; de Lorgeril *et al*, 1994).

A randomized controlled trial was set up among men with angina to test the following hypotheses: (1) coronary mortality and morbidity can be reduced by an intake of oily fish or fish oil that provides about 3 g of eicosapentaenoic acid

***Correspondence: Dr ML Burr, Centre for Applied Public Health Medicine, University of Wales College of Medicine, Temple of Peace and Health, Cathays Park, Cardiff CF10 3NW, UK.**
E-mail: michael.burr@bro-taf-ha.wales.nhs.uk
Guarantor: **Dr ML Burr.**
Contributors: **MLB and AMF designed the study. PALA-W and AMF were responsible for the day-to-day running of the study. Clinical interviews were conducted by PB, MLB and PCE. AMF, PALA-W, TA and PCZ were responsible for the dietary information. NAAH provided the serum cholesterol measurements. PALA-W collated the data, FDJD conducted the analysis and MLB wrote the paper.**
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(EPA) each week; (2) coronary mortality and morbidity can be reduced by increasing the intake of fruit, vegetables and oats, so as to supply about 8 g of soluble fibre per day and corresponding amounts of antioxidant vitamins. With respect to oily fish, this study differs from the previous trials in that the patients had stable angina rather than a recent history of MI.

Subjects and methods

Subjects for the trial were men under the age of 70 y who were being treated for angina. The trial was restricted to men because the case fatality rate among angina patients seems to be higher in men than in women (Krueger *et al*, 1970; Zeiner-Henriksen, 1976). General practitioners were asked to identify patients for whom they prescribed nitrates (as tablets, sprays or patches) or other treatment for angina, which was not defined at this stage: different practices were found to use different ways of classifying their patients with coronary heart disease. An explanatory letter was written to the patients inviting their participation. Those who agreed were seen at a clinic where medical and dietary questionnaires were administered; the latter was derived (with only minor modifications) from a questionnaire that had previously been validated against 7-day weighed dietary records (Yarnell *et al*, 1983; Fehily *et al*, 1988). Height, weight and blood pressure were measured, and a blood sample was taken for measurement of serum cholesterol.

The following subjects were excluded from the trial: men who denied ever having exertional chest pain or discomfort (except for men who never hurried whose pain was brought on by stress); men awaiting coronary artery by-pass surgery; men who already ate oily fish twice a week; men who could not tolerate oily fish or fish oil; men who appeared to be unsuitable on other grounds (eg other serious illness, likelihood of moving out of the area).

A dietitian then randomly allocated the remaining subjects to four groups, using prepared envelopes, to be advised as follows:

- To eat at least two portions of oily fish each week, or to take up to 3 g of fish oil ('Maxepa') as a partial or total substitute.
- To eat four to five portions of fruit and vegetables (apart from potatoes) and drink at least one glass of natural orange juice daily, and also increase the intake of oats, so as to obtain a higher intake of vitamin C and at least 8 g of soluble fibre from all sources every day.
- A combination of both these forms of advice.
- 'Sensible eating'—non-specific advice that did not include either of the above interventions.

Fish oil capsules were supplied to men who were advised to eat fish but found it unpalatable; for part of the trial, the 'fish advice' group was subrandomized to receive either fish advice or capsules.

The advice conformed to 'real life' conditions and was adjusted to the subjects' situations. Those whose body mass index (BMI) exceeded 30 kg/m^2 were given weight-reducing advice in addition to the above. All smokers were strongly advised to give up the habit. The general practitioners were given the results of the blood pressure and cholesterol measurements so that they could take appropriate action where necessary.

Six months after entering the trial the men were seen again at a clinic, where repeat questionnaires were administered. In a subset of subjects plasma EPA was measured at baseline and again at 6 months; in another subset plasma β-carotene was measured at these times. Compliance was also monitored by means of dietary charts sent by post with reply-paid envelopes for their return. Subjects who did not return charts or who provided evidence of poor compliance were contacted by a dietitian and given encouragement.

Deaths (with certified causes) were ascertained by flagging the subjects' records at the central register of the National Health Service. Three years after the last subject was recruited, a letter and questionnaire were sent to all the survivors enquiring about current medication; this served to check that all deaths had in fact been notified. The general practitioners of non-respondents were asked whether these patients were still alive; those who had moved away were traced through the National Health Service. For those men whose deaths were ascribed to a cardiac causes, further details were obtained from hospital records, relatives or other available sources as appropriate, so that the suddenness of the death could be ascertained. Sudden death was defined as in the US Physicians' Health Study (Albert *et al*, 1998): death within 1 h of symptom onset, excluding those where there was evidence of collapse of the circulation preceded disappearance of the pulse (to increase specificity for arrhythmic death). Unwitnessed deaths were also excluded unless the deceased was found within an hour of being known to be asymptomatic.

Ethical permission was obtained for the study, and the subjects gave signed consent to their participation. A prior calculation gave an estimate of 3000 subjects needed to detect a reduction in mortality from about 13% to just less than 10% over a period of 5 y, at a power of 80% and $P < 0.05$.

Results

Recruitment for the trial began in 1990 and continued until 1996; it ceased for 12 months in 1992–1993 owing to an interruption in funding. The subrandomization of the fish group occurred during the second phase of the trial. A total of 3114 men were enlisted, 1111 during the first phase (1990–1992) and 2003 during the second (1993–1996). In the second phase the dietary questionnaire was administered to only 10% of subjects.

Table 1 shows certain characteristics of the subjects at baseline, classified into the four randomized groups. The differences in numbers are attributable to failure to ensure that the groups were balanced at randomization;

Table 1 Characteristics of subjects at baseline

	Dietary advice group			
	Fish	*Fruit*	*Fish + fruit*	*Sensible eating*
No. of subjects	764	779	807	764
Mean age (s.d.) in years	61.0 (6.5)	61.0 (6.5)	61.1 (6.9)	61.2 (6.3)
Percentage of smokers	24.1	21.6	25.1	24.0
Percentage with history of:				
Heart attack	49.6	48.3	49.8	52.2
Hypertension	49.0	45.8	48.1	49.1
Diabetes	11.3	11.6	13.7	13.1
Percentage on β-blockers	42.5	41.6	42.4	39.5
Mean BMI (s.d.) in kg/m^2	28.2 (3.9)	28.2 (4.1)	28.2 (4.0)	28.0 (4.2)
Mean systolic blood pressure (s.d.) in mmHg	142.3 (22.6)	141.9 (22.9)	141.6 (22.6)	141.3 (22.3)
Mean diastolic blood pressure (s.d.) in mmHg	85.1 (12.9)	84.9 (13.1)	84.6 (12.8)	84.3 (12.4)
Mean serum cholesterol (s.d.) in mmol/l	6.43 (1.12)	6.40 (1.19)	6.39 (1.11)	6.35 (1.19)

Table 2 Weighted mean dietary intakes (s.d.) at baseline and 6 months

	Dietary advice group			
	Fish (n = *267 + 32*)[a]	*Fruit* (n = *270 + 29*)[a]	*Fish + fruit* (n = *265 + 42*)[a]	*Sensible eating* (n = *263 + 34*)[a]
EPA (g/week)				
Baseline	0.67 (0.53)	0.61 (0.68)	0.54 (0.49)	0.66 (0.55)
6 months	3.32 (1.35)	0.79 (1.02)	2.65 (1.50)	0.78 (0.80)
Change	2.65 (1.35)	0.17 (0.98)	2.11 (1.57)	0.12 (0.73)
95% CI for change	2.36, 2.94	−0.01, 0.36	1.79, 2.42	−0.02, 0.26
Vitamin C (mg/day)				
Baseline	79.5 (36.1)	66.6 (34.9)	68.5 (36.9)	73.4 (37.6)
6 months	83.5 (40.7)	95.3 (49.7)	91.7 (43.7)	75.2 (37.2)
Change	4.0 (29.5)	28.7 (47.7)	23.2 (34.6)	1.9 (36.8)
95% CI for change	−1.6, 9.5	19.0, 38.4	16.6, 29.8	−5.6, 9.4
Total energy (kcal/day)				
Baseline	1890 (438)	1895 (583)	1894 (448)	1959 (516)
6 months	1805 (442)	1811 (483)	1834 (512)	1825 (412)
Change	−85 (383)	−84 (409)	−60 (458)	−134 (461)
95% CI for change	−158, −12	−163, −5	−156, 35	−228, −40
Total fat (g/day)				
Baseline	66.4 (23.8)	65.1 (27.7)	66.4 (25.3)	68.4 (25.8)
6 months	61.2 (22.3)	57.8 (23.4)	59.6 (21.4)	59.8 (22.8)
Change	−5.2 (21.4)	−7.2 (19.3)	−6.8 (21.8)	−8.6 (20.9)
95% CI for change	−9.5, −0.9	−10.9, −3.6	−11.1, −2.4	−12.7, −4.6
Saturated fat (g/day)				
Baseline	26.8 (12.6)	25.9 (14.4)	26.6 (12.5)	27.0 (12.1)
6 months	24.0 (12.0)	22.8 (12.7)	22.7 (10.6)	23.5 (11.1)
Change	−2.8 (9.4)	−3.1 (9.2)	−3.9 (9.7)	−3.5 (9.3)
95% CI for change	−4.6, −0.9	−4.8, −1.5	−5.8, −2.0	−5.3, −1.8
Polyunsaturated fat (g/day)				
Baseline	12.1 (5.5)	12.4 (6.1)	12.6 (7.3)	12.8 (6.4)
6 months	12.1 (5.4)	11.1 (5.0)	12.3 (6.5)	11.3 (5.0)
Change	−0.1 (5.8)	−1.3 (5.2)	−0.3 (7.4)	−1.6 (5.4)
95% CI for change	−1.1, 1.0	−2.1, −0.5	−1.9, 1.2	−2.5, −0.6

[a]The numbers shown relate to subjects in phase I and phase II, respectively; mean values are weighted to allow for different sampling ratios in the two phases.

Table 3 Plasma EPA concentrations in subjects who were and were not given fish advice

	Mean (s.d.) plasma EPA in mg/dl	
	Subjects given fish advice (n = 39)	*Subjects not given fish advice (n = 29)*
Baseline	3.35 (2.58)	3.19 (1.75)
At 6 months	4.58 (3.54)	3.03 (1.34)
Change	1.23 (3.29)	−0.16 (1.53)
95% CI for change	0.16, 2.30	−0.75, 0.44

Table 5 Deaths in relation to dietary advice (four-way analysis)

	Dietary advice group			
	Fish	*Fruit*	*Fish + fruit*	*Sensible eating*
No. subjects	764	779	807	764
Total number of deaths (%)	141 (18.5)	133 (17.1)	142 (17.6)	109 (14.3)
Number of cardiac deaths (%)	94 (12.3)	72 (9.2)	86 (10.7)	67 (8.8)
Number of sudden deaths (%)	42 (5.5)	30 (3.9)	31 (3.8)	17 (2.2)

the numbers shown comprise all those who were originally allocated to these groups, and all analysis is by intention to treat. The baseline characteristics were broadly similar in the groups; those allocated to sensible eating were slightly more likely than the others to give a history of a heart attack, and slightly less likely to be taking a β-blocker, while the fruit group had a lower prevalence of a history of hypertension than the rest. Age, BMI and blood pressure were very similar in the four groups. Weight reducing advice was given to very similar proportions of men in the four groups (28–30%); the details are not shown here.

Table 2 shows the mean intakes of certain dietary variables among subjects who completed detailed dietary questionnaires at baseline and at 6 months, weighted to allow for the differential application of this questionnaire in the two phases of the study. A substantial rise in EPA intake was reported in the fish and fish + fruit groups, of 2.65 and 2.11 g per week, respectively, whereas in the fruit and sensible eating groups the mean rise was only 0.17 and 0.12 g per week, respectively. Reported vitamin C intake rose in the fruit and fish + fruit groups, by 28.7 and 23.2 mg per day respectively, whereas in the fish and sensible eating groups the mean increase was only 4.0 and 1.9 mg per day, respectively. Data on certain other dietary variables are also shown; these intakes tended to decline, particularly total energy in the sensible eating group. Polyunsaturated fat showed little change in the fish groups but a decline in the others. The consumption of soluble fibre (not shown in the table) did not change very much; in the fruit advice groups, mean daily intakes rose by about 1 g to 7.8 g, while remaining at 6.9 g in the other groups.

Table 3 shows mean plasma EPA concentrations in a subset of subjects, with the changes that occurred from baseline to 6 months; as the numbers are rather small, the subjects are classified into two groups according to whether they received fish advice or not. A significant rise of 1.23 mg/dl occurred in those given fish advice, while a non-significant decline of 0.16 mg/dl occurred in the others. Table 4 similarly shows mean plasma β-carotene concentrations in a subset of subjects according to whether they were or were not given fruit advice. The changes were negligible in both groups. As part of another study, plasma folate was also measured in some subjects at baseline and 6 months. Mean concentrations remained virtually unchanged at 4.4–4.5 μg/l in those given and those not given fruit advice; other details have been published elsewhere (Ashfield-Watt *et al*, 2002).

All subjects except one were traced as being registered with a general practitioner on 1 April 1999 or having died before that date. Table 5 shows the subjects who died, classified in the four dietary advice groups. The subjects not given any specific advice ('Sensible eating') had the lowest mortality from all causes, cardiac death and sudden death, while the group advised only about fish or fish oil had the highest mortality. When the comparisons were made between all subjects given and all not given each type of

Table 4 Plasma β-carotene concentrations in subjects who were and were not given fruit advice

	Mean (s.d.) plasma β-carotene in μmol/l	
	Subjects given fruit advice (n = 36)	*Subjects not given fruit advice (n = 33)*
Baseline	0.278 (0.158)	0.291 (0.166)
At 6 months	0.261 (0.150)	0.297 (0.170)
Change	−0.017 (0.094)	0.007 (0.125)
95% CI for change	−0.049, 0.015	−0.038, 0.051

Table 6 Deaths in relation to dietary advice (two-way analysis)

	Dietary advice group			
	All fish[a]	*No fish*	*All fruit*[b]	*No fruit*
Number of subjects	1571	1543	1586	1528
Total number of deaths (%)	283 (18.0) $P = 0.08$	242 (15.7)	275 (17.3) $P = 0.07$	250 (16.4)
Number of cardiac deaths (%)	180 (11.5) $P = 0.02$	139 (9.0)	158 (10.0) $P = 0.60$	161 (10.5)
Number of sudden deaths (%)	73 (4.6) $P = 0.02$	47 (3.0)	61 (3.9) $P = 0.98$	59 (3.8)

[a]*P*-values relative to no fish group; [b]*P*-values relative to no fruit group.

Table 7 Mortality of subjects advised about fish and fruit: adjusted hazard ratios (HR)[a] relative to subjects not so advised

	Fish advice		*Fruit advice*	
	HR (95% CI)	P-*value*	*HR (95% CI)*	P-*value*
All deaths	1.15 (0.96, 1.36)	0.13	1.12 (0.94, 1.34)	0.20
Cardiac deaths	1.26 (1.00, 1.58)	0.047	1.00 (0.80, 1.25)	1.0
Sudden deaths	1.54 (1.06, 2.23)	0.025	1.01 (0.70, 1.46)	0.94

[a]Hazard ratios adjusted for age, smoking, previous MI, history of high blood pressure, diabetes, BMI, serum cholesterol, medication (see text), and fruit advice (for fish) or fish advice (for fruit).

advice, those given fish advice had a significantly higher mortality from cardiac and sudden death; fruit advice appeared to have no effect in either direction (Table 6). Similar findings emerged when the data were analysed in terms of hazard ratios that take into account duration of survival (Table 7); these were adjusted for various baseline variables that were found to influence cardiac mortality: age, smoking, previous myocardial infarction (MI), history of high blood pressure, diabetes, serum cholesterol, fruit advice, and six types of medication (β-blockers, nitrates, digoxin, lipid-lowering drugs, anticoagulants and diuretics). There was no evidence of any effect of fruit advice. Figure 1 shows the survival curves in respect of cardiac death for subjects given and not given each type of advice. The excess risk for fish advice was fairly consistent over the whole period; for fruit advice there was virtually no difference in either direction at any time.

In order to attempt to explain the unexpected excess mortality associated with fish advice, subgroup analyses were carried out. The apparently adverse effect of fish advice was confined to the second phase of the trial (data not shown), when a much higher proportion of subjects were given fish oil capsules than in the first phase. During this part of the study, some of the subjects allocated to fish advice were subrandomized to receive fish oil capsules, so a survival analysis was carried out to examine the effect on those subrandomized to capsules rather than to dietary advice. Table 8 shows that the hazard ratios for each mortality category were higher in the fish oil than in the dietary fish group, and significantly different from unity only in the former group. The dietary fish group comprises all subjects allocated to fish advice throughout the trial, including those who chose to take capsules instead of fish, but excluding the subrandomized fish oil group.

The possibility was considered that dietary fish or fish oil could adversely interact with drugs commonly given for heart disease. Hazard ratios for cardiac death were calculated in relation to fish advice, with subjects classified into those receiving and those not receiving various types of drug at recruitment into the trial. No evidence was found of any adverse interactions; treatment with β-blockers showed a significant favourable interaction with fish advice.

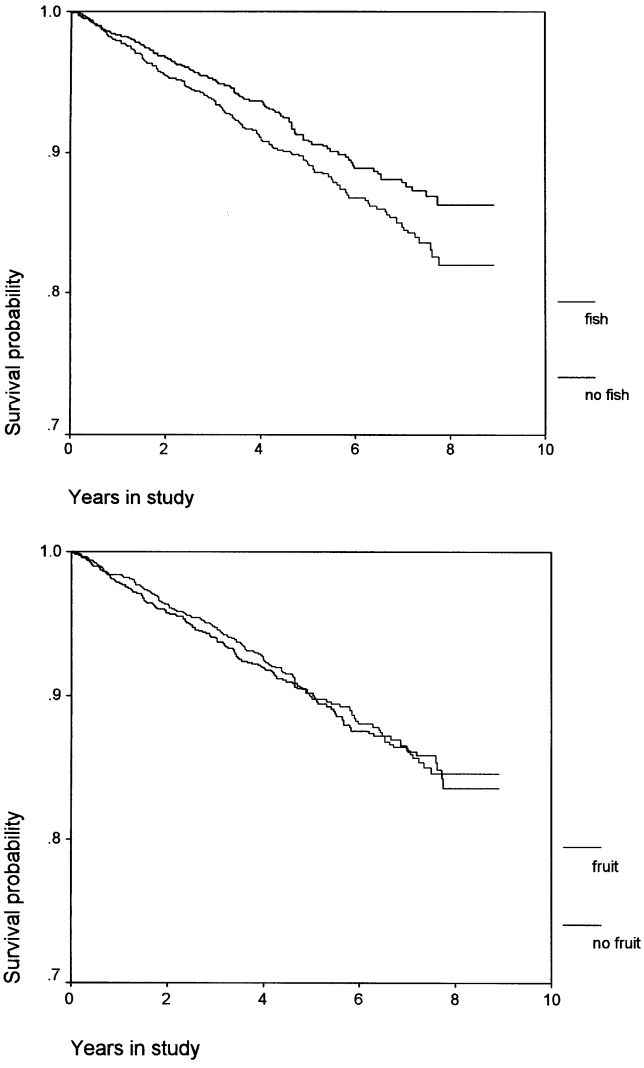

Figure 1 Survival from cardiac death of subjects, classified according to their allocation to fish or fruit advice.

Table 8 Survival analysis of subjects advised on dietary fish or fish oil: adjusted hazard ratios (HR)[a] relative to subjects given no fish advice

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

[a]Hazard ratios adjusted for age, smoking, previous MI, history of high blood pressure, diabetes, BMI, serum cholesterol, medication (see text), and fruit advice.

Discussion

This study was set up to test the hypothesis that advising male angina patients to eat more fruit and vegetables, or more oily fish, reduces their risk of death from heart disease. It was designed as a pragmatic trial of dietary advice in real-life conditions.

Recruitment was initially by means of general practitioners' records of prescriptions for nitrate drugs, followed by administration of a questionnaire that enquired about exertional chest pain or discomfort. It is accepted that this process does not guarantee that a diagnosis of angina would be made on a full clinical investigation. Nevertheless, other studies have shown that the prescription of nitrates (Clarke *et al*, 1994) and reporting of exertional chest pain (Lampe *et al*, 1998) are useful markers of angina and indicate an increased risk of major IHD events. It is therefore reasonable to assume that most subjects who show both these features are likely to have angina and an increased risk of death from IHD.

Ascertainment of all-cause mortality was virtually complete within the study. Cardiac mortality was defined by the certified cause of death except in a few cases where further evidence from hospital records suggested otherwise. Suddenness of death was ascertained from hospital notes, coroners' reports and eyewitness accounts; it was not always possible to be sure of the exact course of the final episode, owing to variations in the quality of evidence and the fact that some deaths were unwitnessed. It was decided in advance of the analysis that the primary endpoint would be cardiac death.

Advice to eat more fruit, vegetables and oats did not reduce mortality. Although some increases occurred in reported intakes of vitamin C and soluble fibre, they were substantially less than intended, and (given the inevitable reporting biases) the actual increases were presumably lower still. The lack of any rise in serum concentrations of folate or carotenoids confirms the impression of poor compliance with the advice, although admittedly the men may have chosen fruit and vegetables that are not good sources of these particular nutrients. The trial cannot therefore be regarded as an adequate test of the hypothesis that these foodstuffs protect against heart disease. Good evidence for this hypothesis is provided by a range of observational studies (Key *et al*, 1996; Ness & Powles, 1997), and by controlled trials where an increased intake of fruit and vegetables formed part of the intervention (Singh *et al*, 1992; de Lorgeril *et al*, 1994). A further trial is warranted which achieves a better degree of compliance with this advice. There may be cultural obstacles to the consumption of adequate amounts of fruit and vegetables among middle-aged men in South Wales.

The lack of benefit from advice to eat oily fish, or to take fish oil capsules, is less easily explained. Reported EPA intakes suggest a reasonable degree of compliance, borne out by the changes in serum levels. Inadequate compliance in our trial cannot be ruled out, given the likelihood of reporting bias, the small number of subjects for whom serum EPA was measured, and the wide confidence intervals for the mean EPA levels. However, there is no obvious reason to suppose that these subjects were more biased in their reporting than those in the DART study (Burr *et al*, 1989), where similar advice produced a similar reported increase in EPA intake. That study, and the trial conducted by the GISSI-Prevenzione Investigators (1999), showed a protective effect in post-MI patients; the present trial was set up to see whether a similar effect occurred in men with angina. Observational evidence on this point is not wholly consistent, but overall it suggests that fish consumption is markedly protective against IND in high-risk populations (Marckmann & Grønbæk, 1999), a designation that certainly applies to angina patients. The trial was also designed to see whether fish oil specifically protects against sudden cardiac death (a marker for fatal arrhythmia), as might be expected from animal studies (Charnock, l994; Billman *et al*, 1997). The Physicians' Heart Study provided some evidence for this hypothesis, in that sudden cardiac death was inversely related to fish consumption (Albert *et al*, 1998) and blood levels of long-chain n-3 fatty acids (Albert *et al*, 2002), but another observational study suggested that the effect is greater for non-sudden cardiac death (Daviglus *et al*, 1997). Data from that study and GISSI-Prevenzione suggest that the protective effect of fish oil is greatest in the immediate post-MI period, and it is possible that there is little or no benefit among patients with stable angina.

The higher incidence of cardiac and sudden death associated with fish advice was wholly unexpected. There are six possible explanations that should be considered.

1. It may have arisen by chance. Misleading associations can always occur, and the reported *P* values do not necessarily require rejection of the null hypothesis if a Bayesian approach is taken, taking prior evidence into account (Sterne & Davey Smith, 2001). Nevertheless it is prudent to consider other possibilities.
2. Fish or fish oil may have an adverse effect in angina patients. No previous study (observational or interventional) specifically addressed this group, so such an effect cannot be wholly excluded. However, the DART and GISSI-Prevenzione studies give no evidence of an adverse effect after the immediate post-MI period, when many of the subjects are likely to have had stable angina. Fish appeared to be protective in a Dutch cohort of elderly people, 19% of whom initially had angina (Kromhout *et al*, 1995). An adverse effect of fish oil as distinct from dietary fish is unlikely: GISSI-Prevenzione used fish oil, and in DART the effects of fish oil and dietary fish were similar (Burr *et al*, 1994). It is difficult to see how fish or fish oil could be protective after MI and in other high-risk groups but harmful in patients with angina.
3. Some contaminant of fish or fish oil could be responsible. A study in Finland showed an excess risk of MI associated with the concentration of mercury in hair and with the intake of fish, which was apparently contaminated with mercury (Salonen *et al*, 1995). Other toxic contaminants

such as dioxin and polychlorinated biphenyls (PCBs) can be found in fish. However, the Finnish study related to non-fatty fish from locally polluted inland waters, whereas this study concerned mainly saltwater fatty fish. Levels of dioxins and PCBs in inland waters, estuaries and seas have declined during recent decades, leading to a substantial reduction in the concentrations found in fish and other foods, so that the average UK dietary exposure has fallen by about 75% since 1982 (Liem & Theelen, 1997; Ministry of Agriculture, Fisheries and Food, 1997; Food Standards Agency, 2001). The fish oil preparation in this study was derived from fish in the southern hemisphere, where pollution is particularly low, so it is likely to have made only a minor contribution to the daily intake of these contaminants.

4. Fish oil could interact adversely with drugs taken by angina patients. There are other examples of common foods that are beneficial in themselves but have potentially adverse interactions with drugs (eg grapefruit juice with calcium-channel blockers, green vegetables with warfarin). There was no evidence of such interactions; indeed, beta-blockers appeared to interact favourably with fish in this study.
5. The taking of fish oil may modify the patient's treatment. It is possible that men who took three large capsules daily were disinclined to take additional capsules or tablets. Their doctors may even have tended not to prescribe further medication in the belief that it would interfere with the trial, despite instructions to the contrary. It is noteworthy that the effect was confined to the second phase of the trial, when a higher proportion of subjects were issued with capsules, and greater in those subrandomized to capsules. Information about medication was obtained on all patients at entry to the trial, after 6 months, and at the end; there were no clear differences between the randomized groups' drug usage, but 6 months was probably too short an interval for such an effect to occur, while the data at the end of the trial related only to the survivors. Thus although there is no evidence that treatment was affected, it is still a possibility.
6. If people believe that taking certain capsules greatly reduces the danger of death from heart disease, they may feel at liberty to increase their risk-taking behaviour in relation to issues such as diet, lifestyle, and compliance with treatment. The phenomenon of risk compensation is well documented in other contexts (Richens *et al*, 2000), and there is no reason to suppose that patients with angina would be immune from it. Furthermore, these men are likely to have a different perception of risk from that of patients recovering from a life-threatening MI, who were the subjects in the DART and GISSI-Prevenzione studies.

There have been other trials of diet and lifestyle factors that have produced paradoxical results. In the Sydney Diet – Heart Study, men with clinical coronary disease were randomly allocated to receive usual care or individually tailored advice to reduce their intake of saturated fat and cholesterol (Woodhill *et al*, 1978). Despite good dietary compliance and a greater reduction in serum lipids, the intervention group had a significantly higher mortality than the control group. A higher net mortality rate (14% difference) occurred in the intervention group of the UK component of the WHO Collaborative Trial of Multifactorial Prevention of Coronary Heart Disease, which used advice on diet, smoking, overweight, blood pressure and exercise (World Health Organization European Collaborative Group, 1983). In a randomized trial among middle-aged men in Finland the intervention consisted of diet, lipid-lowering drugs and antihypertensive treatment; these measures were successful in terms of the risk factors, yet the intervention group had a significantly higher mortality from cardiac disease and from all causes (Strandberg *et al*, 1991).

A recent discussion of 'effect models' in cardiological trials pointed out that, since almost all interventions have the potential to cause harm, the net effect of any intervention in a group of persons depends on the relative proportions of those benefited and harmed as well as the size of these effects (Lubsen & Poole-Wilson, 2000). This principle applies whether the effects are direct or indirect. Research is needed to see whether interventions that are perceived to reduce risk have indirect adverse consequences (possibilities 5 and 6 above), which could outweigh their benefits in some circumstances. Such consequences will be revealed only by open, non-blinded studies; in placebo-controlled trials they are just as liable to occur, but are undetectable, since they affect the intervention and control groups equally.

In summary, this study shows that simple advice increases the intake of some dietary components (such as fish) but has little effect on others (fruit and vegetables). An apparent improvement does not necessarily produce any change in the important outcome variables; indeed, providing fish oil capsules may even have an adverse effect, for reasons that are at present unclear. Further data from this cohort will be examined in order to elucidate this finding. Caution is needed when giving pragmatic dietary advice in case it has unforeseen effects.

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