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# Is Fish Oil Good or Bad for Heart Disease? Two Trials with Apparently Conflicting Results

**M.L. Burr**[1], **F.D.J. Dunstan**[1], **C.H. George**[2]
[1]Department of Epidemiology, Statistics and Public Health, Cardiff University, Heath Park, Cardiff, CF14 4XN, Wales, UK
[2]Wales Heart Research Institute, Cardiff University, Heath Park, Cardiff CF14 4XN, Wales, UK

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**Abstract.** Two successive randomized trials examined the effect of an increased intake of fatty fish, or the use of fish oil supplements, in reducing mortality in men with heart disease. The Diet and Reinfarction Trial (DART) was conducted in 2033 men who were recovering from acute myocardial infarction (MI). Those who were advised to eat fatty fish (or who opted to take fish oil capsules instead) had a 29% reduction in all-cause mortality over the following two years compared with those not so advised. The effect appeared in the first few months of the trial. The Diet and Angina Randomized Trial (DART 2) involved 3114 men with stable angina. Advice to eat fatty fish did not reduce mortality, and taking fish oil capsules was associated with a higher risk of cardiac and sudden death. The adverse effects of fish or fish oil were restricted to men not taking β-blockers or dihydropyridine calcium-channel blockers, and were greater in those taking digoxin. Evidence from other sources strongly suggests an anti-arrhythmic action of fish oil, particularly after MI or in the presence of acute ischemia. The apparently conflicting results of the two trials may reflect different actions of n-3 fatty acids in acute and chronic conditions, together with different effects of eating fish and taking fish oil capsules. A mechanism is proposed that could account for these findings.

**Key words:** Fatty acids — Fish — Heart disease

## Background

The essential fatty acids were discovered in 1929 by the American biochemists Evans and Burr. In 1937 the British physiologist Hugh Sinclair visited Evans and became interested in the possibility that deficiencies in some fatty acids might account for the rise of diseases such as ischemic heart disease (IHD) in Western countries. In 1944 he undertook his first visit to Eskimos (Inuit); he became convinced that their diet protects them against atherosclerosis and other "Western" conditions, and published his hypothesis in a long letter to The Lancet in 1956. This view was contrary to the received wisdom at that time, which regarded all animal fats as harmful.

More detailed studies by the Danish investigators Bang and Dyerberg suggested that certain polyunsaturated fatty acids (PUFAs), particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are the ingredients of seafood that protect native Greenlanders from thrombosis and atherosclerosis. They also drew attention to a sudden fall in IHD and mortality in Oslo in 1940, which they attributed to dietary changes (from meat to fish) consequent to the German invasion (Bang & Dyerberg, 1981). Studies in Japanese populations with different intakes of fish confirmed the observations among Greenlanders. A rapidly growing body of experimental studies explored various effects of fish oil, including its actions on clotting mechanisms, platelet function, plasma lipids, and blood pressure.

## Diet and Reinfarction Trial (DART)

### Purpose of the Trial

In the early 1980s the Medical Research Council Epidemiology Unit (South Wales), where MLB was working, decided to set up a randomized controlled trial to investigate the effects of dietary intervention on the secondary prevention of MI. Up until that time, the main dietary factor in relation to IHD was thought to be saturated fat; several secondary prevention trials of dietary fat modification had been conducted, but they were small and inconclusive. The

*Correspondence to:* M.L. Burr; email: burrml@cf.ac.uk

trial was therefore planned to test the effect of advice to reduce saturated fat intake and increase the ratio of polyunsaturated to saturated fatty acids in the diet.

There was also a growing interest in the possibility that a high fiber diet confers protection against IHD. The evidence for this belief was derived from cohort studies in which intake of dietary fiber (particularly that derived from cereal products) was inversely related to subsequent MI incidence or mortality. No relevant clinical trials had been conducted, so the opportunity was taken to incorporate a test of this hypothesis in the planned trial. In order to examine the effects of fat modification and fiber separately, it was decided to adopt a factorial design: i.e., the subjects would be randomized to receive or not receive dietary advice on fat and independently on fiber. This type of trial design is very economical; it effectively allows two trials to be run simultaneously on the same group of subjects. It also allows the investigation of any interaction between the two interventions.

At the same time, we considered the growing body of evidence pointing to fatty fish as potentially protective against IHD. In 1982 a Finnish study was published showing that serum EPA (in stored samples) was inversely related to subsequent myocardial infarction (MI) and sudden death (Miettinen et al., 1982). We conducted a trial among healthy men that demonstrated that advice to eat at least 100 g fatty fish at least twice a week was acceptable and reduced plasma triglyceride concentration. It therefore seemed reasonable to include this advice as a third factor in the proposed trial.

## Subjects and Methods

In consequence, the Diet and Reinfarction Trial (DART) was set up (Burr et al., 1989). Between 1983 and 1987 we recruited 2033 nondiabetic men aged under 70 years who were recovering from MI. They were randomly allocated to receive advice or no advice on three dietary factors independently of each other: fat modification, cereal fiber, and fatty fish. Men whose diet already conformed to any of the three interventions were excluded prior to randomization. Those who were advised to eat fatty fish but found it unpalatable were given fish oil capsules as a partial or total substitute. The subset of men who were controls for all three interventions were given "healthy eating" advice, which was designed to change their diet as little as possible. Weight reducing advice was incorporated when required. Dietitians contacted the men periodically and reinforced the dietary advice.

After about 6 months, and again after about two years, a dietary questionnaire was administered to each man, blood was taken for various measurements, and enquiries were made about hospital admissions. If the history suggested possible reinfarction, the hospital notes were examined to see whether a diagnosis of a further MI could be established. Deaths and certified causes were ascertained by flagging the subjects' records at the National Health Service (NHS) central register. A copy of the death certificate was obtained for everyone who had died before the second anniversary of his recruitment into the trial, and the cause of death was classified as IHD or non-IHD. Decisions about reinfarction and IHD death were made without the knowledge of the subjects' allocation within the trial.

## Results

The differences in dietary patterns and serum cholesterol attributable to advice on fat modification was disappointing, partly because of poor compliance and partly because of spontaneous changes among the men not given this advice. In contrast, the advice relating to fiber and to fish resulted in adequate dietary differences between the intervention and control groups for these factors; objective evidence of compliance with the fish advice was provided by measurement of plasma fatty acids in a subset.

The primary endpoints were death and reinfarction occurring within two years of entry to the trial. Table 1 shows the differences in outcome between those given and those not given advice to eat fatty fish. Overall mortality was 29% lower in the group advised to eat fatty fish than in those not so advised, the difference being due to a reduction in IHD deaths. The survival curves of the two groups diverged within the first few months of the trial, and then became roughly parallel. No reduction occurred in non-fatal MI, which occurred somewhat more frequently in the intervention group than in the controls. Fish oil capsules appeared to confer a similar degree of benefit to that provided by dietary fish (Burr, Sweetnam & Fehily, 1994). No significant differences were attributable to the advice on fat or fiber.

## Conclusions in the Light of Concurrent Studies

The results of this trial indicated that a modest intake of fatty fish improves the two-year survival of men who have recently recovered from MI. This conclusion fitted in with the findings of several cohort studies that were published at about this time, most (though not all) of which showed an inverse relation between fish consumption and IHD mortality. The possibility that fish oil protects against the early complications of MI was supported by experimental studies: dietary fish oil was shown to prevent ventricular fibrillation following coronary artery occlusion and reperfusion in rats (McLennan, Abey Wardena & Charnock, 1988), and EPA solution was found to protect rat

myocytes in vitro against the arrhythmogenic action of ouabain (Hallaq et al., 1990). It therefore seemed reasonable to postulate that the outcome of the DART study was due to protection by fatty fish (presumably through its n-3 fatty acid content) against the potentially fatal arrhythmias that are liable to occur during recovery from MI.

Fatty fish did not appear to reduce the incidence of MI in this trial. This finding was somewhat surprising in view of some of the known actions of n-3 fatty acids. Several randomized controlled trials showed effects of fish oil on blood platelets and clotting mechanisms that could reduce the incidence and severity of MI, and this possibility was borne out by evidence that fish oil reduces the size of experimentally induced atheromatous and ischemic lesions in animals (for review, *see* Burr, 1989). Perhaps these effects require a larger intake or a longer duration to become clinically evident.

### An Unanswered Question

When the results of this trial were presented at various meetings, the question most often asked was whether there had been a reduction in sudden death, since this is a proxy for fatal arrhythmias such as ventricular fibrillation. Unfortunately this question could not be answered; we had not been aware of the work on the anti-arrrhythmic action of fish oil, so information on the mode of death was not collected, and it seemed too late to obtain details from witnesses after an interval of a few years in some cases.

### Subsequent Follow-up

When the results were published in 1989, a letter was sent to all the surviving subjects explaining the findings and advising them to eat fatty fish, whether or not this advice had been given them at the start of the trial. In 1999-2000 a further follow up was conducted, using a questionnaire and the NHS central register. Long-term survival was not greatly improved in the group originally given fish advice, either because of a diminishing difference in fish intake between the two groups, or because the benefits occurred specifically during the immediate post-infarct period (Ness et al., 2002).

## Diet and Angina Randomized Trial (DART 2)

### Purpose of the Trial

A further trial was planned in order to take forward the findings of DART in several respects:

1. To see whether a moderate intake of fatty fish reduces IHD mortality among people at high risk of MI to a similar degree as among men who have just recovered from MI.
2. To see whether any reduction in IHD mortality attributable to fish occurs mainly among sudden deaths.
3. To investigate concurrently the possible cardioprotective effects of two other factors: the intake of soluble fiber in fruit, vegetables, oats and fruit juice; and a short course in stress management training.

As before, the trial had a factorial design so that the three factors could be investigated independently.

### Subjects and Methods

The subjects for this trial were patients under the age of 70 years who were identified by their general practitioners as under treatment for angina (Burr et al., 2003). The trial was restricted to men because the case fatality of angina seems to be higher in men than in women. The men were interviewed and excluded from the trial if they denied any history of chest pain brought on by exertion or stress, if they already ate fatty fish twice a week, if they could not tolerate fatty fish or fish oil capsules, or if they were awaiting coronary artery bypass surgery. The rest were randomly allocated to receive advice or no advice on each of the three interventions. As before, men advised to eat fish who found it unpalatable were supplied with capsules, and those who were not allocated to a dietary intervention were given "healthy eating" advice.

Subjects were enlisted from 1990 to 1996. The conduct of the trial was complicated by the Medical Research Council's decision to run down its Epidemiology Unit prior to closure on the Director's impending retirement. Recruitment was interrupted for twelve months in 1992-1993 while fresh funding was obtained; the stress management component had to be abandoned. When recruitment was resumed, the fish advice group was subrandomized to receive either advice to eat dietary fish or a supply of fish oil capsules. Certain aspects of the study had to be curtailed: the contact between patients and dietitians was much reduced, detailed dietary information was obtained on a subset rather than on all subjects, and ascertainment of incident MI by examining hospital notes was not undertaken. These changes occurred when about a third of the subjects had been recruited: 1111 out of the ultimate total of 3114.

Deaths and certified causes were ascertained as in DART. Three years after the last subject was recruited, a letter and questionnaire were sent to all the men who were thought to have survived. Other enquiries were made about non-responders, so that on 1 April 1999 all the subjects except one were known to be currently registered with a general practitioner or

**Table 1.** Deaths and reinfarctions in groups advised and not advised to eat fish in DART

| | Randomized advice group | | |
|---|---|---|---|
| | Fish | No fish | *P* (logrank test) |
| No. subjects | 1015 | 1018 | |
| All deaths (%) | 94 (9.3) | 130 (12.8) | < 0.05 |
| IHD deaths (%) | 78 (7.7) | 116 (11.4) | < 0.01 |
| Nonfatal MI (%) | 49 (4.8) | 33 (3.2) | NS |
| IHD events* (%) | 127 (12.5) | 149 (14.6) | NS |

*IHD events = IHD deaths + nonfatal MI.

**Table 2.** Deaths among men given any fish advice and no fish advice in DART 2

| | Randomized advice group | | |
|---|---|---|---|
| | Any fish | No fish | *P* |
| No. subjects | 1571 | 1543 | |
| All deaths (%) | 283 (18.0) | 242 (15.7) | 0.08 |
| Cardiac deaths (%) | 180 (11.5) | 139 (9.0) | 0.02 |
| Sudden deaths (%) | 73 (4.6) | 47 (3.0) | 0.02 |

else to have died before that date. For those whose deaths were attributed to a cardiac cause, further details were obtained from hospital records, coroners, relatives and other witnesses, so that the suddenness of the death could be ascertained. Sudden death was defined as in the US Physicians' Heart Study (Albert et al., 1998), based on death within an hour of the onset of symptoms.

## Results

As in the previous trial, compliance with fish advice was good, indicated by reported fish intake and by plasma EPA concentrations in a subset of subjects (Burr et al., 2003). There was a higher mortality among the group advised to eat fish or take fish oil capsules than among those not so advised, and the difference was significant for cardiac and sudden death (Table 2). No significant differences occurred in relation to advice to eat fruit and vegetables. The excess mortality in the fish advice group was confirmed by hazard ratios (Table 3), which take account of the duration of survival and are adjusted for various baseline variables. Hazard ratios were then calculated separately for the subgroups randomly allocated to receive dietary fish advice or fish oil capsules; the excess mortality was significant only within the latter subgroup.

The possibility was considered that there could be an interaction between fish oil and the medication which the patients were taking. The effect of fish advice was therefore examined separately in men receiving and not receiving various drugs at recruitment. Table 4 shows this analysis in relation to β-blockers: the excess mortality in the fish group was restricted to the men not taking β-blockers, and the interaction was significant for all deaths and cardiac deaths. Table 5 shows a similar result in regard to nifedipine and other dihydropyridine-class calcium-channel blockers, the interaction term for sudden death being statistically significant. Digoxin was the only other drug for which a significant interaction with fish advice occurred (Table 6), but here the interaction was unfavorable—i.e., fish advice was associated with a greater increase in mortality (particularly from all causes) in men who were taking this drug. The total numbers in Tables 4–6 are slightly less than those in Table 2 owing to some missing data on medication at baseline.

## Implications

It therefore appeared that fish oil, which protected post-MI male patients in DART, increased the risk of cardiac death in men with angina, being particularly associated with sudden death. The adverse effect seemed attributable to fish oil taken in capsules rather than to dietary fish, and was very surprising in view of the growing body of evidence suggesting an anti-arrhythmic action of n-3 fatty acids.

Subgroup analysis is hazardous in the absence of a prior hypothesis, so the evidence for interactions with drugs must be treated very cautiously. If indeed these interactions were real, they suggest that β-blockers and dihydropyridine calcium-channel blockers protect the heart against the arrhythmic effects of fish oil, while digoxin exacerbates these

**Table 3.** Hazard ratios (HR)* for death among men randomized to receive any fish advice, dietary fish advice and fish oil capsules

| | Randomized group or subgroup | | |
|---|---|---|---|
| | Any fish advice | Dietary fish advice | Fish oil capsules |
| No. subjects | 1571 | 1109 | 462 |
| All deaths | | | |
| No. | 283 | 198 | 85 |
| HR (95% CI) | 1.15 (0.96, 1.36) | 1.13 (0.94, 1.37) | 1.19 (0.92, 1.54) |
| *P* | 0,20 | 0.20 | 0.19 |
| Cardiac deaths | | | |
| No. | 180 | 121 | 59 |
| HR (95% CI) | 1.26 (1.00, 1.58) | 1.20 (0.93, 1.53) | 1.45 (1.05, 1.99) |
| *P* | 0.047 | 0.16 | 0.025 |
| Sudden deaths | | | |
| No. | 73 | 49 | 24 |
| HR (95% CI) | 1.54 (1.06, 2.23) | 1.43 (0.95, 2.15) | 1.84 (1.11, 3.05) |
| *P* | 0.025 | 0.086 | 0.018 |

*HR = hazard ratio adjusted for age, smoking habit, medication, and other variables. CI, confidence interval.

**Table 4.** Deaths in men taking and not taking β-blockers on recruitment

| | Taking β-blockers | | | Not taking β-blockers | | | |
|---|---|---|---|---|---|---|---|
| | Advice group | | | Advice group | | | |
| | Fish | No fish | *P* | Fish | No fish | *P* | *P* for interaction |
| No. subjects | 665 | 626 | | 902 | 917 | | |
| All deaths (%) | 93 (14.0) | 94 (15.0) | 0.60 | 188 (20.8) | 148 (16.1) | 0.010 | 0.047 |
| Cardiac deaths (%) | 5.8 (9.1) | 57 (8.7) | 0.81 | 120 (13.3) | 82 (8.9) | 0.003 | 0.046 |
| Sudden deaths (%) | 26 (3.9) | 18 (2.9) | 0.31 | 47 (5.2) | 29 (3.2) | 0.031 | 0.61 |

**Table 5.** Deaths in men taking and not taking nifedipine or other dihydropyridine calcium-channel blockers on recruitment

| | Taking nifedipine, etc | | | Not taking nifedipine, etc | | | |
|---|---|---|---|---|---|---|---|
| | Advice group | | | Advice group | | | |
| | Fish | No fish | *P* | Fish | No fish | *P* | *P* for interaction |
| No. subjects | 621 | 584 | | 955 | 946 | | |
| All deaths (%) | 112 (18.0) | 108 (18.5) | 0.84 | 169 (17.8) | 134 (14.0) | 0.021 | 0.10 |
| Cardiac deaths (%) | 68 (11.0) | 60 (10.3) | 0.70 | 110 (11.6) | 79 (8.2) | 0.012 | 0.20 |
| Sudden deaths (%) | 21 (3.4) | 21 (3.6) | 0.84 | 52 (5.2) | 26 (2.7) | 0.003 | 0.045 |

effects. But it must be recognized that the observations could be chance effects.

## Could Risk Compensation Be the Explanation?

One possible explanation was that the issue of fish oil capsules modified the subjects' behavior in some way that was prejudicial to cardiac health. If people believe that a certain medicament infallibly protects them against heart disease, they may feel at liberty to increase their risk-taking behavior with regard to diet, lifestyle, and compliance with treatment. This phenomenon has been described in other contexts (Richens, Imrie & Copas, 2000), and could occur in patients with mild angina. When the subjects were seen at 6 months, no obvious differences had arisen between the randomized groups in respect of change in weight, body mass index, serum cholesterol, or medication. In 2000 a short questionnaire was sent to a subset of 1191 men asking about certain factors that

**Table 6.** Deaths in men taking and not taking digoxin on recruitment

| | Taking digoxin | | | Not taking digoxin | | | |
|---|---|---|---|---|---|---|---|
| | Advice group | | | Advice group | | | |
| | Fish | No fish | *P* | Fish | No fish | *P* | *P* for interaction |
| No. subjects | 74 | 61 | | 1493 | 1482 | | |
| All deaths (%) | 35 (47.3) | 17 (27.9) | 0.022 | 246 (16.5) | 223 (15.1) | 0.33 | 0.009 |
| Cardiac deaths (%) | 23 (31.1) | 12 (19.7) | 0.13 | 155 (10.4) | 126 (8.5) | 0.092 | 0.274 |
| Sudden deaths (%) | 8 (10.8) | 2 (3.3) | 0.12 | 65 (4.4) | 44 (3.0) | 0.058 | 0.28 |

might be relevant to this issue: no differences were found in smoking habit, alcohol intake, self-reported weight or medication between the groups given and not given fish advice (Ness et al., 2004). Thus, although risk compensation cannot be wholly ruled out, it is difficult to postulate the risk-taking activities that would have created the excess cardiac deaths in the fish advice group.

## DART and DART 2 in Relation to Other Studies

### Other Randomized Trials

The large GISSI-Prevenzione Study showed that fish oil (1 g per day of n-3 PUFAs) reduced cardiac mortality (but not nonfatal MI) in patients who had recently recovered from MI; a significant reduction in sudden death was detectable after 4 months (Marchioli et al., 2002). These findings reinforced those of DART in showing a protective effect of fish oil during recovery from MI, and supplied good evidence that this was attributable to a reduction in the incidence of fatal arrhythmia, which is especially liable to occur in the post-infarction period.

A systematic review of randomized trials examined the evidence for an effect of omega 3 (n-3) fatty acids (from fish and plant sources) on cardiovascular disease (Hooper et al., 2004). Overall there was no clear evidence of reduction in mortality by these fatty acids, whether of fish or plant origin; there was significant statistical heterogeneity in this analysis, which disappeared when DART 2 was excluded, the meta-analysis then showing a reduction in risk of death (relative risk 0.83, 95% confidence interval 0.75–0.91). The authors concluded that it is not clear whether dietary or supplemental omega 3 fatty acids alter total deaths or cardiovascular events in the general population or in people with or at risk of cardiovascular disease.

A further randomized trial investigated the effect of fish oil in preventing episodes of sustained ventricular tachycardia (VT) or ventricular fibrillation (VF) in patients with implantable defibrillators (Raitt et al., 2005). The incidence of these episodes was somewhat higher in patients receiving fish oil than in those taking placebo, the difference being statistically significant for recurrent episodes and among persons whose qualifying arrhythmia was VT; there was also a tendency for the association between fish oil and arrhythmia to occur in patients with prior coronary artery disease. The authors considered that fish oil may be pro-arrhythmic in this population. This finding is obviously relevant to DART 2, in that VT and VF would probably cause sudden death in the absence of a defibrillator.

On the other hand, a trial of n-3 PUFAs in patients undergoing coronary artery bypass surgery showed a reduction in the incidence of postoperative atrial fibrillation (Calo et al., 2005). Perhaps the difference between the results of this and of the preceding study is due to the different clinical conditions of the patients: fish oil could be anti-arrhythmic in conditions of acute coronary ischemia (as in GISSI-Prevenzione) but pro-arrhythmic in patients with chronic disease (as in DART 2). Further trials are in progress that may elucidate the issue.

### Cohort Studies

A meta-analysis of cohort studies showed that fish consumption is inversely associated with fatal coronary heart disease (He et al., 2004). Even a small intake of fish conferred some benefit, and each 20 g/day increase was related to a 7% lower risk of coronary heart disease mortality. Individual studies varied as to whether the effect was greater for sudden (Albert et al., 1998) or non-sudden (Daviglus et al., 1997) cardiac death. Another meta-analysis included data relating to any source of n-3 fatty acids (Hooper et al., 2004); this showed protection against total and (less clearly) cardiovascular mortality but not nonfatal MI. This evidence accords with that of DART, though as in all cohort studies some of the effects may be attributable to confounding variables, since people who choose to eat fish or take supplements probably

differ from other people in ways that are difficult to allow for in the analysis.

One cohort study examined the relationship between fish intake and incident atrial fibrillation (Mozaffarian et al., 2004): a reduced incidence was associated with some types of fish meal (tuna and other broiled or baked fish) but not with others (fried fish and fish sandwiches). Another cohort study showed a positive relationship between intake of n-3 fatty acids from fish and the incidence of atrial fibrillation or flutter in persons with no prior history of heart disease (Frost & Vestergaard, 2005). This finding appears to conflict with that of the trial by Calo et al. (2005), unless the effect of fish oil is anti-arrhythmic in the acute circumstances of coronary bypass grafting and pro-arrhythmic in some people in the longer term. Alternatively, the association in the cohort study could have arisen from confounding factors that were not allowed for in the analysis.

### Animal and in Vitro Experiments

There is a large body of experimental studies showing anti-arrhythmic effects of n-3 PUFAs in various animals, including rats (McLennan et al., 1988), dogs (Billman, Kang & Leaf, 1997), and monkeys (Charnock, 1994), when subjected to acute myocardial ischemia or subsequent coronary reperfusion. Experiments using cultured rat cardiomyocytes show that these fatty acids prevent and stop arrhythmia induced by various agents, probably by modulating the ionic currents in the plasma membrane of heart cells (Leaf et al., 2003a).

These findings support the hypothesis that fish oil protects the human heart from fatal arrhythmia following MI or other acute ischemia, thus explaining the rapid reduction in post-MI mortality found in DART and the GISSI-Prevenzione study. They are less relevant to the patients with chronic stable angina in DART 2.

## Why the Discrepancy between DART and DART 2?

### Differences between the Trials

Presumably the difference between the results of DART and DART 2 should be largely explained by the difference between the men in the two studies. All the available evidence suggests that fish and fish oil protect post-MI patients in the short term against cardiac and sudden death by preventing fatal arrhythmias, but the effect may well be different in men with chronic IHD. Admittedly the cohort studies suggest that dietary fish protects a wider population against cardiac death in the longer term, and some of these studies contained patients with chronic IHD: thus, fish seemed to be protective in a Dutch cohort of elderly people, 19% of whom initially had angina (Kromhout, Feskens & Bowles, 1995), so it seems unlikely that there is an important adverse effect in such people.

The distinction between dietary fish and fish oil capsules may be relevant here. Fish contains numerous ingredients besides fish oil, and at least one study showed an inverse relation between the intake of lean fish (which contains relatively low levels of long-chain n-3 PUFAs) and mortality from coronary heart disease (Kromhout, Bosschieter & de Lezenne Coulander et al., 1985). Some of the benefits of dietary fish may be attributable to other constituents of fish, alone or in combination with fish oil. Furthermore, the absorption of fatty acids following a fish meal is likely to occur far more gradually than from the ingestion of fish oil capsules. The subjects who were sent capsules in DART 2 were advised to take three every day; if some of them took all three at the same time on an empty stomach, the resulting bolus of fatty acids entering the circulation might well act quite differently from the slowly-absorbed products of digestion.

It is therefore possible that the higher mortality of men who took fish oil in DART 2 reflects an adverse effect of a sudden upsurge of circulating n-3 fatty acids in patients with chronic IHD. Admittedly this does not explain the lack of any obvious benefit in the subgroup advised to eat fatty fish, but some of these subjects elected to take capsules, the adverse effect of which may have outweighed any benefit of dietary fish in the overall analysis.

### The Pro- and Anti-Arrhythmic Effect of Fish Oil: a Molecular Hypothesis

Normal cardiac function is dependent on the precise co-ordination of sodium ($Na^+$), potassium ($K^+$) and calcium ($Ca^{2+}$) ions, and acute perturbation in these ionic fluxes is arrhythmogenic. The anti-arrhythmic effects of n-3 PUFAs have been attributed to direct inhibition of $Na^+$, $K^+$ and $Ca^{2+}$ channels, pumps and exchangers (Kang & Leaf 1996; Ferrier et al., 2002; Leaf et al., 2003b; Swan et al., 2003; Xiao et al., 2004), or indirectly, via membrane modification (Asano et al., 1998). Thus, it is not possible to assign a discrete molecular basis of n-3 PUFA action. This lack of molecular specificity may underlie the marked beneficial effects of fish oil following acute myocardial damage (e.g., MI), that may be due to a broad resynchronization of acutely disrupted $Na^+$, $K^+$ and $Ca^{2+}$ ion flux within the first few weeks following MI (as in DART). However, such a mechanism cannot explain the recent findings of pro-arrhythmogenic effects of fish oil administration in VT-susceptible individuals (Raitt et al., 2005).

It is emerging that the pro- or anti-arrhythmic effects of PUFA may be inherently linked to the

pre-existing cardiac status, i.e., differential effects of fish oil in acute versus chronic disease. Chronic heart disease is associated with long-term mechanistic adaptation, such that relatively normal myocardial function is maintained by 're-tuning' the normal $Na^+$, $K^+$ and $Ca^{2+}$ ionic flux to a new, stable equilibrium. This re-tuning may occur via altered cellular expression levels of ion channels or altered sensitivity to intracellular effectors (e.g., phosphorylation). Notably, this chronically re-set equilibrium may be exquisitely susceptible to perturbation by fish oil (DART 2). Moreover, we speculate that the pro-arrhythmic effect of fish oil capsules, and not dietary fish, may reflect a 'bolus effect', whereby the acute modification of molecular components, already re-tuned as a result of chronic disease, is pro-arrhythmic. Perhaps a dietary intake of fish oil is more compatible with a more gradual and tolerable modification of ionic co-ordination and therefore is less pro-arrhythmogenic.

The beneficial interactions of PUFA with β-adrenoceptor blockade (β-AR) and the dihydropyridine class of L-type $Ca^{2+}$ channel inhibitors, drugs that suppress cardiac excitability, suggest that they effectively ameliorate the pro-arrhythmic effects of n-3 PUFAs. In contrast, digoxin, a potent inhibitor of the $Na^+/K^+$ ATPase that results in $Ca^{2+}$ overload via altered $Na^+/Ca^{2+}$ exchange, may have exacerbated PUFA-induced perturbation of ionic flux and was associated with increased sudden cardiac death. Such observations are of great interest, since the elevation of intracellular $Ca^{2+}$ is a key event in sudden death via delayed after-depolarizations (DAD) (Pogwizd & Bers, 2004). However, although evidence from DART 2 appears to contraindicate the co-administration of fish oil and agents that augment intra-myocyte $Ca^{2+}$ (Table 6), this is not supported by the marked beneficial effects of n-3 PUFAs on preventing tachyarrhythmias induced by ouabain (a mechanistic analog of digoxin) in cultured cardiomyocytes (Leaf et al. 2003a). Thus, it will be important to more fully understand how the molecular mechanisms of PUFA actions predict the pro- or anti-arrhythmic phenotype, and how this is influenced by the status of the molecular pathways underlying acute and chronic cardiac disorders.

## Conclusions

The two trials described here showed very different effects of fatty fish or fish oil: in DART, mortality was reduced, while in DART 2 there was no evidence of benefit and some evidence of harm. The apparently conflicting findings may be attributable to the different clinical conditions of the subjects (recent MI and chronic stable angina, respectively), together with different effects of dietary fish and fish oil. Other explanations cannot be excluded, however, and further enlightenment may be provided when the results of other large trials become available. A hypothesis is tentatively offered that would account for pro-arrhythmic and anti-arrhythmic actions of fish oil.

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