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EFFECTS OF CHANGES IN FAT, FISH, AND FIBRE INTAKES ON DEATH AND MYOCARDIAL REINFARCTION: DIET AND REINFARCTION TRIAL (DART)

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Summary A randomised controlled trial with a factorial design was done to examine the effects of dietary intervention in the secondary prevention of myocardial infarction (MI). 2033 men who had recovered from MI were allocated to receive or not to receive advice on each of three dietary factors: a reduction in fat intake and an increase in the ratio of polyunsaturated to saturated fat, an increase in fatty fish intake, and an increase in cereal fibre intake. The advice on fat was not associated with any difference in mortality, perhaps because it produced only a small reduction (3–4%) in serum cholesterol. The subjects advised to eat fatty fish had a 29% reduction in 2 year all-cause mortality compared with those not so advised. This effect, which was significant, was not altered by adjusting for ten potential confounding factors. Subjects given fibre advice had a slightly higher mortality than other subjects (not significant). The 2 year incidence of reinfarction plus death from ischaemic heart disease was not significantly affected by any of the dietary regimens. A modest intake of fatty fish (two or three portions per week) may reduce mortality in men who have recovered from MI.

Introduction

ALTHOUGH diet is believed to contribute to the cause of ischaemic heart disease (IHD), no adequate attempt has been made to evaluate dietary advice in the secondary prevention of myocardial infarction (MI). A few small dietary trials have been reported; total mortality was reduced only in the two that were not randomised.[1] As for the type of diet that may be relevant, fat (especially saturated fat) has been positively associated with IHD in several prospective studies.[2-5] Fatty fish consumption may be protective, possibly because of the eicosapentaenoic acid (EPA) content: three prospective studies showed an inverse relation between fish intake and IHD mortality.[6-8] In several prospective studies the intake of total or cereal dietary fibre also seemed to be protective, although the effect was not always independent of other dietary components.[5,9-11] In view of these associations, we set up a randomised controlled trial with a factorial design to see whether dietary advice on fat, fish, or fibre is beneficial in the secondary prevention of MI.

Subjects and Methods

The subjects were men under 70 years of age, admitted to 21 hospitals with a diagnosis of acute MI according to World Health Organisation criteria.[12] The study was explained to the men; those who agreed to participate were visited at home by a doctor, who took blood for serum cholesterol estimation, and later by a dietitian. Diabetic patients, men awaiting cardiac surgery, and men who already intended to eat one of the intervention diets were excluded. The remaining men were weighed, measured, and randomly allocated to receive or not to receive advice on each of three dietary factors; the randomisation for each factor was independent of the other two factors. The three dietary factors were: (1) fat advice, designed to reduce fat intake to 30% of total energy and to increase the polyunsaturated/saturated (P/S) ratio to 1·0; (2) fish advice, at least two weekly portions (200–400 g) of fatty fish (mackerel,

TABLE I—CHARACTERISTICS OF SUBJECTS AT ENTRY

—	Dietary advice group					
	Fat advice (n = 1018)	No fat advice (n = 1015)	Fish advice (n = 1015)	No fish advice (n = 1018)	Fibre advice (n = 1017)	No fibre advice (n = 1016)
Mean age (yr)	56·4	56·8	56·7	56·4	56·6	56·6
Smokers at time of MI (%)	61·2	62·7	61·7	62·2	63·0	60·8
History (%)						
Previous MI	21·9	19·8	19·0	22·7	20·8	21·0
Angina	22·6	22·1	20·8	23·9	21·8	22·8
Hypertension	24·0	23·3	22·7	24·6	23·5	23·7
X-ray appearance (%)						
Cardiomegaly	15·0	12·9	16·4	11·6	13·8	14·2
Lung congestion	10·7	10·7	11·1	10·3	11·8	9·7
Lung oedema	9·2	9·0	9·4	8·8	8 6	9·7
Drug treatment (%)						
β-blocker	30·6	28·2	26·2	32·6	28·1	30·7
Other antihypertensive	33·4	34·0	34·9	32·5	32·4	34·9
Antiangina*	47·7	45·9	46·5	47·2	46·9	46 8
Anticoagulant	6·2	5·5	4·8	6·9	6·7	5·0
Aspirin/antiplatelet†	10·5	10·0	10·1	10 3	10·7	9·7
Digoxin/antiarrhythmic	8·9	10·2	9·2	9 8	9·0	10·0

*Includes nifedipine. †Includes non-steroidal anti-inflammatory drugs.

herring, kipper, pilchard, sardine, salmon, or trout); and (3) fibre advice, increased intake of cereal fibre to 18 g daily. There were thus eight possible combinations of these dietary factors, including a group which received no advice on any of these factors. The dietitians visited and telephoned regularly to reinforce their initial instructions. Weight reduction advice was incorporated when required. Subjects in the fish advice group who could not tolerate fish were given 'Maxepa' capsules and asked to take three daily (0·5 g). All smokers were strongly advised to stop smoking and ex-smokers were encouraged not to relapse. Full details of the study design and the diets have been reported.[13,14]

At 6 months and at 2 years the subjects were weighed, a detailed dietary questionnaire was administered, and blood was taken for assay of total and high-density lipoprotein (HDL) cholesterol. In a subset of subjects the percentages of linoleic acid and EPA in the plasma total fatty acids were measured by gas chromatography. A 25% random sample was asked to weigh and record all food and drink consumed for 7 days. The men were asked whether they had been re-admitted, and in all cases where the history suggested a possibility of reinfarction the hospital notes were examined to establish a diagnosis of MI.[12] Death certificates of those who had died were obtained from relatives or the National Health Service central registry, where the records of all the subjects were flagged. A few subjects could not be contacted at 2 years; their general practitioners were asked whether the men were still alive and if so, whether reinfarction had occurred. All the medical interviews, the decisions regarding diagnosis of reinfarction, and the classifications of death certificates were done by doctors who were unaware of the subjects' allocation within the trial. Before analysis it was decided that the major endpoints were total mortality and IHD events (IHD deaths plus non-fatal MI), and that analysis would be confined to deaths and events occurring within 2 years of entry, because during (but not after) that time the dietitians repeatedly reinforced their advice to the men and because our information about death and reinfarction was complete only up to 2 years. The ethics committee of each hospital gave approval to the trial.

TABLE II—EFFECTS OF DIETARY ADVICE ON INTAKE

—	At 6 months	At 2 years
% fat energy		
Fat advice	32·1 (6·0, 937)*	32·3 (5·9, 869)
No fat advice	35·3 (5·9, 942)	35·0 (5·8, 876)
P/S ratio		
Fat advice	0·78 (0·30, 937)	0·78 (0·32, 869)
No fat advice	0·40 (0·23, 942)	0·44 (0·25, 876)
EPA (g per week)		
Fish advice	2·3 (1·3, 947)	2·4 (1 4, 883)
No fish advice	0·7 (0·7, 932)	0 6 (0·7, 862)
Cereal fibre (g per day)		
Fibre advice	19 (8, 926)	17 (8, 849)
No fibre advice	9 (5, 953)	9 (5, 896)

*Mean (SD, no of subjects).

Results

Selection and Randomisation

During recruitment, 4371 eligible men were identified. Since each hospital was visited weekly, this number represents virtually all the cases of MI except those who died soon after admission. 2101 were excluded for various reasons[13] (1044 because they intended to eat one of the diets under investigation) and 237 died before they could be randomised. The remaining 2033 entered the trial, at a mean interval of 41 days after MI (table I). "X-ray appearance" refers to chest X-rays taken during the relevant hospital admission. For 20% of the subjects no X-ray was reported; their 2 year survival was better than that of the subjects with a normal X-ray, who in turn survived better than those with cardiomegaly, pulmonary congestion, or oedema. The prevalence of these three signs is therefore shown as a percentage of all subjects, whether they had had an X-ray or not.

Dietary Changes

Table II shows the effects of the three dietary interventions on dietary intakes. The data are from the questionnaires, which gave estimates of intake close to those obtained from 7 day weighed intake records for 459 subjects.[13] There was considerable overlap between the fat

TABLE III—DEATHS AND REINFARCTIONS IN RELATION TO DIETARY ADVICE

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

Fish advice *vs* no fish advice: *$p < 0·05$ and †$p < 0·01$ (logrank test).

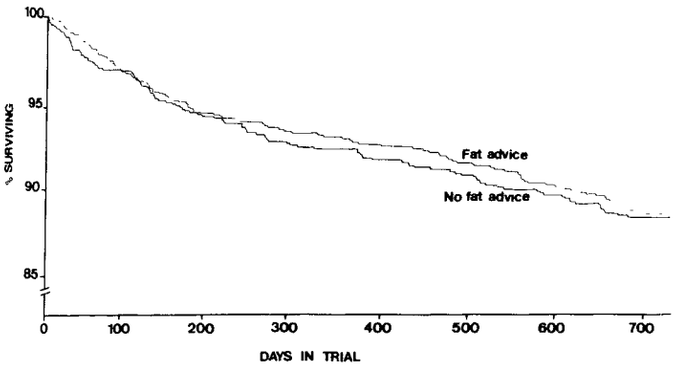

Fig 1—Life-table survival curves up to 2 years: fat advice.

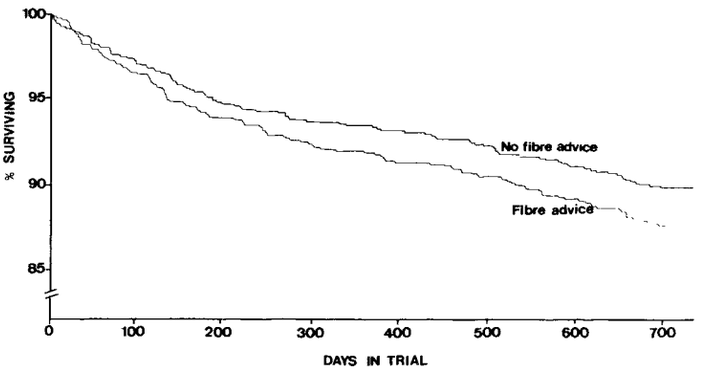

Fig 3—Survival: fibre advice.

advice and no fat advice groups for fat intake but less of an overlap for P/S ratio. In the fish advice group 136 subjects (14%) took maxepa capsules at 6 months and 191 out of 883 (22%) at 2 years as a partial or total substitute for fatty fish. Fish advice produced a fourfold difference at 2 years in EPA intake. Cereal fibre intake in the fibre advice group was double that in subjects not given fibre advice; mean intakes of other sources of dietary fibre remained constant at about 11 g per day in both groups.

Deaths and Reinfarctions

Table III shows the numbers of deaths and reinfarctions. The IHD deaths are those men whose death was certified as due to International Classification of Diseases codes 410–414. Subjects who had a reinfarction, recovered, and subsequently died of IHD during the 2 years are included as IHD deaths and not as non-fatal MIs, so these two groups are mutually exclusive. There were no cases of reinfarction that died of a non-IHD cause. There were no significant differences between the groups given and not given advice on fat or fibre. Total mortality was significantly lower in the fish advice group than in the no fish advice group, the difference being entirely attributable to a reduction in IHD deaths. There was no significant differences in IHD events between the fish advice and no fish advice groups because more non-fatal infarcts occurred in the fish advice group.

Life-table survival curves were similar in subjects given and not given fat advice (fig 1); for most of the period the fat advice group had a slightly better survival but the differences were small. The difference in favour of fish advice (fig 2) appeared early and persisted up to 2 years. Subjects given fibre advice tended to have a lower survival than the other subjects (fig 3).

There were various potential confounding factors. In so far as the randomised groupings were slightly unbalanced for these factors, some bias may have been introduced. From numerous potential confounders, ten were selected because, by a combination of imbalance between any pair of diet groups and prognostic power, they might have introduced a bias of 0·1% or more into the comparisons of total mortality. These confounders were: history of MI, angina, or hypertension; X-ray evidence of cardiomegaly, pulmonary congestion, or pulmonary oedema; and treatment (at entry) with β-blockers, other antihypertensives, digoxin/antiarrhythmics, or anticoagulants. With the dietary allocations these confounders were entered into a Cox proportional hazards regression model. Table IV shows the relative risk of death and IHD events for each of the dietary interventions before and after allowing for the confounding factors. For all deaths, the effect of fish advice had a relative risk of 0·71 (ie, a 29% reduction in risk of death compared with the group not given fish advice), which was not altered by adjustment for the confounding variables. After adjustment for the confounders, the fat advice group had the same risk of death as the no fat advice group; the relative risk of the fibre advice group was not significantly different from unity. For IHD events, adjustment for the same confounders made little difference to the relative risks, which tended to be favourable for fat and fish advice, and unfavourable for fibre, although none differed significantly from unity.

In each of the four combinations of fat and fibre advice, the subjects given fish advice had a lower mortality than subjects not given fish advice (table V). There were no significant interactions between the three dietary interventions.

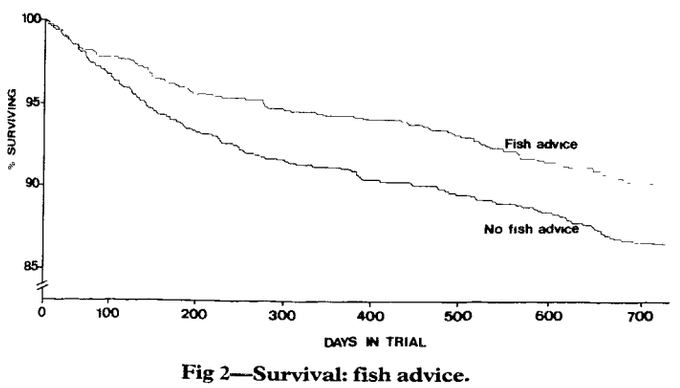

Fig 2—Survival: fish advice.

TABLE IV—ADJUSTMENT FOR CONFOUNDERS

Advice	Effects on all deaths	Effects on IHD events
Fat		
Unadjusted	0·97 (0·75–1·27)*	0·91 (0·71–1·15)
Adjusted	1·00 (0·77–1·30)	0·91 (0·72–1·16)
Fish		
Unadjusted	0·71 (0·54–0·92)†	0·84 (0·67–1·07)
Adjusted	0·71 (0·54–0·93)†	0·84 (0·66–1·07)
Fibre		
Unadjusted	1·23 (0·95–1·60)	1·21 (0·95–1·53)
Adjusted	1·27 (0·99–1·65)	1·23 (0·97–1·57)

*Relative risk (95% confidence interval). †$p < 0·05$.

TABLE V—EFFECTS OF FISH ADVICE ON TOTAL MORTALITY, WITHIN OTHER DIETARY GROUPINGS

Other dietary advice	Mortality		
	Fish advice group	No fish advice group	Difference (Fish − No fish)
Fat, fibre	8·0%	13·5%	−5·5%
Fat, no fibre	8·9%	13·2%	−4·3%
No fat, fibre	12·4%	14·5%	−2·1%
No fat, no fibre	7·8%	9·9%	−2·1%

TABLE VI—SERUM CHOLESTEROL CONCENTRATIONS IN RELATION TO FAT ADVICE

—		Total cholesterol (mmol/l)	HDL cholesterol (mmol/l)
At entry			
Fat advice	(n = 982)	6·47 (1 24)*	0·96 (0·27)
No fat advice	(n = 978)	6·47 (1 23)	0·98 (0·31)
At 6 months			
Fat advice	(n = 924)	6·31 (1·14)†	1·04 (0·31)
No fat advice	(n = 931)	6 57 (1·16)	1·05 (0·30)
At 2 years			
Fat advice	(n = 855)	6·29 (1·13)	1·04 (0 29)
No fat advice	(n = 860)	6·55 (1·10)	1·05 (0·28)

*Mean (SD). †Fat advice *vs* no fat advice, $p < 0.001$.

Serum Cholesterol and Plasma Fatty Acids

At 6 months and at 2 years the subjects given fat advice tended to have lower cholesterol levels than the other subjects, although the differences were not great (table VI). HDL cholesterol rose equally in both groups during the first 6 months and thereafter remained constant. Among 1791 men whose cholesterol levels were measured initially and at 6 months, those given fat advice showed a fall of 0·14 mmol/l whereas the rest showed a rise of 0·09 mmol/l ($p < 0.001$) —ie, there was a net reduction of 3·6% attributable to fat advice. Similarly a net reduction of 3·5% in total cholesterol was attributable to fat advice over the 2 years. During the first 6 months a small but significant ($p < 0.01$) net increase of 2·1% in total cholesterol was attributable to fish advice; however, over the 2 years, the net change attributable to fish advice was not significant. No significant changes in serum cholesterol were attributable to fibre advice. In 111 men given fat advice the mean percentage of linoleic acid was 28·1% (95% confidence interval [CI] 26·9–29·2%) compared with 25·0% (24·0–26·0%) in 92 men not given fat advice ($p < 0.001$). In 107 men given fish advice and 96 men not given fish advice, geometric mean percentages of EPA were 0·59% (95% CI 0·52–0·67%) and 0·46% (0·41–0·51%), respectively ($p < 0.01$).

Changes in Body Weight

On average the weights of the subjects did not change much during the trial: the overall mean weight rose by 0·6 kg. The only significant difference in weight change between the paired dietary groups occurred at 6 months, when the subjects not given fat advice showed a rise of 0·4 kg compared with no change in the fat advice group ($p < 0.05$).

Discussion

We decided at the outset that total mortality would be the primary end-point and we calculated that 2000 subjects would be required to detect a 30% reduction in total mortality or a 25% reduction in IHD events at $p < 0.05$ with a power of 90%. The magnitude of these changes is reasonable in the light of evidence from prospective studies.[13] About 50% of all available patients entered our trial, drawn from 21 hospitals in a large geographical area; so the results are applicable to a wide range of men who recover from acute MI. The excluded subjects tended to be of higher social class, readier to change their diet, and less likely to be smokers.[13]

The issue of compliance raises peculiar difficulties in dietary trials. Subjects in an intervention group will not eat exactly what they are advised (despite repeated exhortations) while controls may spontaneously change to the diet being tested, even if they had no such intention at the start. The difference between the intervention and control groups is thus liable to erosion at both ends. Inevitably there was some overlap between intervention and control groups for our three factors. Monitoring of compliance was primarily by means of questionnaires, which were open to bias in that a subject may have told the dietitian what he thought she wanted to hear. Nevertheless the results correlated well with those from 7 day weighed intake records in a 25% subset of subjects.[13,14] Objective evidence of compliance with the fat and fish advice was obtained from the serum cholesterol and plasma fatty acid measurements.

The randomised groupings were well balanced for most aspects of medical history that were likely to predict survival, and the results were not substantially altered when adjustments were made for the slight imbalances that occurred. There may have been unexpected differences between the diets of the randomised groups, in that the dietary recommendations could have induced unforeseen changes in the subjects' patterns of eating. The weighed intake records showed that the dietary changes were largely a matter of simple substitutions; the largest unintended effect was a difference in energy intake between the fat advice and no fat advice groups (7·3 and 7·7 MJ respectively at 6 months),[14] which was reflected in a difference in weight gain of 0·4 kg.

Five randomised trials have been published in which a diet low in fat or with a high P/S ratio was given to subjects who had recovered from MI.[15–19] All these trials contained less than 500 subjects and none showed any reduction in deaths; indeed, one showed an increase in total mortality in the subjects who took the diet.[19] In our trial the fat advice, if fully complied with, would give a fat intake supplying 30% of total energy and a P/S ratio of 1·0; the mean values achieved at 6 months were 32·1% and 0·78, respectively. In the group not given fat advice it is likely that some spontaneous reduction in fat intake and increase in P/S ratio occurred: at 6 months the mean values were 35·3% energy and 0·40, respectively, whereas a random sample of healthy men in a South Wales town had a higher fat intake (37·3% energy) and a lower P/S ratio (0·30).[20] The consequential narrowing of the difference between the groups given and not given fat advice was reflected in the small difference in the change in serum cholesterol (a net fall of 3·6% in the fat advice group relative to the other subjects at 6 months). In contrast, the Oslo trial of primary prevention achieved a 13% net reduction in serum cholesterol.[21] If serum cholesterol had decreased more in our trial, mortality might have been reduced. It is perhaps surprising that so little change in cholesterol occurred in view of the repeated contacts made by dietitians. This was partly attributable to the initial exclusion of those subjects most likely to comply. In any case, changes in dietary fat may take more than 2 years to affect mortality, so the subjects will be followed up to see whether any benefit emerges in the future.

Our study is the first controlled trial of dietary fish advice in the secondary prevention of MI. Compliance was reasonably good, and there was little spontaneous tendency to eat fatty fish in the group not given fish advice. The results suggest that fatty fish (and fish oil) reduces mortality in men after MI, by about 29% during the first 2 years. The effect appeared early in the trial, and it may be questioned whether it is likely that a dietary change would act so quickly. At the start of the second world war IHD mortality in Norway fell sharply within a year of a sudden change in the national diet,

which included a rise in fatty fish intake; mortality rose again within a year of the end of the war, when dietary habits returned to their previous pattern.[22] Fish oils appear to have a favourable effect on clotting mechanisms and blood platelets,[23-25] and reduce the rate of restenosis in the coronary artery within 3 to 4 months of angioplasty.[26] Fish oil may prevent ventricular fibrillation during acute myocardial ischaemia;[27] if this effect is confirmed it could explain the effect of fish on mortality rather than on IHD events in our trial. The amount of fish in our study was small, supplying 2·5 g EPA weekly (corresponding to about 300 g fatty fish every week), and thus involved no radical change in diet. There were of course other changes in the diet of the fish advice group following the increase in fish consumption: small reductions occurred in the intakes of meat, meat products, cheese, and eggs.[14] These changes were less than those induced by the fat advice diet, and serum cholesterol levels tended to rise in the fish advice group relative to the no fish advice group. So it is unlikely that the effect of fish advice on mortality was attributable to a reduction in foods containing saturated fat and cholesterol.

Compliance with fibre advice was good, and a reasonable difference was achieved between the daily cereal fibre intakes of the groups given and not given fibre advice (19 g and 9 g, respectively, according to the questionnaires). There was no evidence of any benefit; mortality was somewhat higher in the fibre advice group, but this was presumably fortuitous since the difference was not statistically significant. No cohort studies have shown an unfavourable relation between cereal fibre and IHD or total mortality, whereas several have suggested favourable associations.[5,9-11] These associations may have been non-causal, especially since a high-fibre diet is currently regarded as an indispensable part of a healthy life-style and is therefore characteristic of individuals whose mortality rates are below average for different reasons. A high-fibre diet—or the intention to change to such a diet—was a major reason for excluding MI patients from our trial. Apparently it is widely believed that cereal fibre confers protection against IHD. Our trial suggests that ingestion of modest amounts of fatty fish reduces mortality in men after MI.

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DETECTION OF A SECOND WIDESPREAD STRAIN OF EPSTEIN-BARR VIRUS

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Summary The prevalence of Epstein-Barr virus (EBV) type B, which was previously found mainly in equatorial Africa, was investigated with the polymerase chain reaction in a population of healthy adults in Memphis, Tennessee. EBV was detected in the throat washings of 34 (22%) of 157 randomly selected donors, 14 (41%) of whom had type B virus and 17 (50%) type A; 3 donors (9%) had both strains. 18 additional adults with human immunodeficiency virus (HIV-1) infection and 6 severely immunocompromised children were also investigated. Results indicated that type B EBV is widespread in nature and may be reactivated by immunodeficiency.

Introduction

THE Epstein-Barr virus (EBV) is a human herpesvirus that causes widespread but largely symptomless infection worldwide. EBV-associated diseases are diverse and have an

M. L. BURR AND OTHERS: REFERENCES—*continued*

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