Further reduction in mortality following myocardial infarction

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Omacor is a new omega-3 fatty acid product that is licensed for secondary prevention post-myocardial infarction. It confers an additional 20% reduction in all-cause mortality, based on the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico prevenzione (GISSI-P) study data. The GISSI-P results are compared with other trials of secondary prevention.

The *National Service Framework for Coronary Heart Disease* (CHD) (Department of Health, 2000) has established clear standards for prevention and treatment of CHD.

CHD is an important part of the overall public health problem, as it is common, frequently fatal and largely preventable. CHD is a leading cause of death, killing over 110 000 people in England in 1998, including more than 41 000 under the age of 75 years (Office for National Statistics, 1998).

Saving Lives: Our Healthier Nation (Department of Health, 1999) sets out the national strategy for improving health. It sets challenging targets for improving health and proposes the creation of an integrated strategy for action to reduce the burden of CHD. All public agencies, including the NHS, will be expected to contribute to improving the health of the population and to achieving the target set out in the White Paper to reduce mortality from CHD, stroke and related disorders by 40% in people aged less than 75 years by the year 2010.

SECONDARY PREVENTION POST-MYOCARDIAL INFARCTION AND OMEGA-3 FATTY ACIDS

The past 25 years have seen increased use of aspirin, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors and lipid-lowering therapies to lower the risk of future vascular events in high-risk patients such as those post-myocardial infarction (MI).

The benefits of each class of drug appear to be largely independent, so that when used together in appropriate patients it is reasonable to expect that up to three-quarters of future vascular events could be prevented (Yusuf, 2002). The standard therapy, therefore, for post-MI patients, includes all of these four classes of drugs.

Since the late 1970s, interest in the possible cardioprotective effects of omega-3 fatty acid has grown markedly. Epidemiological studies (such as Bang and Dyerberg, 1981) in Greenland Eskimos and in the Japanese population have suggested that a diet rich in fish oil and marine animals can prevent heart disease.

The beneficial effects of fish oils are attributed to their omega-3 fatty acid (also known as n-3 PUFA) content, in particular eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).

Studies have supported the antiatherogenic, antithrombotic and antiarrhythmic effects of omega-3 fatty acids, as reviewed by Demaison and Moreau (2002), although the exact mechanism of action has not yet been fully elucidated. A protective role in the secondary prevention of CHD was seen for fatty fish in the Diet and Reinfarction Trial (DART) (Burr et al, 1989). In the DART study, those subjects advised to eat fatty fish had a 29% reduction in 2-year all-cause mortality compared with those not so advised.

OMACOR

Omacor (Pronova Biocare, Norway) is a new omega-3 fatty acid product. It contains high concentrations of omega-3 fatty acids (90% EPA+DHA) and is the only one in its class that is licensed for use in the secondary prevention of MI. It reduces the cardiovascular mortality by a further 30% when added to the standard post-MI treatment regimen (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico (GISSI) Prevenzione Investigators, 1999).

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Omacor shows significant efficacy in secondary prevention post-MI, with a 20% reduction in all deaths and a 45% reduction in sudden deaths (GISSI-Prevenzione Investigators, 1999). These reductions were not only seen in concomitant treatment with antiplatelet drugs, statins, beta-blockers and ACE inhibitors but also in addition to a Mediterranean diet.

The GISSI-Prevenzione trial

These data are taken from the GISSI-Prevenzione (GISSI-P) trial, which was conducted in Italy by the GISSI group.

The GISSI-P study involved 11 324 patients who had survived a recent (<3 months, median 16 days) MI. Patients were randomized to four treatment groups: Omacor (1 g daily, *n*=2836), vitamin E (300 mg daily, *n*=2830), both (*n*=2830) or none (control, *n*=2828) for 3.5 years. Patients also adhered to their recommended preventative treatments – aspirin, beta-blockers, ACE inhibitors and statins. The primary combined efficacy end-points included all-cause death, non-fatal MI and non-fatal stroke.

GISSI-P in comparison with other trials of secondary prevention

This article analyses the GISSI-P data to assess its robustness in comparison with other trials of secondary prevention. The purpose of this endeavour is to see if the GISSI-P data are as sound and hence comparable to these landmark studies.

As the standard post-MI drug therapy includes aspirin, beta blockers, statins and ACE inhibitors in a large proportion of patients, the important large clinical trials which used these drugs were identified. The following four were chosen as they were landmark trials which had been published around the same time:

- 4S (The Scandinavian Simvastatin Survival Study Group, 1994)
- CARE (Cholesterol and Recurrent Events Trial; Sacks et al, 1996)
- LIPID (Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group, 1998)
- HOPE (The Heart Outcome Prevention Evaluation Study Investigators, 2000).

The first three of these studies involved statins and HOPE was a trial of ramipril, an ACE inhibitor, all of whose importance and relevance in secondary prophylaxis has been established. The trial designs and the patient characteristics have been analysed. The data have been taken from the treatment arm of each study. These are all randomized controlled trials. GISSI had a prospective randomized, open, blinded end-points design like the Hypertension Optimal Treatment trial (Hansson et al, 1998).

Most of these trials are based on patient populations that are geographically, socially and culturally diverse, as can be seen from *Table 1*.

The patient characteristics show noteworthy findings (*Table 1*). The age range is reasonably similar across the trials, although 4S and LIPID included much younger patients as well. GISSI-P included more patients than the other trials.

TABLE 1.
Baseline characteristics from secondary prevention trials

Trial		GISSI	4S	LIPID	CARE	HOPE
Drug		Omacor 1g	Simvastatin 20g	Pravastatin 40mg	Pravastatin 40mg	Ramipril 10mg
Countries		Italy	Scandinavia	Australia and New Zealand	US and Canada	Canada, USA, Europe and South Africa
Recruited		1993–1995	1988–1989	1990–1992	1989–1991	1993–1995
Duration (mean in months)		42	64	74	60	50
Patient characteristics	Total no of patients	11324	4444	9014	4159	9297
	No of patients in study arm	2836	2221	4512	2081	4645
	Age range (years)	<50–>80	35–70	31–75	50–68	>55
	% male patients	85	82	83	86	72.5
Other conditions (%)	Hypertension	36	26	41	42	47
	Diabetes mellitus	14	5	9	14	38
	Smokers	42	24	9	21	14
	CABG/PTCA	24	9	41	54	44
	Myocardial infarction	11	62	64	All	51

CABG/PTCA = coronary artery bypass surgery/percutaneous transluminal coronary angioplasty; NS= not specified. GISSI = Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico (GISSI) Prevenzione Investigators (1999); 4S = The Scandinavian Simvastatin Survival Study Group (1994); LIPID = Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group (1998); CARE = Cholesterol and Recurrent Events Trial (Sacks et al, 1996); HOPE = Heart Outcome Prevention Evaluation Study Investigators (2000)

There were fewer hypertensive patients in 4S than the other studies and many more diabetic patients in HOPE than in the statin studies. This is probably as a result of the inclusion criteria of HOPE. A much higher percentage of participants was current smokers in GISSI, and the revascularization procedure rate was much lower in GISSI than in the other contemporary trials, such as HOPE.

Compared to other studies, 4S had a much smaller proportion of participants who were taking aspirin (*Table 2*). This may be because the study took place much earlier than the others. The figures express the percentage use at the end of the trial. The use of beta blockers was found to be similar across all the trials.

The discontinuation rates are higher in population-based trials like GISSI (28%), and are one of their drawbacks, but there were similar discontinuation rates in HOPE (29%), a double-blind trial which had excluded non-compliant patients.

TABLE 2.
Percentage drug use by patients at the end of secondary prevention trials

Trial	GISSI	4S	LIPID	CARE	HOPE
Aspirin	83	37	83	83	75
Beta blockers	39	57	46	41	39
Calcium channel blockers	26	32	35	40	46
Nitrates	64	31	35	32	NS
Statins	46	All	All	All	28.4
Omega-3 fatty acids	All	13	NS	NS	NS
ACE-Is	46	NS	16	15	All
Diuretic	10	7	16	11	15.3

ACE-I = angiotensin-converting enzyme inhibitor; NS= not specifed. GISSI = Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico (GISSI) Prevenzione Investigators (1999); 4S = The Scandinavian Simvastatin Survival Study Group (1994); LIPID = Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group (1998); CARE = Cholesterol and Recurrent Events Trial (Sacks et al, 1996); HOPE = Heart Outcome Prevention Evaluation Study Investigators (2000)

Assessment of results

For the assessment of results, the method described by Otterstad and Sleight (2001) has been used as this is a simplified approach to evaluating clinical trials that can be readily used by a busy clinician. The method is described below with an example.

Explanation of calculations: Let us consider the calculations carried out for the 4S study in *Table 3*. During this trial, with a mean follow-up of 64 months, the placebo mortality was 256/2223 (11·5%) and treatment mortality was 182/2221 (8·2%).

The relative risk in the treatment group was 8·2%/11·5%= 0·71. The relative risk reduction was accordingly: 1–0·71=0·29 or 29%. The absolute risk reduction (ARR) was: 11·5%–8·2%=3·3% over a 64-month period.

These figures enable us to calculate the number needed to treat (NNT) to postpone one death over a 64-month period. The treatment difference is 256–182=74 deaths. There were 2221 patients randomized to simvastatin. NNT is then derived from: 2221/74=30 or 1/ARR: 1/0·033=30.

To adjust for the study duration, the treatment difference has been extrapolated to 1 year of treatment, according to: 74/64x12=14, when using 64 months as the mean study duration of 4S. This means that on average, 14 deaths were postponed per year during the study period. The NNT to postpone one event per year (NNT-1y) is then 2221/14=159.

Table 3 compares the stated primary end-points from each trial. The results of GISSI compare well with the other trials in terms of NNT and risk reduction for secondary prevention of MI.

All of these trials have different end-points. Hence an attempt was made to compare the results for total mortality and cardiovascular

TABLE 3.
Comparison of primary end-points in secondary prevention trials

	GISSI	4S	LIPID	CARE	HOPE
Primary end-point	TM+NFMI+NFS	TM	CD	CD+NFMI	CVD+NFMI+stroke
Incidence in control group (%)	414/2828 (14.6)	256/2223 (11.5)	373/4502 (8.3)	274/2074 (13.2)	826/4652 (17.8)
Incidence in treatment group (%)	356/2836 (12.3)	182/2221 (8.2)	287/4512 (6.4)	212/2081 (10.2)	651/4645 (14)
Relative risk	0.85 (0.74–0.98)	0.71 (0.58–0.85)	0.77 (0.65–0.88)	0.77 (0.64–0.91)	0.78 (0.70–0.86)
Absolute risk reduction	2.3	3.3	1.9	3	3.8
NNT over the trial period	43	30	52	33	26
Deaths postponed/year	17	14	14	12	42
NNT to postpone one event per year	167	159	322	173	110

CD = cardiac death; CVD = cardiovascular death; NFMI = non-fatal myocardial infarction; NFS = non-fatal stroke; NNT= numbers needed to treat; RRR= relative risk reduction; TM = total mortality. GISSI = Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico (GISSI) Prevenzione Investigators (1999); 4S = The Scandinavian Simvastatin Survival Study Group (1994); LIPID = Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group (1998); CARE = Cholesterol and Recurrent Events Trial (Sacks et al, 1996); HOPE = Heart Outcome Prevention Evaluation Study Investigators (2000)

TABLE 4.
Comparison of total mortality in secondary prevention trials

	GISSI (*n*=11324)	4S (*n*=4444)	LIPID (*n*=9014)	CARE (*n*=4159)	HOPE (*n*=9297)
Control group: incidence of total mortality (%)	293/2828 (10.4)	256/2223 (11.5)	633/4502 (14.1)	196/2078 (9.4)	569/4652 (12.2)
Treatment group: incidence of total mortality (%)	236/2836 (8.3)	182/2221 (8.2)	498/4512 (11)	180/2081 (8.6)	482/4645 (10.4)
Relative risk	0.8	0.71	0.79	0.91	0.85
Absolute risk reduction	2.1	3.3	3.1	0.8	1.8
NNT to postpone one death over the trial period	49	30	33	125	56
Deaths postponed per year	16	14	22	3	21
Lives saved/1000 patients/year	5.7	6.2	4.8	1.5	4.5
NNT to postpone 1 event per year	177	159	205	694	221

NNT= numbers needed to treat. GISSI = Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico (GISSI) Prevenzione Investigators (1999); 4S = The Scandinavian Simvastatin Survival Study Group (1994); LIPID = Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group (1998); CARE = Cholesterol and Recurrent Events Trial (Sacks et al, 1996); HOPE = Heart Outcome Prevention Evaluation Study Investigators (2000)

TABLE 5.
Comparison of cardiovascular mortality in secondary prevention trials

	GISSI (*n*=11324)	4S (*n*=4444)	LIPID (*n*=9014)	HOPE (*n*=9297)
Control group: incidence of cardiovascular mortality (%)	193/2828 (6.8)	207/2223 (9.3)	433/4502 (9.6)	377/4652 (8.1)
Treatment group: incidence of total mortality (%)	136/2836 (4.8)	136/2221 (6.1)	331/4512 (7.3)	282/4645 (6.1)
Relative risk	0.7	0.66	0.76	0.75
Absolute risk reduction	2	3.2	2.3	2
NNT to postpone one cardiovascular death over the trial period	50	31	43	50
Deaths postponed per year	16	13	17	23
Lives saved/1000 patients/year	5.7	6	3.6	4.9
NNT to postpone one event/year	177	171	265	202

NNT= numbers needed to treat. Cholesterol and Recurrent Events Trial (CARE) did not report cardiovascular deaths. GISSI = Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico (GISSI) Prevenzione Investigators (1999); 4S = The Scandinavian Simvastatin Survival Study Group (1994); LIPID = Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group (1998); HOPE = Heart Outcome Prevention Evaluation Study Investigators (2000)

mortality individually (*Tables 4* and *5*). Again the aim is to see the place of GISSI-P among its peers. As can be seen, GISSI-P results remain in the same range as these major studies.

The control group mortality for GISSI-P and other studies is shown in *Table 6*, both in absolute terms and averaged per year. It is interesting to see that in spite of the Mediterranean diet, the control group mortality rate in GISSI populations was in fact one of the worst in these studies.

CONCLUSION

The GISSI trial was designed to assess the effect of omega-3 fatty acids on secondary prevention post-MI. From the assessment of the results it is clear that although the major trials of secondary prevention have been conducted across the world, the patient characteristics remain reasonably comparable.

We can also see that the results of the study seem to fit in well with the other studies of secondary prevention.

Thus, given the results of major trials of secondary prevention, an evidence-based argument can be made for the addition of Omacor to the current standard pharmacological treatment post-MI to provide additional benefits in terms of saving lives. HM

The author wishes to thank Jeff Ashford and Dr Marie Bakowski for their helpful comments.

TABLE 6.
Comparison of total mortality in control groups

	GISSI	4S	LIPID	CARE	HOPE
Control group mortality (%)	10.4	11.5	14.1	9.4	12.2
Control group mortality per year (%)	2.9	2.2	2.3	1.9	2.9

GISSI = Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico (GISSI) Prevenzione Investigators (1999); 4S = The Scandinavian Simvastatin Survival Study Group (1994); LIPID = Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group (1998); CARE = Cholesterol and Recurrent Events Trial (Sacks et al, 1996); HOPE = Heart Outcome Prevention Evaluation Study Investigators (2000)

Conflict of interest: Dr Abhyankar works as a medical adviser for Solvay Healthcare Ltd which holds the marketing authorization for Omacor in the UK.

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KEY POINTS

- Secondary prevention of myocardial infarction (MI) is an important public health problem.
- The standard drug therapy for secondary prevention consists of aspirin, beta blockers, statins and angiotensin-converting enzyme inhibitors.
- The role of omega-3 fatty acid products in the secondary prevention post-MI has been evolving.
- Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico (GISSI-P) study was a large trial looking at the effect of Omacor on the secondary prevention post-MI.
- The results of the GISSI study compare very well with other trials of secondary prevention.
- Omacor promises to be an important additional therapy for secondary prevention post-MI.