Study of the Effectiveness of Additional SEARCH Reductions in Cholesterol and Homocysteine

British Heart Foundation

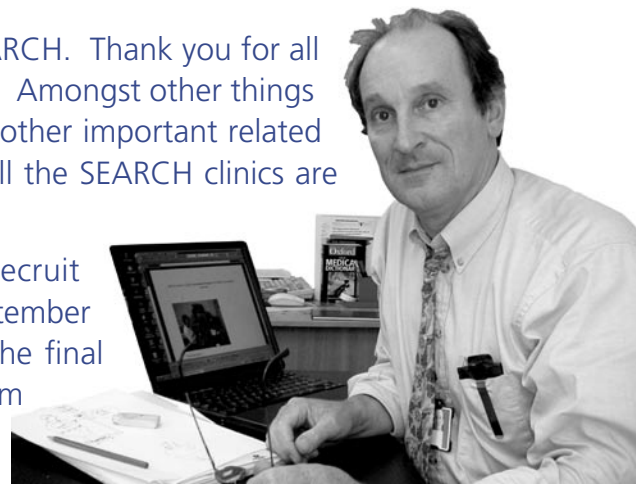
ReSEARCH

No 2 *Autumn 2002*

The newsletter for people taking part in SEARCH

We've hit the 12,000 recruitment target!

Welcome to another edition of *Re***SEARCH**, our newsletter for volunteers taking part in SEARCH. Thank you for all the positive feedback to the first edition. We hope you find this edition a worthwhile read too. Amongst other things it includes news of the study's progress, a reminder about some safety issues, results from another important related trial, and an article about the health hazards of obesity. It also has a map showing where all the SEARCH clinics are located around the UK.



David Simpson, Editor of *Re***SEARCH**

As you will remember, our target was to recruit 12,000 heart attack survivors into SEARCH by September 2001, and this was successfully achieved with the final total being 12,064. The 12,000th volunteer, Mr Tim Minchin, came from the SEARCH clinic at Bristol Royal Infirmary. The picture shows him (seated) with Dr David Stansbie, the local Consultant Pathologist who oversees SEARCH at Bristol Royal Infirmary, together with Senior Clinic Nurses Margaret Halestrap and Gale Andrews. Thank you to everyone who has agreed to join the study and so help answer two of the most important current questions in the on-going battle to prevent heart disease.

This edition of the newsletter also provides some information about the type of people taking part in SEARCH. For example, the bottom figure on page 2 shows that there are a lot of older men and women participating. In the past, older people tended to be excluded from heart disease trials. As our population ages and stays healthy for longer, however, it is particularly important to include older people in medical research studies. Women have also tended to be under-represented in studies of heart disease. This has been partly because they get heart problems at an older age than men, but also because it has proved more difficult to persuade women to take part in studies than men. There are probably lots of reasons for this and we would be interested to hear your views. Also, if you have questions to ask or interesting stories to relate please write to me at *Re***SEARCH**, FREEPOST, Harkness Building, Radcliffe Infirmary, Oxford OX2 6YZ (or ask your local clinic nurse to pass your letter on).

David Simpson, Editor

Letter from the Coordinators

The SEARCH study has now successfully completed recruitment of over 12,000 participants and it is well on its way with the planned treatment and follow-up of 4-5 years. This is thanks to a lot of hard work by many people in the 88 participating hospitals around the country (see map on page 4) and in the coordinating centre at Oxford University's Clinical Trial Service Unit. We are also particularly grateful to all of you for being willing to volunteer to help answer the important questions that SEARCH is addressing.

The first question being addressed by SEARCH is whether more intensive cholesterol-lowering using higher doses of simvastatin is worthwhile. The importance of this has been highlighted by the recent results of the MRC/BHF Heart Protection Study (described in more detail on page 2). That study has shown very clearly that lowering cholesterol with standard doses of simvastatin produces very worthwhile benefits in a wide range of people at increased risk of heart problems – even those presenting with very low cholesterol levels. This suggests that reducing cholesterol as much as possible with more intensive treatments will reduce heart disease risk, but we do not know whether problems with higher statin doses might off-set such benefits.

The second question being addressed by SEARCH is whether or not lowering blood levels of homocysteine by using folic acid and vitamin B12 supplements will reduce the risks of heart attacks and strokes. Folic acid has also been in the news lately. The Food Standards Agency recently decided – for the time being at least – not to recommend routine fortification of foods with folic acid. The reason fortification was being considered was to increase the folate intake of women around the time of conception in order to reduce the risk of babies being born with neural tube defects (spina bifida). However, there was considerable uncertainty as to whether fortification would produce any beneficial, or even harmful, effects in the rest of the population. The results of SEARCH should help to resolve this uncertainty by demonstrating whether or not increased folate consumption reduces heart attack and stroke rates.

As you will see from this newsletter, SEARCH is going extremely well. We are most grateful to you for agreeing to participate in the first place, and hope that you will keep attending the study clinics regularly and, whenever possible, continue taking the study treatments.

Once again a very big thank you for taking part!

Dr Jane Armitage Professor Rory Collins
Oxford University

Results of the Heart Protection Study

Good news for many people at risk of heart disease

The results of the MRC/BHF Heart Protection Study (HPS), which were published recently in the prestigious medical journal The Lancet, provide substantial new evidence about the benefits of cholesterol-lowering with statins. It was a large randomised trial run by the same team of scientists who coordinate SEARCH in Oxford, and involved about half of the doctors and nurses who are now conducting SEARCH.

20,536 volunteers were recruited into HPS between 1994 and 1997 and all were at increased risk of heart disease. People were included (aged 40-80) who were considered to be at high risk because of a history of a heart attack, angina or having had coronary bypass surgery or angioplasty, or a history of a stroke or circulatory problems elsewhere, or having diabetes. This was a much wider range of people than had been studied before with cholesterol-lowering therapy. At the start of the study their own doctors were not considering using statins and so participants were randomly allocated to take 40mg simvastatin daily or placebo (dummy) for five years. These high-risk individuals were included regardless of their cholesterol levels in order to find out whether it would be worthwhile lowering even an "average" or "low" level.

The study showed that simvastatin not only reduced the risk of heart attacks, but also the risk of strokes and the need for coronary or other bypass surgery or angioplasty. On average, the reduction in cholesterol was about 1 mmol/l and this was associated with a reduction in the risk of heart attacks or strokes or revascularisations by about one-quarter. However, taking 40mg simvastatin regularly would reduce cholesterol by about 1.5 mmol/l and so the reduction in risk for those taking this dose regularly would be about one-third. Benefits were seen not just in middle-aged people but in older individuals (even among those who didn't start treatment until their late seventies) and in women as well as in men.

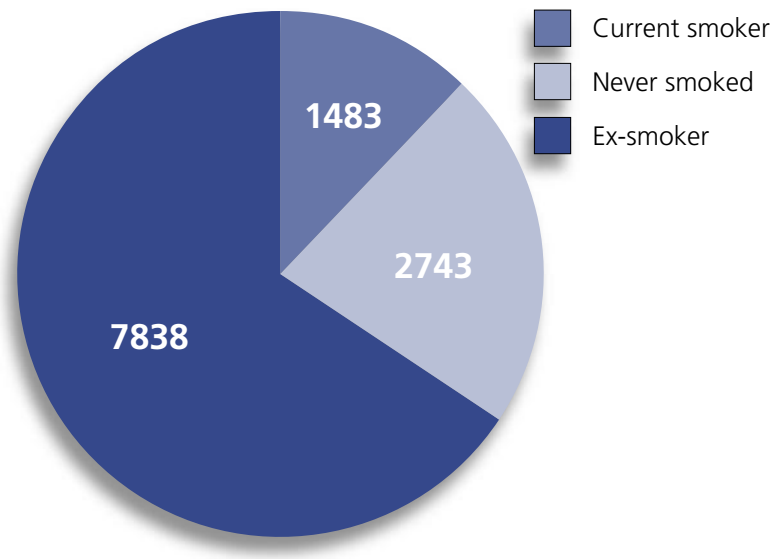
One of the findings that has most surprised doctors around the world is that these benefits were seen regardless of the initial cholesterol level. So, even in people who were at risk because of a history of circulatory problems or diabetes but had "low" cholesterol, lowering the cholesterol further was clearly beneficial. This result makes it much simpler for doctors, as it means that worrying about the exact levels of cholesterol in high-risk people before starting to treat is not necessary. What is important in such people is to ensure that all of them are considered for treatment with a statin regimen that will lower their cholesterol level substantially.

The Heart Protection Study also assessed the safety of 40mg simvastatin daily. With this regimen the excess risk of "myopathy" (that is, serious muscle problems) was very low – only about 1 in 10,000 people per year. No other problems with this simvastatin regimen were detected during HPS, but higher statin doses (such as 80mg simvastatin daily, as used in SEARCH) may cause more problems. So, although the HPS results suggest that bigger reductions in cholesterol will produce bigger reductions in the risk of heart attacks and strokes, it remains uncertain whether such benefits will outweigh any increased risk of side-effects. SEARCH can answer this important question. But, for SEARCH to do so reliably requires as many participants as possible to keep taking their study tablets. For those who are interested, more information about HPS can be found on the study web-site http://www.hpsinfo.org.

Who else is in SEARCH?

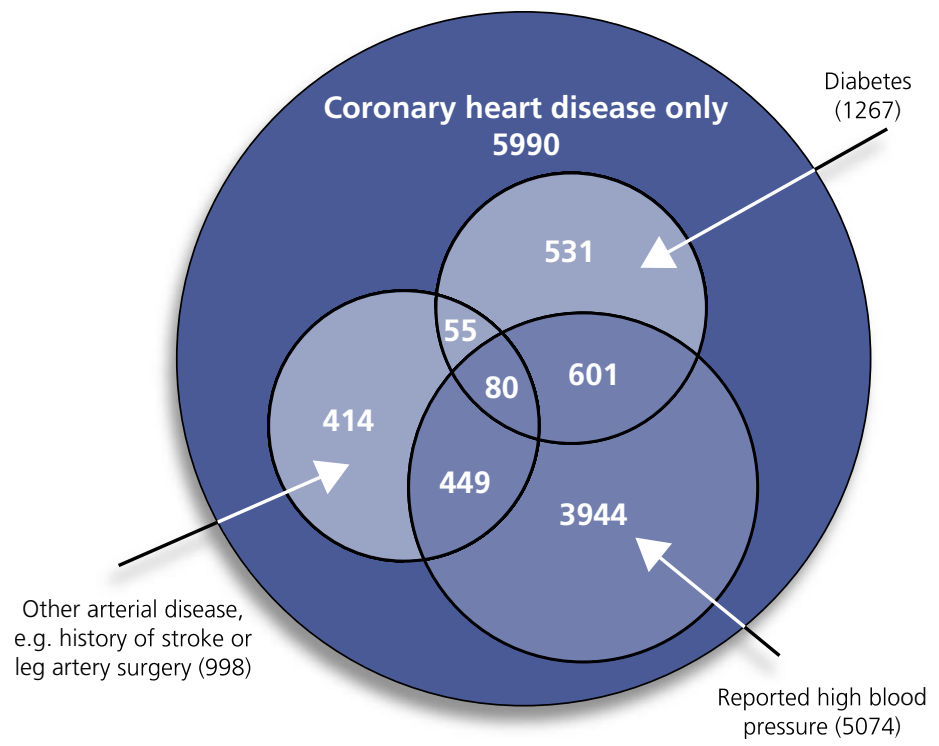
Some characteristics of the 12064 participants

Smoking history

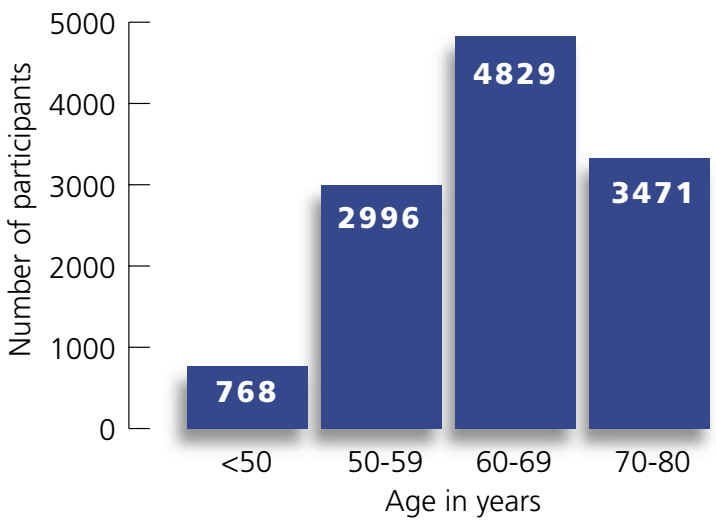


Other medical conditions

(All participants have had a heart attack)



Age distribution



Weighing up the risks

Almost all of us know someone who is trying to lose weight. Newspapers and magazines regularly carry features on losing weight and staying slim, and earlier this year press reports suggested that – as a nation – we are rapidly becoming obese. In the UK, average weight is going up. Underlying the public debate about weight are some scientific facts linking excess body fat to disease. It is particularly important for people who have had a heart attack or other cardiovascular problems to know the facts, and have some idea of their ideal weight.

First, a little background. When we talk about "fat" here, we do not mean blood fats, which are associated with the blocking of the blood vessels (and reduced by statin drugs). In the context of weight and obesity, we mean body fat – the soft flesh composed of adipose tissue that can build up all over us, especially around our middles. Not all body fat is a bad thing; in fact, a certain amount of it is vital for life. It is a bit like a car's fuel tank. A car uses petrol all the time it is running, but only takes on a new supply when filled up at the garage. Similarly, we constantly expend energy, but only intermittently acquire it, mostly at mealtimes. In other words, we have to store energy until we need it; and fat tissue is where much of it is stored. Typically, we store enough for about 50 to 60 days' normal use.

In extreme cases, when energy sources are virtually absent, fat tissue can become very important. The most obvious example is people faced with serious food shortages (such as during a famine), when the only way their bodies can get energy is by converting it from fat tissue. In terms of human evolution, populations are more likely to survive through times of famine if some members are particularly good at storing energy. This may be why a large proportion of most human populations seems to be genetically predisposed to putting on weight: literally, we may be the descendants of people who survived past times of extreme food shortage by being better-than-average at storing energy.

Major changes in the composition of genes in a population probably take hundreds of generations. Clearly, therefore, some other influences must also be at work to explain the recent increases in obesity, and the most obvious culprits are to be found in what we eat (too much of it, particularly fatty or sugary foods) and physical activity (too little of it). The greater availability of energy-dense foods, particularly processed foods and snacks high in fat and sugar, the massive rise in the use of private cars at the expense of walking or cycling, and our apparently steady metamorphosis into television-watching couch-potatoes, point the finger of suspicion strongly at our changing lifestyle being a key problem!

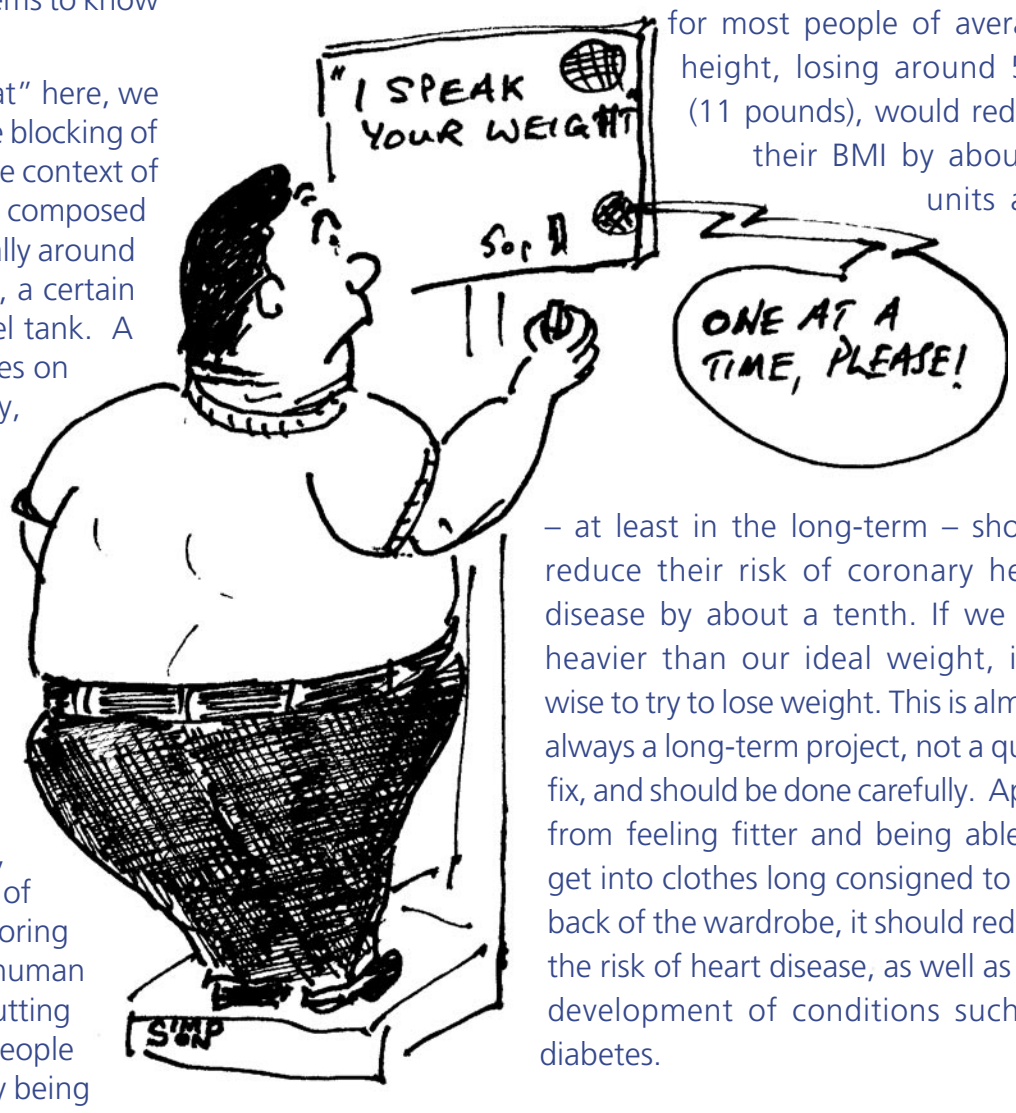
How can we tell if we're overweight?

So how can we know if we have too much body fat, and what each of us should weigh? What the bathroom scales tell us is not of itself a good measure of body fat, because even the slimmest person who happens to be tall and broadly-built can weigh more than a short person shaped like the Michelin man. Clearly, if we are going to use weight to measure body fat, we need to make a correction for height. Probably the most accurate and widely used method is a simple mathematical formula that takes account of both height and weight in what is called the Body Mass Index (BMI). This takes a person's weight in kilograms and divides it by the square of their height in metres. To take an example out of the blue (but uncomfortably similar to the editor of ReSEARCH), the BMI of a man weighing 83.9 kg (13 stones 3 pounds) who is 1.73 metres (5ft 8ins) tall is calculated as 83.9 ÷ (1.73 x 1.73). This gives a result of 28 which is well above the ideal range of 18.5 to 25!!

As a volunteer in the SEARCH trial, you will recall having your height and weight checked by the nurse at your local centre so that BMI could be calculated in this way. Based on that result, you may also have been given advice on whether you should aim to lose some weight.

Does being overweight harm your health?

Overall, from an amalgamation of large studies, there seems to be a simple, positive association between BMI and risk of coronary heart disease – put simply, the more overweight the more risk of heart problems. Looking at it the other way round, this means that people with lower weight are at lower risk of heart disease – but by how much? These studies suggest that for people with a BMI above 22, every 2 units lower BMI is associated with about a 10% lower relative risk of coronary heart disease. So, for most people of average height, losing around 5kg (11 pounds), would reduce their BMI by about 2 units and



– at least in the long-term – should reduce their risk of coronary heart disease by about a tenth. If we are heavier than our ideal weight, it is wise to try to lose weight. This is almost always a long-term project, not a quick fix, and should be done carefully. Apart from feeling fitter and being able to get into clothes long consigned to the back of the wardrobe, it should reduce the risk of heart disease, as well as the development of conditions such as diabetes.

Are "Vitamin pills useless"?

Some of you may have seen the recent newspaper headlines which claimed that "Vitamin pills are useless". These related to results published from the other part of the Heart Protection Study on the effects of dietary supplementation with a combination of 600mg vitamin E, 250mg vitamin C and 20mg beta carotene daily. Despite 10,000 volunteers at risk of heart problems having taken this supplement for an average of 5 years, there was no evidence of any reductions in heart attacks, strokes, cancers or, indeed, any other health problems compared to the 10,000 who took placebo (dummy) supplements. It had been hoped that these vitamins might also protect against cataracts, fractures and dementia, but none of those hopes was confirmed. So, rather than spending money on pills containing these particular vitamins, it would be better to spend it on a better diet – with more fresh fruit and vegetables and less saturated animal fat from meat and dairy products.

So are all vitamin pills useless?

Most of us probably get sufficient amounts of the different vitamins we need from eating a balanced diet. The Heart Protection Study, and other similar large-scale studies, indicate that supplementation with vitamins E, C and beta-carotene does not improve health in well nourished populations such as ours. Certain groups do, however, benefit from extra amounts of other vitamins: for example, vitamin B12 needs to be given to people with pernicious anaemia, and folic acid taken around the time of conception can reduce the risk of a baby having a neural tube defect (spina bifida). Whether or not people at high risk of heart problems will benefit from these two vitamins is one of the important questions currently being addressed by SEARCH.

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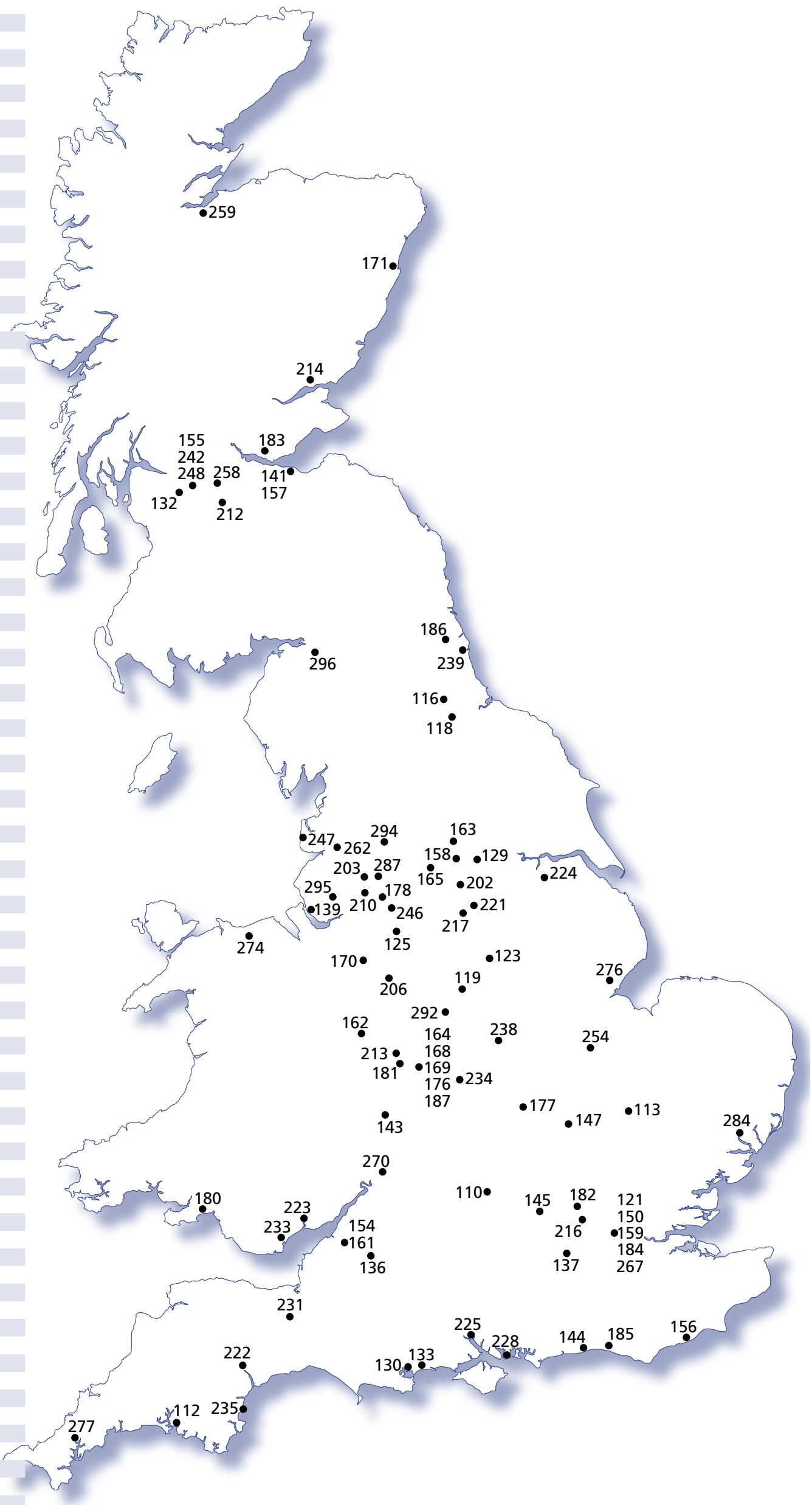
Collaborating Hospitals

Centre Number	Hospital
110	Radcliffe Infirmary, Oxford
112	Derriford Hospital, Plymouth
113	Addenbrooke's Hospital, Cambridge
116	Bishop Auckland General Hospital
118	Memorial Hospital, Darlington
119	Derbyshire Royal Infirmary
121	Hillingdon Hospital
123	King's Mill Centre, Sutton-in-Ashfield
125	Macclesfield Hospital
129	Castleford & Normanton District Hospital
130	Poole General Hospital
132	Russell Institute, Paisley
133	Royal Bournemouth Hospital
136	Royal United Hospital, Bath
137	St Peter's Hospital, Chertsey
139	Walton Centre, Liverpool
141	Western General Hospital, Edinburgh
143	Worcestershire Royal Hospitals, Worcester
144	Southlands Hospital, Shoreham-by-Sea
145	Wycombe General Hospital
147	Bedford Hospital
150	St Helier Hospital, Carshalton
154	Blackberry Hill Hospital, Bristol
155	Glasgow Royal Infirmary
156	Conquest Hospital, Hastings
157	Edinburgh Royal Infirmary
158	Dewsbury and District Hospital
159	Guy's and St Thomas' Hospital, London
161	Bristol Royal Infirmary
162	Princess Royal Hospital, Telford
163	St James's University Hospital, Leeds
164	City Hospital, Birmingham
165	St Luke's Hospital, Huddersfield
168	Queen Elizabeth Hospital, Birmingham
169	Manor Hospital, Walsall
170	Leighton Hospital, Crewe
171	Aberdeen Royal Infirmary
176	Birmingham Heartlands Hospital
177	Northampton General Hospital
178	North Manchester General Hospital
180	Singleton Hospital, Swansea
181	Russells Hall Hospital, Dudley
182	Watford General Hospital
183	Queen Margaret Hospital, Dunfermline
184	Ealing Hospital
185	Royal Sussex County Hospital, Brighton
186	North Tyneside General Hospital, North Shields
187	Sandwell General Hospital
202	Barnsley District General Hospital
203	Royal Bolton Hospital
206	City General Hospital, Stoke-on-Trent
210	Hope Hospital, Salford
212	Wishaw General Hospital
213	New Cross Hospital, Wolverhampton
214	Ninewells Hospital, Dundee
216	Northwick Park Hospital, Harrow
217	Northern General Hospital, Sheffield
221	Rotherham District General Hospital
222	Royal Devon and Exeter Hospital, Exeter
223	St Woolos Hospital, Newport
224	Scunthorpe General Hospital
225	Royal South Hants Hospital, Southampton
228	St Mary's Hospital, Portsmouth
231	Musgrove Park Hospital, Taunton
233	University Hospital of Wales, Cardiff
234	Coventry and Warwickshire Hospital, Coventry
235	Torbay Hospital, Torquay
238	Leicester General Hospital
239	Monkwearmouth Hospital, Sunderland
242	Victoria Infirmary, Glasgow
246	Stepping Hill Hospital, Stockport
247	Victoria Hospital, Blackpool
248	Hairmyres Hospital, Glasgow
254	Peterborough District Hospital
258	Monklands Hospital, Airdrie
259	Raigmore Hospital, Inverness
262	Sharoe Green Hospital, Preston
267	Whipps Cross Hospital, London
270	Gloucestershire Royal Hospital, Gloucester
274	HM Stanley Hospital, St Asaph
276	Pilgrim Hospital, Boston
277	Treliske Hospital, Truro
284	Ipswich Hospital NHS Trust
287	Fairfield Hospital, Bury
292	Queen's Hospital, Burton-upon-Trent
294	Burnley General Hospital
295	Newton Hospital, St Helens
296	Cumberland Infirmary, Carlisle



Who and what are Monitors?

Some of you may have come for your follow-up appointment and wondered why a second person was sitting in with your nurse. We thought it would be a good idea in this newsletter to give a brief explanation.

SEARCH has 88 UK participating hospitals, as you can see from the map opposite. All the nurses working in the clinics are monitored every 6-9 months during the study to ensure that volunteers are being properly looked after, and that good quality and accurate data are being recorded. This is important for the management and integrity of the study, as well as providing feedback and ongoing education for the nurses taking part. Currently there is a team of 5 monitors who are based in different parts of the country. All are highly trained senior nurses with considerable experience of SEARCH who also run their own SEARCH clinics locally. As you will appreciate from the map they cover many miles in their job and have to cope with the unpredictability not only of the British weather but also of public transport!

Monitors' duties include:

- Checking standards of the nurses conducting clinic visits.
- Helping to ensure procedures in the study protocol are adhered to consistently.
- Maintaining contact between the coordinating centre in Oxford and the collaborating hospitals.
- Providing training and supporting nurses, particularly when they are newly in post.
- Reporting back on local issues or problems to the coordinators or administrative staff.
- Sharing ideas for the smooth and efficient running of all of the study clinics.

Maureen Nash and Helen Lochhead

The monitoring team submit reports about each visit and meet on a regular basis to share information and provide feedback to the study coordinators. It is overseen by two Senior Monitors: Maureen Nash based at Leighton Hospital, Crewe and Helen Lochhead based in Oxford (shown in the first photo).

The other monitors are: Anne Robinson, based in Macclesfield, and Elaine Walton, based at Manor Hospital, Walsall (shown in the second photo), and Julie Fitzgerald, based in Huddersfield.

The monitoring team would like to thank the participants for their invaluable support and contribution to SEARCH and for also allowing observation during study appointments.

Anne Robinson and Elaine Walton

Why are cholesterol levels not monitored routinely in everyone in SEARCH?

Both participants and their general practitioners quite commonly ask why cholesterol levels are not measured routinely in all the study volunteers during follow-up. The simple answer is that it is not required for the study: a random sample of volunteers is sufficient to assess reliably the difference between the two treatment groups (see table at the bottom of this page) and is more efficient. Participants' GPs are, however, free to measure cholesterol levels in their patients at any time (as they would do normally) and to change the statin treatment if they feel that their patient is not sufficiently well controlled on the SEARCH treatment regimen.

Guidelines written for doctors to help them treat people with heart disease (such as those in SEARCH) generally recommend lowering total cholesterol below 5 mmol/l. As can be seen in the table, the average levels among those on the lower 20mg daily simvastatin dose in SEARCH are already well below this target (and those on the higher 80mg daily simvastatin dose are still lower). Hence, it is not likely that many participants in SEARCH will need to have their study simvastatin regimen changed by their own doctors in order to produce a bigger cholesterol reduction.

Ringing the changes

We hear many interesting stories about volunteers in the SEARCH trial, providing living proof of what full lives and wide-ranging interests are enjoyed by many people who have had a heart attack. Among the more unusual stories sent in recently was that of Mr Vivian Williams of Pontefract, West Yorkshire. He is not only a bell ringer, or "campanologist" if we want to get technical, but he has been ringing for no less than seventy years. Mr Williams' father learned to ring during the First World War, and when new ringers were sought by the vicar of Redruth, Cornwall – their home at the time – Williams junior, aged seven, duly volunteered. Thus he began his journey into a whole new world that he has continued to explore with relish, not just near his home, but all over the country, and even in the United States. He says that he finds Britain's forty thousand bell ringers a friendly crowd, that no two bells sound or handle alike, and that he is always learning more ways to produce the 'changes'. He finds the mathematics of his hobby fascinating – he explains that when six bells are used, subtle variations in the order of ringing offer more than seven hundred different ways in which the seven hundred and twenty changes can be produced. With twelve bells, the possibilities boggle the mind – it would take some thirty-seven years of non-stop ringing, he says, to perform the maximum number of changes. Mr Williams adds that there are always new towers to ring in, so next time you hear the bells ring out, you never know, perhaps a fellow SEARCH volunteer has come to a church near you.

Cholesterol differences during SEARCH

Although cholesterol levels are not routinely monitored in everyone taking part in SEARCH, they are measured in a randomly selected sample of about 1300 volunteers every year. The information on individual participants in this sample is not made available to the SEARCH nurses or doctors, nor to participants' own doctors. Instead it is used to determine overall results for the whole study population. The results from the first two years of follow-up are shown in the table. You will see that the average cholesterol levels among those allocated to take the higher 80mg dose of simvastatin are about 0.5 mmol/l lower than among those allocated to take simvastatin 20mg daily.

The percentage of SEARCH volunteers taking their study simvastatin tablets regularly is about 90%. Provided this continues to be high, the study has a very good chance of providing reliable answers to the question: "Will fewer people allocated 80mg simvastatin suffer heart attacks, strokes or the need for revascularisation procedures than among those allocated 20mg simvastatin?" It will also allow us to determine whether any benefit from a bigger reduction in cholesterol outweighs any increase in side effects with a higher statin dose.

Average levels of total cholesterol (mmol/l) during SEARCH

Months since randomisation	Total cholesterol (mmol/l)		Difference in cholesterol (mmol/l)
	Volunteers on 20mg simvastatin	Volunteers on 80mg simvastatin	
2-4	4.3	3.7	0.6
8-12	4.3	3.8	0.5
18-24	4.4	3.9	0.5

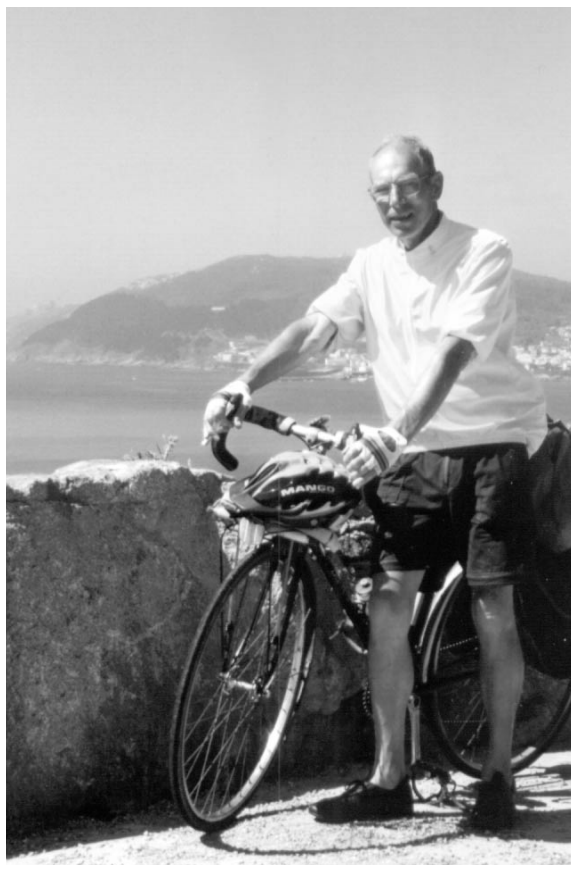
Taking other treatments with SEARCH study medication

The study medication used in SEARCH does not appear to react with most of the other common treatments taken by people with heart problems (but see below). The table shows the numbers of participants taking other commonly used treatments.

Name of treatment	Approx. number (and %) of participants
Aspirin	11,000 (91%)
Warfarin	600 (5%)
Beta blockers (e.g. atenolol, bisoprolol, metoprolol)	6,000 (50%)
Nitrates (e.g. isosorbide mononitrate or dinitrate)	5,000 (42%)
Calcium channel blockers (e.g. nifedipine, diltiazem, amlodipine)	3,000 (25%)
ACE inhibitors (e.g. captopril, lisinopril, enalapril)	600 (5%)

Life cycle

Pictured here is Leslie Smith, 67, a SEARCH participant from Lincolnshire who had a heart attack in 1995, when still five years off retirement from his job as a production manager in the food industry. As is obvious, Mr Smith enjoys a full and active life. The bicycle is his preferred method of transport from his home in Spalding to the local SEARCH clinic at the Pilgrim hospital in Boston, at least in fairer weather. However, the more than 30 mile round trip is nothing compared to his pedal epic in 2000. Combining his cycling with a long-standing interest in Spain and all things Spanish, and an aptitude for languages, he made a solo trip, starting in France, along the famous pilgrim route to Santiago de Compostela, in northern Spain. This picture was taken along the way, with Cape Finistère in the background.



Some tablets increase the risk of muscle problems

Very rarely, statins can cause unexplained muscle pain or weakness, which is called "myopathy" when it is accompanied by a significant increase in the muscle blood test called "creatine kinase" (or, for short, "CK"). That is why volunteers in SEARCH are asked to report any new or unexplained muscle pain at each clinic visit and a blood sample is taken to measure CK levels in the blood. Some types of other treatment can increase the risk of myopathy with simvastatin and other statins, and these are listed in the boxes below. So, when such treatments are started by participants in SEARCH it is recommended either that the study simvastatin be stopped when the risk may be increased substantially (Box 1), or that the study simvastatin may be continued when the increase in risk is smaller (Box 2). In the latter case, however, particular care is needed to ensure **reporting of any unusual or unexplained muscle pain or weakness** as soon as possible to the clinic nurse or coordinating centre.

Box 1: Drugs that can increase the risk of myopathy substantially, and so should NOT be taken with the study simvastatin tablets

For kidney and heart transplants:

- **Ciclosporin** (Neoral, Sandimmum, SangCya)

For lowering cholesterol:

- Non-study statins: **Simvastatin** (Zocor)
  Atorvastatin (Lipitor)
  Fluvastatin (Lescol)
  Pravastatin (Lipostat)
- "Fibrates": **Bezafibrate** (Bezalip, Bezalip Mono, Zimbacol XL)
  Ciprofibrate (Modalim)
  Clofibrate (Atromid-S)
  Fenofibrate (Lipantil, Lipantil Micro)
  Gemfibrozil (Lopid)
- High dose niacin: **Nicotinic acid** more than 1 gram per day
  Acipimox (Olbetam)

For depression:

- **Nefazodone** (Dutonin)

If you are prescribed any of these treatments then you should stop the study simvastatin tablets (the tan-coloured round ones and the dark pink capsule-shaped ones) and contact your study nurse (or ring the Freefone service on 0800-585323) for further advice.

Box 2: Drugs that can increase the risk of myopathy to a lesser extent, and so may be continued with study simvastatin tablets

For some irregularities of heart rhythm ("arrhythmias"):

- **Amiodarone:** (Cordarone, Cordarone X, Amidox)
- **Verapamil:** (Berkatens, Cordilox, Ethimil, Geangin, Securon, Univer, Verapress, Vertab, Zolvera)

For infections:

- **Erythromycin:** (also sold as Arpimycin, Erycen, Erymax, Erymin, Erythrocin, Erythroped A, Erythrolar, Erythromid, Ilosone, Ilotycin, Retcin, Rommix)
- **Clarithromycin:** (Klaricid, Helimet, Heliclear)

For fungal infections (only when these drugs are given by mouth or injection; ointments or lotions are fine to use):

- **Fluconazole:** (Diflucan)
- **Itraconazole** (Sporanox)
- **Ketoconazale:** (Nizoral)
- **Miconazole:** (Daktarin)

If you are newly prescribed any of these drugs, or have unexplained muscle pain or weakness, then continue to take your study treatment (unless advised otherwise), but contact your study nurse (or ring the Freefone service) for further advice. Sometimes this advice will involve an extra clinic visit to measure CK levels in the blood. In other cases, for example with certain short courses of treatments for infections, you may be advised to stop the study simvastatin temporarily until the other treatment has been completed.

The study vitamins are not known to cause any adverse effects when taken with any other treatments. Folic acid can, however, disturb the effects of methotrexate (given for severe arthritis or psoriasis, and for some other conditions) which works by interfering with the body's handling of folic acid. So, if you are prescribed methotrexate, you should stop the white study tablets (which contain folic acid or dummy) and contact the study nurse (or ring the Freefone service on 0800-585323) for further advice.