Welcome to the third edition of ReSEARCH, our newsletter for volunteers taking part in SEARCH. Thank you for all your letters and for continuing to send ideas for items to include. The emphasis in this edition is on the importance of staying in the study for a bit longer. SEARCH needs to continue for at least another year if reliable results are to emerge. On page 2, the Study Coordinators explain the reasons for needing your continued support, and why it is difficult to be precise about the exact end date of the study.

We also have news about other relevant medical research studies. Since our last newsletter in 2002, several important studies of the effects of statins for cholesterol-lowering in different types of people have been published. We have summarised the key findings of these studies, and any implications for people taking part in SEARCH. As you may know, statins are now available over-the-counter without a prescription and while this is not directly relevant to people taking part in SEARCH (who are all taking prescribed statins), the article on page 5 may be helpful if friends or relatives ask you about it.

Letter from the Editor

A surprise party was held recently to mark the departure of Jacqui Wisby, the long-standing receptionist at Blackberry Hill Hospital, Bristol. This was combined with a meeting for local SEARCH participants who heard a useful and informative presentation about the study from Dr Richard Bulbulia, who is based at the Oxford coordinating centre. This was followed by a lively question and answer session.

Jacqui has worked for Dr Papachadou, Consultant Cardiologist and SEARCH investigator, on clinical trials for about ten years, firstly for our Heart Protection Study and then for SEARCH. She is very popular with volunteers, providing a welcoming and homely atmosphere. Jacqui is moving to Peterborough to be near to her family. Her enthusiasm, humour and professionalism will be greatly missed.

SEARCH Surprise

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Another prize for Sir Richard Doll

Many volunteers will have heard of Sir Richard Doll, one of the world’s best-known medical researchers. He is particularly well known as one of the two scientists who first demonstrated conclusively the link between smoking and lung cancer in the 1950s. Only last June he was on national radio and television summarising the fifty year follow-up results of his British Doctors Study. Like previous instalments, this revealed findings showing long-term smoking to be even more damaging to health than had previously been thought.

Sir Richard helped establish the Oxford unit which runs SEARCH, and at 92 years of age, when not speaking at scientific meetings around the world, he can still be seen climbing the two flights of stairs to his office every day. He is chairman of the Data Monitoring Committee of SEARCH, a committee of independent scientists who monitor the progress of the study from data to which the coordinators do not have access.

Recently, Sir Richard was awarded the valuable and prestigious Shaw Prize in Life Science and Medicine, adding to an already long string of honours and prizes. The Shaw Prizes - there are others for astronomy and mathematics - are awarded by a foundation set up in 2002 by Run Run Shaw, the famous Hong Kong businessman. Their aim is to honour individuals who have achieved significant breakthroughs in academic and scientific research, and whose work has resulted in a positive and profound impact on mankind. The prize recognises the extraordinary contribution made by Sir Richard over many years. His work on SEARCH illustrates his continuing commitment to important medical research.
Letter from the Coordinators

Dr Louise Bowman reports on the results of a new study of more intensive statin treatment

Dr Louise Bowman

10 years ago, the first major study of statin drugs showed that cholesterol-lowering treatment plays a very important part in preventing heart disease, particularly in people who have already had a heart attack. Since then, further studies (including our own Heart Protection Study) have shown the benefits of statins in a much wider range of people, including those with diabetes, those who have previously had a stroke or a mini-stroke and those with poor circulation in the legs. Statins prevent strokes as well as heart attacks and, at standard doses, are found to be very safe and well tolerated, with little in the way of side effects.

Perhaps more surprising to some, the benefits of lowering cholesterol are seen even in people with ‘normal’ or ‘low’ cholesterol levels (probably because these levels are still too high). However, what is not yet clear is whether everyone should have their cholesterol lowered as much as possible (e.g. with more intensive statin treatment), or whether there might be problems with such an approach, and standard statin doses are actually sufficient for most people.

As you know, SEARCH is the largest study addressing this important question. Recently, however, results have been announced from a much smaller study which, when considered with the final results from SEARCH and the other large on-going trials, should help improve current treatments for heart disease. The 'PROVE-IT' trial enrolled about 4,000 people in 8 countries, who had been admitted to hospital with either a stroke or a heart attack within the previous 10 days. They were treated (by random allocation) with either standard therapy (40mg pravastatin, which is roughly equivalent to taking 20mg simvastatin) or intensive therapy with atorvastatin 80mg daily (which is somewhat smaller than we had anticipated at this stage. As a result of these two factors, SEARCH probably needs to continue for a total of 5 to 6 years, rather than our original estimate of 4 to 5 years.

An independent committee of experts not involved in the day-to-day running of SEARCH (known as the Data Monitoring Committee, and chaired by Sir Richard Doll: see front page) has been looking at the study results as they accumulate. If at any time they feel that SEARCH has produced a clear answer to either of the main questions, they will inform those of us running the study. Otherwise, SEARCH will continue until at least 1,900 people have had a confirmed cardiovascular event during the study. On current projections, this is likely to be around the end of 2005 or early 2006. So, we are very keen for all participants to continue in the study for about another 12-18 months.

Dr Louise Bowman discusses this in more detail in the article below.

Cholesterol: is lower better?

Dr Jane Armitage Professor Rory Collins

Around the world there are 3 large

Cholesterol-lowering margarines and yoghurts can be used safely with study treatment (see pages3).
Does folic acid protect the heart?

Dr Robert Clarke, our expert on homocysteine, describes some recent findings and puts them in context for SEARCH participants.

Research over the last several years has linked high blood levels of homocysteine with an increased risk of heart disease and strokes. Homocysteine, which is an amino acid (one of the body’s protein building blocks), circulates normally in the blood, but higher than usual levels are seen in people who eat a diet which is low in folic acid or in vitamin B12. As you will know, SEARCH is trying to find out whether reducing homocysteine levels with supplements of folic acid (also known as folate) and vitamin B12 helps protect against heart disease and strokes which, at present, looks possible but by no means certain.

As well as this possible benefit, folic acid has a different and well demonstrated beneficial effect when taken during early pregnancy. Folic acid supplements help protect women from having babies with certain developmental problems, in particular spina bifida. Because of this, the American government decided in the 1990s to add folic acid to all cereal grain (2.5 mg) or very low dose (0.25 mg) folic acid to foods. This food change has led to a marked increase in folate intake and lower blood homocysteine levels in the whole US population. Consequently, the VISP trial alone could have shown a clear benefit of folic acid for the prevention of heart disease and strokes, as both studies were relatively small and did not continue for long. On the other hand, in SEARCH, 12,000 volunteers are taking either folic acid and vitamin B12 or dummy tablets, and we expect the study to last at least 5 years. So far, blood tests during the study show that the vitamins are producing the expected lowering in homocysteine levels (about 15%) with heart problems took either folic acid (5 mg) or a placebo (dummy) tablet. This trial was stopped early (after less than 2 years) because the folic acid supplements had only lowered homocysteine levels by about 15% compared with the expected 25-30% in this population. No effect was seen on heart disease or strokes.

In North America, the ‘VISP’ trial included 3,680 people who had already had a stroke. They were treated with either high-dose (2.5 mg) or very low dose (0.25 mg) folic acid for 2-year period. This trial started in 1998 at around the time of the introduction of the US law requiring addition of folic acid to foods. This food change has led to a marked increase in folate intake and lower blood homocysteine levels in the whole US population. Consequently, the VISP trial also showed a smaller than expected reduction in homocysteine levels (about 15%) with folic acid and the treatment had no significant impact on the risk of recurrent strokes or heart disease.

Although disappointing, it is unlikely that either the CHAOS II or VISP trials alone could have shown a clear benefit of folic acid for the prevention of heart disease and strokes, as both studies were relatively small and did not continue for long. On the other hand, in SEARCH, 12,000 volunteers are taking either folic acid and vitamin B12 or dummy tablets, and we expect the study to last at least 5 years. So far, blood tests during the study show that the vitamins are producing the expected lowering in homocysteine levels of 25-30%. Therefore, assuming the study continues as at present, SEARCH has a good chance of answering the important question of whether folic acid and vitamin B12 supplements reduce the risk of heart disease or strokes.

Ken works wonders on aged beauty

Ken Matchett, a SEARCH participant from the West Midlands, is a retired coach-builder. For most of his working life he built passenger coaches for British Rail Engineering (BREL). When he started his career, much of a railway coach was made of wood, apart from the chassis, so Ken was in a trade where specialised wood-working met heavy engineering. In his last few years of work, as metal and plastics began to take over, Ken left BREL and found an outlet for his skills in the shop and bar-fitting trade. He is now 70 and retired, but not long ago he answered a call to help on an unusual project that was more like his original work.

Intrigued by an ad in his local paper for a coach-builder, Ken found that the advertiser was a car enthusiast who was trying to re-build a 1935 Fiat Belilla, a small, two-seat sports car. The car, whose body frame had been built of wood on a steel chassis, had been found in a sorry state in an old barn in France. Time and woodworm had taken their toll, and only a few parts of the frame remained. Luckily the new owner, a tool-maker by trade, was able to show Ken another example of the car that belonged to a local club, so the pair were able to set about making drawings, and then getting down to some reconstruction. At last the complete frame was ready to go to a firm in Manchester to have an aluminium skin fabricated, and the first reward for a great deal of hard work was when they were told that the frame was the best the fitters had ever worked with. Ken’s labours are largely complete, and now it is up to others to finish the job, so the little Fiat can take to the roads again. When we last heard from Ken he was on his way to the owner’s garage to check how things were coming along. We can be sure he will be among the first to have a ride in the completed machine.
New results confirm the benefits of statins

Dr Richard Bulbulia explains the results of some recent trials

The benefits of statins for people who have survived a heart attack have been well known for many years. Some of you may remember that in the Autumn 2002 edition of ReSEARCH we reported the results of our Heart Protection Study, which included over 20,000 people with circulatory problems or diabetes. This study showed that reducing cholesterol by about 1 mmol/l with simvastatin reduced the risks of heart disease and strokes by about one quarter, regardless of a person’s age, sex or cholesterol level. These results have had a huge impact both in the UK and around the world, and have contributed to a worldwide increase in prescribing of statin drugs.

Since then, several other studies have reported results that extend and reinforce the recognised benefits of statins. Two studies looked at the role of statins in people with high blood pressure, one more in the elderly, and another in people with diabetes. In ASCOT (Anglo Scandinavian Cardiac Outcomes Trial), just over 10,000 people with high blood pressure who were considered at high risk of arterial disease were given either atorvastatin 10mg daily or dummy tablets. This trial ran for just over three years, and participants who had atorvastatin from the trial had a reduction in the risk of a heart attack, stroke or bypass surgery of about one-third. The Collaborative Atorvastatin Diabetes Study (CARDS) also assessed atorvastatin 10mg daily, this time in 2,838 volunteers with diabetes. That study also showed a clear reduction of about one third in the chances of developing heart problems or having a stroke in such patients.

ALLHAT-LTT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack-Lipid Lowering Trial) was an American study involving over 10,000 volunteers with high blood pressure. Participants were either prescribed pravastatin 40mg daily or given ‘usual care’ by their own doctors, who were therefore free to prescribe any drugs that they thought appropriate (including statins). In fact, many of the volunteers in the usual care group were treated with a statin, which meant that the difference in blood cholesterol levels between the two groups was rather small. So, although slightly fewer people in the pravastatin group had heart attacks, strokes or bypass operations (vascular events), the effect was not large enough to be clear cut. Put in the context of the other studies, it is likely that this first disappointing result from a statin trial was because so many of the ‘control’ group were taking a statin.

In conclusion, there is no clear evidence linking statin use to memory problems. In contrast, there is an overwhelming body of evidence confirming the long-term benefit of statins in preventing illness and saving lives in a wide range of people, including those with vascular disease. So, it would be unwise for people to stop their statin treatment due to fears of memory problems without first discussing it with either their GP, the SEARCH nurse, or one of the SEARCH doctors.

Where have I left my keys?

Is there any connection between statins and memory loss?

The possibility of a connection between statin use and memory loss has been raised by a group of researchers in America. These reports have received a significant amount of publicity in the popular press in this country. What is the evidence behind these claims?

Researchers at Duke University Medical Centre, North Carolina collected a series of about 60 cases of people who experienced varying degrees of short- or long-term memory loss and who were also taking a statin. The most celebrated case was a retired NASA astronaut who suffered a complete loss of memory (a condition called transient global amnesia), which occurred six weeks after starting atorvastatin. His memory returned fully once he stopped these tablets, and, interestingly, the problem recurred on starting them again.

Whilst at first sight these reports might seem alarming, it is important to place them in context. Worldwide, tens of millions of patients are taking a statin. Memory loss and forgetfulness are very common symptoms, particularly as people get older and if they have heart disease – exactly the sort of people who should and do receive statin therapy. It is highly likely that the association between memory loss and statins is a chance finding, since no such memory problems have been seen in properly controlled studies.

For example, in our Heart Protection Study, in which 20,000 volunteers took either simvastatin 40mg daily or placebo for 5 years, there was no difference in various memory tests at the end of the study between those who were allocated to take the statin and those who were not, or in reports of memory loss between the two groups. Similarly, in the PROSPER Study (see above) which tested pravastatin in 6,000 older individuals, no adverse effects were seen for a variety of memory tests.

In conclusion, there is no clear evidence linking statin use to memory problems. In contrast, there is an overwhelming body of evidence confirming the long-term benefit of statins in preventing illness and saving lives in a wide range of people, including those with vascular disease. So, it would be unwise for people to stop their statin treatment due to fears of memory problems without first discussing it with either their GP, the SEARCH nurse, or one of the SEARCH doctors.
At the end of the study, will I be told which treatments I was taking?
A. After the study ends, if you would like to know what you had been taking, either you or your GP will be able to find out by telephoning the Freephone number. You will be told whether you were on 20mg or 80mg simvastatin, and whether you were on active or dummy vitamins.

Am I on the real thing?
A. Everyone who is taking all the SEARCH tablets is on active (real) simvastatin. No-one gets only dummy (placebo) cholesterol-lowering treatment. Half of the participants in SEARCH have been randomly allocated to take a standard 20mg daily dose of simvastatin and the other half to take the higher 80mg daily simvastatin dose. For the vitamin part of the study, half of the participants are taking active vitamins (2mg folic acid plus 1mg of vitamin B12 daily) and the other half are taking dummy (placebo) vitamins.

Do I take the same dose throughout the study?
A. Yes. Whichever simvastatin dose you were allocated to take at the beginning will remain the same during the study. An exception to this is the few people who also take the heart drug amiodarone. For safety reasons, all these people are given the lower 20mg simvastatin dose regardless of the dose they were originally allocated. If these people stop their amiodarone, they can go back to taking their original dose of simvastatin. Whether or not volunteers are taking active or dummy vitamins was decided by random allocation by computer at the beginning of the study. The type of study treatment (active or dummy) stays the same during the study, as does the dose of vitamins for those on active vitamins.

What will happen at the end of the trial? Where will I get my tablets from?
A. You will be told whether you had been taking the standard 20mg or higher 80mg dose of simvastatin. This result was sent to each participant’s GP if a volunteer is taking 20mg simvastatin in the trial then the cholesterol level should remain much the same as at the start, whereas for those taking 80mg simvastatin in the trial it should be somewhat lower. GPs are free to monitor cholesterol levels during the trial if they consider it necessary, and many do so.

How much longer will the study go on?
A. Probably another 12-18 months (see Letter from Study Coordinators on page 2).

Should I eat cholesterol-lowering margarines and yogurts?
A. These products have been shown to be effective at lowering blood cholesterol levels and do so safely. However, they do not have as big an effect as statins and have not been shown conclusively to reduce heart disease risk. They should not be seen as an alternative to statins but may be safely used alongside a statin if you wish.

Do I have to keep taking the tablets?
A. We would like you to do so if at all possible. To get the most benefit from statins they need to be taken regularly over several years. Similarly, for the study to be able to demonstrate a difference in the risk of heart attacks and strokes between those on the higher versus the standard dose takes time. This is why it is important for the success of the study for people on both the higher and lower doses of simvastatin to keep taking the tablets. The difference in cholesterol of about 0.5 mmol/L needs time to translate into a difference (if there is one) in heart attacks and strokes.

Am I still at risk of muscle problems if I take simvastatin? Should I eat cholesterol-lowering margarines and yogurts?
A. Yes, but the risk is much, much lower than in the first few months after starting to take a statin. A change in circumstances, such as starting a new drug, can also increase the risk of muscle problems. There is a reminder on the back of this newsletter about other drugs which increase the risk of muscle problems when taken with simvastatin. Advice can be obtained from the Freephone number (0800 585323) if you are ever unsure about any new tablets or medicines.

Some frequently asked questions
Here we try to answer some of the most commonly asked questions about participation in SEARCH.

Statins over the counter

Britain has recently become the first country to allow sale of a statin cholesterol-lowering drug over-the-counter without a prescription. However, “behind-the-counter” might be a better description, since customers will have to consult their pharmacist in order to buy the new Zocor-Heart-Pro. It contains the same type of statin – simvastatin – that is being used in SEARCH, but at a lower dose. Zocor-Heart-Pro contains simvastatin 10mg to be taken daily, whereas SEARCH is comparing the value of 20mg versus 80mg daily. Anyone who already has circulatory problems, diabetes or high blood pressure who tries to buy a statin in the chemist should be advised by the pharmacist to see their own GP, since these people are probably eligible for a statin on prescription. It is people at somewhat lower risk of heart disease who are being targeted for over-the-counter statin treatment. People likely to be at these more moderate levels of risk of heart disease include any men over the age of 55 or, men aged 45-54 and women aged over 55 years if they have one or more of the following risk factors: a family history of coronary heart disease in a close relative (e.g. parent, brother or sister), or being a current smoker (or within one year of giving up), overweight, or of South Asian ethnicity.

It may seem surprising that having a high cholesterol level is not necessary for those who want to buy statins. This is because it has been recognised that the level of cholesterol is fundamentally important whatever it may be. As a population, people in the UK have average cholesterol levels that are too high to be good for us. So, if other factors (such as age, smoking, and family history) mean that we are likely to develop heart problems, then lowering the levels of bad LDL-cholesterol is likely to be worthwhile whatever the cholesterol level.
ReSEARCH

Soaring away

Iain Pickering is a SEARCH volunteer in Gloucestershire. Telephoning him for the first time, it is easy to think the ‘phone has been answered by his son. In fact, it is Iain himself, but it takes a while to accept that you really are talking to someone of 75. Perhaps this is the first clue to how, after being laid low a few times in the past, he now finds himself not only living life to the full, but sometimes, quite literally, on top of the world.

Iain was born and brought up in Surrey, and at 16 was apprenticed to Vickers-Armstrongs in Weybridge as an aircraft fitter. This training marked the beginning of an association with aviation that has continued ever since. In 1958, a new job took him to Gloucestershire, and the following year, seeing gliders soaring above a ridge in the Cotswolds, he made up his mind that one day he would take up gliding, a decision he put into practice two years later.

In 1992, a couple of years off retirement, Iain had his first heart attack. When a second one struck two years later, his firm retired him. He then set about getting fit and enjoying a well-earned retirement. At last he and his wife could enjoy doing all the things that had been put off for so long due to his busy career. Sadly this golden time was cruelly cut short eighteen months ago, when his wife died of cancer. After that, as a gliding man might have put it, Iain found himself sinking rather low. However, as would come as no surprise to anyone who has talked to Iain, it was not long before he took charge of matters, realising that he alone could do something to get back his life. He decided to take to the skies again, and in due course became the co-owner of a high performance Astir glider. To do something practical to help others, Iain also volunteered to take part in the SEARCH study.

Iain Pickering

Gilding is far from the sedentary sport it may seem to the uninitiated. There are always gliders to push out of the hangar to the launch position, or back from where they land (sometimes far away on the airfield) and many other jobs to be done. On his first flight this year, after being towed up to about 2,000 feet by an aeroplane, Iain was released to soar with whatever lift he could find from updrafts caused by the wind below blowing on ridges, or under the few clouds around. He got up to about 5,000 feet, and spent two and a half hours soaring like a bird over the Cotswolds on a glorious early summer’s day. SEARCH wishes him many more years of the uplifting life he has made for himself.

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 assistance.

Safety reminder: 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 other treatments can increase the risk of myopathy when taken with simvastatin or some other statins. These are listed in the boxes below. So, if any of these medications are started by SEARCH participants, we recommend either that the study simvastatin tablets are stopped (when the risk may be substantially increased: Box 1), or that the study simvastatin tablets are continued (when the increase in risk is smaller: Box 2).

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 heart irregularities (arrhythmias):
- Amiodarone (Cordarone, Cordarone X, Amiadox) (see ‘frequently asked questions’ on page 5)

For lowering cholesterol:
- Non-study statins: Simvastatin (Zocor, Simwador, Ranzolont), Atorvastatin (Lipitor), Fluvastatin (Lescol), Pravastatin (Lipostat), Rosuvastatin (Crestor)
- “Fibrates”:
  - Bezafibrate (Bezalip, Bezalip Mono, Bezalex XL, Liparol XL, Zimcolol XL)
  - Ciprofibrate (Modalim)
  - Fenofibrate (Lipantil, Lipantil Micro, Supralip)
  - Gemfibrozil (Lipid)
- High dose niacin: Nicotinic acid (Niaspan) more than 1 gram/day (Olbetam)

For depression:
- Nefazodone (Dutonin)

If you are prescribed any of these drugs then continue to take your study treatment (unless advised otherwise), but contact your study nurse (or ring the Freefone service on 0800 585323) 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 antibiotics, you may be advised to stop the study simvastatin temporarily until the other treatment has been completed.

Box 2: Drugs that can increase the risk of myopathy to a lesser extent, and so may be continued with study simvastatin tablets (but with increased vigilance about muscle symptoms)

For some irregularities of heart rhythm (arrhythmias):
- Verapamil: (Berkatens, Cordilox, Securon, Univer, Tarla, Verapress, Vertab, Zol vera, Ethimil, Ranvera, Vera-tl, Geanqin)

For infections:
- Erythromycin: (also sold as Arpimycin, Erycin, Erymax, Erymin, Erythrocin, Erythroped A, Erythrolar, Erythromed, Kerymax, Tilyruth, Ilsonene, Ilcyrin, Retcin, Rommisa) (Klaricid, Helimet, Heliclear)
- Telithromycin: (Ketek)

For fungal infections: (only if these drugs are given by mouth or injection, ointments or lotions are fine to use):
- Fluconazole: (Diffucan)
- Itraconazole: (Sporanox)
- Ketoconazole: (Nizoral)
- Micronazole: (Daktarin)

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