

The newsletter for people taking part in SEARCH

Letter from the Editor

Once again thank you, on behalf of the SEARCH team, for your participation in the study, and for your continued commitment over the last several years. With your help we are on target to complete the largest and longest trial which has ever assessed the safety and effectiveness of intensive cholesterol-lowering treatment, and of homocysteine-lowering therapy with B vitamins. Regardless of the outcome of the study, the results will make a valuable contribution to how doctors manage patients with heart disease.

As the study end soon, this is the last issue of ReSEARCH. You will find information about the final phase of SEARCH on the bottom of this page as well

as other features that we hope you will find interesting and informative on the following pages. You or your friends might like to take part in some other studies being conducted at Oxford University's Clinical Trial Service Unit (CTSU) such as HPS2-THRIVE (page 2) or ASCEND (page 3). Also the visionary UK Biobank study, directed by Rory Collins, has opened its doors to the first 10 000 volunteers and you may, in due course, receive an invitation. It aims to help future generations live healthier disease-free lives (page 2).

Every week we seem to be bombarded with a new headline about statins. One week they are reported to protect against cancer and the next week to cause

cancer. This sort of reporting is extremely confusing for doctors as well as for patients. In this ReSEARCH we explain the background behind some of these scare stories and I hope provide some reassurance about the safety of statins. To help you further, the study team are always happy to answer individual questions.

Thank you for all your encouraging feedback and help over the years. We look forward to being able to share the results of this important study with you later next year.

Best wishes

David Simpson, Editor, ReSEARCH

The beginning of the end: *Less than one year to go*

The SEARCH study is rapidly approaching its scheduled end, with all participants to be seen in the study clinic for the last time between October 2007 and April 2008. By that time, the average follow-up for study volunteers will be just over 7 years, so although some people will have taken the study treatment for "only" 6 years, others will have done so for as long as 9 years! This is a tremendous contribution and so thank-you to everyone. Throughout this period there has been fantastic support for the study, and more than 85% of volunteers continue to take one or more of their study tablets. With your continued help during this final year, SEARCH will provide important new information about the prevention of heart disease.

To keep the regular follow-up visits in SEARCH reasonably brief, information has been sought from study volunteers only about any serious medical events (such as heart attacks and strokes) that may have occurred. At the final follow-up, however, we plan to record some extra information so that the study can assess the effects of long-term treatment with the cholesterol-lowering drugs and with the vitamins on some additional measurements that are of interest. Because it is especially important to assess as many as possible of the original volunteers at the end of the study, we are keen that anyone who has stopped attending the study clinics regularly does come to this final visit.

Blood pressure

Neither the cholesterol-lowering treatment nor the vitamin supplement being studied in SEARCH are thought to affect blood pressure. But, in order to be sure that any effects of the study treatments on heart disease are due to their effects on blood levels of cholesterol and vitamins (rather than due to effects on some other risk-factors), blood pressure will be



recorded routinely in all participants attending the final follow-up visit.

Memory and other aspects of mental functioning

Gradual narrowing and blockage of small blood vessels supplying the brain can lead to a decline in mental function with increasing age. Lowering blood homocysteine levels may improve blood flow to the brain. Consequently, there has been considerable interest in whether the treatments being studied in SEARCH (especially the vitamins) help improve memory loss. Therefore, at the final follow-up the clinic nurses will be asking all volunteers some extra questions designed to assess memory and some other aspects of mental function, but don't worry, the questions are very straightforward and relate to everyday things and only take about 10 minutes! To help obtain complete information, anyone who is unable to attend their final appointment visit will be asked to answer these questions over the telephone.

Hearing

As many volunteers will be all too aware, ageing is often associated with hearing problems. Although not traditionally considered to be related to the same underlying circulatory disease as strokes and decline in mental functioning, some recent information suggests there might be a link. A recently published Dutch study

of the effect of folic acid (one of the vitamins included in SEARCH) on mental functioning and on hearing suggested small benefits in both areas. However, this particular study only



One of the programming team trying out the hearing test

included a few hundred people and so was not large enough to be definitive. With the many thousands involved in SEARCH, we have the opportunity to assess whether or not folic acid and vitamin B12 really do improve hearing or brain power. Hence, at the final visit we shall be asking you some questions about your hearing and doing a simple hearing test.

Treatment after the final follow-up visit

We shall not know which dose of simvastatin or whether the study vitamins being studied in SEARCH are of value for people until Autumn 2008. It will not be until then that all of the final follow-ups will have been conducted that the data checked, and the results analysed. Consequently, at the time of the final follow-up visit, the results of the study will not be available to help guide participants about their subsequent dose of cholesterol-lowering "statin" therapy or use of vitamin supplements. Instead, study volunteers will be asked to see their own doctor for a new prescription of statin treatment using the current recommendations. We shall be writing to your GP after your final visit to explain this.

Nothing Ventured

As Jock Dunlop, who attends the SEARCH clinic in Bournemouth Dorset, approached his eightieth birthday last year, he decided to use



Photo courtesy of The Community Magazine, part of Blackmore Vale Publishing, Dorset

the event to raise funds for charity. He hit on the idea of getting himself sponsored to take

eight different methods of transport, one for each decade. Sponsors signed up and when the big day arrived Jock was joined by a variety of well-wishers, including his three children – one visiting from Australia, another from Ireland – and some of his grandchildren. Having spent his life in the world of aviation engineering – he became managing director of Flight Refuelling Electronics – Jock started his challenge by flying a light aircraft, with an instructor from the local flying club. Jock used to fly anyway and is one of few people who can say they flew with the late Sir Alan Cobham, the legendary pilot who founded Jock's old firm. Safely back on the ground, the second task was driving a car, a practical solution to getting between each activity, while the third was more pedestrian – literally – as he walked on the golf course, playing three holes.

The next three challenges were all forms of riding: number four was on a horse, despite

having last ridden aged fourteen, and fifth was riding a motorcycle, accompanied by local bikers called the Brotherhood of Street Racers. As with the horse, Jock had not ridden a motorcycle for a very long time, at least fifty years. Next, he swapped two-wheelers and like many boys at heart, rode a bicycle backwards in the local school playground. Then he drove to Poole harbour and sailed a dinghy, number seven, and finally jumped onto a boardsail for a spot of windsurfing.

Jock raised £3,400 that day, sending £850 to each of four medical charities, including the British Heart Foundation. When we caught up with him, he had just taken a lesson in fly fishing – as he said, "Nothing ventured..." – and was looking forward to a holiday at a favourite spot near Oban, in the west of Scotland. We can picture him setting off, fishing rod and waders in the car, dinghy on the roof rack; but it is anybody's guess what else he might try once he's there...

Cholesterol – it's not all bad HPS2-THRIVE A new study investigating good cholesterol

At Oxford University's Clinical Trial Service Unit we are investigating various different ways in which to protect people against heart and circulatory problems. There is a long-standing interest in cholesterol and, thanks to a large number of studies (including the Heart Protection Study), we know that lowering cholesterol with statins is very effective at preventing heart attacks and strokes. However, the full cholesterol story is a bit more complicated!



Cholesterol is carried around the body in special particles known as lipoproteins, and there are two major types of lipoprotein. The more common particle is called "low-density lipoprotein", or "bad" LDL-cholesterol. High levels of LDL cholesterol are known to cause circulatory problems, and lowering LDL cholesterol with statins is a very effective treatment for preventing such problems. However, despite taking statin treatment, some people still have circulatory problems.



The other major lipoprotein is called "high-density lipoprotein", or "good" HDL-cholesterol. High levels of HDL cholesterol seem to protect against circulatory disease. However, until recently, there have not been any effective, widely-applicable treatments to increase HDL cholesterol levels in the blood.

A new medication (which is not yet available to prescribe) is now being tested in a large trial being run by the same team that is coordinating SEARCH. This new treatment, called ER niacin/laropiprant, is a combination of an extended release (ER) form niacin (a B vitamin which raises "good" HDL cholesterol and lowers "bad" LDL cholesterol) and laropiprant (which blocks a common side effect of niacin known

as "flushing"). It has been known for over 50 years that high dose niacin (2 to 4 g per day) improves cholesterol levels, but it has not been widely used because of its side-effects. The most troublesome one is "flushing" which makes the skin go red and hot and can be unpleasant. Laropiprant has been developed to prevent this flushing, and is very effective at doing so.

HPS2-THRIVE, a new study of 20 000 volunteers, is investigating whether ER niacin/laropiprant will reduce the risk of circulatory problems when given in addition to a statin. The effects on the good and bad cholesterol make this highly likely but, since it is a new preparation it needs careful testing. HPS2-THRIVE: Treatment of HDL to Reduce the Incidence of Vascular Events, started recruitment earlier this year and will be recruiting patients from 6 countries (including the UK) over the next year or so. Many SEARCH hospitals will also be running HPS2-THRIVE clinics and most SEARCH volunteers will be suitable to take part if they would like to when SEARCH ends. We will be in touch with you in due course.

VISIONARY MEDICAL RESEARCH PROJECT BEGINS RECRUITMENT

UK Biobank, one of the most detailed medical research projects ever undertaken, has begun its recruitment across Britain. It will help untangle the complex interplay of nature (that is, genes) and nurture (such as lifestyle) in the development of many different diseases, and try to explain why some people get certain illnesses and others do not. It should help future generations live healthier lives, freer of disease.

UK Biobank will follow the lives of 500 000 people aged 40-69 to find out more about curing life threatening, painful and debilitating illnesses such as cancer, heart disease, diabetes, stroke, dementia, arthritis and depression. Hosted by the University of Manchester, and



Staff processing a blood samples at a UK Biobank centre

with the support of the NHS and leading universities and medical charities, researchers believe that UK Biobank will be an extraordinarily important resource for scientists for many years to come. The project is led by Professor Rory Collins, who is co-director of CTSU, and is also the Chief Investigator of SEARCH. Many of the people behind the scenes at Oxford University involved in running SEARCH are also involved in UK Biobank.



Samples are processed by state-of-the-art robots

Statins: *The truth behind the headlines*

Over the last few months there have been numerous articles about statins in the newspapers. We often receive calls or letters from participants worried about the content of these articles, and asking for advice and reassurance about statins. Unfortunately, many of the articles are alarmist and give a negative view of statins. Below we provide some informed responses to the commonly raised questions and put them in the context of the scientific evidence. Muscle symptoms are discussed in detail in the Safety Update on the back page of *ReSEARCH*.

or no treatment. There is also now almost 10 years follow-up of the 20 000 people who took part in the Heart Protection Study and took simvastatin 40 mg or dummy treatment for 5 years. Again the results are reassuring with similar numbers of people developing cancer among those who took statins as among those allocated placebo or dummy treatment.

2. "Statins do not prevent death in some patient groups such as women and patients older than 70 years."

3. "Cut-price statins are associated with an increased rate of patient death."

When particular drugs are no longer under patent many different companies can manufacture them, and sell them as generic products. This has the effect of pushing the price down. In the UK, simvastatin and pravastatin are now both available as generic products and therefore might be called 'cut-price' statins. However, in order to be allowed to market a generic statin, the manufacturer has to prove that the drug behaves in a similar way to the patented version of that drug. Generic 'cut-price' statins are likely to be just as effective as the earlier expensive



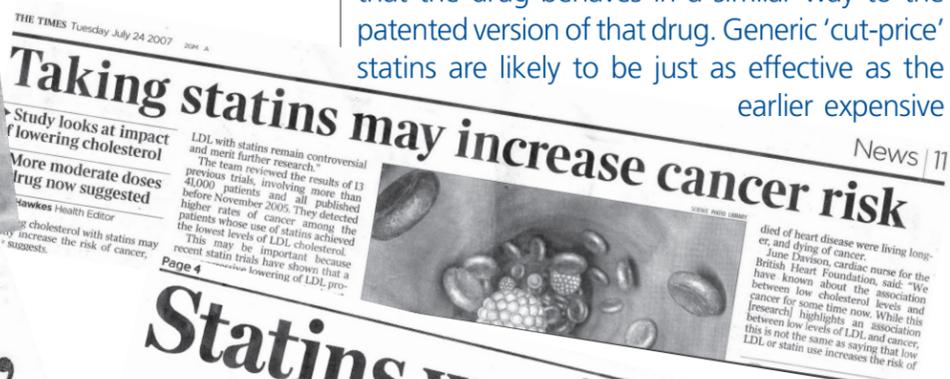
1. "Taking statins may increase cancer risk"

There is no evidence that statins increase the risk of cancer, but the article which prompted this particular headline was reporting an apparent relationship between low cholesterol levels and cancer in people on statins. Having

carefully looked at this article we believe the association and the analysis did not properly take account of peoples' age and came to the wrong conclusion. Much more reliable information comes from a combined analysis of 90 000 people who took part in various statin trials lasting about 5 years (published in the *Lancet*, a leading UK medical journal, in 2005). In these studies, a similar number of people developed cancer among those who took statins as among those who took dummy

Heart disease 'wonder drug' to save extra 10,000 lives

We know that statins do prevent heart attacks, strokes and the need for arterial bypass or angioplasty in a whole range of different types of patient (older and younger, men and women, high and low cholesterol, smokers and non-smokers etc). However, fewer older people and women were included in the statin trials than younger men, and so the information in these groups has been more limited, hence this sort of headline. Nevertheless, all the evidence points to women and older patients receiving just a similar benefit from statins as all other groups.



Statins won't prevent women getting heart disease, claim doctors

versions, and have the advantage that the money saved can be used for other things. So, there is no proper evidence to support the above statement, and there is overwhelming evidence that statins save lives.

4. "Statins may cause Parkinson's disease"

One small study suggested an association between low cholesterol levels and Parkinson's disease but this has not been replicated in larger studies. None of the good quality studies where people have been randomly allocated to take 5 years of a statin or a dummy pill have suggested a link between statin use and Parkinson's disease

Other Research at CTSU: *Do you know anyone with diabetes?*

As well as the HPS2-THRIVE study discussed on page 2, CTSU is also coordinating a large study in diabetes. People with diabetes are at slightly higher risk of circulatory problems (such as heart attacks and strokes) than people without. ASCEND (A Study of Cardiovascular Events in Diabetes) is a large national study supported by the British Heart Foundation which is investigating two treatments, aspirin and fish oils, to prevent the development of circulatory problems in people with diabetes.

ASPIRIN

There is very good evidence to support the use of aspirin in people who already have circulatory disease, but at present there is not enough evidence to support recommending aspirin for everyone with diabetes who doesn't have circulatory disease. Since aspirin occasionally causes bleeding, we need to know if the benefits of aspirin outweigh the risk. We are trying to provide the evidence so doctors can know whether or not

aspirin should be given routinely to people with diabetes without circulatory disease.

OMEGA-3 FATTY ACIDS ("fish oils")

It is thought that people who eat oily fish are less likely to develop heart disease. Recent guidance from the National Institute for Health and Clinical Excellence (NICE) recommends that people who have had a heart attack should eat at least 2 portions of oily fish per week, or in some instances, should take fish oil supplements. ASCEND is investigating whether taking omega-3 fatty acid supplements can prevent the development of circulatory problems in people with diabetes.

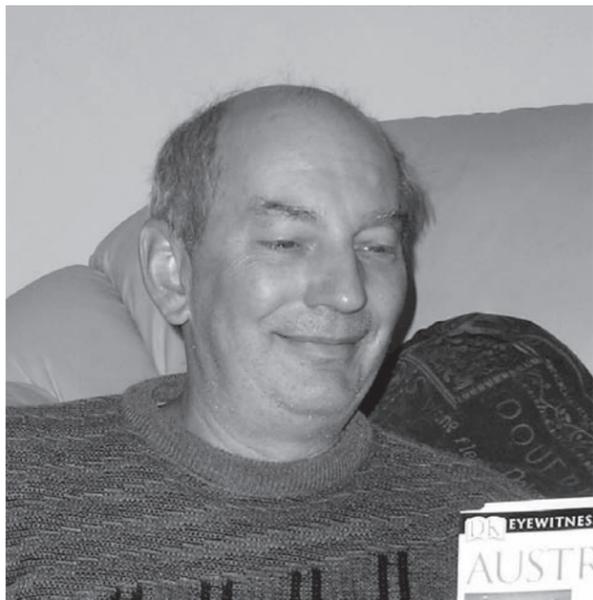
ASCEND is a study for people with diabetes who have not had heart disease or a stroke. Unlike SEARCH, there are no study clinics to attend. The treatments being assessed, aspirin and fish oils, do not need monitoring with safety blood tests. It is

therefore possible to run the study predominantly by mail, with backup from the 24 hour Freephone number for any medical advice needed in relation to the study.

As everyone currently taking part in SEARCH has previously had a heart attack (and most people will already be taking aspirin) you will unfortunately not be able to participate in ASCEND yourself, even if you have diabetes. However, if you have any friends or relatives over the age of 40 who have diabetes but who have not had a heart attack or stroke in the past, please tell them about ASCEND. If they are interested in helping with this important medical research study they can get more information from the study website (www.ctsu.ox.ac.uk/ascend) and can even register for the study there. They could also phone (Freephone) 0800 585323 and speak to one of the study team who could give them more details, and find out whether it would be a suitable study for them.



Bees in his bonnet



Leslie Stevens of Pontefract had a heart attack at the early age of 49. A senior manager in a Southampton-based frozen food company, he had come north to establish a new base in North Yorkshire. Since stopping full time work,

he has resumed many long-established hobbies and taken up others, some rather unexpected. Still only 58, Leslie first mentions flying, which he continues to enjoy even though he can no longer hold a pilot's license. For most private flyers, this might mean joy rides in a light plane, but Leslie had to repeat the name of his usual lift in case we had heard it wrongly. He flies in a Hawker Hunter, the jet fighter that was the mainstay of the RAF in the 1950s and early '60s. A friend owns a rare two-seat training version and for the price of half the fuel Leslie enjoys the ultimate Boy's Own experience of flight.

Back down on earth, Leslie's other activities include an allotment – there was mention of a fourteen inch runner bean in a national competition – and something he took up rather unexpectedly just two years ago. A

farming friend who kept bees was seriously ill and told Leslie that it was traditional for a beekeeper to hand his hives on to a person of his choice when he could no longer tend them himself. The friend had decided that Leslie was the man to look after his bees. Leslie honoured his friend's request and set about attending beekeeping courses and reading as much as he could about his new hobby.

While Leslie tends his bees and his allotment, or visits his mother on the south coast, his wife works as a staff nurse at a local hospital and his daughter, too, is a staff nurse at another hospital. So participation in SEARCH is probably a natural contribution to medical research for Leslie, though attending clinics must seem rather mundane compared to dealing with a swarm of bees, or hurtling through the air at just below the speed of sound.

Safety reminder: Some tablets increase the risk of muscle problems

Rarely, statins cause unexplained muscle pain or weakness, which is called 'myopathy' when it is accompanied by a significant increase in the muscle blood test called 'creatin 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 other statins. These are listed (with tradenames in brackets) 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 with care (when the increase in risk is smaller: Box 2). Some UK pharmacies buy their drug

supplies from outside the UK, in which case drug names may differ from those listed. If you are in any doubt about whether your SEARCH tablets react with any of your other medication, please ring the Freefone service (0800-585323) to check with one of the study doctors. In all cases, however, any unusual or unexplained muscle pain or weakness should be reported via the Freefone number as soon as possible

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, Sandimmun, SangCya)

For heart irregularities (arrhythmias):

- **Amiodarone** (Cordarone, Cordarone X, Amidox, Amyben)

For lowering cholesterol:

- Non-study statins: **Simvastatin** (Zocor, Zocor Heart-Pro, Simvador, Ranzolont, Simzal, Simlup, Lipex, Inegy)

Atorvastatin (Lipitor, Atorlip)

Fluvastatin (Lescol)

Pravastatin (Lipostat, Eptastatin, Pravachol)

Rosuvastatin (Crestor)

- "Fibrates":

Bezafibrate (Bezalip, Bezalip Mono, Bezagen XL, Liparol XL, Zimbacol XL)

Ciprofibrate (Modalim)

Fenofibrate (Lipantil, Lipantil Micro, Supralip, Fenogal)

Gemfibrozil (Lopid)

- High dose niacin: **Nicotinic acid** (Niaspan) more than 1 gram/day
Acipimox (Olbetam)

If you are prescribed any of these treatments, 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 assistance.

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, Tarka, Verapress, Vertab, Zolvera, Ethimil, Ranvera, Vera-Til, Geangin, Hypaneze)

For infections:

- **Erythromycin:** (also sold as Arpimycin, Erycen, Erymax, Erymin, Erythrocin, Erythroped A, Erythrolar, Erythromid, Kerymax, Tiloryth, Ilosone, Ilotycin, Retcin, Rommix, Primacine)

- **Clarithromycin:** (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):

- **Itraconazole:** (Sporanox)

- **Ketoconazole:** (Nizoral)

- **Miconazole:** (Daktarin)

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.

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.