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

British Heart Foundation

*Re*SEARCH

No 1 *Spring 2001*

The newsletter for people taking part in SEARCH

WELCOME TO *Re*SEARCH

Welcome to the first edition of *Re***SEARCH**, which has been specially written for volunteers taking part in SEARCH (Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine).

The idea of publishing *Re***SEARCH** has built up over time. Volunteers, study nurses and receptionists have all suggested that producing a newsletter once or twice each year would be a good way to keep everyone up to date about the study. It also allows us to explain any developments which may affect participants in the study.

We hope you find this newsletter interesting and helpful. Feel free to pen a letter to us if you have any ideas for things we should include in the next edition. Or if you have any questions about the study (other than about your own health, which would be better addressed to your own doctor) then be sure to let us know — the answer may help others, as well as yourself.

Please write to David Simpson, *Re***SEARCH** Editor, CTSU, Harkness Building, Radcliffe Infirmary, Oxford OX2 6HE (or ask any member of your local clinic staff to pass your letter on).

*David Simpson, Editor of Re***SEARCH** *— currently director of the International Agency on Tobacco & Health (IATH), and previously director of Action on Smoking & Health (ASH).*

HOW DOES THE STUDY WORK?

A brief reminder about how the study works. For the cholesterol-lowering part of the study, you will be taking one small tan tablet (containing either a standard 20 mg dose of simvastatin, or a similar-looking inactive substance called a "placebo") and one pink capsule-shaped tablet (containing either a larger 80 mg dose of simvastatin, or a matching placebo). Only one of these two tablets will really contain simvastatin — that is, by taking both tablets each day you would receive either 20 mg or 80 mg simvastatin.

In addition, for the vitamin-supplement part of the study, you will be taking one white tablet (containing either 2 mg folic acid plus 1 mg vitamin B_{12}, or a matching placebo).

Neither the study participant, nor any of the clinic staff, nor the participant's own doctor — nor even the doctors in Oxford who are coordinating the study — knows whether any particular participant is getting standard-dose or larger-dose simvastatin, or active or placebo vitamin-supplement. This information is known by just a few people and is kept confidential.

Doing a study in this way ensures that the results

– and why it is so important to keep attending the study clinics

are as free as possible from any bias. (It is called a "double-blind" study because neither study participants nor medical staff can see which type of study treatment any particular participant is on.) Of course, if it is considered medically necessary, a participant's own doctor or one of the Oxford doctors can always arrange for a participant's treatment to be "unblinded".

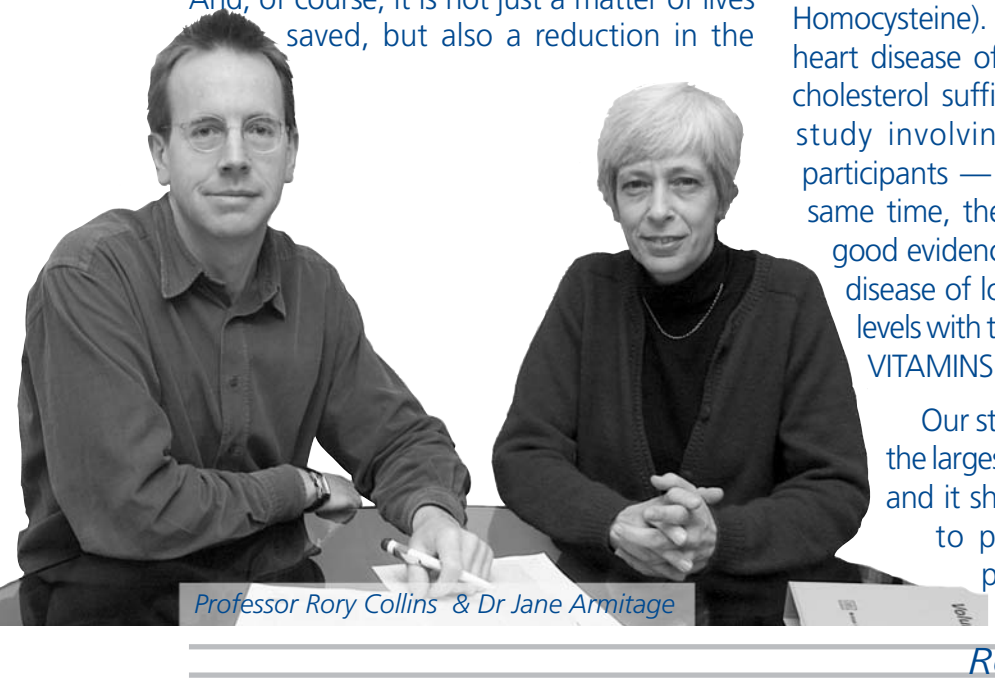
At the end of the trial, in about five years, we shall be able to work out which treatment, or combination of treatments, is most effective at preventing disease. But, again to avoid bias, it is important that we find out how each and every person who entered the study has got on. That is why we ask study participants to keep on coming back to the clinics regularly (at 2, 4, 8 and 12 months in the first year, and 6-monthly thereafter) even if, for some reason, they have had to stop taking their study tablets.

CTSU — WHO ARE WE?

The coordinating centre for SEARCH is based in Oxford University's Clinical Trial Service Unit (typically abbreviated to "CTSU"), which is located at the Radcliffe Infirmary in Oxford. The CTSU is one of the UK's best known medical research units, and it is supported by the British Heart Foundation, the Medical Research Council and the Imperial Cancer Research Fund. Not only does the CTSU coordinate SEARCH in all of the hospitals participating throughout Britain, but it also conducts several other major studies of the prevention and treatment of heart disease and cancer in the UK and elsewhere. Previous research by the CTSU has led to substantial improvements in health care, and this is preventing hundreds of thousands of unnecessary deaths (and much avoidable disability and misery) around the world each year.

A BIG, BIG "THANK YOU" FROM THE COORDINATORS

Heart disease is Britain's biggest killer. Even a small reduction in the number of people who suffer from it each year could save far more lives than a much larger reduction in the number who suffer from rare forms of disease. And, of course, it is not just a matter of lives saved, but also a reduction in the suffering and disability caused by heart disease.



Professor Rory Collins & Dr Jane Armitage

It is this simple fact — measuring a small change in a common disease — that underlies SEARCH (Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine). For, measuring the effects on heart disease of bigger reductions in blood cholesterol sufficiently accurately requires a study involving very large numbers of participants — more than 10,000. At the same time, the study will provide the first good evidence about the effects on heart disease of lowering blood homocysteine levels with the vitamin folic acid (see WHY VITAMINS?).

Our study — your study — is by far the largest of its type to be undertaken, and it should tell us a lot about how to prevent heart disease. As participants in the study will recall, during the first two months of the study you were invited to withdraw if you had any second thoughts or problems with study treatment or clinic attendance. If, following this initial period, you decide to continue, then **we really do want to see you regularly for the next five years or so to check on your health** — even if you stop taking the study tablets for some reason. (And, although you are free to stop study treatment at any time if you wish, we hope this won't be necessary as the study will be most informative if as few people as possible stop.)

We're very grateful to you for taking part in the study. By mid-2001 we expect that all 12,000 participants will have been recruited. With your continued cooperation we are going to get some really important answers that should benefit many people.

MANY THANKS!

Prof Rory Collins *Dr Jane Armitage*

WHO IS BEHIND THE SCENES — WHAT IS "*ROOM 13*"?

In the coordinating centre offices, based at the Radcliffe Infirmary in Oxford, there are about 20-25 people beavering away to make sure that the study runs smoothly on a day-to-day basis.

Staff in "Room13" (from the left): Sue Knight, Angela Radley and Cathy Hope

Most of you, at some time or another, will have had some reason to ring the Freefone number (0800-585323), either to change an appointment or to seek advice about matters relating to the study. The telephone service is known within the coordinating centre as "Room 13". That name has been used for about 20 years, dating back to the time when the research unit started running its first heart disease study and the telephone service was housed in the 13th room along a somewhat gloomy corridor.

In the current building the name has stuck. Mrs. Angela Radley and Mrs. Sue Knight (pictured here) lead a team of 4 staff who deal with all the appointment changes and refer queries to the central administrative and medical staff. The role of Room 13 is not only to handle calls about SEARCH but also to provide a similar service for about 20 other studies in which the unit is involved. Some of these studies are run directly by the unit, while some are run by other groups in the UK and around the world. As well as handling calls, the Room 13 staff also manage much of the data from the government-supported studies of the treatment of leukaemia in children and adults.

WHY VITAMINS?

Although a person's level of blood cholesterol affects their chances of having a heart attack, other factors (particularly cigarette smoking and high blood pressure) also play a part. Recently, raised levels in the blood of homocysteine (which is an "amino acid", one of the building blocks of proteins) have been found to be associated with increased risks of heart disease. Consequently, there have been suggestions that consumption of folic acid and vitamin B_{12}, which lower blood homocysteine levels, might help to protect against heart attacks. But, so far, this remains unproven.

Moreover, taking regular supplements of these vitamins may have little or no beneficial effect among people living in a country, such as Britain, where most get adequate amounts in their diet. It is also possible that long-term use of these vitamins could, on balance, be slightly harmful. But this, too, is unproven.

At present, therefore, it is not known whether these vitamins are of any importance in reducing the chances of having a heart attack. With your help, SEARCH will answer this question.

COMMONLY ASKED QUESTIONS AND ANSWERS

SEARCH clinics are now starting to arrange meetings for people taking part in the study —often including a spouse or friend as well. Usually a speaker will be invited, who in many cases is the local doctor involved in the study, and sometimes one of the coordinating team from Oxford will come along too. There has normally been lively discussion after the talks, and we hope that you find them helpful and informative (and fun!). For those of you who have not yet had the opportunity to attend one of these meetings, here are the answers to just some of the questions that people taking part in the study have asked:

Q Does it affect the study if I take other vitamins, cod-liver oil, garlic or other products bought at the chemist or health food shops?

A The only vitamin we ask you not to take large amounts of, in addition to the study treatment, is folic acid. Most multi-vitamins contain relatively small amounts of folic acid (approximately 100-200 micrograms), and so are OK to take.

Q What about other drugs (e.g. antibiotics, sleeping tablets, anti-depressants or arthritis tablets) that my own doctor might prescribe?

A Almost all other tablets and medicines are quite safe when taken with study treatments. When you come to the clinic for your follow-up visit, you will be asked what other medicines you are taking. If you are on a statin prescribed by your own doctor, a fibrate or high-dose niacin (for cholesterol-lowering), cyclosporin (generally following transplants) or nefazodone (for depression) then you will be asked to stop your study simvastatin tablets (but can still continue the white folic acid/placebo tablets). Most other medicines are fine, but it is as well to remind your own, or any other doctor, of your involvement in SEARCH when you are being prescribed new treatments. Carrying your SEARCH card may help to do this.

Q How do I know if the blood tests show anything abnormal?

A The blood sample taken at each clinic visit is used to measure one test of the function of the liver called an "ALT", and one test for muscle problems called a "CK". If either of these tests is significantly abnormal you will receive a letter from the coordinating centre asking you to come back to have it checked again. Usually the blood tests will have gone back to normal, but if not you may be asked to stop the study simvastatin tablets either temporarily or permanently.

Q Is the blood cholesterol level monitored during the study?

A No. The cholesterol level is not routinely measured, other than at the beginning when the result is sent to your own doctor. The reason for not measuring it after entry into the study is that, for those people taking the 80 mg simvastatin tablets, the cholesterol level will be lower than for those people who are taking the 20 mg tablets. This would "unblind" the treatment allocation. But as you will remember, we don't want you or the clinic nurse to know which dose you are taking, so that the study results are really reliable. If, however, your own doctor considers there is a good reason to measure your cholesterol then he or she is always free to do so.

Q How will I get to hear the results of the study?

A When the study results are available in about 5 years, we plan to write to people taking part in the study with the important findings.

Q At the end of the study will I be told which treatment I have been taking during the study?

A One of the aims of the study is to assess the **long-term** effects of the treatments being used. In general, therefore, we would prefer volunteers not to know which treatments they had been taking during the study. The reason for this is that information about what happens to people beyond the end of the study is likely to be most reliable if people are not routinely told which study treatments they were taking. In other words, if the study remains "blind". (But, of course, treatment after the end of the study would be determined by each person's own doctor — and may be influenced by the study results, irrespective of the treatments received during the study.)

Q If I take lots of exercise, begin to eat a healthier diet and stop smoking to reduce my risk of heart problems, will it affect the findings of the study?

A No. We encourage everyone to try to adopt a healthier lifestyle. With such a large study we anticipate that there will be similar numbers of people in the different treatment groups who will make such lifestyle changes. Consequently, such changes will not affect the study's ability to assess the effects of the study treatments.

Q Will the study tablets make me feel better?

A No. Neither of the treatments should make you feel any different. The study medicines are trying to prevent heart disease problems from developing. So, even if you feel no different, please keep on taking the tablets anyway!

John knows his onions

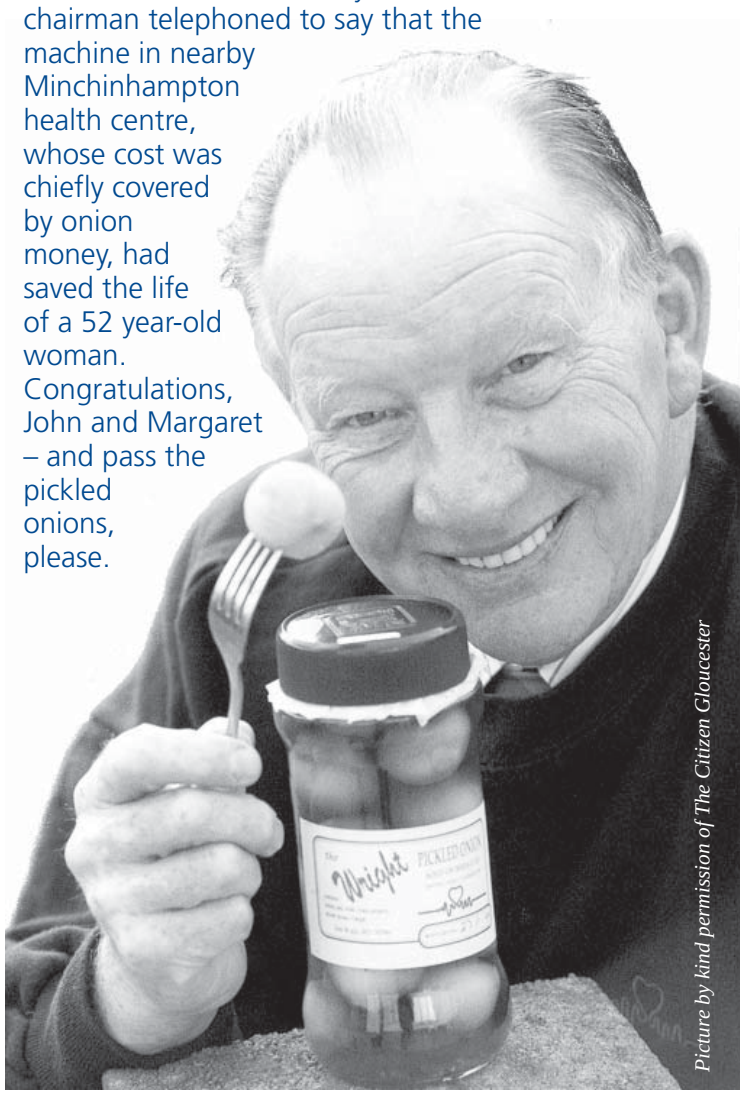
Visit John Wright of Stroud in Gloucestershire during the autumn, and you are likely to find him in a bit of a pickle – right up to the elbows in it sometimes. But before you jump to any wrong conclusions, let us explain.

John, 66, formerly a manager with British Telecom for 42 years, is a SEARCH volunteer whose local centre is at the Royal Hospital in Gloucester. John's story begins in 1990, when he felt a slight tightness in the chest while up a ladder, decorating the outside of his home. Feeling better quite quickly, he shrugged it off, though he remembers telling his wife, Margaret, that if he knew about first aid he would have thought that he had just had a heart attack. Unfortunately, he knew more than he thought he did, and later that day (after watching a football match in Cirencester) John found himself in an ambulance en route for Cheltenham, when his heart stopped. Paramedics applied a defibrillator, in effect giving his heart an electric shock to re-start it. The ambulance did a U-turn back to Cirencester to add a doctor to the team, who later commented that he reckoned John "had had about thirty seconds left on the clock" if it hadn't been for the defibrillator. Not surprisingly, a seed was sown - not exactly an onion seed, but the germ of an idea that would later involve the pungent vegetable.

Happily, John recovered and later took retirement. But he is a very active man, and has always kept himself busy with a wide range of activities, not least as a magistrate, and has worked on a long list of committees serving causes such as youth football, playing fields, and the British Legion. At home, too, he doesn't sit around much. For many years now he has had a date in autumn, usually in September, with a bag or two of onions. He would pickle a couple of pounds for his family and a few discerning friends, using his mother's old war-time recipe. After retirement, he decided to do a few pounds extra, partly just to make himself sit still a bit more. His daughter-in-law, another BT worker, sold them in the office. One day, while conveying the compliments of some satisfied customers, she asked if he had thought of pickling them for charity. This prompted the idea of turning onions into defibrillators.

After talking to his GP, whose surgery already had one of these life-saving machines, John went the local branch of the British Heart Foundation. They enthusiastically accepted his offer, and John's production line began to grow. Nowadays, in the three-month pickling season, John and Margaret buy, peel, wash, pickle, bottle and label as many as 900 kilograms of onions, or well over three quarters of a ton. The peeling process alone, which is entirely John's department, can wear out four pairs of rubber gloves. In keeping with the practice of Mrs Wright senior, if a glove is about to "throw in it's hand" it is turned inside out for continued ambidextrous service. To complete production, the onions are packed in jars that have been put through the dish-washer twice, with printed labels supplied by a fellow Justice of the Peace (with generous donations also provided by Sarcen's vinegar).

Offering the finished product to friends, family and other contacts in return for a small donation, John and Margaret have so far raised over £10,000. Most of this has been used to buy defibrillators for the British Heart Foundation, with another substantial sum sponsoring their son's boss to take part in a Save the Children yacht race (in that case raised from pickling eggs). Until not long ago, John was telling people that if one of the defibrillators his pickled onions helped to buy were to save someone's life, it would be all the proof needed that it had been worthwhile. Recently, the local BHF chairman telephoned to say that the machine in nearby Minchinhampton health centre, whose cost was chiefly covered by onion money, had saved the life of a 52 year-old woman. Congratulations, John and Margaret – and pass the pickled onions, please.



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Salt and blood pressure

Does salt intake in the diet matter? There has been a great deal of controversy around this question, but the answer is probably **"Yes"**.

As a person's blood pressure rises, so too does their risk of suffering a heart attack. Consequently, people who have had a heart attack are more likely to have high blood pressure. That is why so many of the volunteers taking part in SEARCH also take tablets to lower their blood pressure. In addition, many will have had advice to try to reduce the amount of salt in their diet.

The complex relationship between salt intake and blood pressure has been difficult to disentangle. Large international studies have shown that there is a bigger rise in blood pressure with age in populations who eat a lot of salt in their diet than in those populations who eat less salt. Moreover, reducing salt in the diet has been shown to reduce blood pressure both in people and in animals. This effect seems to be more marked among those starting with higher blood pressure (although some other types of people may also be more sensitive to salt intake).

The typical British diet contains much more salt than we really require: on average we eat about 9 grams (about a quarter of an ounce) of salt each day. The current recommendation from the government committee which advises about food intake is that this should be reduced by a third, to about 6 grams per day. (This is also sometimes expressed as a reduction from 150 mmols salt per day to 100 mmols per day.)

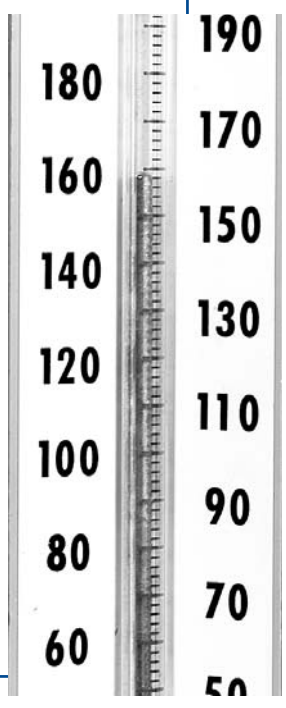
Common salt (sodium chloride) is added to many foods during the manufacturing process to add flavour, help consistency, and to prolong shelf-life. About three-quarters of the salt in the British diet comes from salt added to manufactured foods. This salt is not just in obviously salty foods (such as salted snacks), but also in bread, biscuits, soups, tinned products, cereals, and sauces. Bread is one of the most important sources of this "hidden" salt. So, food manufacturers will need to make changes if the whole population is to reduce their salt intake substantially.

Even so, for many people, it is easy and possible to eat less salt. This can be done by not adding salt during cooking, and by adding little or no salt at the table. Those people who are used to a lot of salt in their diet may at first find their food tastes a bit dull. But, slow reductions in salt intake soon lead to changes in the perception of saltiness: after a few months foods that previously didn't taste salty will do so.

Hypertension and blood pressure

Everyone who attends the SEARCH clinics will have had their blood pressure measured at some time or other. This is a measure of the pressure in the arteries created by the pumping of the heart. Two numbers are given to describe blood pressure. The higher figure ("systolic" blood pressure), usually given first, is the maximum pressure in the arteries created by each heart beat. The lower figure ("diastolic" blood pressure) is the pressure between each beat. The measurement is made in millimetres of mercury (mmHg) and represents the pressure that would support that height of a column of mercury.

Blood pressure is usually measured on the upper arm. A cuff is applied around the arm and squeezed until the blood stops flowing. The pressure in the cuff is then released slowly until the sound of the blood beginning to flow is detected. This is picked up either with a stethoscope or by an electronic sensor on automatic machines. The pressure at which the blood flow starts to be heard is the systolic blood pressure, and the pressure at which the sounds disappear is the diastolic pressure.



What is meant by hypertension?

Hypertension means having high blood pressure: "hyper" is the Greek word for "above", and" tensio" is the Latin word for pressure. It can be defined in different ways depending on what values of blood pressure are described as normal or abnormal. Usually blood pressure readings up to about 140/90 are considered normal and levels above 160/95 considered high. Using these definitions, hypertension is a very common condition — found in about 20% of the population as a whole, and in some 40% of volunteers taking part in SEARCH.

What is considered an acceptable blood pressure for an individual varies — but, in general, the lower the better. Levels of blood pressure vary during the day and are lower at night. Sometimes, when treatment is being considered, people have their blood pressure monitored throughout a whole day. This means that the daily average can be used to decide on whether or not treatment is necessary.

WHAT'S WHAT?

Even before you joined SEARCH, you may have become quite an expert in medical terminology. But, in case some of the terms are not too familiar, here's a brief guide:

Artery: one of the two types of blood supply pipes through which blood flows around the body. Arteries are the ones through which blood carrying oxygen, picked up in the lungs, supplies oxygen to muscles and other tissues throughout the body. (Veins bring the blood back to the lungs, where some of the body's waste products, such as carbon dioxide, are expelled as we breathe out.)

Angina: pain that people suffer as a result of heart disease (especially when they exert themselves), typically in the chest but also in the left arm.

Atherosclerosis: a fatty coating on the inside walls of arteries which narrows them. This is a bit like what happens when water pipes "fur up" in hard water areas, causing the water to flow too slowly or even stop flowing altogether.

Cerebral arteries: the name of the arteries that take oxygen-carrying blood to the brain.

Cholesterol: a type of fat present in the blood, which is a prime cause of atherosclerosis (see above) and, thus, of heart disease. The main purpose of SEARCH is to find out whether people who are liable to suffer from heart disease get more protection from bigger reductions in blood levels of cholesterol (using the drug simvastatin).

Clot: a blood clot is a solid mass of blood cells and proteins. Clots can get stuck in arteries, especially if these blood vessels are narrower than they should be because of atherosclerosis (see above). A clot that gets stuck like this can block the flow of blood: if this happens in a coronary artery it may cause a heart attack, and if it happens in a cerebral artery it may cause a stroke.

Coronary arteries: the name of the arteries that take oxygen-carrying blood to the heart muscle itself.

Coronary Artery Bypass Graft (sometimes abbreviated to CABG and pronounced "cabbage"): the operation in which blocked coronary arteries are by-passed, usually with veins taken out of the legs, to improve blood supply to the heart muscle.

Coronary (or ischaemic) heart disease: the disease in which the arteries supplying blood to the heart are narrowed by atherosclerosis (see above)— causing angina and, sometimes, a heart attack.

Cardiovascular disease: the whole range of heart and blood vessel diseases — including coronary heart disease, stroke and peripheral vascular disease.

Heart Attack (or myocardial infarction): this is what happens when the supply of oxygen-rich blood flowing through one or more of the coronary arteries to the heart muscle is cut off (which is why a heart attack is also sometimes called a "coronary"). Oxygen is needed to power all our muscles, including the all-important muscle of the heart. If the supply of oxygen is severely reduced, the muscle of the heart indicates this with pain, and then can malfunction or cut out.

Ischaemic (pronounced iskeemic): this means inadequate blood supply. Commonly used in the term ischaemic (or coronary) heart disease, which results from the blood supply to the heart's own muscle being restricted or cut off.

Myocardial Infarction: a more technical way of describing a heart attack. The myocardium is the heart muscle, and an infarct (or infarction) means that some of the muscle has died.

Percutaneous Transluminal Coronary Angioplasty (also known as "PTCA" or "balloon angioplasty"): this non-surgical alternative to a coronary artery bypass graft involves passing a long tube with a small balloon on the end through the blood vessels – usually starting in the groin – up to the coronary arteries. At the narrowing in the coronary artery the balloon can be inflated to get rid of the narrowing.Sometimes a small piece of metal, a "stent", is inserted to help keep the narrowing open.

Peripheral vascular disease: the disease in which the arteries supplying blood to the legs are narrowed by atherosclerosis (see above) – causing pain in the legs on walking (sometimes known as "claudication").

Stroke: the illness, usually involving loss of movement or feeling on one side of the body, caused by the blood supply in the cerebral arteries being blocked (called an "occlusive" or "ischaemic" stroke) or by a bleed into the brain (called a "haemorrhagic stroke; haemorrhage just means bleed).

Transient Ischaemic Attack (or TIA): this describes the effects of a temporary restriction of blood supply to the brain which causes symptoms that last less than 24 hours, and is like a mini-stroke (except that the symptoms of a stroke last for longer). Patients with a TIA may suffer a temporary loss or impairment of their sight.

Vascular: this is the word used to describe anything to do with either arteries or veins, the blood's pipework.

Vein – see under Artery

Taking other treatments with study tablets

Most prescribed and over-the-counter medicines can be safely taken with the SEARCH treatment. A few drugs, however, may occasionally lead to muscle pain when taken with the study simvastatin tablets (see the box on the right).

If you do suffer any **unusual or unexplained muscle pain or weakness** then let us know by contacting your local study nurse, or by ringing the Freefone number (0800-585323) and talking to one of the study doctors.

Muscle problems caused by the study cholesterol-lowering treatment can be detected by a simple blood test. This "CK" test can be done easily in the SEARCH clinic or by your general practitioner. A normal CK value would indicate that it is unlikely that the study tablets are affecting the muscles (in which case, some other cause may need to be looked for).

Names of drugs (typically used for particular medical conditions) that may interact with the study simvastatin tablets

Kidney and heart transplants: cyclosporin (Neoral, Sandimmun)
Depression: nefazodone (Dutonin)

Some types of cholesterol-lowering treatment:

- Non-study statins: atorvastatin (Lipitor), cerivastatin (Lipobay), fluvastatin (Lescol), lovastatin (Mevacor), pravastatin (Lipostat), and simvastatin (Zocor)
- 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), nicofuranose (Bradilan)

The study simvastatin tablets must be stopped if a participant's own doctor considers there to be a need for any of these treatments, but the white vitamin (or dummy) tablets can still be continued. Please call the Freefone number (0800-585323) if you want to discuss this with one of the study doctors.