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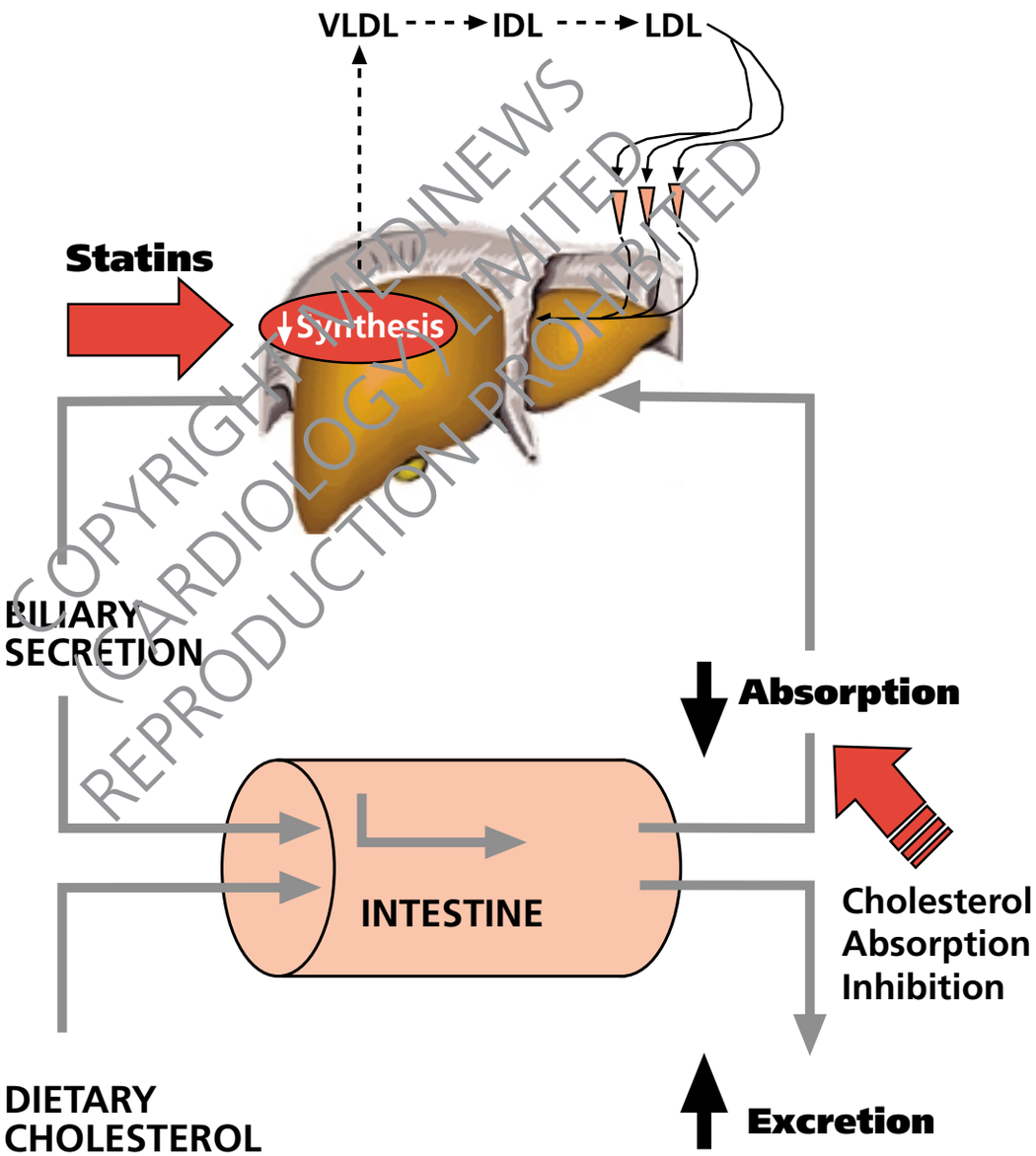


Abridged product information can be found on the back cover.

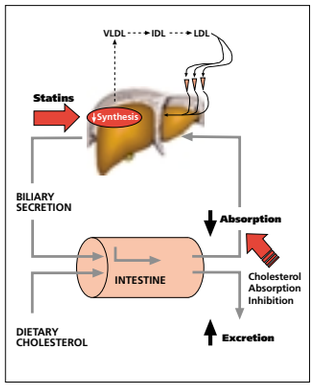
DUAL INHIBITION OF CHOLESTEROL ABSORPTION AND CHOLESTEROL SYNTHESIS

SUPPLEMENT 3
2004

THE BRITISH JOURNAL OF Cardiology

A NEW CLASS IN CHOLESTEROL MANAGEMENT

CONTENTS



Front cover: Dual inhibition of cholesterol absorption and cholesterol synthesis
(Credit: Dr Anthony Wierzbicki)

Editorial Office and Publishers
MediNews (Cardiology) Limited
3 Duchess Place,
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Tel: +44 (0) 121 454 4114
Fax: +44 (0) 121 454 1190
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Introduction

Participants at the meeting

Dr Howard Swanton	*Consultant in Cardiology, Cardiac Services Directorate, The Middlesex Hospital, London, (Chair)*
Professor James Shepherd	*Full Professor, Head of Department and Honorary Consultant in Pathological Biochemistry, University of Glasgow and Royal Infirmary, Glasgow, (Chair)*
Dr Mark Davis	*General Practitioner, Moorfield House Surgery, Garforth, Leeds*
Dr Alan Rees	*Consultant Physician in Endocrinology & Diabetes and Metabolism, University Hospital of Wales, Heath Park, Cardiff*
Professor David Wood	*Garfield Weston Chair of Cardiovascular Medicine, Imperial College London, London*
Dr Anthony Wierzbicki	*Senior Lecturer in Chemical Pathology, St Thomas' Hospital, Lambeth Palace Road, London*
Dr Harry Davis	*Distinguished Research Fellow, Cardiovascular/CNS Biological Research, Schering-Plough Research Institute, Kenilworth, New Jersey, US*
Dr Chris Allen	*Senior Medical Director, Merck/Schering-Plough, Whitehouse Station, New Jersey, US*
Professor Richard Hobbs	*Professor of Primary Care and General Practice, Department of Primary Care and General Practice, The University of Birmingham, Birmingham*
Dr Clive Weston	*Consultant Cardiologist, Singleton Hospital, Swansea*
Dr Elizabeth Hughes	*Consultant Chemical Pathologist, Sandwell General Hospital, West Bromwich*
Dr Adrian Brady	*Consultant in Cardiology, Glasgow Royal Infirmary*

Over the past 15 years, a number of randomised controlled trials have shown that lowering the low-density lipoprotein (LDL) cholesterol results in a reduction in coronary heart disease (CHD) events. There appears to be a continuous relationship between vascular risk and plasma cholesterol levels, with no lower threshold level.

We are not hitting lipid targets in patients who are at high risk of cardiovascular events. For example, EUROASPIRE II data show that 58% of coronary patients had not achieved a total cholesterol below 5 mmol/L despite intervention.

Statins are very successful in targeting cholesterol synthesis in the liver but we face the challenge of moving therapy back to the first-line organ in cholesterol metabolism, the gut.

The management of dyslipidaemia is likely to follow the example of hypertension. Better regulation of the lipid profile will be achieved using a combination of drugs that have actions on various parts of the cholesterol homoeostatic pathway.

Intestinal-acting cholesterol-lowering agents include the bile acid sequestrants, which have marked gastro-intestinal side effects; and the plant stanol and sterol esters, which lack selectivity and are expensive. Another agent is needed that is effective without these side effects of poor tolerability, lack of selectivity, non-compliance and expense.

Cholesterol absorption inhibitors, such as ezetimibe, target the exogenous cholesterol pathway. Their effects are complementary and additive to those of statins. Ezetimibe is a potent and specific inhibitor of dietary and biliary cholesterol absorption. It is also a cholesterol uptake inhibitor. It does not affect the absorption of bile acids or fat-soluble vitamins. Ezetimibe and its glucuronide metabolite circulate enterohepatically, which means that there is little peripheral exposure to these compounds.

In animal studies, ezetimibe has been shown to lower plasma cholesterol and to inhibit the development of atherosclerosis. In clinical studies, ezetimibe co-administered with low-dose statin may give an additional 10% reduction in triglycerides, 14% reduction in LDL, and a 5% rise in high-density lipoprotein (HDL) cholesterol compared to treatment with statin alone. In one study, significantly better NCEP goal reduction was achieved with co-administration of ezetimibe and statin compared to statin alone.

Coronary heart disease management in the UK

MARK DAVIS

Abstract

There are health inequalities in distribution of coronary heart disease (CHD). The National Service Framework (NSF) for CHD sets national clinical and organisational standards, defines service models, and establishes performance indicators. The four waves of the primary care collaborative have shown that, by offering structured and systematic care, secondary prevention can be improved. The basic remit of primary care trusts is to improve the health of their population, to provide access to appropriate services, and to integrate these services.

Key words: coronary heart disease, National Service Framework, primary care, primary care collaborative.

Br J Cardiol 2004;**11**(suppl 3):S2–S4

Mark Davis

Introduction

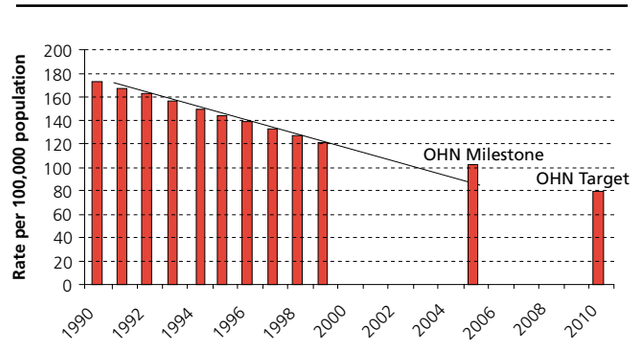
The management of coronary heart disease (CHD) in the UK is changing. Different primary care trusts will have different challenges: there are health inequalities in disease distribution, with greater CHD prevalence and mortality in less prosperous areas, and in interventions such as revascularisations.

The 'eternal rules of health systems' have been described by Uwe Reinhart, a Professor of Economics at Princeton. He says:

- All health services are currently undergoing reforms
- The last reform was a disaster
- Somebody somewhere is saying that the current reforms will be bad for patients
- Health ministers must have been bad people in previous lives, because to sort out any health service is a big challenge.

Figure 1 shows standardised mortality rates (SMR) for people under 75 since 1990. The 'Our Healthier Nation' target to reduce SMR is marked on the graph, and the changes that have been made mean that we will hit the target sooner than expected.

Figure 1. Standardised mortality rates (three-year averages for all persons under 75)



The NSF for CHD

Of particular importance was the National Services Framework for Coronary Heart Disease (NSF for CHD). This was a practical, evidence-based and flexible approach to tackling CHD. It sets national clinical and organisational standards, defines service models and establishes performance indicators.

Certain standards of the NSF for CHD are especially relevant to primary care. Standard 3 addresses secondary prevention and Standard 4 addresses primary prevention. Standards 11 and 12 are also relevant.

The initial priority for primary care was secondary prevention.

Moorfield House Surgery, 11 Wakefield Road, Garforth, Leeds, LS25 1AN.
Mark Davis, General Practitioner
Correspondence to: Dr M Davis
(email: markdavisbspa@aol.com)

Table 1. NSF implementation: Prevention/Health promotion

Improving diet and exercise

- School fruit scheme (250,000 children in 2,000 schools)
- Five-a-day pilots, NOF grants to 66 PCTs
- Nine Local Exercise Action Pilots in conjunction with Sport England and the Countryside Agency

Smoking

- Cessation clinics, NRT, buproprion
- Bill banning tobacco advertising now law

Figure 2. First wave practices – NPDT

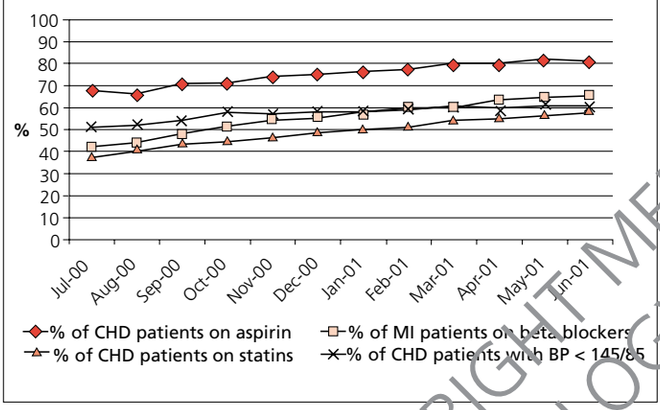
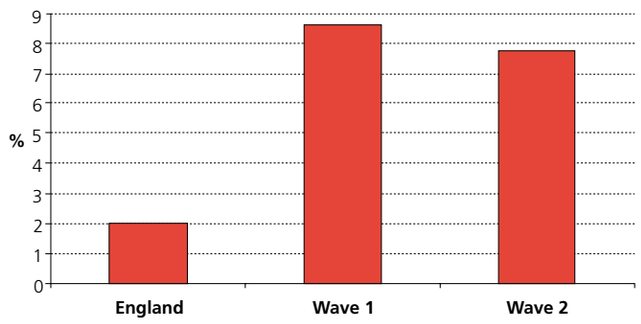


Figure 3. Percentage improvement in CHD deaths all ages over 12 months



There are both threshold targets and therapeutic targets for total cholesterol and low density lipoprotein (LDL) cholesterol, for example. At the moment, the aim is to lower the total cholesterol to < 5 mmol/L or by 20–25%, whichever is the lower. The equivalent figures for LDL cholesterol are 3 mmol/L or 30%.

Primary prevention is used to identify people who are likely to be at highest risk, especially those with hypertension or diabetes. A risk calculator is employed, and the blood pressure (BP) and cholesterol are treated to target as required. Patients are treated with cholesterol-lowering drugs if their 10-year risk of CHD is greater than 30%.

Great efforts are being made in the Department of Health to try to implement the NSF (table 1). All of these efforts should make an impact on the health of the community in the next 10–15 years.

Statin prescribing in the UK is rising exponentially, and statins are probably being prescribed appropriately. There are data on the prescribing for each strategic health authority based on standardised mortality rates: the general trend is that, the higher the disease burden, the higher the statin prescribing.

Primary care collaborative

One source of information about the prevention of CHD is the primary care collaborative. There have now been four waves, and about five million people are covered by the primary care collaborative. Figure 2 shows some of the secondary prevention achievements that have been made in the first wave practices, with each line representing a different intervention such as aspirin or post-MI beta blockers. Within these groups, it can be seen that by offering structured and systematic care, secondary prevention can be improved. This may well translate into a reduction in mortality and morbidity.

In July 2000, in the first wave practices, fewer than 40% of their secondary prevention patients were on a statin. This had risen to almost 70% two years later. Each of the succeeding waves started at a higher baseline and, by getting organised, was able to offer better care to their secondary prevention patients.

Looking at the change in CHD death rates within first and second wave practices during the first 12 months shows a greater reduction than the 2% reduction in England over that period. The numbers are small but the general trend is towards an improvement.

Figure 3 shows the percentage improvement in CHD deaths in all ages over 12 months. In England as a whole, there is a 2% reduction in CHD death rates. In first wave practices, they saw an 8–9% reduction, and in second wave practices an 8% reduction. By intervening with statins and controlling BP, a marked difference in mortality can be achieved.

Secondary care

A great deal more information has been obtained from hospitals than from primary care. The Myocardial Infarction National Audit Project (MINAP) looked at the door-to-needle time. Clearly, by getting organised and having systematic structured care and management support systems in place, the length of time taken to provide thrombolysis can be reduced. This, of course, reduces myocardial damage and improves outcomes.

There are also data to show that the use of secondary prevention measures such as aspirin, ACE inhibitors, beta blockers and statins in acute MI patients is improving (though they were already at quite a high level).

The government has put a lot of money and effort into reducing waiting times for coronary artery bypass graft surgery (CABG). Nobody is waiting more than 12 months now for a CABG, and it is now projected that the number of people waiting six months for a CABG is also falling.

The government has put its faith in primary care trusts. These are new managerial organisations and they are as yet unproven. Their basic remit is to improve the health of their population, to provide access to appropriate services, and to integrate these services. These integrated services are perhaps the most interesting aspect of all this because different ways of working will be needed. Each model of care will require some of the following:

- Appropriate care in an appropriate setting
- Multidisciplinary working
- Expertise within primary care
- Primary/secondary care interface
  - Care pathway
  - Diagnostic and treatment centres
  - Intermediate care
  - Complex care

We shall need more resources in primary care if these services are to be commissioned and designed. By March 2006, practice-based registers and systematic treatment regimes should also cover the majority of patients at high risk of CHD, and in particular those with hypertension, diabetes and a BMI > 30 kg/m^2.

The new contract

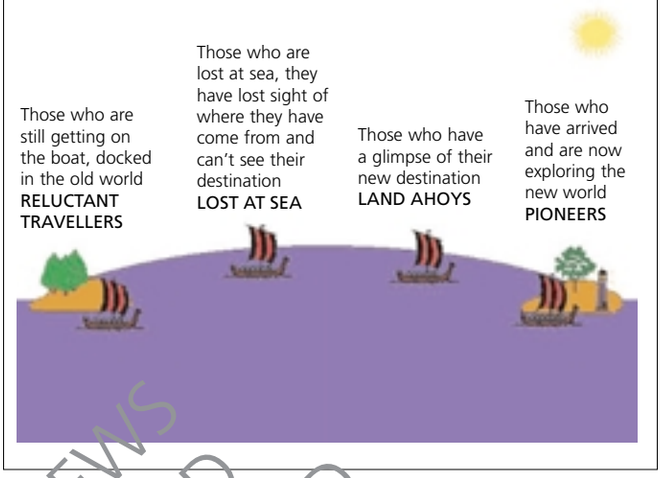
The new contract embraces core payments, quality payments and enhanced services. If this is accepted, then primary care will go forward.

There is much work to be done in building up morale. In internal NHS research on the NHS Plan, various groups of health workers were asked whether they liked the plan. Senior nurses, practice nurses and health visitors were all extremely positive; GPs and consultants thought that it was 'political fluff, unachievable, insulting, ambitious and Utopian'. Perhaps the truth lies somewhere in between.

People were also asked how long it would be before those working in the NHS will be able to deliver the aims of the NHS Plan in the form of some major improvements. Eighteen per cent of hospital doctors thought there would be change within five years, as did 11% of GPs – but more than half the hospital nurses thought it would make a difference.

It is very important in primary care that we seize the opportunity. Figure 4 is a pictorial representation of the journey that we make in, for example, facing changes in services. Some people, the pioneers, have already arrived in the Promised Land and are already devising and using new services. Others are still cowering behind their desks and have not yet set sail. Most of us are probably somewhere in the middle.

Figure 4. The journey in, for example, facing changes in services



Q: Where do you think you are personally, or where do you think your organisation is, on that journey?

A: (after audience vote) 41% are lost at sea, and 29% at the 'land ahoy!' stage.

Questions from the audience

Q: The CHD mortality was falling in the UK before the statins came in, wasn't it?

A: Yes, it has been falling for 20 years now. That is in part because of the sterling work of the cardiologists, but mainly because of changes in lifestyle. Thirty years ago, the CHD mortality in social classes 1 and 5 was much the same, but now there is a three-fold difference. The better educated people, living and working in a better environment, have changed their lifestyle and their mortality rate.

Q: What about giving up smoking? How successful have we been?

A: Before they were disbanded, the health authorities put in place people who were essentially smoking cessation counsellors. About 40% of smokers gave up for four weeks. By 12 months, the quit rate with counselling, nicotine replacement and other interventions is about 20%.

Q: Let us ask the audience. How many of you are smokers?

A: (after audience vote) That is about 13%, which shows how difficult it is to give up smoking.

Current strategies in the management of high cholesterol

ALAN REES

Abstract

Randomised controlled trials uniformly show that lowering low-density lipoprotein (LDL) cholesterol results in a predictable and consistent reduction in coronary heart disease (CHD) events. The Heart Protection Study showed that the relative risk reduction in major vascular events was consistent irrespective of the LDL level at baseline. There appears to be no lower threshold level. Trials show that the greater the reduction in LDL, the greater the CHD risk reduction observed.

The management of dyslipidaemia is likely to follow the example of hypertension, such that the effective regulation of the lipid profile will be achieved by combination drug therapy.

Key words: guidelines, Heart Protection Study, statins, combination therapy.

Br J Cardiol 2004;**11**(suppl 3):S5–S7

Alan Rees

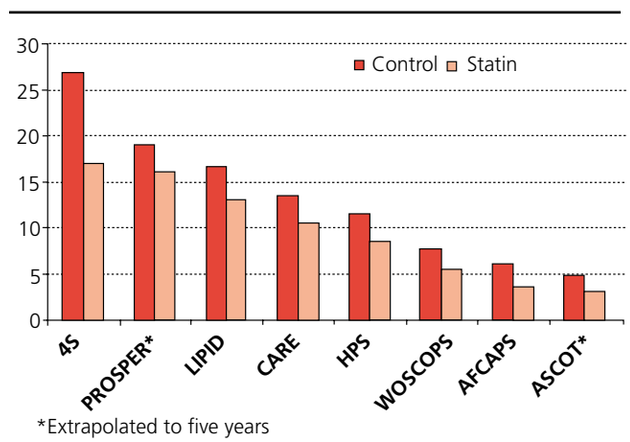
Introduction

The history of lipoprotein metabolism is a distinguished one. Hewson gave the first description of lipoproteins in 1771 in London: he discovered the lymphatic system and observed chylomicrons in lymph. Nearly 100 years later, Chevreul gave the first description of cholesterol in 1861 in Paris.

Our gold standard epidemiological data come from the Framingham study, which started in a small town outside Boston in 1949. A few years later, two pathologists discovered raised fatty streaks in the blood vessels of young American GIs who died during the Korean War. This discovery implied that it may take several decades to develop atheromatous plaques.

The first National Cholesterol Education Program (NCEP) guidelines, established in 1988, were based mainly on epidemiological data and data from Framingham. They were modified in 1993 with results from the regression studies and introduction of the statins. The third set of guidelines was introduced in 2001 after results from the randomised controlled studies such as 4S, CARE, LIPID and WOSCOPS and the move to global risk assessment. These guidelines will no doubt evolve further over the next 10 years as we learn more about the metabolic syndrome, lipoprotein A, homocysteine and apoB. A number of trials are due to report, including IDEAL, SEARCH and PROVE-IT: they will probably show that the further low density lipoprotein (LDL) cholesterol is reduced, the better.

Figure 1. Five-year major coronary events



*Extrapolated to five years

University Hospital of Wales, Heath Park, Cardiff, CF4 4XW.
Alan Rees, Consultant Physician in Endocrinology & Diabetes and Metabolism

Correspondence to: Dr A Rees
(email: alan.rees@uhw-tr.wales.nhs.uk)

Figure 2. CHD events in primary and secondary prevention trials

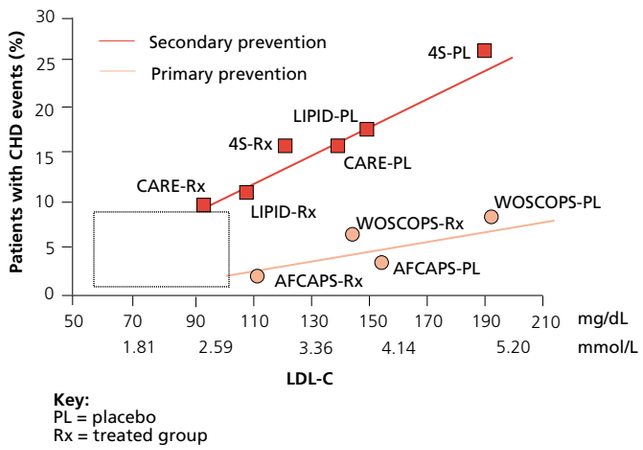


Figure 1 is a summary slide of a number of randomised controlled trials. They uniformly show that lowering LDL cholesterol results in predictable and internally consistent reduction in coronary heart disease events.

The Heart Protection Study

The Heart Protection Study (HPS) was published in the *Lancet* in July 2002. Interestingly, 33% of people at randomisation had plasma LDL below the current target of 3 mmol/L, and 20% had a total cholesterol below the current target of 5 mmol/L. The HPS showed that the relative risk reduction in major vascular events of 22–24% was consistent irrespective of the LDL level at baseline: even people with relatively low levels of LDL benefited from treatment with 40 mg simvastatin.

Figure 2 shows the number of people with coronary heart disease (CHD) events in the primary and secondary prevention trials according to their LDL levels. We do not yet have the data for very low levels of LDL, but the HPS suggests that it is probably a linear relationship.

In the ALLHAT lipid-lowering trial, which reported in December 2002, the benefit observed was proportional to the LDL lowering. In this trial pravastatin did not alter either the all-cause mortality or the CHD event rates. However, the patients included in this trial were older patients with well-controlled hypertension and moderately elevated LDL. There were modest differentials in total cholesterol and LDL between the usual care arm and the intervention arm compared to previous statin trials.

Table 1 shows the results of a number of recent intervention trials. It can be seen that the greater the reduction in LDL, the greater the CHD risk reduction observed.

Past and recent developments in the understanding of cholesterol management may be summarised thus:

- There appears to be a continuous relationship between vascular risk and plasma cholesterol levels.

Table 1. Change in LDL-C and CHD risk reduction

Trial	Control LDL mmol/L	Change in LDL mmol/L	LDL % ↓	CHD % ↓
GREACE	4.6	1.9	41	54
4S	4.9	1.7	35	35
WOSCOPS	5.0	1.3	26	31
AFCAPS	4.0	1.1	25	37
ASCOT	3.4	1.1	34	36
HPS	3.4	1.0	29	26
CARE	3.6	1.0	28	24
LIPID	3.9	1.0	25	24
PROSPER	3.8	1.0	27	19
ALLHAT	3.3	0.6	18	9

- There appears to be no lower threshold level
- Recent trial evidence supports the benefit of intensive cholesterol reduction
- Recent treatment guidelines suggest that even great cholesterol reductions may be beneficial
- Newer, innovative cholesterol-lowering drugs have been developed

Statins

Statin prescribing has increased enormously over the past few years as clinicians attempt to bring down elevated plasma lipids. However, clinicians in this country are very conservative in their prescribing. For example, simvastatin has been shown in the trials to be mostly effective at 20 mg daily (though the HPS used 40 mg daily). Despite this evidence base, 42% of prescriptions for simvastatin in the UK are for simvastatin 10 mg daily.

This reluctance to adopt evidence-based prescribing may be due to lack of awareness, lack of confidence, inertia, fiscal pressures or worry about side effects – though the statins are relatively well-tolerated drugs. Myopathy is a class effect: in preclinical toxicology it is observed with all statins, and in clinical practice it is observed with all statins but to different degrees. Its frequency is dose- and exposure-related, it is commonly the result of drug–drug interactions which elevate systemic levels, and there are predisposing factors such as age, hypothyroidism and exercise.

This conservative prescribing means that we are not hitting lipid targets. For example, EUROASPIRE II data show that 58% of all coronary patients had not achieved a total cholesterol below 5 mmol/L despite intervention.

Simvastatin came off-patent in May 2003 in the UK. With its genericisation, its cost will eventually come down and this may influence prescribing habits. Simvastatin is likely to become available over the counter in the next couple of years, another factor that will influence prescribing.

New approaches to lipid lowering include cholesterol absorption inhibitors such as ezetimibe. New drugs in development, such as the ACAT inhibitors, are perhaps a couple of years away from

the marketplace. And new statins include rosuvastatin, which has just been licensed.

Combination therapy

The management of dyslipidaemia is likely to follow the example of hypertension. The effective regulation of the lipid profile will be achieved by combination drug therapy such as statins with cholesterol absorption inhibitors. Pharmacotherapy will target different aspects of the lipid homoeostatic mechanisms. The big growth factor in the next 10 years will be drugs developed to raise high density lipoprotein (HDL) levels, as well as those to lower LDL. This approach will produce complementary, additive and perhaps synergistic benefits for the lipid profile.

Questions from the audience

Q: Do you have concerns about the use of high-dose statins, such as 80 mg simvastatin?

A: The number of people in my practice who require 80 mg simvastatin is extremely small, but I imagine that if you were to use a lot of high-dose statins then you would see a commensurate increase in side effects.

Q: I started using statins a long time ago but am put under pressure for using too much money.

A: If all the people who would benefit from statin therapy were to be prescribed statins, it would cost an enormous amount of money and would probably bankrupt the NHS. I think the government will be very keen, because of the tolerability of statins long-term, to see over-the-counter availability. There are a great many practical issues to be resolved, though.

Q: Why did you not mention HDL?

A: I had to be selective in my talk. HDL is an extremely important component of the lipid profile and it is probably the commonest dyslipidaemia in coronary care. Over the next 10 years we will be developing drugs to raise the HDL more than the statins. Fibric acid derivatives do that, and there is great interest in the combination of fibric acid derivatives and statins.

Q: Could you say something more about the mechanism of myopathy with statins?

A: The mechanism may have to do with glucuronidation. Myopathy is not an all-or-nothing phenomenon. There is mild myositis at one end of the spectrum and rhabdomyolysis at the other end. Aches and pains are common in clinical practice, and it is very difficult to distinguish between the aches and pains of everyday life and those caused by statins. Many doctors withdraw statins on the presumption that they are causing myopathy, thereby denying their patients the benefits of statin therapy. I want to know what the patient's CPK level is before attributing muscle aches to a statin. And because the intra-individual variation of CPK varies three or four-fold, CPK levels have to be 8–10 times the upper limit of normal before I stop a statin.

Changing goals and guidelines

DAVID WOOD

Abstract

The Joint British Societies guidelines on the prevention of coronary heart disease (CHD) are being revised. Target populations will be patients with any symptomatic presentation of atherosclerotic disease, whatever the vascular territory. The first-degree relatives of patients with premature cardiovascular disease also need to be targeted. Third, individuals at high multifactorial risk of developing cardiovascular disease need to be targeted.

New risk prediction charts are being produced. Patients with a cardiovascular risk of > 20% over 10 years (equivalent to a CHD risk of 15% over 10 years) will require investigation and treatment to blood pressure and lipid targets. Those with a cardiovascular disease risk below this threshold require lifestyle advice.

Key words: guidelines, coronary heart disease, cardiovascular disease, risk threshold.

Br J Cardiol 2004;**11**(suppl 3):S8–S10

David Wood

Introduction

In 1998, the British Cardiac Society joined forces with the British Hyperlipidaemia Association and the British Diabetic Association to publish joint guidance on the prevention of coronary heart disease (CHD) in clinical practice. The British Heart Foundation sent fact files on secondary and primary prevention to every GP in the country. Most important, the British National Formulary adopted the coronary risk prediction charts and reproduced them in colour in every version of the book. So the charts sit on the desk of every practitioner in hospital practice and general practice.

Patients with established CHD or with other symptomatic atherosclerotic disease were given top priority in this document. Such patients are at high risk of recurrent disease and of dying from this disease, and the evidence for modification of that risk is compelling.

The second priority is apparently healthy, high-risk individuals in the population with risk factors such as hypertension, diabetes or a family history of CHD. These individuals require risk-factor modification to reduce their risk of developing disease in the first place.

In these recommendations we tried to move forward the traditional model of thinking about the management of each risk factor in isolation, to thinking about the clustering of risk factors which puts an individual at high multifactorial risk.

Goals for prevention of CHD

We set lifelong goals regarding smoking, diet and exercise. We also set a blood pressure (BP) goal of < 140/85 mmHg, a total cholesterol goal of < 5 mmol/L, and low density lipoprotein (LDL) goal of < 3 mmol/L, and good glucose control in diabetes. Where these could not be achieved by changes in lifestyle, the use of appropriate antihypertensive and lipid modification therapies was recommended. The same goals were set for both priority groups – for patients with atherosclerotic disease and those at high risk of developing the disease.

The recommendations gave guidance on the use of prophylactic drug therapies such as antiplatelet agents, beta blockers, ACE inhibitors, cholesterol-lowering agents and anticoagulation. They recommended follow-up of close relatives of patients with premature coronary disease (that is, men under 55 and women under 65). The relatives should be screened for cardiovascular risk, and where familial dyslipidaemia is suspected.

Imperial College London, Fulham Palace Road, London, SW6 8RF.
David Wood, Garfield Weston Chair of Cardiovascular Medicine
Correspondence to: Professor D Wood
(email: d.wood@imperial.ac.uk)

Table 1. Target populations

- Patients with any symptomatic presentation of atherosclerotic disease
  - Coronary artery disease
  - Acute coronary syndromes
  - Angina pectoris
  - Cerebral arterial disease
  - Peripheral arterial disease
- First-degree relatives of patients with premature cardiovascular disease
- Individuals at high total (absolute) risk of developing cardiovascular disease

New British guidelines

These guidelines are being revised. Three aspects of this revision are discussed here: the target populations for prevention of coronary or cardiovascular disease; the risk thresholds for initiating antihypertensive or lipid-lowering medication; and treatment goals, specifically for cholesterol.

Target populations

There is enough new evidence since 1998 to target in the same way patients with *any* symptomatic presentation of atherosclerotic disease. Whatever the vascular territory, whether the patient presents with coronary disease or peripheral arterial disease or cerebral arterial disease, the disease is the same. These patients should all be treated as high risk and managed to the same BP and lipid targets. The first-degree relatives of patients with premature cardiovascular disease also need to be targeted. Third, individuals in the population at high multifactorial risk of developing cardiovascular disease need to be targeted.

Table 1 summarises the target population, as defined in the new guidelines. The commonest cause of death in patients presenting with cerebral or peripheral arterial disease is in fact coronary disease.

A coronary register in London identified all first presentations of CHD in the community in 578 cases. The first presentation of CHD in 14% of these patients was sudden cardiac collapse and death. The commonest manifestation of coronary disease is angina, with stable angina in 49% of these cases, and unstable angina in 8%. Thus, rapid access chest pain clinics are clearly important in tackling CHD.

We know that the first-degree relatives of patients with premature cardiovascular disease are at high risk themselves of developing cardiovascular disease compared to the general population. However, as physicians we frequently miss the opportunity to target and manage these high-risk individuals.

In EUROASPIRE II, we followed up the relatives of men who had presented with coronary disease under the age of 55, or women under the age of 65. The relatives were asked whether they had had any assessment of cardiovascular risk factors as a consequence of premature disease in their family. The answer was yes in only 10% of the siblings and 5–6% of the offspring. The answer was no in 43% of brothers, 53% of sisters, 69% of sons and 71% of daughters.

The development of the coronary risk prediction chart moved the concept of primary prevention from single risk factors such as hypertension, dyslipidaemia and diabetes, to multifactorial risk. It was recommended that individuals whose CHD risk exceeded 15% over 10 years should be treated with antihypertensive and lipid-lowering agents if they did not reach targets using lifestyle measures alone. Since targeting such a huge number of apparently healthy people is such an enormous job, a staged approach to primary prevention was proposed. First, those with an absolute CHD risk > 30% over 10 years would be identified and treated. As resources allow, this target could be progressively moved down to a CHD risk of 15% over 10 years.

The physician now needs to work out the patient's total risk of developing coronary or cardiovascular disease. Second, he needs to work out the components of that risk, which will vary between one person and another. Third, he needs to work out how the individual risk components are to be managed.

Risk thresholds

Risk thresholds for treatment currently stand at a CHD risk of 15% over 10 years for the general population. (Patients who present with symptomatic atherosclerotic disease or who come from families with premature cardiovascular disease do not require risk thresholds because they are already deemed to need intervention.)

The risk prediction charts have been changed from coronary disease to cardiovascular disease, and this is of relevance to the risk assessment of apparently healthy individuals. A CHD risk of 15% over 10 years is equivalent to a cardiovascular disease risk of > 20% over 10 years, and that will be the recommended risk threshold.

The new risk prediction charts, which will appear in the BNF, will only have two colours – orange and green. The patients in the orange area, with a cardiovascular risk > 20%, require investigation and treatment to BP and lipid targets, whereas those in the green area simply require lifestyle advice.

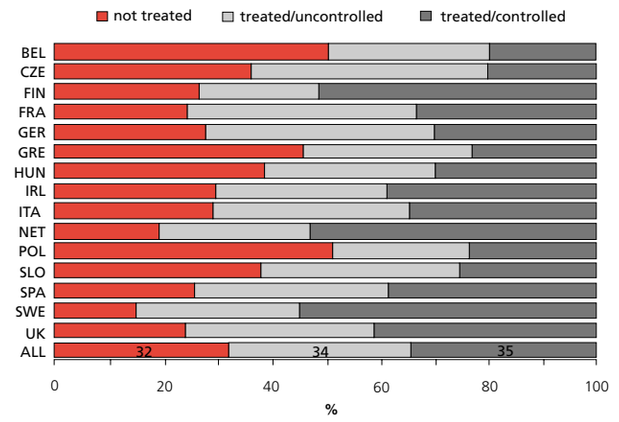
Treatment goals

The BP and lipid goals should be the same for each of the high-risk groups – patients with symptomatic atherosclerosis, relatives from families with premature disease, and apparently healthy individuals at high absolute risk.

Should a new and more challenging cholesterol target be set in the revised Joint British guidelines? There are two schools of thought about this. One view is that the scientific evidence since 1998, such as the Heart Protection Study, shows that there is benefit from lowering the cholesterol in high-risk patients below 5 mmol/L. As a result, lower total and LDL cholesterol targets should be set.

The other view is that meeting current targets is already very difficult. EUROASPIRE II data collected in 1999/2000 show that 58% of all coronary patients had not achieved the target of 5.0 mmol/L despite intervention. In the UK centres, 54% of

Figure 1. Control* of cholesterol at interview – by center



*among those with total cholesterol ≥ 5 mmol/L and/or taking lipid-lowering drugs

patients had not reached this target, though this was a big improvement compared to the first EUROASPIRE survey in 1995/6.

The proportion of patients achieving target improved dramatically between one survey and the next as a consequence of the almost doubling in the prescription of lipid-lowering drugs, principally statins, across Europe. The use of lipid-lowering drugs went from 32% to 63%. Figure 1 shows that 35% of patients are on lipid-lowering therapy and have reached the target; 34% are on lipid-lowering therapy but are not to target; and 32% have a total cholesterol above 5 mmol/L but are not receiving lipid-lowering medication. In analysing the data, it was found that the commonest reason for patients not achieving targets despite a prescription of a lipid-lowering drug was that these drugs are used at considerably lower dose than those used in the clinical trials.

Thus the new developments in the revision of the guidance are:

- Focus on cardiovascular disease as a whole, with all manifestations of atherosclerotic disease
- Concept of absolute multifactorial risk replaces traditional classification into primary, secondary and tertiary prevention
- Revised risk estimation model based on cardiovascular risk
- Revised risk treatment threshold of 20% over 10 years

Questions from the audience

Q: Should the absolute risk threshold for drug intervention in apparently healthy high-risk individuals remain at 30% CHD risk over 10 years or be lowered to 15% CHD risk over 10 years?

A: (after audience vote) 79% vote to lower the risk threshold to 15% CHD risk over 10 years.

Q: Should the target total cholesterol in patients with atherosclerotic disease remain at 5 mmol/L, or be lowered to 4 mmol/L?

A: (after audience vote) 72% vote to lower the target to 4 mmol/L.

Q: Should the target total cholesterol in apparently healthy high-risk individuals (> 15% CHD risk over 10 years) remain at 5 mmol/L, or be lowered to 4 mmol/L?

A: (after audience vote) 60% vote to lower the target to 4 mmol/L.

Q: In patients with type 2 diabetes, should absolute CHD risk determine whether to prescribe lipid-lowering therapy, or should all patients with type 2 diabetes be treated?

A: (after audience vote) 80% vote to treat all patients with type 2 diabetes.

Audience discussion

Q: If you are a non-smoking female, you are hardly ever treated with the present recommendations.

A: That is a very important point. We are doing patients a disservice: an absolute risk of > 30% over 10 years (among healthy individuals) is considerably higher than the risk for many patients with symptomatic atherosclerosis.

Q: At what sort of age would you start screening for atherosclerosis?

A: There is not a recommendation about that, except that if you think the family has FH then screening is justified at a younger age. Very few people in their twenties and thirties reach the risk threshold, but many have adverse lifestyles which will put them at risk in later life. One way of overcoming that is to project the risk calculated to age 60, to see whether they are on track to become high-risk patients.

Q: It would have been easier to take diabetes out of equation altogether, wouldn't it?

A: What we are talking about here is an arbitrary medical diagnosis of hyperglycaemia, classifying people into diabetes or no diabetes. In fact, glycaemia is continuously related to the risk of cardiovascular disease, just like BP and lipoproteins. It would be better to incorporate glycaemia into risk estimation and to forget about the notion of type 2 diabetes – but that is a controversial view.

Targeting multiple pathways in cholesterol management

ANTHONY WIERZBICKI

Abstract

There is a wide variation in plasma total cholesterol levels in populations that are genetically similar: these variations are driven by the environment. We absorb 40–50% of our cholesterol from the diet, and synthesise 50–60% in the liver. Cholesterol absorption inhibitors target the exogenous pathway of cholesterol absorption.

Agents that act on different pathways in cholesterol metabolism, such as statins and cholesterol absorption inhibitors, can be co-administered in an attempt to achieve complementary or synergistic effects on lipid control.

Key words: cholesterol, statins, stanols and sterols, bile acid sequestrants, cholesterol absorption inhibitors.

Br J Cardiol 2004;**11**(suppl 3):S11–S13

Anthony Wierzbicki

Introduction

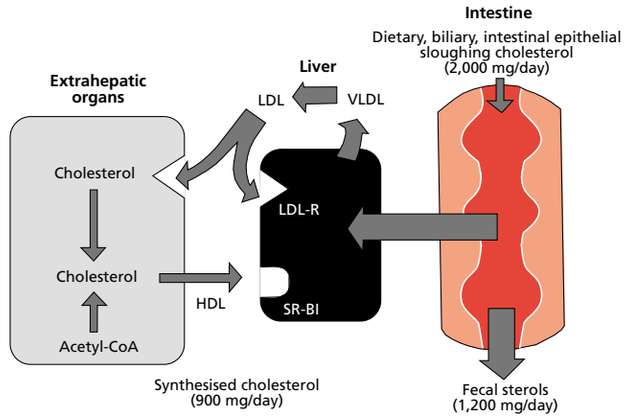
There is a wide variation in plasma total cholesterol levels in populations which are genetically similar. These variations are driven by the environment, and the food content of our diet needs to be considered carefully. Vegetarian diets lower low density lipoprotein (LDL) cholesterol by 1.0–1.5 mmol/L on average. Strict diet control can lower it by as much as 1.8 mmol/L. It is also possible to regulate the amount of cholesterol that you take up: the case of the Oklahoma egg addict was reported in the *New England Journal of Medicine* in 1991. He ate at least 25 eggs a day, which is about 2,500 mg cholesterol a day, and yet he maintained his total cholesterol at 6.2 mmol/L.

Cholesterol metabolism

There are two sources of cholesterol. The first-line organ in cholesterol metabolism is the gut. We absorb 40–50% of our cholesterol and we make 50–60% of our cholesterol in the liver, but the cholesterol that we synthesise in the liver is derived from saturated fat. Also, the liver absorbs cholesterol as chylomicrons, and repackages and secretes it as very low density lipoprotein (VLDL). Statins are very successful in targeting the liver but we face the challenge of moving therapy back to the first-line organ in cholesterol metabolism, the gut. For the past 20 years the intestine, the chylomicron production and the proteins that are stimulated by the presence of fatty acids or cholesterol in the gut have been neglected.

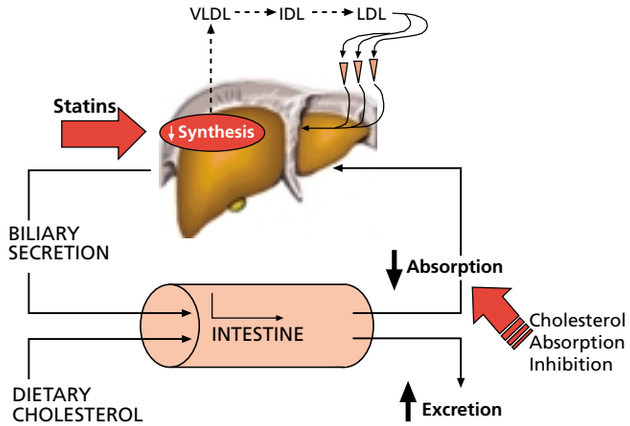
Cholesterol balance within the gut is quite complicated (figure 1).

Figure 1. Net cholesterol balance in humans



St Thomas' Hospital, Lambeth Palace Road, London, SE1 7EH.
Anthony Wierzbicki, Senior Lecturer in Chemical Pathology
Correspondence to: Dr A Wierzbicki
(email: Anthony.Wierzbicki@kcl.ac.uk)

Figure 2. Cholesterol absorption inhibition may be combined with statin treatment for broader lipid control



Daily cholesterol intake is about 300 mg but there is also a considerable amount of cycling of cholesterol between the gut and the plasma. Fecal sterols can add up to about 1,200 mg/day, and about 900 mg is synthesised. Breaking into that cycle could have a large effect on reducing cholesterol absorption and cholesterol levels. In addition, the efficiency of cholesterol absorption varies greatly between individuals (unlike the uniformly high efficiency of absorption of other lipids). Although cholesterol absorption depends partially on the baseline diet, there are both hyperabsorbers and hypoabsorbers. Again, this implies a potential for successful intervention.

There are various targets on which such a drug can act. One possibility is a sterol transporter: this protein has not yet been isolated but is believed to exist and to facilitate uptake of sterols by the enterocyte. The adenosine triphosphate-binding cassette transporters (ABC) pump cholesterol into the gut, and ABCG5 and ABCG8 are behind the rare disease sitosterolaemia, which leads to early coronary heart disease (CHD). Lastly, the ileal bile acid transporter (IBAT) facilitates reabsorption of bile acids in the terminal ileum. The bile acid sequestrants interfere with this pathway, and a new generation of agents to attack IBAT is in the pipeline.

Figure 2 is a diagram of the steps involved in cholesterol metabolism. It shows how agents that work on different pathways – in this case statins and cholesterol absorption inhibitors – can be combined in an attempt to produce complementary or synergistic effects on lipid control. It is the same principle used in the treatment of hypertension, most obviously with ACE inhibitors and diuretics.

Benefits of cholesterol absorption inhibition

Cholesterol absorption inhibition targets the exogenous pathway, which some patients may find a preferable proposition. Their effects are complementary and additive to those of statins. The co-administration of a statin and cholestyramine also works, but has disadvantages. The co-administration of a statin and a cholesterol absorption inhibitor may be helpful in achieving broader lipid control, with beneficial effects on high density lipoprotein (HDL) and triglycerides (TG). Cholesterol absorption inhibition offers a new and much needed additional approach within CHD prevention.

Table 1. Intestinal-acting cholesterol-lowering agents

- Surgery – POSCH trial
- Inhibition of bile acid reabsorption
  - Bile acid sequestrants (BAS)
    - Cholestyramine, colestipol, colesevelam
- Inhibition of cholesterol absorption
  - Plant stanol and sterol esters
  - Selective cholesterol absorption inhibitors
    - Ezetimibe

Table 1 shows the intestinal-acting cholesterol-lowering agents that may be used. The Programme On Surgical Correction of Hyperlipidaemia (POSCH) showed that LDL can be reduced by 35% after ileal bypass surgery. The other agents mentioned have their pros and cons but one definite advantage of ezetimibe is that it inhibits cholesterol absorption selectively, with no effect on the absorption of fatty acids or fat-soluble vitamins.

Plant sterol and stanol esters

The stanol esters lower LDL by 10–15% at best in trials. (There is no real evidence base about their influence on cardiovascular events.) They may interfere with the absorption of fat-soluble vitamins. The main problem is that their absorption is very low and, because they are put in foods, this makes them an expensive approach to lipid lowering for the patient. About 1% of patients taking them experience side effects.

Bile acid sequestrants

The bile acid sequestrants such as cholestyramine and colestipol can be quite effective in reducing LDL, averaging at about 20%. They raise HDL by about 3–5% but they may also raise TG. Their principal disadvantage is side effects such as gastro-intestinal distress and constipation: the bile acids are an irritant to the colon. Their other disadvantage is that they slow the absorption of almost all lipid-soluble drugs. This may result in difficulties with dosing of drugs and difficulties with spacing the various agents that the patient may require. There are some contra-indications to their use, including dysbetalipoproteinaemia and elevated TGs.

Two early trials, the LRC and Upjohn studies, showed that these agents do work. The LDL fell by about 20%, and CHD events also fell by 19–20%. A similar figure of a 1% LDL lowering equating to a 1% fall in CHD events is seen in the statin studies. Fibrates and surgery of the ileum also reduce LDL and CHD events. It is possible that any form of reduction will give long-term benefit – all we have to do is find a method by which we can do it which is well-tolerated by and acceptable to patients, and which is effective.

The limitations of bile acid sequestrants are:

- Non-compliance
- Poor GI tolerability
- Decreased absorption of fat-soluble vitamins
- Elevation of TG in patients with hypertriglyceridaemia

The limitations of plant stanol and sterol esters are:

- Lack of selectivity
- Some patients may find it difficult to incorporate them into their diet
- High dose and expense

Another agent is needed that does not have these side effects of poor tolerability, lack of selectivity, non-compliance and expense. It should be simple, well-tolerated, and given once a day.

It needs to be synergistic with the agents already in use because as lipid targets move lower, the effects of the statins are becoming exhausted and their usefulness is becoming limited by side effects.

In summary, cholesterol metabolism involves multiple, complex pathways. The current therapies work on the endogenous pathway and cholesterol synthesis, and ignore the exogenous pathway. Using logical combinations of treatments means that there is the possibility of very powerful lipid-lowering, and that the side effects caused by high-dose statins may be avoided.

Lastly, when a new drug class is introduced it may turn out to have other benefits. For example, we now know that lipid-lowering agents work not only on CHD but also in stroke and peripheral vascular disease. There may be some interesting discoveries as cholesterol absorption inhibitors are developed and introduced into clinical practice.

Questions from the audience

Q: There was a scare a few years ago that we could lower cholesterol too much and cause cancer. Do you think that is possible?

A: No. The immune changes in cancer activate cytokines and drop cholesterol levels. We are seeing the effect of the cancer manifesting itself on lipid levels, not the other way round.

Q: Do you use orlistat in your practice?

A: Orlistat does work, and we use it in treating some of our type 1 and type 5 hyperlipidaemias with very high TG levels. It inhibits about 30% of triglyceride synthesis in the gut and it lowers cholesterol by about 10%. However, it is very unpleasant to take, and only about 5% of patients are still on it after a year.

Q: What about diet in these patients?

A: All patients with raised cholesterol should receive lifestyle advice and be put on a diet. There are cases in the literature of people literally eating their way through the lowest doses of lovastatin. If patients eat what they like, the price is dose escalation of statins.

Ezetimibe – the first in a new class

HARRY DAVIS

Abstract

In animal models, ezetimibe has been observed to lower plasma total, chylomicron, very-low density lipoprotein (VLDL) and low-density lipoprotein (LDL) cholesterol levels.

It inhibits the development of atherosclerosis in ApoE knockout mice. In combination with statins in dogs, it reduces plasma cholesterol in a synergistic manner.

In a study in humans, treatment with ezetimibe gave a 54% reduction in absorption of cholesterol. There was a wide range of cholesterol absorption and drug activity among these individuals.

Key words: cholesterol absorption, ezetimibe, animal models, potency of action.

Br J Cardiol 2004;**11**(suppl 3):S14–S16

Harry Davis

Introduction

Cholesterol is a very insoluble molecule, and therefore it has to be made soluble before it can be absorbed. First it is emulsified with bile in the lumen of the intestine. Then it is transferred from the bile acid micelle to the brush border membrane. From there it is transferred to the endoplasmic reticulum and esterified by the enzyme ACAT. It then needs to be secreted from the basolateral surface and move into the lymph.

Ezetimibe has a low molecular weight, about 409 kilodaltons. It is an extremely potent and specific inhibitor of dietary and biliary cholesterol absorption.

Animal studies

The animal model that was used to screen for the compound was a seven-day, cholesterol-fed hamster model, dosed once daily. Over seven days, there is a 30-fold increase in cholesterol accumulation in the liver. There is a dose-responsive reduction in liver cholesterol ester levels with ezetimibe: the ED_{50} in this animal is 40 mcg/kg/day.

It was found to be extremely potent in cholesterol-fed Rhesus monkeys. At 3 mcg/kg/day, it totally inhibits cholesterol absorption.

In humans, biliary cholesterol represents far more intestinal cholesterol than is in the diet. About two-thirds to three-quarters of the cholesterol in the lumen of the intestine comes from the bile. Typically, people eat about 300 mg cholesterol a day and excrete about 1 g of cholesterol in the bile. Thus a greater effect can be expected from a cholesterol absorption inhibitor than from eating a zero-cholesterol diet.

It was necessary to find out where the cholesterol absorption was being blocked by ezetimibe. A simple cholesterol absorption model in rats was used – the animals are treated with ezetimibe and then given radio-labelled cholesterol in the lumen of the small intestine. The ezetimibe kept more than 90% of the cholesterol from entering the plasma.

On rinsing out the intestine, it became apparent that ezetimibe keeps the radio-labelled cholesterol in the lumen of the intestine: it keeps cholesterol from entering the enterocytes which line the intestine, and keeps it from entering the intestinal wall. So ezetimibe is not only a cholesterol absorption inhibitor but it is also a cholesterol uptake inhibitor.

Numerous absorption studies have been performed with ezetimibe. Unlike pancreatic lipase inhibitors (such as orlistat), it does not affect the intestinal hydrolysis of triglycerides or the absorption of fatty acids. Unlike bile acid sequestrants (such as cholestyramine), it does not affect the absorption of bile acids or fat-soluble vitamins.

Schering-Plough Research Institute, Kenilworth, New Jersey, USA.
Harry Davis, Distinguished Research Fellow, Cardiovascular/CNS Biological Research

Correspondence to: Dr H Davis
(email: harry.davis@spcorp.com)

Comparison of ezetimibe and bile acid sequestrants (resins)

- Ezetimibe does not inhibit the absorption of bile acids, whereas resins do
- Ezetimibe does not affect the absorption of fat-soluble vitamins, whereas resins sequester them
- Ezetimibe has no gastro-intestinal side effects, whereas the resins have tremendous gastro-intestinal side effects
- Ezetimibe is taken in milligram quantities, at any time of day, whereas gram quantities of resins are necessary, preferably at mealtimes
- Ezetimibe lowers plasma triglycerides by a modest amount whereas resins increase them
- Resins have poor compliance, whereas compliance issues are not anticipated with ezetimibe

Figure 1 shows the steps involved in cholesterol absorption, and the sites of action of various interventions. We know that ezetimibe blocks cholesterol absorption specifically at the brush border membrane of the enterocyte, at a step prior to its esterification by ACAT. It blocks both biliary and dietary cholesterol absorption.

The metabolism of ezetimibe is very simple. It has only one metabolite, its glucuronide, and it does not go through any cytochrome P450 metabolic pathways. This lowers the potential for drug/drug interactions with this compound, and patients who take lipid-lowering therapy will typically be on many drugs. In phase I studies, no drug/drug interactions with drugs that are metabolised by the cytochrome P450 pathways were found. Ezetimibe and its glucuronide metabolite are both potent inhibitors of dietary and biliary cholesterol absorption.

Potency and tolerability of ezetimibe

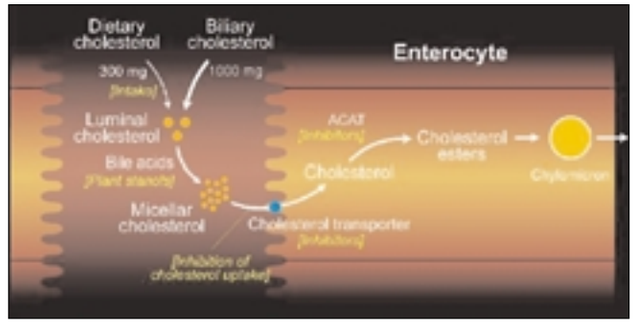
Ezetimibe undergoes rapid and extensive glucuronidation in the intestinal wall, and appears in the portal system and bile within minutes as the glucuronide. The glucuronide is itself a potent cholesterol absorption inhibitor.

Ezetimibe or its glucuronide circulate enterohepatically, repeatedly delivering the agent back to the site of action. There is very little peripheral exposure to these compounds, and ezetimibe appears to be extremely tolerable because the peripheral plasma levels are so low. Ezetimibe went through the entire preclinical toxicology programme without any issues. The half-life in humans is about 22 hours.

After ingestion of ezetimibe, its glucuronide goes into the portal plasma and then to the liver. It sits in the bile in the gall bladder. When the next meal is eaten, another load of ezetimibe is excreted into the lumen of the small intestine, where it localises at the brush border membrane of the enterocyte. This enterohepatic circulation is an ideal drug delivery system for a cholesterol absorption inhibitor.

Ezetimibe is a highly potent and specific inhibitor of cholesterol absorption. Its onset of action is rapid, in less than 90 minutes. It may act on a specific cholesterol or related plant sterol transporter: this is the subject of ongoing research. Extensive preclinical studies have shown that the mechanism of action of ezetimibe is unlike that of resins, plant sterol margarines, statins or fibrates.

Figure 1. Inhibition of cholesterol absorption



Once the cholesterol is absorbed, it forms a chylomicron particle, which is triglyceride-rich with cholesterol ester. As the chylomicrons enter the circulation, the triglyceride is hydrolysed by lipoprotein lipase. The chylomicron remnant takes up ApoE particle, which is the ligand for the LDL receptor for the chylomicrons to be cleared. These chylomicron remnants are very atherogenic as well; they may be deposited into the artery wall to form atherosclerotic plaques.

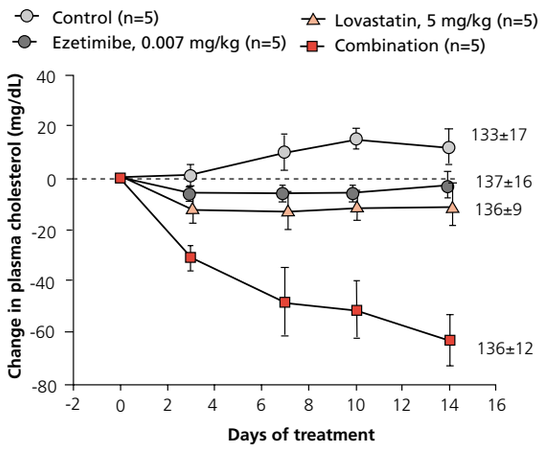
The effect of ezetimibe on chylomicron composition was examined, using a very close analogue of the agent. Monkeys were fasted overnight and fed a single high-cholesterol, high-fat meal with or without the cholesterol absorption inhibitor. Five hours later the composition of the chylomicrons was analysed. The chylomicron particles in the monkeys treated with the ezetimibe analogue were depleted of cholesterol ester and free cholesterol, but there was no effect on triglyceride absorption.

In a parallel study, it was found that the ezetimibe analogue had no effect on the number of chylomicrons, but that it depleted them of their cholesterol content.

The effect of ezetimibe was studied in the ApoE knockout mouse, which is a model of atherosclerosis. Without ApoE, these mice do not clear the chylomicron remnants and they become very hypercholesterolaemic. Three different diets were administered: a Western diet, a low-fat diet containing cholesterol, and an absolutely cholesterol-free diet. Ezetimibe reduced the very low density lipoprotein (VLDL) and chylomicron remnant cholesterol in all groups by greater than 80–90%. The low density lipoprotein (LDL) cholesterol was reduced by about 50%. The atherosclerosis was quantitated in these mice. Ezetimibe inhibited by more than 90% the development of atherosclerotic plaque.

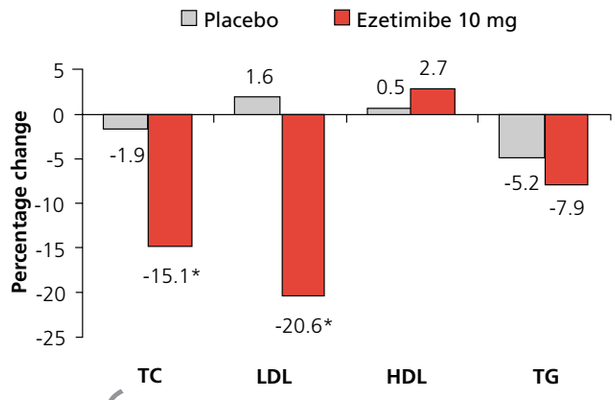
In animals fed diets without cholesterol, ezetimibe has fairly modest effects on plasma cholesterol levels, lowering them by about 15–20%. Since ezetimibe reduces the delivery of cholesterol to the liver, it leads to the reduction of hepatic cholesterol stores and the upregulation of hepatic HMG-CoA reductase activity. Since statins block HMG-CoA reductase activity, ezetimibe should work in a complementary fashion to the statins. Theoretically, plasma cholesterol should be lowered via a dual mechanism inhibiting both absorption and synthesis of cholesterol.

Figure 2. Ezetimibe + lovastatin lowers plasma cholesterol in chow-fed dogs in a synergistic manner



Davis *et al. Metabolism* 2001;**50**:1234-41.

Figure 3. Cholesterol absorption study results



*p<0.001 *vs.* placebo

Key: TC = total cholesterol; LDL = low density lipoprotein cholesterol; HDL = high density lipoprotein cholesterol; TC = triglycerides

Studies were performed in dogs to investigate this possibility. In dogs, neither lovastatin 5 mg/kg nor ezetimibe 7 mcg/kg had an effect on plasma cholesterol on its own. However, when the two agents were given together, there was a greater than 50% synergistic reduction in plasma cholesterol levels within two weeks (figure 2).

In summary, in animal models, ezetimibe:

- lowers plasma total, chylomicron, VLDL and LDL levels in cholesterol-fed animals
- inhibits the development of atherosclerosis in ApoE knockout mice
- in combination with statins in dogs, reduces plasma cholesterol in a synergistic manner

These results suggest that, in patients with hypercholesterolaemia, ezetimibe in combination with a statin should produce additional reductions in plasma cholesterol levels.

Human cholesterol absorption study

A human cholesterol absorption study was carried out in Germany. Young male mildly hypercholesterolaemic individuals were given ezetimibe 10 mg a day, or placebo, for two weeks and then crossed over. The cholesterol absorption studies were done during the ezetimibe treatment phase, and they acted as their own controls under placebo treatment. A continuous feeding, dual-isotope method was used.

On average, the placebo group absorbed 50% of their cholesterol, and in the ezetimibe group cholesterol absorption was reduced by 54%. There was a range of both absorption and activity. Under placebo, individuals absorbed anything from 20% to 80% of the cholesterol. In some individuals, ezetimibe did not reduce cholesterol absorption very much, but in one there was > 90% reduction in cholesterol absorption.

Figure 3 shows the mean percentage changes in plasma lipid and lipoprotein concentrations after two weeks of treatment with ezetimibe. Compared to placebo, there was a 15% reduction in total cholesterol; a 20% reduction in LDL; an 8% reduction in triglyceride; and a 3% rise in high density lipoprotein (HDL).

Whole body cholesterol synthesis rates were measured in this study by two techniques. A fecal balance method showed that whole body cholesterol synthesis was increased by about 89%, and another method using lathosterol to cholesterol ratios showed that whole body cholesterol synthesis was increased by about 72%.

When you take ezetimibe, the cholesterol content of the liver is reduced, which should increase the numbers of LDL receptors, and LDL cholesterol levels fall. Also, there is increased cholesterol synthesis in the liver. If ezetimibe is combined with a statin, then the statin will block this increase in cholesterol biosynthesis, and plasma LDL cholesterol levels should in theory decrease even further.

In summary, then, cholesterol absorption inhibition by ezetimibe can be combined with other agents, such as statins, for additional lowering in LDL levels. This type of combination offers clinicians the potential for broader lipid control, enabling more patients to achieve effective lipid lowering.

Questions from the audience

Q: Why do some people absorb more cholesterol than others?

A: There are many factors that affect cholesterol absorption, such as the type of bile acid that you produce. We are also searching for the putative cholesterol transporter.

Q: Theoretically, if you could target the patients who absorbed the most cholesterol, they would be the ones to receive ezetimibe, wouldn't they?

A: That is right, because theoretically they would be the best responders.

Ezetimibe – maximising cholesterol reduction through dual inhibition

JAMES SHEPHERD

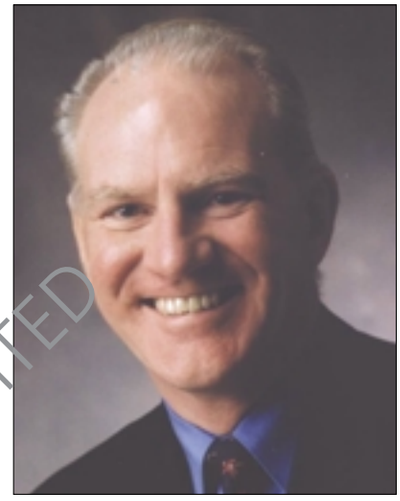
Abstract

Statins cannot always bring plasma lipoprotein levels to target because they only attack one element of the cholesterol homoeostatic pathway. By inhibiting cholesterol absorption as well, using ezetimibe, additional benefits may be obtained. Ezetimibe co-administered with low-dose statin may give an additional 10% reduction in triglyceride, 14% reduction in low-density lipoprotein (LDL) cholesterol, and a 5% rise in high-density lipoprotein (HDL) cholesterol compared to statin alone.

In one study, significantly better National Cholesterol Education Program goal achievement was seen with co-administration of ezetimibe and a statin compared to statin treatment alone. Ezetimibe plus a statin is generally well tolerated.

Key words: ezetimibe, statin, cholesterol target, lipoprotein control.

Br J Cardiol 2004;**11**(suppl 3):S17–S20



James Shepherd

Introduction

It is not as easy as the literature might suggest to reach lipid targets. We tend to be cautious with the drugs that we have, partly because we are worried about side effects, and partly because we do not want to push up the doses. The new approach using ezetimibe in combination with other agents means that doctors can achieve powerful cholesterol reduction without increasing the dose of the statin.

The gold standard for managing vascular risk is to suppress cholesterol production, especially in the liver. The statins do that, but even with the maximum dose of statins, patients do not necessarily reach their cholesterol target. Some statins bring down low density lipoprotein (LDL) by 35–40% at maximum dose, and rosuvastatin will achieve up to 50–60% LDL reduction at maximum dose.

We cannot bring down cholesterol as far as we want with the statins because they only attack one element of the cholesterol homeostatic pathway. Every day, we not only generate substantial amounts of cholesterol in our liver but we also absorb significant amounts from the diet and from secretion of cholesterol in the bile. If we were able to block cholesterol synthesis (with statins) and inhibit cholesterol absorption, we would have two complementary ways of bringing cholesterol levels down. Until now, no-one has been able to get a handle on blocking cholesterol absorption.

We should be able to lower LDL levels further because we are inhibiting the input of cholesterol from the diet for very low density lipoprotein (VLDL) synthesis, and we are also promoting the removal of cholesterol from the bloodstream in the form of LDL by activating LDL receptors with statins.

When ezetimibe was first examined in clinical studies, it was clear that even if you block cholesterol absorption maximally, you would typically only lower the level of cholesterol in the bloodstream by about 20%. Thus the option had to be considered of giving ezetimibe with other drugs. It has been studied in combination with the whole range of statins.

Clinical programme

Clinical trials were set up to address various questions about ezetimibe:

- Would there be any pharmacokinetic interaction with statins?
- Would ezetimibe work in combination with a statin?

University of Glasgow and Royal Infirmary, Glasgow, G4 0SF.
James Shepherd, Full Professor, Head of Department and Honorary Consultant in Pathological Biochemistry

Correspondence to: Dr James Shepherd
(email: jshepherd@gribiochem.org.uk)

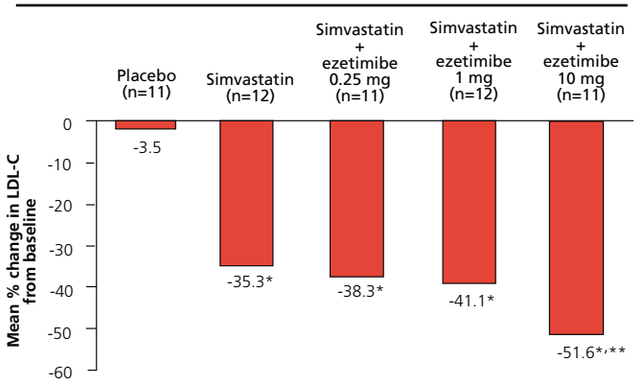


Figure 1. Combined ezetimibe/simvastatin therapy. PK/PD co-administration study

*p<0.01 *vs.* placebo
**p<0.01 *vs.* simvastatin 10 mg

Adapted from Kosoglou T *et al. Br J Clin Pharmacol* 2002;**54**:1-16.

Table 1. Ezetimibe/statin co-administration

Statin	Statin alone (pooled results)	Combination Ezetimibe plus statin (pooled results)	Δ	p value
Lovastatin	-24.7±0.9% n=220	-39.0±1.0% n=192	14.3%	p<0.01
Simvastatin	-36.0±0.9% n=263	-49.9±0.9% n=273	13.9%	p<0.01
Pravastatin	-24.3±0.9% n=205	-37.7±0.9% n=204	13.4%	p<0.01
Atorvastatin	-42.4±1.0% n=248	-54.5±1.0% n=255	12.1%	p<0.01
Pooled – any statin	-31.9±0.5% n=936	-45.2±0.5% n=924	13.3%	p<0.01

- Could consistent, incremental and favourable effects on the lipid profile be shown?
- Could the combination of statin plus ezetimibe produce greater reductions in cholesterol than either agent given on its own?
- Could patients achieve lipid targets on lower doses of statins, in combination with ezetimibe?
- How well tolerated is ezetimibe?
- Would the combination of statin plus ezetimibe be better tolerated than high-dose statin monotherapy?

In one study, simvastatin alone was given to individuals at a dose of 10 mg, and the plasma concentration was measured over 24 hours. The peak level of simvastatin occurs after about two hours. Then ezetimibe in doses of 0.25 mg, 1 mg and 10 mg was coadministered with the statin. There was no interaction between simvastatin and ezetimibe in relation to their pharmacokinetics, and no difference in the peak plasma concentration of simvastatin. Data from all the other statins show the same thing: there is no ezetimibe/statin interaction of any consequence that will change the level of either agent in the plasma.

Figure 1 shows the reductions in LDL in individuals given simvastatin plus incremental doses of ezetimibe. With the statin alone, there is about a 35% reduction in the plasma LDL level. When a 0.25 mg dose of ezetimibe is added to the statin, a 38% reduction is seen. With coadministration of 10 mg ezetimibe and 10 mg simvastatin, there is a 52% reduction in LDL. Thus ezetimibe, when added to a statin, can increase the LDL reduction by 15–20% compared to that given by the statin alone.

Factorial studies

Four phase III factorial studies were set up to examine in greater detail the potential of giving the combination of statin plus ezetimibe. They were multicentre, double-blind, randomised and placebo-controlled. The LDL at entry had to be 145–250 mg/dL, which is about 3.8–6.5 mmol/L, and the triglycerides (TG) had to be below 350 mg/dL (4.0 mmol/L).

If individuals were receiving a statin at the beginning of the study, they had a 10-week washout period and were then stabilised on a National Cholesterol Education Program (NCEP) diet. If, after four weeks, they were compliant with the drug therapy and taking the diet, they were given a blinded 12-week drug treatment study.

During this study period they took two tablets. Some individuals had two placebo tablets, while others had placebo and ezetimibe 10 mg. Some had statin 10 mg plus placebo, and others statin 10 mg plus ezetimibe 10 mg. Individuals might take a statin at 20 mg, 40 mg or 80 mg plus either placebo or ezetimibe. The maximum dose for atorvastatin and simvastatin was 80 mg, and for pravastatin and lovastatin it was 40 mg. The primary comparison was ezetimibe plus statin versus statin alone, and determination of the overall treatment effect. The secondary comparisons were pairwise comparisons between the treatment arms. A total of 2,382 patients were enrolled, so there were roughly 65 patients in each treatment group.

Table 1 shows the pooled results for the different statins, alone and in combination with ezetimibe. If you put all doses of lovastatin together, for example, LDL is reduced by about 25%. If you add ezetimibe to that, LDL is reduced by a further 14%. With all the statins, adding ezetimibe made a highly significant difference.

Further, a comparison of the LDL changes shows that the same benefit is achieved with the statins at their highest dose or with a low-dose statin plus ezetimibe.

Similar benefits are seen in relation to high density lipoprotein (HDL). For instance, lovastatin 40 mg gives an 8% increase in HDL level, and the lowest dose of lovastatin in combination with ezetimibe gives at least that beneficial incremental change in HDL. Similar results are seen with pravastatin and atorvastatin. There is also a similar reduction in plasma TG for the high-dose statin alone or the low-dose statin plus ezetimibe.

Thus physicians have the options of using the high-dose statin

Figure 2. Ezetimibe plus statin combinations: the effects on lipids

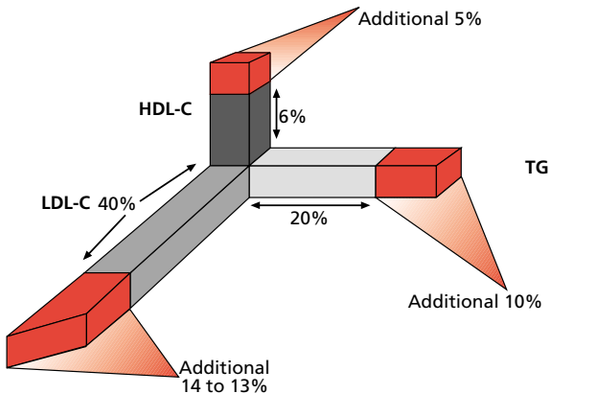
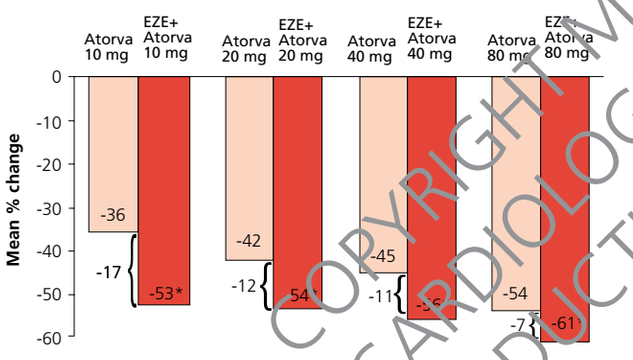


Figure 3. Ezetimibe plus atorvastatin study. Mean percentage change from baseline to end point in LDL



*p<0.01 Combination versus statin alone

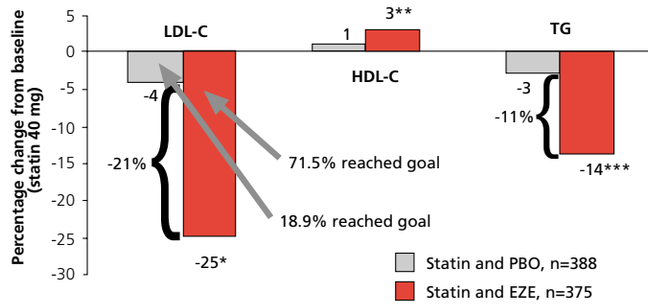
all the time; starting with low-dose statin and uptitrating the statin until the desired LDL level is reached; or giving the lowest dose of the statin plus ezetimibe and achieving the same result, or even better.

Figure 2 summarises the effects on lipids of adding ezetimibe to a statin. For example, you will achieve about a 20% reduction in TG with the average statin, and by adding ezetimibe you will achieve a further 5–10% reduction. So ezetimibe co-administered with low-dose statin offers broader lipid control than that achieved by increasing the dose of statin alone.

Ezetimibe plus atorvastatin study

Some patients have extremely high levels of cholesterol. If you give atorvastatin 10 mg, you will see a 36% reduction in LDL. As you double the dose of statin, there is a 6% further benefit each time. Thus with atorvastatin 80 mg, there will be a 54% reduction in LDL

Figure 4. Key efficacy results from the ezetimibe add-on study. Patients entered into the study (n=769) were on statin and not at NCEP goal



*p<0.001 *vs.* statin + placebo
**p<0.05 *vs.* statin + placebo
***p<0.01 *vs.* statin + placebo

level. Figure 3 shows that if you add ezetimibe to atorvastatin, you will achieve a 17% further reduction even at the lowest dose of statin. If you push the dose of atorvastatin to 80 mg and give ezetimibe, you will still achieve a further 7–10% reduction in LDL cholesterol in those patients who are giving you the biggest problem.

As you raise the dose of atorvastatin from 10 mg to 80 mg, the beneficial rise in HDL tends to fade away. Thus with atorvastatin 10 mg, a 6% rise in HDL is observed, but with atorvastatin 80 mg there is only a 3% rise in HDL. If ezetimibe is added to the atorvastatin, the attenuation of the rise in HDL in response to rising doses of atorvastatin is alleviated.

A similar change is seen for TG reduction. At the highest dose of atorvastatin plus ezetimibe, a 40% reduction in TG is seen. So this combination is extremely powerful, but most patients will not need the maximum dose of the statin.

Ezetimibe add-on study

What can be done for patients in whom doctors do not want to increase the statin dose any further, but who are not to target? The ezetimibe add-on study investigated 769 patients who had been taking a statin at the maximum dose their physician wanted to give for at least six weeks but who had not reached their target NCEP Adult Treatment Panel (ATP)-II target LDL. After a six-week washout phase, either a placebo or ezetimibe 10 mg was added to the statin on a randomised, double-blind basis for eight weeks.

At baseline, about 30% of patients were taking simvastatin and about 40% were taking atorvastatin. Of the 390 individuals in this part of the study, about 9% were in NCEP category I (fewer than two risk factors) and 20% were in NCEP category II (more than two risk factors, but no coronary heart disease). This meant that 71% of patients were in NCEP category III, at the highest level of risk (already suffering from vascular disease or diabetes and/or other risk factors), and therefore were the most worrying group of patients. The target LDL cholesterol levels for each of these three categories are 160, 130 and 100 mg/dL, respectively.

The key efficacy results are seen in figure 4. Those who received statin plus placebo took their drugs more assiduously, perhaps, and reduced their LDL by a further 4%. However, those who had statin plus ezetimibe reduced their LDL by 25%. HDL levels increased by 3% in the combination therapy group – a small but significant change – and TG fell by a further 11% in the combination therapy group versus the placebo group.

Of the patients receiving statin plus placebo, 19% reached target. In patients who received statin plus ezetimibe, however, 72% reached target LDL.

Side effects

In the studies described, the side-effect profiles from treatment with ezetimibe were minimal. Ezetimibe added no further risk of increased levels of creatine kinase levels greater than 10 times the upper limit of normal in patients taking statins. Likewise, there was no differential in increased liver function abnormalities, as measured by ALT/AST elevations greater than three times the upper limit of normal, between patients taking statin plus placebo and patients taking statin plus ezetimibe.

In conclusion, ezetimibe plus a statin gives additional benefits compared to statin alone.

- Additional efficacy ezetimibe and statin
  - Lowered LDL by 21.5% *vs.* placebo
  - Raised HDL by 2% *vs.* placebo
  - Lowered TG by 11% *vs.* placebo
- Significantly better NCEP goal achievement
  - 72% statin plus ezetimibe patients reached goal
  - 19% statin plus placebo patients reached goal
- Ezetimibe plus a statin is generally well tolerated

Questions from the audience

Q: Why shouldn't I use top-dose statins rather than 10 mg statin and 10 mg ezetimibe?

A: You can either titrate upwards until you reach the top dose, with many safety and lipid checks. Alternatively, you can use the lowest dose of the statin plus ezetimibe, and try to get the patient straight to goal without these multiple and time-consuming steps. In making the latter choice, you are giving the patient the lowest exposure to statins which, although they are relatively safe drugs, in unusual situations will raise the levels of liver function enzymes and creatine kinase.

Q: Are the anti-inflammatory effects of having a patient on a low-dose statin plus ezetimibe as good as those from having them on a higher dose of a statin?

A: In studies, the CRP values fall with the low-dose statin plus ezetimibe as they would with a high-dose statin on its own, so there is suppression of inflammation. The anti-inflammatory effect seems to be due to the lowering of oxidised LDL.

Ezetimibe – future development

CHRIS ALLEN

Abstract

The ENHANCE study will assess the effect of ezetimibe plus simvastatin in patients with heterozygous familial hypercholesterolaemia. Carotid artery intima-media thickness will be measured, which is able to predict a progression to cardiovascular or cerebrovascular events.

The SEAS study will evaluate whether treatment with ezetimibe and simvastatin, compared with placebo, will reduce the risk of major cardiovascular events in patients with aortic stenosis.

The SHARP study will measure major vascular events in patients with chronic kidney disease or who are receiving dialysis. Ezetimibe and simvastatin treatment will be compared with placebo.

Key words: ezetimibe, familial hypercholesterolaemia, aortic stenosis, chronic kidney disease.

Br J Cardiol 2004;**11**(suppl 3):S21–S22

Introduction

Even at this stage in the development of ezetimibe, it is clear that this is an outcomes-driven market. An active outcomes study programme is under way looking at the combination of ezetimibe with three of the currently available doses of simvastatin (20 mg, 40 mg and 80 mg). In addition, data from the phase III programme to investigate this combination with all four simvastatin doses will be filed with the regulatory authorities towards the end of 2003. By late 2004, a combination tablet of ezetimibe with simvastatin will probably become available.

The ENHANCE study

One ezetimibe study currently under way is the ezetimibe and simvastatin in hypercholesterolaemia enhances atherosclerosis regression (ENHANCE) study. This is a carotid artery intima-media thickness (IMT) study. Carotid IMT is a non-invasive and reproducible parameter that is measured using ultrasound. Carotid thickening is increased in patients with coronary artery disease and raised lipids, and has been validated in long-term investigations as able to predict a progression to cardiovascular and cerebrovascular events. Data show that patients in the top quintile of carotid IMT have a 25% risk over seven years of developing either a cardiovascular or cerebrovascular event.

Changes in carotid IMT independently predict coronary events such as myocardial infarction, coronary death or coronary artery bypass graft surgery. Carotid IMT can be used to evaluate changes in the carotid vessels, even before any plaque develops.

Details of the ENHANCE study are shown in table 1. This will be the largest study of IMT done to date in heterozygous familial hypercholesterolaemia (FH). The hypothesis is that ezetimibe plus simvastatin compared to simvastatin will attenuate the rate of progression of atherosclerosis, as measured by change in intimal medial thickness.

Merck/Schering-Plough, Whitehouse Station, New Jersey, USA.
Chris Allen, Senior Medical Director
Correspondence to: Dr C Allen
(email: chris_allen@merck.com)

Chris Allen

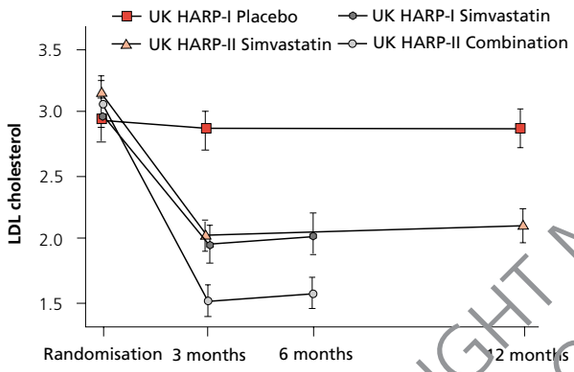
Table 1. ENHANCE: Ezetimibe and simvastatiN in Hypercholesterolemia enhANces atherosClerosis rEgression

- Patients with heterozygous familial hypercholesterolaemia
- 725 patients
- Ezetimibe 10 mg + simvastatin 80 mg *vs.* simvastatin 80 mg
- Primary outcome: mean change from baseline to end point in carotid artery intima media thickness

Table 2. SEAS: Simvastatin and Ezetimibe in patients with Aortic Stenosis

- Evaluates whether treatment with ezetimibe 10 mg/day and simvastatin 40 mg/day compared to placebo will reduce the risk of major cardiovascular events (n=1,400)
- Primary outcome: reduction in risk of composite cardiovascular end point (including aortic valve replacement)
- Key secondary outcome: progression of aortic stenosis by echocardiography

Figure 1. Ezetimibe plus simvastatin lowers LDL in patients with chronic kidney disease



The SEAS study

It is rare nowadays to see aortic stenosis (AS) as a consequence of untreated rheumatic disease. Many patients develop AS as a consequence of the calcification that occurs with age or because they have a congenital bicuspid valve. The risk of developing degenerative aortic stenosis doubles every 10 years above the age of 75 years, and is twice as high in men compared to women. Smoking and hypertension also increase the risk, and markers such as raised lipoprotein(a) and raised low density lipoprotein (LDL) are predictors of degenerative AS.

In this condition, an inflammatory process seems to be taking place in the aortic valve. For example, CD4+ lymphocytes, macrophages, T-lymphocytes, oxidised LDL and even *Chlamydia pneumoniae* may be present, and matrix metalloproteinases are upregulated. An abstract presented at the American College of Cardiology meeting earlier this year indicated that statins may actually reduce aortic valve calcification. There is growing interest in finding out whether cholesterol lowering might prevent or attenuate the progression of degenerative aortic stenosis.

The likelihood of an event – aortic valve replacement, sudden death or a serious cardiovascular event – depends on the flow over the valve. With a comparatively unstenosed valve and a comparatively slow flow rate of about three metres per second, the chance of developing an event is low. As the valve becomes more stenotic, the flow rate increases and so does the chance of rapid progression.

Details of the simvastatin and ezetimibe in patients with aortic stenosis (SEAS) study are shown in table 2. Since this population has not been studied before, there is justification for trial of these active agents against placebo. The study will provide information about the effect of fairly aggressive lipid lowering on both the morphological progression of aortic valve disease and major cardiovascular end-points.

Table 3. SHARP: Study of Heart And Renal Protection

- Patients with chronic kidney disease (creatinine (≥ 130 µmol/L in women or ≥ 150 µmol/L in men), or receiving dialysis
- Ezetimibe 10 mg + simvastatin 20 mg *vs.* placebo (n=9,000)
- Primary outcome: major vascular event (stroke, MI, revascularisation)
- Oxford University Clinical Trials Unit (HPS investigators)

The SHARP study

Patients with renal failure have a very high mortality from cardiovascular disease. Current trials are not able to show the benefits and/or risks of LDL lowering in patients with CKD because they have been excluded from the outcome studies. It is possible that the effects of lipid-lowering therapy may be different in patients with chronic kidney disease, and their high risk may not just reflect atherosclerotic disease. For example, many patients develop ventricular hypertrophy, possibly as a consequence of uraemia. There is a pressing need to know whether lowering cholesterol in these patients might attenuate their cardiovascular morbidity and mortality.

Two pilot studies into the effect of lipid lowering in patients with chronic kidney disease have been carried out by the Clinical Trials Unit in Oxford. Patients were treated with simvastatin 20 mg, simvastatin 20 mg plus ezetimibe, or placebo. There was a 0.5 mmol/L incremental benefit in LDL level when the ezetimibe was added to the simvastatin (see figure 1). The side-effect profile over a year was very good, with 90% compliance.

The results were reassuring enough for progression to the SHARP study, the study of heart and renal protection. The design of SHARP is shown in table 3. This will be a four-year study involving 200 centres, and recruitment is just beginning.

Questions from the audience

Q: We now know that type 2 diabetes is an atherosclerotic disease. In patients with metabolic syndrome and insulin resistance, are there any studies planned using aggressive lipid-lowering therapy with combinations of ezetimibe and statins?

A: We have just received the results of a study looking at combination therapy with ezetimibe in thiazolidinedione (TZD)-treated diabetics. Ezetimibe appears to have an incremental benefit on lipid lowering in patients treated with TZDs, compared to doubling the dose of simvastatin.

The need for a new approach in cholesterol management

RICHARD HOBBS

Abstract

By the year 2020, cardiovascular disease will be the world's biggest cause of premature death. As the plasma cholesterol is lowered, the incidence of coronary heart disease (CHD) events is reduced. European data on secondary prevention show that many patients have not had a plasma cholesterol recorded – even those with a diagnosis of CHD. English data show that only half of patients with a cholesterol measurement are being prescribed a statin, and only half of those are being treated to target. Poor public understanding of this subject area is one obstacle to progress.

Key words: cholesterol, coronary heart disease, prevention, targets.

Br J Cardiol 2004;**11**(suppl 3):S23–S25

Richard Hobbs

Introduction

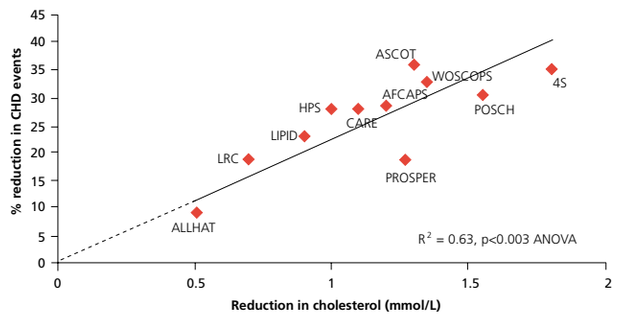
Doctors should not be apologetic about concentrating on reducing the risk of cardiovascular disease. Coronary heart disease (CHD) is the commonest cause of death in the world, and stroke is the second commonest. Even in developing economies, more people die from cardiovascular disease than from any other cause of death.

By the year 2020, cardiovascular disease will be the world's biggest cause of premature death (death before 65). And by 2020, ischaemic heart disease and stroke will move up to the number one and number four causes of death and disability. So tackling cardiovascular disease is important not just for individuals but to healthcare systems, which have to deal with the consequences of cardiovascular disease.

The other reason to justify concentration on this subject is that there is no more evidence-based area of medicine than interventions to reduce cardiovascular disease. Data show that if you treat hypertension, there will be a 42% reduced risk of stroke and a 14% reduced risk of CHD. We underachieve in terms of CHD – we would expect a 20–25% reduction from epidemiological data. The obvious reason for the discrepancy is that the relationship between blood pressure (BP) and lipids is crucial: as the cholesterol level is reduced, so the incidence of CHD events is reduced.

If the reduction in incidence of CHD events is plotted against the reduction in cholesterol, the results from all the trials are remarkably consistent (figure 1). This applies to both secondary and primary prevention, and to trials that used statins, surgery and

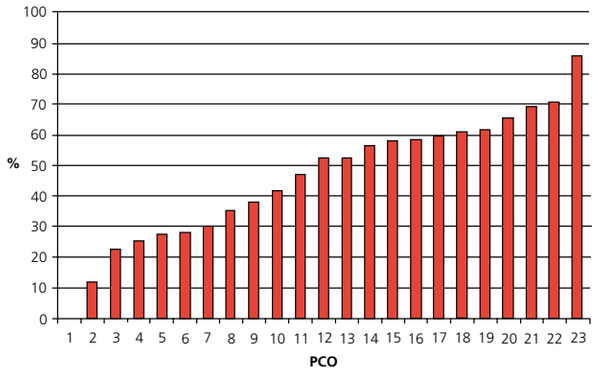
Figure 1. Reduction in CHD events with lipid-lowering strategies



Adapted from: Brady A, Betteridge J. *Br J Cardiol* 2003

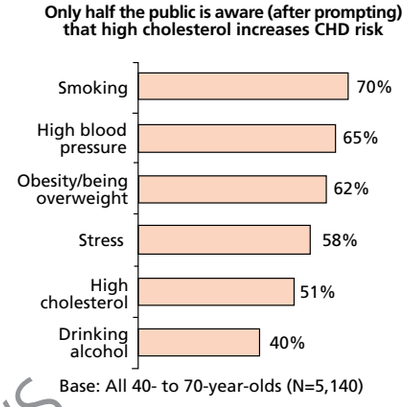
Department of Primary Care and General Practice, The University of Birmingham, B15 2TT.
Richard Hobbs, Professor of Primary Care and General Practice
Correspondence to: Dr R Hobbs
(email: f.d.r.hobbs@bham.ac.uk)

Figure 2. Percentage of CHD patients with a valid lipid measurement recorded: variations in primary care organisation performance



Adapted from: de Lusignan S, Dzregah B, Hague N, Chan T. *Br J Cardiol* 2003;**10**:223–8

Figure 3. Public unaware of cholesterol as CHD risk factor



Adapted from Erhardt, Hobbs, REACT Study, *IJCP*, 2002

bile acid sequestrants. (Incidentally, this figure implies that there are no pleiotropic effects with statins, but that the important target is a reduction in level of cholesterol, obtained by whatever means.)

Government has recently lent support to doctors' efforts to manage cardiovascular disease. The National Service Framework for CHD discusses both secondary and primary prevention, and deals with specific interventions and targets. The new GP contract for England and Wales has the potential to act as an impetus for change. Even if the new contract is not voted in, the same sort of financial incentives for medical services that are suggested under the contract may still be seen. Some 35% of the clinical markers in the proposed new contract relate to cardiovascular disease; they refer to CHD, hypertension and diabetes.

How well is cardiovascular disease prevention working in primary care?

EUROASPIRE data on secondary prevention probably represent best practice in Europe. The surveys took place largely among patients discharged from teaching hospitals, having had an event such as a myocardial infarction or a revascularisation. Among those patients, 58% are still not reaching their cholesterol target, compared to the 86% not to target in the first EUROASPIRE survey six years ago. Worryingly, there was very little change in the number of patients with hypertension or still smoking, and there was even an increase in the proportion of patients who were obese at follow-up.

The Healthwise Survey was a survey of 548 computerised general practices in the UK in 1997/8. A total of 24,341 patients with CJD were identified from practice records; their risk factors and secondary preventive measures were noted. The survey found that 25% of men and 20% of women were still smoking, and that just over a third of all patients had inadequately controlled BP. Even though they had a diagnosis of CHD, a third of men and just over half the women had no recorded cholesterol measurement in their records, and 48% of men and 40% of women still had a raised total cholesterol.

The largest audit in secondary prevention in English general practice, by de Lusignan and colleagues, was published recently in *The British Journal of Cardiology*. Valid data regarding statin use and cholesterol levels were available for 78,600 patients with a diagnosis of CHD, mainly in London and the South East. The major finding from this study was that the rule of halves applies to the management of cholesterol in patients with CHD: half had a record of a cholesterol measurement, half of these were being prescribed a statin, and half of these had been treated to target.

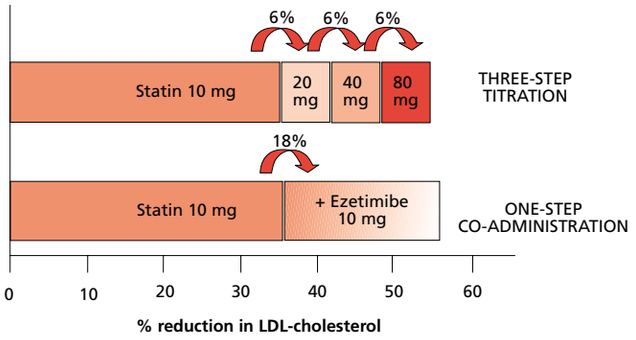
Figure 2 shows the percentage of CHD patients with a valid lipid measurement by primary care organisation. It can be observed that at least half the practices have a huge task ahead of them, even in identifying those at risk – and this was a survey of secondary prevention.

Poor public understanding

One reason for the difficulties that clinicians have in getting patients to target is poor public understanding of this subject area. The REACT survey, published three years ago, was conducted among 5,000 members of the general public in six European countries. CHD is the leading cause of death in middle-aged and elderly adults throughout Europe, but only 45% of the population surveyed correctly identified CHD as the leading cause of death in their country.

More than 90% of physicians surveyed as part of this research thought that their patients knew that high cholesterol was associated with increased risk of CHD. In fact, this was an overestimate: only half the public were aware (after prompting) of this association. Patients were fairly well informed about the risks of smoking and hypertension, but they thought that stress was a more important risk factor for CHD than was cholesterol (figure 3). In addi-

Figure 4. Rationale for therapy with combination of ezetimibe plus statin



Data on file, Merck Sharp & Dohme Ltd and Schering-Plough

tion, three quarters of patients did not know about low density lipoprotein (LDL) or high density lipoprotein (HDL) cholesterol. So it appears that patients are not well informed about the importance of high cholesterol levels.

Primary prevention

Nearly all the surveys of our clinical practice in relation to prevention of CHD are surveys of secondary prevention. The primary prevention of CHD is an enormous target, but it does need to be tackled. If we wait until patients develop CHD before we offer them treatment, only half will have relatively benign presentations of CHD. In about 14% of patients, the first presentation of CHD is sudden cardiac death, and in another 25% the first presentation is an acute myocardial infarction (MI). It does not seem ethical to allow people who may be at very high risk to wait for treatment until after they develop angina, especially since we have no way of determining what an individual's first manifestation of CHD might be.

It is right for us to concentrate on secondary prevention, but only in the recognition that, at some stage, we have to tackle primary prevention more seriously than we do at present.

The Health Survey for England 1993 shows just how high-risk our population is, and the data would probably be even worse if Scotland were surveyed. Of the 13,500 adults over 45 years of age surveyed, 67.5% had a total cholesterol above 5 mmol/L (with 22.1% above 6.5 mmol/L) and 26.6% had a TC:HDL above five. Of these adults, 2.2% were on a statin.

Measures to help us deal with this enormous disease burden include increased access and advice about lifestyle. Cholesterol reduction through lifestyle intervention is beneficial but it is difficult to achieve, and we need more government involvement in food policy and exercise provision. We need to increase our lipid measurements in patients with cardiovascular disease and those who are at risk. Unless we take these measurements, we will miss patients in whom treatment is necessary or who are not to target.

We have to consider increasing doses of statins in patients who are not to target. In some patients this will be the right strategy, but it is true that doubling the dose of statin will only achieve a further 6% LDL reduction, and side effects are increasingly likely at higher doses.

With the advent of ezetimibe, doctors can now choose between uptitration of a statin or co-administration of a statin with ezetimibe. Figure 4 shows the percentage reduction in LDL achieved with these two options: it can be observed that a three-step uptitration of a statin or a one-step co-administration of ezetimibe plus statin give equivalent reductions in LDL. Such options are important in medicine because patients are different, and indeed so are physicians.

We will increasingly be evaluated for our ability to reach targets in medicine. American data suggest that ezetimibe added to a statin will get patients to target in nearly three quarters of cases, compared to 19% of patients who remain on low doses of statin alone.

Questions from the audience

Q: From the practical point of view, do we accept the lower dose of statin with ezetimibe as a starter, or do we keep ezetimibe as a reserve for patients who do not respond despite a maximum dose of statin?

A: In many patients the start dose of statin will not achieve the necessary reduction in cholesterol. For these patients, the prescribing decisions include whether to start low and uptitrate, or to start at the higher dose straight away, or to use a combination treatment. In time these strategies will become clearer. For the moment, with a single strategy for everybody, we know that some patients will fall by the wayside.

Q: Could you comment on the GP's job in screening?

A: We have fantastic interventions available now for cardiovascular disease prevention, and we have the means to identify those at risk. What we do not yet have is organised systems that allow us to search systematically for those who are at risk and then to put into effect systematically, strategies to modify that risk.

Q: I am worried about compliance. Some of our patients are already taking so many pills, and here is another one.

A: Multiple pill treatment is a problem. Cardiovascular prescribing will lead the way because the need to combine prophylactic treatments with symptomatic treatments has already been recognised. Next year, the combination of ezetimibe and simvastatin is expected to become available. There will almost certainly be combinations of antihypertensive plus statin plus ezetimibe in the future.

Case study. Thirty years on

CLIVE WESTON

Introduction

The natural history of hyperlipidaemia over 30 years was shown in this case presentation. The patient was first seen when he was a boy of 14. By the age of 21 he had developed atypical chest pain. At the age of 35 he suffered an acute myocardial infarction. By his late thirties he had diffuse three vessel disease, and by his mid-forties he had developed symptomatic heart failure.

1972–1977

The patient was referred as a boy of 14, in 1972, by his GP. He had been complaining of palpitations after swimming. His cholesterol was checked at that time. The physician's letter says; 'The ECG is normal but apparently the cholesterol was 325 mg% which was peculiar…and may not be quite correct…If you want to put him on a diet, please do, but I cannot find anything wrong with him.'

The GP repeated the cholesterol estimate and referred him again, saying that the cholesterol was now 350 mg% and that there was a family history of coronary heart disease. He asked whether the boy should be on a diet or on Atromid S. The mother's cholesterol was found to be 300 mg% but no treatment was suggested for her, and the boy's treatment was left to the GP.

At the age of 17, the patient's cholesterol was 440 mg%: his GP had put him on Atromid S and a diet.

Q: What is a total cholesterol of 350 mg% expressed in SI units?

A: (after audience vote) It is in fact almost exactly 9 mmol/L.

Q: Should a teenager with a total cholesterol of 9 mmol/L be:

- referred to a dietician?
- referred to a specialist lipidologist?
- referred to a cardiologist?
- managed in primary care?

A: (after audience vote) 82% would refer to a lipidologist.

Singleton Hospital, Swansea, SA2 8QA.
Clive Weston, Consultant Cardiologist
Correspondence to: Dr C Weston
(email: cfmw@lycos.com)

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1977–1993

At the age of 19, the patient was referred to the lipid clinic by a cardiothoracic surgeon who had just done a coronary artery bypass graft on his mother. He was prescribed a diet, and cholestyramine 4 g t.d.s. However, he was not compliant with his medication and he defaulted from clinic. His total cholesterol at this time was about 11.9 mmol/L.

When the patient was 21 he was referred to a DGH cardiologist with atypical chest pain, by which point he was smoking 10 cigarettes a day. He was unable to take clofibrate or cholestyramine 4 g t.d.s. The cardiologist could find no abnormal clinical signs but prophetically said that the patient was in danger of developing arterial disease.

The patient married and had two children, though the marriage broke up soon after the second child was born. He was referred at his own request at the age of 25 because he was generally tired and achy; he had recently stopped smoking. His total cholesterol was 11.7 mmol/L. He defaulted from clinic after one consultation.

The patient was referred once more with exertional chest pain at the age of 29. He was found to have minor ST segment changes on exercise, early corneal arcus and possibly tendon xanthomata. He agreed to take cholestyramine 1 g t.d.s. again and his total cholesterol fell to 9.8 mmol/L, though his high density lipoprotein (HDL) fell too, to 0.8 mmol/L. He refused additional bezafibrate at that time. He was put on simvastatin 10 mg but stopped it because he felt nauseated.

At the age of 35, he suffered an acute myocardial infarction. On admission to hospital his total cholesterol was 10.6 mmol/L and his low density lipoprotein (LDL) was 8.8 mmol/L. The plan was for him to go onto pravastatin 10 mg/day prior to any intervention, and to double the dose if necessary.

Q: What is the effect on LDL of doubling the dose of a statin? Is it a reduction in LDL of approximately:

- 20%
- 6%
- 10%
- 50%

A: (after the audience vote) Most of you voted correctly, for 6%.

1994–2000

The patient's coronary angiogram revealed diffuse three-vessel disease. He had an angioplasty to the left anterior descending artery. He started taking pravastatin 40 mg/day but felt nauseated and dizzy. He was referred to a university hospital lipid clinic with a total cholesterol of 11.0 mmol/L, triglycerides 3.0 mmol/L

and HDL 1.7 mmol/L. The clinic letter stated: 'He was over an hour late for his appointment…He had been told that he might be able to take part in a trial of a new statin. When he was told that he might not be able to stay on the statin after the study, he left with ill grace. Good luck!'

He was put on atorvastatin 20 mg by the local lipid-lowering specialist, but he felt generally achy and stopped taking it.

2001–2003

He was admitted as an emergency, at the age of 42, in heart failure. In a period of months he had gone from being able to exercise in the gymnasium to being extremely short of breath and looking very unwell. He was put on bisoprolol, losartan, bumetanide, digoxin and warfarin. A PET scan suggested hibernating myocardium. He underwent coronary artery bypass grafting (CABG), and had recurrent ventricular tachycardia afterwards. He required an implantable defibrillator, and his cardiac output was so poor that a biventricular pacing system was put in place. And his total cholesterol was still 11.7 mmol/L.

He agreed to take atorvastatin 20 mg again: his total cholesterol fell to 7.7 mmol/L, his LDL to 5.5 mmol/L and his HDL to 1.8 mmol/L. When he was put on atorvastatin 40 mg, his total cholesterol was 6.7 mmol/L, his LDL 4.7 and his HDL 1.5 mmol/L. However, he is very unhappy about the generalised aches and pains and wants to reduce his dose.

Q: Would you settle for the reduction of cholesterol from the starting point of 11.0 to 6.7 mmol/L?

A: (after audience vote) 70% voted no.

Panel discussion

(Key: AB = Adrian Brady; RH = Richard Hobbs; AR = Alan Rees.)

AB: This man is 44, and has symptomatic heart failure from which he will die in three to four years unless he has a transplant. His cholesterol treatment should have been started many years ago.

RH: He will have been told that his diagnosis is terminal, but there is merit in helping him to make a sensible decision about reducing his risk. If he does have a transplant, you want his arteries in as good a shape as possible. We do not yet know whether statins are effective in heart failure.

AR: It is very difficult to know what to do about these patients. The response to statins in individual patients has to do with intrinsic and extrinsic factors, and the commonest extrinsic factor is compliance. Whether this patient is having side effects from the statins or he believes he is having side effects from the statins is an academic question – he is obviously not taking the stuff.

Q: How would you attempt to reduce the total cholesterol and LDL further?

- Increase the dose of the existing statin?
- Change to another statin?
- Add a fibrate?
- Add ezetimibe?

A: (after the vote) 93% of the audience voted to add ezetimibe to this man's treatment.

Case study. A woman with high lipid levels and poor drug tolerance

MARK DAVIS

Introduction

The case presented was a 59-year-old woman, who was 50 years old at the beginning of the story. She was married, but had various family and domestic problems. She had been seen a great deal by the practice for her anxiety and depression. She also had a number of gastro-intestinal problems, which had been diagnosed as irritable bowel syndrome.

She had a strong family history of coronary heart disease. Her father was 62 when he had his first myocardial infarct (MI) and he died eventually of another infarct at the age of 76. A paternal uncle died suddenly of an acute MI at the age of 58.

Q: She has no symptoms and a moderately strong family history. What cardiovascular investigations are indicated?

- None
- Lipid profile and blood pressure
- Lipids, blood pressure and others

A: (after audience vote) 2% voted for no investigations, 33% for lipid profile and blood pressure, and 65% for lipids, blood pressure and other investigations.

In fact, said Dr Davis, we did no cardiovascular investigations other than measure her blood pressure (BP) at intervals – it was always less than 160/100 mmHg. For reasons that will become apparent, that was the wrong decision. In view of her family history we should have carried out a lipid profile, even though she usually consulted us about her troubles in life.

In 1995 she developed episodic headaches. We thought there was 'something not right about them' – they were sometimes associated with vague feelings or sensations of numbness in various locations – so we referred her to a neurologist. The CT scan showed no evidence of abnormality and the neurologist diagnosed her as having migraine.

The probable reason for her headaches was revealed in 1998 when she had a definite hemiparesis, which resolved completely within 24 hours. An MRI scan showed that she had bilateral high-grade stenosis of her internal carotids and she had a carotid endarterectomy and patch angioplasty.

She was discharged without any secondary prevention, so we evaluated her cardiovascular risk status. We made sure that she did not have diabetes and gave her lifestyle advice, even though she was a non-smoker and had a body mass index of 26 kg/m^2. As she was now in the secondary prevention category, her BP of 156/90 mmHg needed treatment. We treated her with an ACE inhibitor and a thiazide, and within three months her BP was below 140/85 mmHg.

All her risk factors were under control except her lipids. She had a total cholesterol of 8.6 mmol/L and an HDL of 1.1 mmol/L. We started her on simvastatin, but she could not tolerate either simvastatin or atorvastatin for more than a short time because she developed various gastro-intestinal symptoms.

We settled on pravastatin 40 mg, and this was reasonably effective, bringing her total cholesterol down to 6.7 mmol/L, and she tolerated it most of the time. She was still at high risk as she kept on having small transient ischaemic attacks (TIAs) on aspirin alone. The neurologists though she should have clopidogrel. This was started but she could not tolerate it.

Q: What next?

- Nothing, you have done your best
- Do a lipid profile and consider the need for a fibrate
- Wait for new therapeutic agents

A: (after audience vote) 3% voted to do nothing, 27% opted to wait, and 70% voted to do a lipid profile and consider a fibrate.

Panel discussion

(Key: EH = Elizabeth Hughes; MD = Mark Davis; JS = James Shepherd; AB = Adrian Brady.)

(EH) You need to do something in this situation, rather than just waiting. Sometimes, like Godot, new therapeutic agents do not arrive when they are expected. I would probably have gone for a combination treatment.

(MD) We know from past experience that this woman can take almost no medication. Every time we give her something, she has problems with it.

(JS) Did you try her on a combination of aspirin and dipyridamole?

(MD) She was tried on that by the neurologist, who had been asked to advise because of her ongoing problems. She could not take that combination either.

Moorfield House Surgery, 11 Wakefield Road, Garforth, Leeds, LS25 1AN.
Mark Davis, General Practitioner
Correspondence to: Dr M Davis
(email: markdavisbspa@aol.com)

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Case report

She was not to target and she was at high risk, intolerant of many drugs. On a named-patient basis, I put her on ezetimibe 10 mg in February 2003 and monitored various blood tests. Her cholesterol came down from 6.7 mmol/L to 5.5 mmol/L by April. She was still taking the pravastatin.

(EH) That is a pretty reasonable outcome for somebody who clearly has difficulty with side effects and compliance. The question is, how far should you push it?

Q: She is still not to target, so what should we do?

- Nothing, we have done our best
- We try simvastatin or atorvastatin again (despite this patient's previous experience)
- We try rosuvastatin, which is now available
- We wait for new therapeutic advances
- We wonder why so many of our high-risk patients cannot take any of our tablets.

A: (after audience vote) 60% vote to try rosuvastatin.

(MD) That is our plan: we hope she will be able to tolerate it.

(EH) She may be able to tolerate it because it is very similar to pravastatin, in my experience.

(JS) Will you be keeping the ezetimibe going?

(MD) We will. She seems to tolerate it well, and does not seem to have any direct symptoms with it.

(AB) Would you do an exercise test?

(MD) I was wondering that. There is obviously a high likelihood that she has coronary artery disease. Would you recommend an exercise test?

(AB) What will you do if she asymptomatic ischaemia? If you perform an exercise test, you will have to be prepared to investigate her with angiography and so forth.

(MD) She is already quite anxious and we are probably doing as much as we can, unless interventional cardiologists are brought in.

(JS) This is a real-life problem. It is the kind of thing we are all dealing with, patients who will not take their medication. They cannot or will not take it, and you are never quite sure whether it is a function of the medication or of the patient, or a combination of both.

EZETROL®▼ (ezetimibe)
ABRIDGED PRODUCT INFORMATION

Refer to Summary of Product Characteristics before Prescribing

PRESENTATION: 10 mg Tablet containing 10 mg of ezetimibe.

USE: As adjunctive therapy to diet in: *Primary hypercholesterolaemia:* For co-administration with an HMG-CoA reductase inhibitor (statin) for patients with primary (heterozygous familial and non-familial) hypercholesterolaemia not appropriately controlled with a statin alone. *Monotherapy:* For use in patients with primary (heterozygous familial and non-familial) hypercholesterolaemia in whom a statin is considered inappropriate or is not tolerated. *Homozygous Familial Hypercholesterolaemia (HoFH):* For co-administration with a statin, for use in patients with HoFH. Patients may also receive adjunctive treatments (e.g., LDL apheresis). *Homozygous sitosterolaemia (phytosterolaemia):* For use in patients with homozygous familial sitosterolaemia. Studies to demonstrate the efficacy of 'Ezetrol' in the prevention of complications of atherosclerosis have not yet been completed.

DOSAGE AND ADMINISTRATION: For oral administration. Put patients on an appropriate lipid-lowering diet and continue during treatment. Recommended dose is one 'Ezetrol' 10 mg tablet daily, administered at any time of the day, with or without food. When added to a statin, either continue with the indicated usual initial dose of that particular statin or the already established higher statin. Consult the statin dosage instructions. *Co-administration with bile acid sequestrants:* Dosing should occur either ≥2 hours before or ≥4 hours after administration of a bile acid sequestrant. *Use in paediatric patients:* Children <10 years: Not recommended as no clinical data are available. *Use in hepatic impairment:* No dosage adjustment is required with mild hepatic insufficiency (Child Pugh score 5 to 6). Not recommended in patients with moderate (Child Pugh score 7 to 9) or severe (Child Pugh score >9) liver dysfunction.

CONTRA-INDICATIONS: Hypersensitivity to any component. When co-administered with a statin, refer to the statin SPC. 'Ezetrol' co-administered with a statin during pregnancy and lactation. 'Ezetrol' co-administered with a statin in patients with active liver disease or unexplained persistent elevations in serum transaminases.

PRECAUTIONS: *Liver enzymes:* When co-administered with a statin, perform liver function tests at initiation of therapy and according to the statin SPC. *Hepatic insufficiency:* Not recommended in patients with moderate or severe hepatic insufficiency due to the unknown effects of the increased exposure to 'Ezetrol'. *Fibrates:* Co-administration is not recommended as the safety and efficacy of co-administration have not been established. Fibrates may increase cholesterol excretion into the bile, leading to cholelithiasis. *Cyclosporin:* Exercise caution when initiating 'Ezetrol' in patients taking cyclosporin. *Interactions: Cholestyramine:* Concomitant cholestyramine administration decreased the mean AUC of total 'Ezetrol' approximately 55%. The incremental low-density lipoprotein cholesterol (LDL-C) reduction due to adding 'Ezetrol' to cholestyramine may be lessened by this interaction. *Statins:* No clinically significant pharmacokinetic interactions were seen upon co-administration with atorvastatin, simvastatin, pravastatin, lovastatin, or fluvastatin. *Pregnancy and lactation:* 'Ezetrol' co-administered with a statin is contra-indicated during pregnancy and lactation, refer to the SPC for that particular statin. *Pregnancy:* 'Ezetrol' should be given to pregnant women only if clearly necessary. No clinical data are available on the use of 'Ezetrol' during pregnancy. *Lactation:* 'Ezetrol' is contra-indicated.

SIDE EFFECTS: Clinical studies demonstrated that 'Ezetrol' was generally well tolerated; adverse reactions were usually mild and transient. The overall incidence of side effects reported with 'Ezetrol' was similar between 'Ezetrol' and placebo. Similarly, the discontinuation rate due to adverse experiences was comparable between 'Ezetrol' and placebo. The following common (≥1/100, <1/10) drug-related adverse experiences were reported in patients taking 'Ezetrol' alone (n=1691) or co-administered with a statin (n=1675): *'Ezetrol' administered alone: Nervous system disorders:* headache. *Gastro-intestinal disorders:* abdominal pain and diarrhoea. *Ezetrol' co-administered with a statin: Nervous system disorders:* headache and fatigue. *Gastro-intestinal disorders:* abdominal pain, constipation, diarrhoea, flatulence and nausea. *Musculoskeletal and connective tissue disorders:* myalgia. The following adverse reactions have been reported in post marketing experience: [Rare (≥1/10,000, <1,000)] *Immune system disorders: rare:* hypersensitivity including angioedema and rash. *Laboratory values:* In controlled clinical monotherapy trials, the incidence of clinically important elevations in serum transaminases (ALT and/or AST ≥3 X ULN, consecutive) was similar between 'Ezetrol' (0.5%) and placebo (0.3%). In co-administration trials, the incidence was 1.3% for patients treated with 'Ezetrol' co-administered with a statin and 0.4% for patients treated with a statin alone. These elevations were generally asymptomatic, not associated with cholestasis, returning to baseline after discontinuation of therapy or with continued treatment. Clinically important elevations of CPK (≥10 X ULN) with treatment with 'Ezetrol' alone or co-administered with a statin were similar to elevations seen with placebo or statin administered alone, respectively.

PACKAGE QUANTITIES AND BASIC NHS COST:
28 Tablets: £26.31

Marketing Authorisation number: PL 19945/0001

Marketing Authorisation holder: MSD-SP Limited, Hertford Road, Hoddesdon, Hertfordshire EN11 9BU, UK

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MSD
Merck Sharp & Dohme Limited
Hertford Road, Hoddesdon, Hertfordshire EN11 9BU

Schering-Plough Ltd