THE BRITISH JOURNAL OF
Cardiology

JANUARY/FEBRUARY 2003 VOLUME 10 SUPPLEMENT 2

Socratic dialogue: the future management of hyperlipidaemia

Socratic dialogue participants

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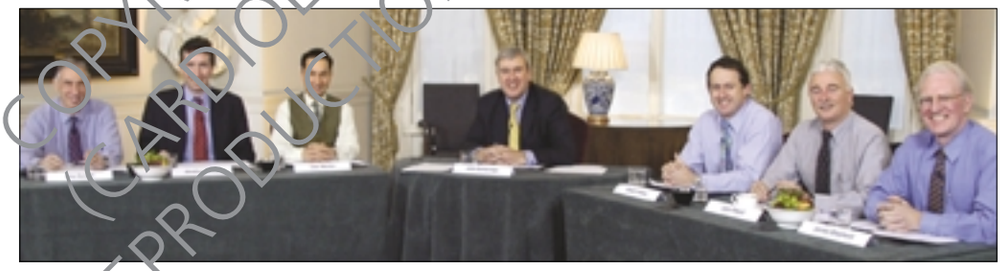


Professor John Betteridge (Chair) and the panel participants. The Socratic dialogue was held on 12th December, 2002

Introduction

The Greek philosopher Socrates developed the technique of challenging accepted wisdom through rigorous questioning, with the aim of establishing a better understanding of a subject through a logical assessment of the facts, rather than the pressures of convention. In the Socratic dialogue on the future management of hyperlipidaemia, Professor John Betteridge was joined by six multidisciplinary experts to discuss the strengths and weaknesses of current treatment pathways in cholesterol management, the opportunities, and the barriers to best practice.

Professor Betteridge challenged the group with the statement that current cholesterol management often fails the patient: treatments do 'marvellously well' in clinical trials yet clinicians fail their patients by not effectively explaining the benefits of cholesterol management to them. In addition, he asked the group to consider why patients receiving treatment are often not achieving the cholesterol-lowering goals currently set by the National Service Framework for Coronary Heart Disease (NSF for CHD). These are: total cholesterol (TC) < 5 mmol/L and low-density lipoprotein (LDL) cholesterol < 3 mmol/L or reduced by 30% (whichever is greater).[1] Professor Betteridge emphasised the importance of addressing the clinical and organisational reasons for this, in order to ensure that patients are properly and adequately treated on the basis of the best available scientific data.

The size of the problem

Cardiovascular disease (CVD) is the main cause of death in the UK, accounting for more than 235,000 deaths a year.[2] CVD is also responsible for 36% of premature deaths in men and 28% in women. In England alone there are 294,000 admissions annually for ischaemic heart disease, with the mean duration of admission being 5.8 days, accounting for a total of 1.71 million bed days.[3]

Despite a wealth of data supporting cholesterol reduction, European and UK audits show that many patients have cholesterol levels above goals set by the NSF for CHD. The 1998 EUROASPIRE II study of more than 5,500 patients across Europe (including 362 from the UK) revealed that 58% of all clinical cardiovascular disease patients had a total cholesterol > 5 mmol/L.[4,5] Yet only 61% of these patients were prescribed a lipid-lowering therapy.

John Betteridge

More recently, The British Regional Heart Study,[6] a long-term cohort study of 3,700 men, revealed that amongst 646 participants with established cardiovascular disease, only 29% were prescribed lipid-lowering therapy, with just 56% of these individuals receiving treatment having total cholesterol levels < 5 mmol/L.

These studies suggest that in many cases clinicians are failing both those with established disease and those at high risk.

The case reports

Four case reports based on clinical experience were presented by the Chair to highlight aspects of our current challenges in achieving best care and getting patients to goal. The group's objective was to discuss each case study from their own perspective while keeping the patient's point of view in mind.

Case study 1. Mrs Risk

Patricia is 49, and first presented at her GP's surgery 18 months ago requesting a cholesterol test after she had read an article about risk factors for heart disease. Her father died of a myocardial infarction (MI) at 50. She smokes seven cigarettes a day and is worried about her health. Her TC was 7.9 mmol/L, LDL 5.2 mmol/L, high-density lipoprotein (HDL) cholesterol 0.8 mmol/L and triglycerides (TG) 4.1 mmol/L. At that time her blood pressure (BP) was 138/92 mmHg and her body mass index (BMI) 28.

Despite her worries, she was not keen to take tablets every day. After initial dietary advice failed to reduce her cholesterol significantly, she was started on pravastatin 20 mg, which was later increased to pravastatin 40 mg. She has not been seen by a cardiologist or lipidologist and did not present for her annual review.

The practice nurse tried by letter to encourage Patricia to attend the cardiovascular clinic. At the follow-up visit that she eventually attended, the patient was found to have TC 6.2 mmol/L, LDL 3.5 mmol/L, HDL 1.0 mmol/L and TG 3.8 mmol/L. She was still smoking five cigarettes a day.

During the discussion the Chair later asked the group to consider the following: the patient tells the practice nurse that she is concerned about taking high-dose medications in the long term; the patient is from an Indian subcontinent ethnic group; she has a fasting glucose of 6.8 mmol/L.

Case study 1 discussion

Professor Shepherd registered his concern since Patricia is a smoker and has mixed hyperlipidaemia. He noted that she will have small dense LDL in her blood and that her lipid profile needs to be addressed, especially since she is not at goal despite statin therapy.

Using CHD risk charts

Coronary heart disease (CHD) risk charts calculate an individual's risk of CHD in the subsequent 10 years, based on traditional risk factor data such as age, gender, BP, cholesterol and diabetes status.

James Shepherd

This patient's 10-year CHD risk was revealed as 28%. Professor Betteridge initiated the discussion by asking the group's opinion of using these charts in primary care and also of revealing the risk calculation figure to the patient. Professor Barnett emphasised that in this case the chart was immaterial – she had every risk factor 'in the book' and needed treating. He rightly suspected that she might be diabetic.

Other members of the group agreed that the charts are not always useful and that the clinical situation is the driver for treatment. It was also thought that if the patient knew she had a 28% risk it could prompt her to comply with treatment. Furthermore, recent National Institute for Clinical Excellence (NICE) guidelines state that statins should be prescribed in diabetic patients at CHD risk of 15% over 10 years.

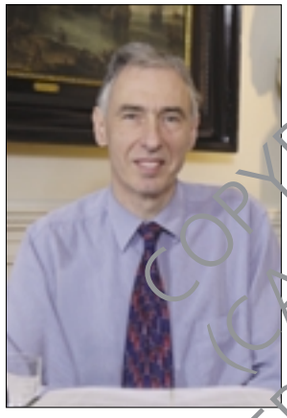
The group agreed that the footnotes for CHD risk charts are often overlooked. These state that a family history of premature CHD increases the risk by a factor of 1.5, and that in people originating from the Indian subcontinent it may be assumed that the charts underestimate risk. This particular patient is also at risk because she has raised TG. Professor Betteridge suggested that this type of lipid profile may be something that primary care physicians need guidance on, because mixed hyperlipidaemia is more difficult to treat than hypercholesterolaemia.

Adherence

The discussion then focused on adherence, including the patient's willingness to take her medication, polypharmacy, intolerance, side effects, dose frequency, interaction with food/alcohol and concerns over high doses/long-term medication. The group agreed that although there was plenty this patient could do for herself

in terms of diet, weight reduction and smoking, her case also raised issues of adherence. Dr Weston felt it was not unusual to have a patient who is worried about her health and at the same time worried about the effect of tablets on her health, and added that it was impossible to frighten patients into taking tablets.

Dr Pittard underlined the importance of exploring the individual patient situation very carefully if the patient is not engaging with smoking, diet and exercise advice in order to see the risks in their true light. He also highlighted the difficulty of raising the statin dose in general practice, as the full picture needs to be teased out for the individual patient. An explanation that statins entail an adjustment to the body biochemistry and need to be built up slowly is necessary, as is not giving up on the first failure of a statin. Others believed that spending time explaining the whys of treatment and the importance of long-term continuation of therapy was a major role for the practice nurse and the pharmacist.



Anthony Barnett

Goals of treatment

What should the goal of treatment be for this patient? The NSF for CHD requires reduction of cardiovascular risk both through secondary and primary prevention. National goals for total cholesterol lowering are < 5 mmol/L and LDL cholesterol < 3 mmol/L or reduced by 30% (whichever is greater). With the further information we have from the Heart Protection Study, for example, it may be necessary to modify these goals further. Professor Betteridge said the secondary goal proposed by the NCEP-ATP III of non-HDL cholesterol is useful when LDL cholesterol is to goal and raised triglycerides persist. In this patient the non-HDL cholesterol is 5.2 mmol/L compared with the NCEP goal of $\leq$ 3.4 mmol/L so there is a significant drop to achieve.

Professor Shepherd thought single statin therapy alone would be unlikely to give the lipidologist the goals that he wanted in this patient. If failure to follow lifestyle advice requires clinicians to do more, then combination of a statin with another treatment would be appropriate. Most GPs would refer rather than use combined statin and fibrate therapy, said Dr Belsey, because the message that this is a dangerous combination has been extensively highlighted. Professor Barnett said that he would give a statin to this patient, and would control her diabetes, which might well improve her lipid profile, particularly the TG and perhaps the HDL.

Statins and fibrates

There is some nervousness amongst primary care physicians regarding the combination of statins and fibrates due to the well known interaction between these drugs. Dr Lindsay would be happy to give a statin and fibrate together if he was sure that the patient was trying to take a higher dose of statin but with limited success. It was noted that some of the group would not use gemfibrozil with a statin even though most of the evidence base is with gemfibrozil. Professor Shepherd reminded the group that problems from the combination arose with lovastatin and gemfibrozil; in fact, minimal risk is associated with second generation fibrates such as fenofibrate in combination with simvastatin or pravastatin. More about statins and fibrates is expected as an outcome from the abortive Lipids in Diabetes Study.

Ethnic issues

One of the main issues regarding increased CVD risk in Indoasian populations is differences in the lipid profile: there is a tendency for this population to have low HDL and raised TG. The timing of onset of diabetes may also be a factor. In populations such as the Indoasians where the genetic burden is high, and particularly in people who migrate to other countries, as weight increases the metabolic syndrome tends to develop at an earlier age. Being Indoasian counts against you in cardiological terms, said Dr Lindsay, because the nature and extent of coronary disease are often so devastating. Professor Barnett underlined that in the diabetes field, Indoasians have 50% greater cardiovascular risk than the white Caucasian population, even

Jonathan Belsey

when BP is low. The UK Asian Study is looking at the large Indoasian population of Birmingham and Coventry and involves community-based diabetes specialist nurses, Asian link workers and extra practice nurse time. In the first year of the pilot involving 400 Asian people with type 2 diabetes, the CHD risk in the active practices fell by 10%.

Case study 2. Mrs 'difficult to treat'

Mary is 64 and was diagnosed with type 2 diabetes three years ago. She lives alone and looks after foreign students on an ad-hoc basis. She has two daughters who are supportive, and she works full-time at the local school canteen.

On diagnosis, Mary's HbA_{1C} was 8.4%, her BMI was 32 and she had moderately elevated BP (155/95 mmHg); her lipids were TC 6.7 mmol/L, LDL 4.1 mmol/L, HDL 1.0 mmol/L and TG 3.5 mmol/L.

Mary is taking metformin 850 mg bd, atorvastatin 10 mg, lisinopril 10 mg and bendrofluazide 2.5 mg. Gliclazide 80 mg bd was later added. Mary was referred to the dietician and attends her diabetic clinic regularly. At her last annual review three months ago, her BP was 140/80 mmHg and her HbA_{1C} was 7.3%. However, she complained of a gastric upset, and of weakness and muscle pains. Her statin was switched and she was able to tolerate pravastatin 10 mg, but not 20 mg. Mary tried cholestyramine but then refused to take it. Her current TC is 5.9 mmol/L, LDL 3.6 mmol/L, HDL 1.1 mmol/L and TG 2.7 mmol/L. Mary has stage 2 diabetic retinopathy and microalbuminuria.

During the discussion the Chair

revealed that in the previous week the patient attended her GP complaining of pains in her calves on walking uphill; the local pharmacist notices that over the past three months he has dispensed only 20 doses of pravastatin per month to the patient.

David Lindsay

Case study 2 discussion

The group agreed that the patient is typical of the type of patients seen every day in diabetic clinics. She has multiple risk factors for cardiovascular disease (the microalbuminuria is a risk in its own right) and requires intervention, but the intervention itself is causing difficulties, with possible side effects from the statin and/or metformin, intolerance of cholestyramine and perhaps compliance issues as well.

It is important to measure the muscle enzyme CPK in patients on statins with muscle symptoms. If she did have a genuine intolerance to statins, then fenofibrate was an alternative and there was a need to refer Mary to the diabetes clinic to tackle her lipid management.

Blood pressure control

The British Hypertension Society recommends stricter BP control in diabetic individuals compared with non-diabetics. Microalbuminuria and proteinuria are markers of increased cardiovascular risk, and if the proteinuria exceeds 1 g/day then the target BP is < 125/75 mmHg. Although Mary's initial BP appeared to be only modestly elevated above the target < 140/80 mmHg, in view of her constellation of risk factors and her diabetes it was considered to be very significantly elevated; therefore the dose of lisinopril needs to be increased. Mary should also be taking aspirin: controlled hypertensive patients are advised to take 75 mg aspirin if their 10-year CHD risk exceeds 15%.

Moderate exercise such as walking is of benefit in patients such as Mary. If she cannot undertake sufficient exercise, her care team needs to be aware of her potential for occult ischaemia. Further, if she does have peripheral vascular disease then her risk is dramatically increased to 50% five-year mortality. Her peripheral vascular disease is probably not a threat to her legs, but it may be a marker of significant coronary disease, and nuclear perfusion scanning or coronary angiography could be supported.

Polypharmacy

Similar patients are often taking multiple tablets (perhaps 8–10) to control their BP, diabetes and dyslipidaemia. The solution is to choose cooperative drugs to work together rather than providing therapy for each problem separately. Since this patient is not picking up all her prescriptions, she would be a good candidate for a medicines management domiciliary visit from the local pharmacist. Fixed dose combination tablets were favoured by some of the group, but it was suggested that pharmacist advisers within primary care trusts may be penalised for using these combination tablets.

Case study 3. Mr MI

Richard is 62 and was discharged from hospital one year ago after an MI. He is a self-employed electrician and lives at home with his wife. His father died of a stroke, aged 68. He is now very aware of the dangers of heart disease and both he and his wife are concerned about the future.

Richard's first hospital blood sample showed TC 8.2 mmol/L, LDL 5.6 mmol/L, HDL 1.0 mmol/L, TG 3.6 mmol/L, BP 162/90 mmHg and BMI 31. He is now taking simvastatin 20 mg, aspirin 75 mg, ramipril 2.5 mg bd and atenolol 50 mg.

He attended the post-MI clinic following discharge and was seen by the hospital dietician. He currently attends a practice nurse-run secondary prevention clinic where he has been given further advice about diet, lifestyle and smoking cessation.

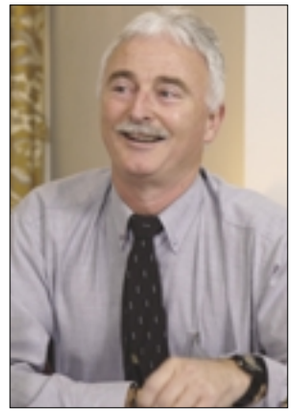
Following initial discussion, the Chair revealed that at review Richard's TC was 6.1 mmol/L, LDL 3.6 mmol/L, HDL 1.2 mmol/L and TG 2.3 mmol/L, despite increasing simvastatin to 40 mg; his liver function tests showed ALT 70 IU/L, bilirubin 24 µmol/L, AST normal, gamma GT normal, CPK 220 IU/L; his fasting glucose is 6.4 mmol/L and his BMI remains at 31.

Case study 3 discussion

The group agreed that the outlook for this patient could be substantially improved – his BP is very poorly controlled, he is overweight and his lipid profile is very detrimental. At the very least he should have the doses of simvastatin and ramipril significantly raised. In the year since his MI he should have been risk-stratified to assess the risk of further events and the need for revascularisation. Assuming that he does not need revascularisation, he does require very aggressive secondary prevention.

Rehabilitation programmes

Most hospitals invite patients to a cardiac rehabilitation programme, which usually includes exercise sessions and advice on lifestyle such as healthy eating and relaxation techniques. Richard ideally should have been enrolled on a cardiac rehabilitation programme: patients expect it and do feel better for it. Weight loss would help many of his risk factors, but some combination of lipid-lowering therapy will probably be needed.



John Pittard

Acute measurement of blood lipids significantly improves patient care. Previously, a stabilisation period of three months preceded measuring lipids but nowadays blood is drawn in casualty following an acute event and used to measure total and HDL cholesterol. (The TG level is unreliable because the patient is unlikely to be fasted.)

Drugs at discharge

The group agreed that the patient's drug doses

needed to be changed: they were almost certainly the drugs prescribed at discharge. Dr Pittard explained that when patients leave hospital they have undue reliance on the credibility of the SHO's prescription; and the GP assumes that the prescription comes directly from the consultant and does not wish to change it. Dr Pittard added that we need to be more proactive in managing the patient's transition from secondary to primary care.

In the practice nurse-run secondary prevention clinic, it is critical that the nurses should have appropriate guidance, perhaps with algorithms, to prompt treatment and changes in treatment. "This man's clinical picture is correctable," said Dr Belsey, "but I fear that for organisational reasons it may not be corrected."

Dr Weston described his local scheme that employs four nurses to span the link between secondary and primary care. Hospital-trained 'interface' nurses follow patients and do a domiciliary visit; they then liaise with practice nurses and transfer the patients to them.

Creatine kinase (CK)

The patient's borderline CK level engendered some debate. Some felt that it was clinically irrelevant in terms of his statin whereas others felt nervous about pushing up the statin dose. Another view was that his liver enzymes were of greater concern than his raised CK level. We do not routinely measure CK levels in patients taking statins, and when we do we find quite a few randomly elevated levels. This is partly explained by the fact that reference CK levels are set in the hospital population. When people lie in bed for extended periods CK levels tend to decrease, whereas in a free-living population these levels tend to be higher.

Dr Belsey pointed out that if we wanted to increase this patient's dose of statin we could check his enzyme levels in 3–4 weeks and decide what action to take on the basis of these repeat levels. Dr Weston commented that this patient's CK was high enough to provoke a suspicion of minor myocardial infarction if he went to hospital complaining of chest pain, unless troponin levels were measured as well.

Diabetes

Professor Betteridge found it interesting that this patient's fasting glucose is 6.4 mmol/L in relation to a recently published study from Sweden where an oral glucose tolerance test was done in hospital on 186 people admitted to the coronary care unit (CCU). The findings revealed that at discharge roughly one third of patients had impaired glucose tolerance and roughly one third had diabetes; these test results persisted at three months. So are we underdiagnosing glucose intolerance, diabetes and metabolic syndrome in the CCU, and do we need to target these as well?

Fish and fish oils

A fish oil supplement, and oily fish as part of healthy eating, may be of some help to this man, though we do not know yet where fish oil stands in terms of secondary prevention. The DART trial showed that eating oily fish reduced events in secondary prevention; and the GISSI Prevenzione trial using one Omacor capsule a day showed a reduction in sudden death, possibly due to its antiarrhythmic effects.

Clive Weston

Getting this patient to goal will take some effort since his starting cholesterol was 8.2 mmol/L. Although he is being given simvastatin 40 mg, a dose shown to be effective in clinical trials, he is not to goal. One further issue to explore in this man is his alcohol consumption, since he is overweight and both his ALT and his TG are elevated. The raised ALT could be related to fatty liver secondary to glucose intolerance and hypertriglyceridaemia. Since Richard still had a cholesterol of 6.1 mmol/L and evident vascular disease at review, Professors Betteridge and Shepherd agreed that there was no room for complacency about his lipid profile.

Beta blockers

It is clear that beta blockers save lives post-MI but there is debate over their effect on their dyslipidaemic profile, how long patients should take these drugs and at what dose. Dr Weston was reassured that concern over the dyslipidaemic profile associated with beta blockers had previous relevance but that the new generation of beta blockers make no difference to the lipid profile. "We are talking about a trivial or even a negligible variation," said Professor Shepherd. There might be issues concerning atenolol in the longer term in cases of frank diabetes, however, as suggested by the LIFE trial.

Dr Pittard commented that we use a lot of atenolol in this country whereas trials typically use metoprolol: perhaps we should consider switching patients to the latter agent by six months. About half of patients treated for hypertension with atenolol come off by six months because they cannot tolerate the side effects. As an alternative, he switches patients to bisoprolol or nebivolol, which are more beta-selective and have higher tolerability. Many doctors give up on beta blockers without looking at other options in the class, he said. Professor Betteridge concurred, saying that EUROASPIRE data show that we are down to about 40% beta blocker use in the UK compared to 80% in Scandinavia.

Case study 4. Mr Familial Hypercholesterolaemia

Jason is 34 and was diagnosed at 29 with heterozygous familial hypercholesterolaemia (FH) after his brother was admitted to hospital with an MI at the age of 36. At diagnosis, Jason's TC was 10.3 mmol/L, LDL 8.7 mmol/L, HDL 1.1 mmol/L and TG 1.1 mmol/L. His mother died aged 57 (sudden death) and his maternal uncle died aged 47 (sudden death). Jason is very health-conscious, eats a balanced diet and is part of a local rowing team. He works as a financial adviser based in the City of London and lives with his wife and two-year-old daughter.

He was started on atorvastatin 20 mg, but with little response, and titrated up to atorvastatin 80 mg and cholestyramine 4 g bd, which he has now been taking for three years. Jason was referred to a dietician on diagnosis. He attends yearly review with his lipidologist.

The Chair then revealed to the group that although the patient's cholesterol measurements have been stable for about six months at TC 7.0 mmol/L, LDL 4.9 mmol/L, HDL 1.4 mmol/L and TG 1.5 mmol/L, 10 days ago the patient was admitted with an episode of chest pain. There were no obvious changes on ECG and his troponin T was not raised. In addition, it was revealed that Jason has another brother and sister.

Case study 4 discussion

Much is known about the science of FH, but little is known about how to manage it properly because the tools at our disposal sometimes do not match the severity of the disease. This patient has quite severe FH and his response to treatment is inadequate so other ways need to be found to reduce his lipid profile.

Investigations

There was extended discussion of the investigations that might be performed for this patient, in particular to determine the extent of coronary disease and to search for any fixed stenosis. An exercise test and myocardial perfusion scanning were suggested and, in view of his recent episode of chest pain, angiography might well be performed. Electron beam CT scanning for calcification scoring, carotid Doppler studies and ankle:brachial indexes were further possibilities.

"It is important to treat the whole patient rather than just the lipid levels," said Professor Betteridge. "In my practice I have a low threshold for non-invasive cardiac testing."

Treatment

Professor Shepherd explained the wide variation in responsiveness to statins. When considering a disease that results in a raised lipid profile where the levels in the circulation depend on a number of genes, then modifying one gene or stimulating the activity of one gene (as statins do) will not solve the problem. It will give some sort of benefit, but this may be counteracted in the individual by an increased propensity to absorb cholesterol. If multiple genes are interacting with the process that you are trying to deal with, you have to look at the possibility of giving multiple therapies to deal with that process.

Since the advent of the statins, partial ileal bypass (with its associated problems of dumping syndrome, etc.) has largely become of historical interest only.

Assessing the family

The group agreed that they should be assessing other members of this patient's family. His daughter should be investigated when she is about 12 years of age. Screening individuals from families with known FH is very rewarding as there is a 50/50 chance of identifying the disease given that it is an autosomal dominant condition.

Conclusions

The case histories have been approached from the perspectives of the multidisciplinary team – primary care, secondary care, practice nurses, dieticians, rehabilitation clinics and the patients themselves, said Professor Betteridge. A co-ordinated effort is required to get patients to goal.

As yet, treatments for metabolic syndrome in its entirety are not available, therefore multiple risks require individual treatment. The ethnic origin of patients is also highly relevant, in that south Asian people seem to be at particularly high risk of metabolic syndrome. When considering treatment, clinicians need to consider the impact of treatment on other risk factors. To do this effectively requires education – healthcare professionals must talk patients through their health problems and explain why they need each drug in order to improve adherence.

The challenges to best practice in hyperlipidaemia consist of translating the evidence from clinical trials into best care for individual patients. EUROASPIRE and other recent research findings reveal improvement, but there is still great potential for improving patient care.

Barriers to best care in hyperlipidaemia

- Patients' and doctors' perceptions and their experience of current medications and doses.
- Side effects which may or may not be attributable to the drug.
- Failure to titrate.
- Inadequate treatment for other risk factors such as raised glucose levels.
- Doses given in clinical practice do not match those shown in clinical trials to have effect.
- Multiple cardiovascular risk factors lead to polypharmacy, itself a tremendous barrier to adherence and a challenge for prescribers.

The way forward

Many of our patients will be given appropriate treatment and are straightforward to manage. But a substantial proportion will have multiple risk factors, a worrying family history, will present complex difficulties in treatment and will not reach the goals set by national guidelines. Newer agents and combination therapy may give us another opportunity to address these patients and help them to reach cholesterol goals.

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This supplement has been sponsored by Merck Sharp & Dohme Limited and Schering-Plough Limited. It was written by staff writers of The British Journal of Cardiology and independently reviewed by members of the editorial board. The report was edited by supplements editor, Dr Rachel Arthur.