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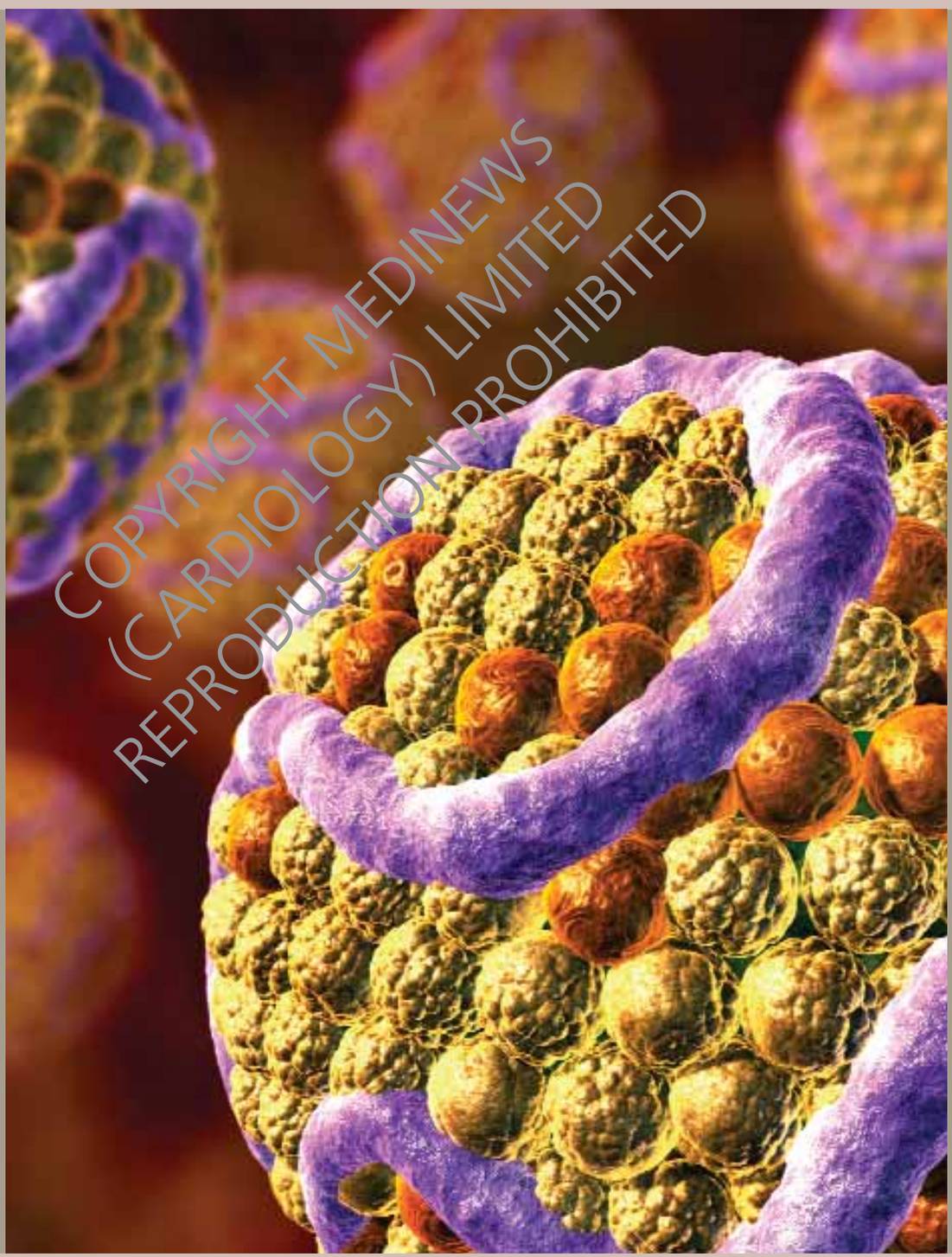
Cholesterol metabolism

Treating to lower targets

Treatment options

New treatment algorithm

The multidisciplinary approach



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BEST PRACTICE PRINCIPLES FOR CHOLESTEROL LOWERING

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Front cover: Computer artwork of balls of cholesterol in a blood vessel.
(Credit: David Mack/Science Photo Library)

The best practice principles laid out in this document were developed following a panel meeting which took place in February 2006. The panel of experts was a multidisciplinary group of medical professionals who were convened to develop an effective treatment algorithm and to discuss and raise the profile of cholesterol management in the UK.

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Best practice principles for cholesterol lowering

NIGEL CAPPS, MARC EVANS, TERRY MCCORMACK, JAN PROCTER-KING, GERSHAN DAVIS, STEWART FINDLAY, CLIVE WESTON, JONATHAN MORRELL

Introduction

In 2006, 78% of patients with coronary heart disease (CHD) achieved the National Quality and Outcomes Framework (QOF) of the General Medical Services (GMS) target of 5.0 mmol/L for total cholesterol.[1] This is a significant achievement in secondary prevention and shows that the standard of care in the UK is becoming aligned with that of the rest of Europe.[2] Nevertheless, the UK still has one of the highest CHD mortality rates in Europe,[2] and we need therefore to continue to work towards improving the quality of care and achieving more clinically meaningful targets for high-risk patients. The current targets outlined by the GMS for lipid lowering are less stringent than the newer evidence-based recommended targets of <4.0 mmol/L for total cholesterol and <2.0 mmol/L for low-density lipoprotein cholesterol (LDL-C) suggested by the recent Joint British Societies' Guidelines on Prevention of Cardiovascular Disease in Clinical Practice (JBS2).[3] This supplement outlines a new treatment algorithm for suggested best practice for cholesterol lowering, incorporating the latest strategies and thinking.

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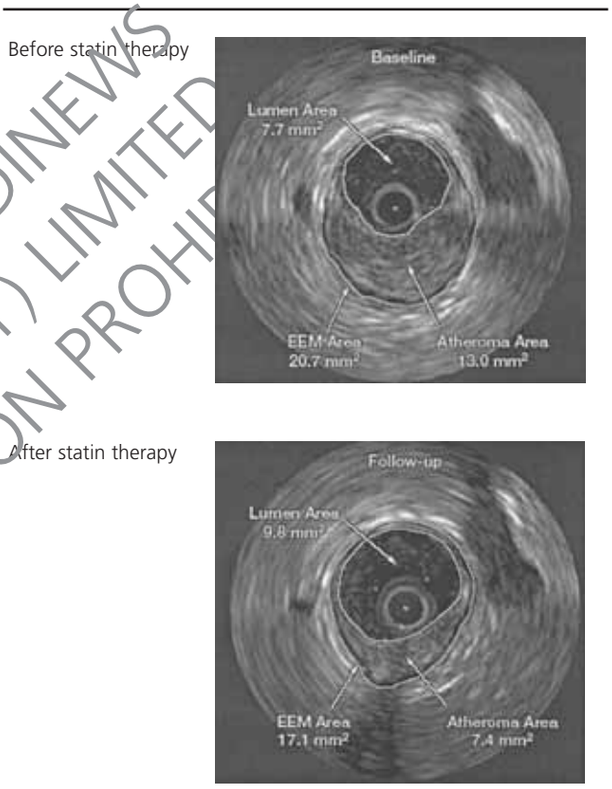
Figure 1. Lesion showing plaque regression and concomitant constrictive remodelling before and after 18 months of statin therapy in the Reversal of Atherosclerosis with Aggressive Lipid Lowering Therapy (REVERSAL) trial



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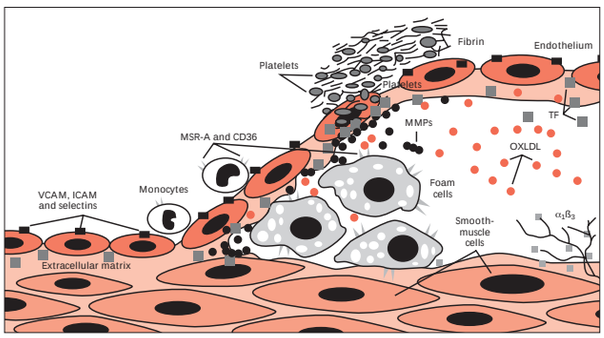
With many clinical issues competing for our attention, it is easy to forget that cholesterol is the single biggest risk factor for coronary heart disease (CHD) – greater than the individual risks

Br J Cardiol 2007;**14**(suppl 1):S1–S16

Figure 2. Illustration of a high-risk atherosclerotic plaque – with its thin fibrous cap, large lipid core, numerous inflammatory cells and high thrombosis, re-thrombosis and stenosis potential

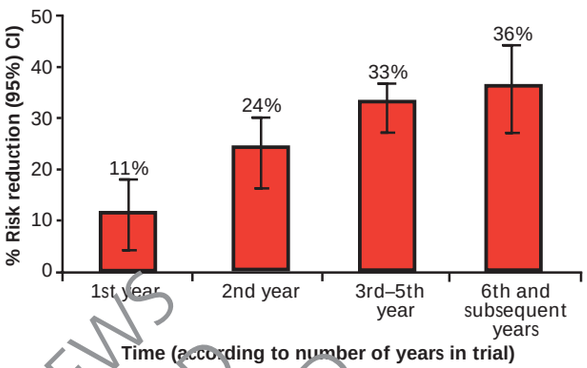


Reproduced with permission from Lipinski MJ, Fuster V, Fisher EA, Fayad ZA. Technology insight: targeting of biological molecules for evaluation of high-risk atherosclerotic plaques with magnetic resonance imaging. *Nat Clin Pract Cardiovasc Med* 2004;**1**:48-55

- Atherosclerosis begins when excess low-density lipoprotein (LDL) accumulates within the arterial wall and triggers an inflammatory response
- Fat-laden macrophages and T-cells produce the earliest form of atherosclerotic plaque
- As inflammation continues, the plaque grows, and a fibrous cap forms over the fatty core
- With time, inflammatory substances can weaken the fibrous cap
- If the plaque ruptures, a thrombus forms
- If the thrombus blocks blood flow to the myocardium, a myocardial infarction occurs

Key: VCAM = vascular cellular adhesion molecule; ICAM = intercellular adhesion molecule; OXLDL = oxidised low-density lipoprotein; MMP = matrix metalloproteinase; TF = tissue factor; MSR-A = anti-human macrophage scavenger receptor

Figure 3. Reduction in risk (95% CI) of ischaemic heart disease events (IHD death and non-fatal myocardial infarction) for every 1.0 mmol/L decrease in serum low-density lipoprotein cholesterol (LDL-C), according to the duration of cholesterol treatment



Based on data from: Law MR, Wald NJ, Rudnicka AR. *BMJ* 2003[19]

associated with high blood pressure, smoking, obesity or lack of exercise.[4] According to the latest statistics from the British Heart Foundation, there are 1.2 million people in the UK who have had a myocardial infarction (MI), 40% of whom are under the age of 65 years.[5] Prevalence rates of MI increase with age and are higher in men than in women.[6] The majority (70%) of the working population over the age of 45 years have raised cholesterol levels, which are above the current GMS target of 5.0 mmol/L.[7]

The clinical benefits of reducing low-density lipoprotein cholesterol (LDL-C) have recently taken on a new significance with the results of the Reversal of Atherosclerosis with Aggressive Lipid Lowering Therapy (REVERSAL) trial, which demonstrated that greater than 50% reductions in LDL-C were associated with a regression in atheroma volume (figure 1).[8,9] This study suggested, for the first time, that intensive lipid-modulating strategies could slow or even reverse the advance of atherosclerosis. Furthermore, the A Study To Evaluate the effect of Rosuvastatin On Intravascular ultrasound-Derived coronary atheroma burden (ASTEROID) trial, which looked at the impact of high-dose statin therapy on the rate of atheroma progression, showed that a reduction of LDL-C by 53% and an increase in high-density lipoprotein cholesterol (HDL-C) by nearly 15% over the 24-month treatment period correlated with a 7–9% reduction in plaque volume, suggesting that intensive modification of lipid levels with high-dose statin therapy can promote atheroma regression.[10]

Based on increasingly compelling evidence for the benefits of cholesterol lowering, the Joint British Societies (JBS) have defined new lower targets for the effective treatment of cholesterol.[3] This second set of guidelines suggests that in high-risk patients clinicians should be aiming for optimal control with a target of <2.0 mmol/L for LDL-C and <4.0 mmol/L for total cholesterol, or a 30% reduction in LDL-C and a 25% reduction in total cholesterol, whichever is the lower absolute value.[3]

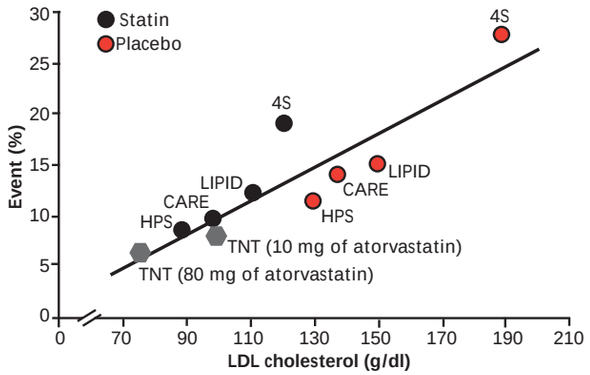
The science of cholesterol and its metabolism

Primary adviser: Dr Nigel Capps

Cholesterol is an important biological molecule that has a central role in membrane structure as well as being a precursor for the synthesis of the steroid hormones. There are two main sources: cholesterol which is synthesised *de novo* and that which is absorbed by the intestine from dietary and recycled biliary sources.

Because cholesterol is an insoluble molecule, it must be packaged and transported by special particles in the plasma called lipoproteins. The same is true of cholesteryl esters, the form of cholesterol that is stored in cells. High-density lipoproteins (HDL) remove excess free cholesterol from cells in peripheral tissues, while low-density lipoproteins (LDL) move cholesterol into the tissues.

Figure 4. The correlation between event rates* and low-density lipoprotein cholesterol (LDL-C) during statin therapy in secondary prevention studies (where 1 mmol/L = 39 mg/dL)

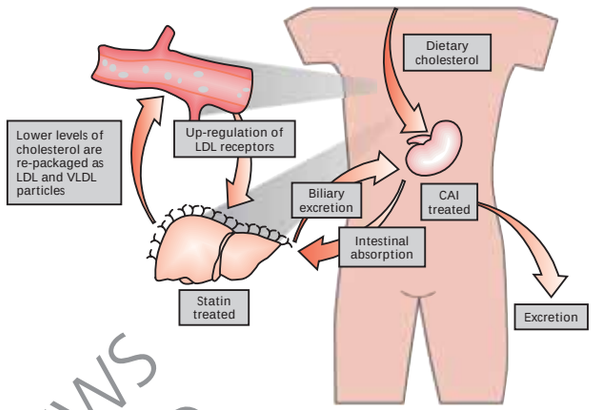


Based on data from LaRosa JC, Grundy SM, Waters DD *et al. N Engl J Med* 2005[21]

* Event rates for HPS, CARE and LIPID are for death from CHD and non-fatal myocardial infarction. Event rates for 4S and the TNT study also include resuscitation after cardiac arrest

Key: HPS = Heart Protection Study; CARE = Cholesterol And Recurrent Events; LIPID = Long-term Intervention with Pravastatin in Ischaemic Disease; TNT = Treating to New Targets; 4S = Scandinavian Simvastatin Survival Study; CHD = Coronary Heart Disease

Figure 5. Cholesterol lowering by dual inhibition of cholesterol absorption (with ezetimibe) and the *de novo* synthesis of cholesterol (with a statin)



- Statins inhibit cholesterol synthesis by inhibiting hydroxymethylglutaryl (HMG)-CoA reductase, a key step in the biosynthesis of cholesterol[25]
- By inhibiting cholesterol production in the liver, statins reduce hepatic cholesterol stores. This produces an up-regulation of low-density lipoprotein (LDL) receptors and increased clearance of cholesterol from the blood
- The reduced absorption of cholesterol with ezetimibe reduces the amount of cholesterol delivered to liver as chylomicron particles, for re-packaging and re-secretion into the blood as very low-density lipoprotein (VLDL) and LDL particles[25]
- Ezetimibe also reduces the stores of hepatic cholesterol and so augments the action of statins by promoting the more rapid clearance of circulating LDL cholesterol from the blood vessels through the up-regulation of the LDL receptors within the liver[25]
- Through these complementary mechanisms statins and ezetimibe, used in combination, produce marked reductions in plasma cholesterol levels[25]

Adapted from data on file, Merck Sharp and Dohme: http://www.vytorin.com/ezetimibe_simvastatin/vytorin/hcp/physician_resources/clinical_slide_sets.jsp?WT.svl=2

Key: CAI = cholesterol absorption inhibitor

The synthesis and utilisation of cholesterol must be tightly regulated in order to prevent its over-accumulation and abnormal deposition within the body. Of particular importance clinically is the abnormal deposition of cholesterol and cholesterol-rich lipoproteins (most notably LDL-C) in the coronary arteries. Such deposition, eventually leading to atherosclerosis, is the principal contributory factor in diseases of the coronary arteries (figure 2).[11] By contrast, early aggressive intervention to lower plasma concentrations of LDL-C promotes the removal of cholesterol from the vessel wall and plaque regression.[9]

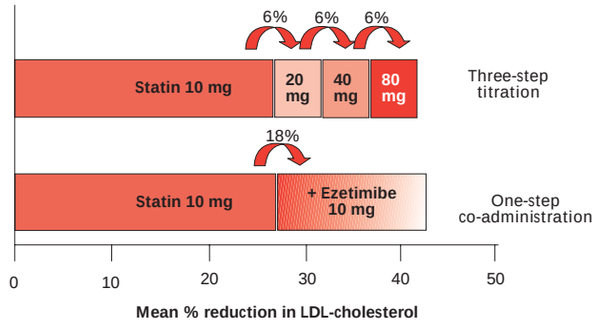
In the past, concern has been raised about potential dangers of reducing LDL-C to very low levels.[12] However, no causal link has been established between certain morbidities (such as depression and cancer) and cholesterol lowering with current treatment options.[13] There is a striking mismatch between normal physiological levels of total cholesterol (between 1.06 mmol/L and 2.58 mmol/L) recorded in newborns and current targets of 4.0 mmol/L with modern therapies.[3,14]

The liver is the centre of cholesterol homeostasis in the body. Cholesterol must be transported through blood to the liver for processing, degradation and secretion into bile. It is clear from a number of clinical studies that about two-thirds of the population has little, if any, change in plasma cholesterol levels when dietary cholesterol is increased, while the rest exhibit a high sensitivity to cholesterol intake because of high levels of cholesterol absorption.[15,16]

On average, healthy adults synthesise cholesterol at a rate of approximately 1.0 g per day and consume approximately 0.3 g per day. A relatively constant level of cholesterol in the body is maintained primarily by controlling the level of *de novo* synthesis. Cholesterol that is absorbed in excess of the body's requirements is re-packaged and secreted into the blood as very low-density lipoproteins (VLDL) and LDL particles.

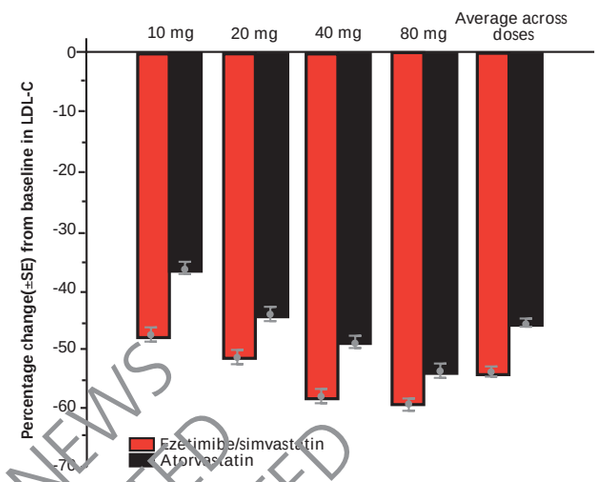
Cholesterol is also secreted by the liver into the bile. As a consequence, most of the free cholesterol delivered to the intestine is not from dietary sources but from biliary cholesterol and also from the sloughing of epithelial cells. The body absorbs approximately 50% of the free cholesterol in the intestine – and so effectively recycles much of the cholesterol secreted in the bile. The reason for the evolution of this mechanism for cholesterol re-absorption is unclear since the body is able to produce all the cholesterol needed for cellular homeostasis.

Figure 6a. The rule of six and the rationale for dual inhibition



Based on data from Stein E. *Eur Heart J* 2001[26]

Figure 6b. Mean low-density lipoprotein cholesterol (LDL-C) reduction from baseline with ezetimibe/simvastatin (10/20 mg) compared with atorvastatin 20 mg, 40 mg or 80 mg



Data from Ballantyne CM, Abate N, Zhong Y *et al. Am Heart J* 2005[30]

Why we should treat to lower targets

Primary adviser: Dr Nigel Capps

LDL-C is the primary target for reducing CHD risk and for lowering the overall burden of atherosclerosis in an individual.[3,17] Trials consistently show that the greater the reduction in LDL-C and the longer the duration of treatment, the greater the reduction in coronary events.[3,18] The most compelling evidence comes from the statin trials, which show that cholesterol lowering reduces morbidity (by lowering the risk of non-fatal events) and prolongs survival (by reducing the incidence of fatal events) both in patients with atherosclerotic cardiovascular disease (CVD) and those at high risk of atherosclerosis (figure 3).[19]

According to recent calculations by the Cholesterol Trialists' Collaborators, every 1.0 mmol/L reduction in LDL-C is associated with a 12% decrease in all-cause mortality, a 19% decrease in coronary mortality and a 19% decrease in stroke, independent of the LDL-C level prior to the start of treatment.[15,20]

There can be no doubt that statin studies have fundamentally revised our thinking on the ideal serum cholesterol levels, showing a continuous relationship between vascular risk and serum cholesterol levels with no apparent lower threshold level (figure 4).[21] Data from the Treating to New Targets (TNT) trial showed that aggressive lipid lowering to mean LDL-C levels of 2.0 mmol/L (77 mg/dL) with atorvastatin 80 mg was associated with a 22% relative risk reduction of cardiovascular events (hazard ratio = 0.78; 95% CI 0.69, 0.89; p=0.0002) compared with moderate reduction to LDL-C levels of 2.6 mmol/L (101 mg/dL) with atorvastatin 10 mg. While dose titrations with atorvastatin only achieved relatively modest reductions in LDL-C, nevertheless the consequence was a significant decrease in cardiovascular events in high-risk patients.[8]

Moreover, trials with statins have found that the value of cholesterol lowering in terms of relative risk reductions is the same for all people with atherosclerotic disease, regardless of age, sex or type of vascular event or initial cholesterol levels.[3] The findings from statin trials reinforce the need for prolonged and substantial reductions in cholesterol in all high-risk patients.

The treatment options for cholesterol lowering

Primary adviser: Dr Nigel Capps

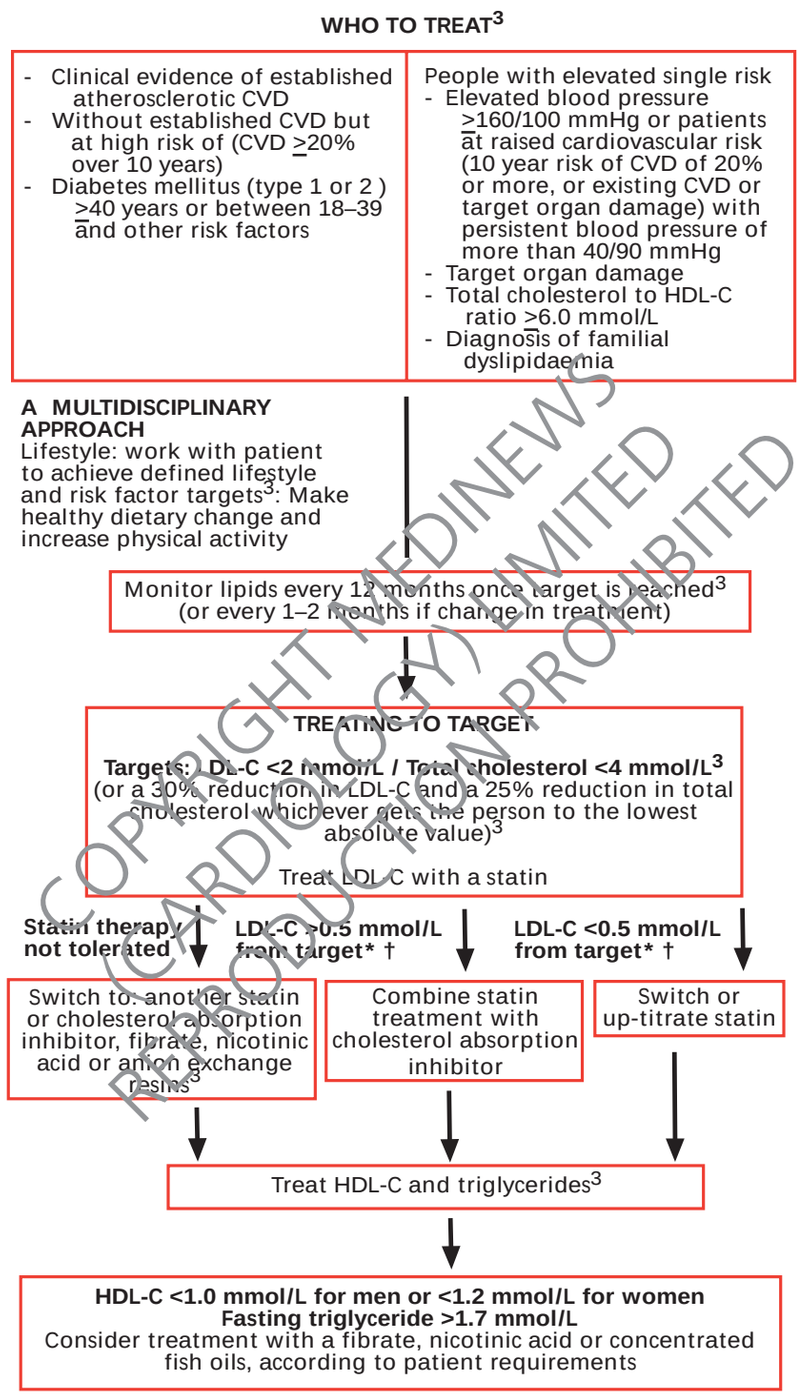
Among a number of far-reaching recommendations for cardiovascular risk management, the JBS2 guidelines now give new emphasis to LDL-C as one of the primary targets for lipid lowering, while recognising HDL-C, triglycerides and non-HDL-C as secondary parameters once LDL-C has been treated to target (especially in people with a mixed dyslipidaemia, which is most commonly seen in the metabolic syndrome and diabetes mellitus).[3]

In line with current evidence, the JBS2 recommend statins as the first-line treatment for all high-risk people with established atherosclerotic disease, diabetes mellitus (type 1 or type 2) or total cardiovascular disease (CVD) risk of ≥20% over 10 years (equivalent to a 15% CHD risk).[3] The statin class is the most potent of the lipid-lowering drug classes for lowering total cholesterol and LDL-C and has a good long-term tolerability record. The principal effect of statins is to lower LDL-C but they also raise HDL-C and lower triglycerides to some extent.[3]

For people with mixed dyslipidaemias, nicotinic acid, fish oils (n3 fatty acids; docosahexaenoic acid [DHA]/eicosapentaenoic acid [EPA]), and some fibrates (but not gemfibrozil) may be added to statin therapy on specialist advice to treat hypertriglyceridaemia and to raise HDL-C levels.[3] Fibrates and nicotinic acid increase HDL-C and reduce triglycerides but have only a modest effect on LDL-C whereas fish oils, at high doses, can reduce triglycerides.[3]

Bile acid sequestrants (binding agents) such as cholestyra-

Figure 7. A proposed new treatment algorithm for cholesterol lowering



* Or TC </> 1 mmol/L from target
† Refer to figure 8 for calculations to provide rationale

Figure 8. Joint British Societies' CVD risk prediction charts in men and women who are not diagnosed with diabetes

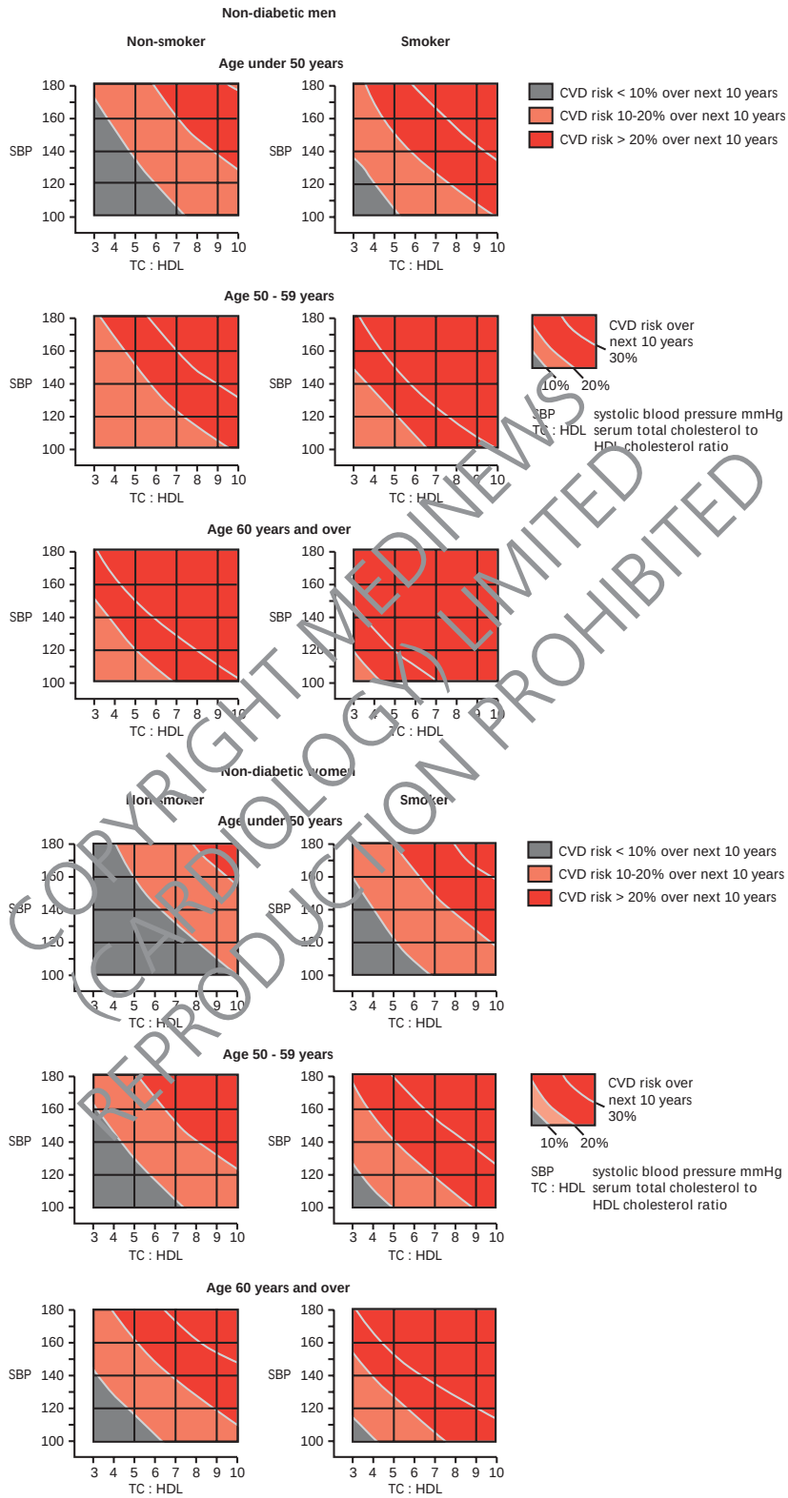


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Figure 9. Percentage reductions based on data from the STELLAR and VYVA trials to provide rationale for the benchmark treatment options in the patient algorithm

	%LDL-C reduction from baseline	Source	%TC reduction from baseline
Simvastatin 40 mg	-39	From STELLAR	-28
Simvastatin 80 mg	-46	From STELLAR	-33
Atorvastatin 40 mg	-48	From STELLAR	-36
Atorvastatin 80 mg	-51	From STELLAR	-39
Rosuvastatin 10 mg	-46	From STELLAR	-33
Ezetimibe 10 mg + Simvastatin 40 mg	-57	From VYVA	-41

Key: STELLAR = Statin Therapies for Elevated Lipid Levels compared Across doses to Rosuvastatin; VYVA = Vytorin Versus Atorvastatin; LDL-C = low-density lipoprotein cholesterol; TC = total cholesterol

Figure 10. Calculator for 25% reduction in total cholesterol and 30% reduction in low-density lipoprotein cholesterol (LDL-C)

Total cholesterol

Initial value	6.0	5.9	5.8	5.7	5.6	5.5	5.4	5.3	5.2	5.1	5.0
25% reduction	4.5	4.43	4.35	4.28	4.2	4.13	4.05	3.98	3.90	3.82	3.75

Initial value	4.9	4.8	4.7	4.6	4.5	4.4	4.3	4.2	4.1	4.0
25% reduction	3.67	3.60	3.52	3.45	3.37	3.30	3.22	3.15	3.07	3.00

LDL-C

Initial value	4.0	3.9	3.8	3.7	3.6	3.5	3.4	3.3	3.2	3.1	3.0
30% reduction	2.80	2.73	2.66	2.59	2.52	2.45	2.38	2.31	2.24	2.17	2.10

Initial value	2.9	2.8	2.7	2.6	2.5	2.4	2.3	2.2	2.1	2.0
30% reduction	2.03	1.96	1.89	1.82	1.75	1.68	1.61	1.54	1.47	1.40

Table 1. Recommendations of the JBS2 guidelines[3]

Equal priority given to all patients with:

- Clinical evidence of atherosclerotic CVD
- Diabetes mellitus (type 1 or 2) who are 40 years and over
- Diabetes mellitus (type 1 or 2) between 18 and 39 years and who have at least one of the following:
  - retinopathy (pre-proliferative, proliferative, maculopathy)
  - nephropathy, including persistent microalbuminuria
  - poor glycaemic control (HbA_{1C} >9 per cent)
- A total CVD risk of ≥20% over 10 years (equivalent to a 15% CHD risk)
- Elevated blood pressure ≥160 mmHg systolic or ≥100 mmHg diastolic or patients at raised cardiovascular risk (10 year risk of CVD of 20% or more, or existing CVD or target organ damage) with persistent blood pressure of more than 140/90 mmHg
- Elevated total cholesterol to HDL-C ratio ≥6.0
- Diagnosis of familial hypercholesterolaemia or dyslipidaemia.

mine can be used, but they are difficult to take and frequently cause gastro-intestinal upsets.[22,23] Plant stanol ester margarines such as Benecol™* and Flora pro-activ™† are also safe to use in combination with statins.[24]

If LDL-C targets are not achieved with a statin alone, despite the use of the maximum licensed statin dose or the maximum tolerated statin dose, the JBS2 also recommends that other classes of lipid-lowering drugs be used. In addition to those named above, these include the cholesterol absorption inhibitor ezetimibe, the first in a new class of drugs which augments the efficacy of statins through the inhibition of cholesterol absorption.[3]

Ezetimibe

Ezetimibe is a potent and selective inhibitor of cholesterol absorption from the small intestine,[25-27] and inhibits both dietary and recycled biliary cholesterol absorption from the intestine by blocking the action of the cholesterol transporter, Niemann-Pick C1 Like-1 Protein or an associated protein.[28,29] This mechanism is distinct from that of statins, which inhibit the *de novo* synthesis of cholesterol and thereby reduce hepatic cholesterol stores. By adding ezetimibe to a statin therefore, we take advantage of these two distinct mechanisms to promote a notable reduction in circulating levels of total and LDL-C (figure 5).[25]

From clinical trials, it has been observed that the initial LDL-C reduction with a statin depends on the potency and dose of that statin. However, for every subsequent doubling of the statin dose, there is generally a mean 6% incremental reduction in LDL-C.[26] As a consequence, a three-step titration, equivalent to increasing the dose from 10 to 80 mg, will result in approximately an additional 18% reduction in LDL-C (figure 6a).[26] Adding ezetimibe 10 mg to the lowest dose of a statin provides an equivalent LDL-C reduction to that of three dose titrations with that statin (figure 6a).[26] In the Vytorin Versus Atorvastatin (VYVA) study,[30] the combination of ezetimibe and simvastatin was compared with atorvastatin in patients with hypercholesterolaemia. The results are shown in figure 6b.

A proposed new treatment algorithm for lipid lowering

Primary adviser: Dr Marc Evans

This section discusses a suggested treatment algorithm for cho-

* Benecol™ is a registered trademark of Raisio plc, Finland; † Flora pro-activ™ is a registered trademark of Unilever Bestfoods UK Ltd

lesterol and LDL-C lowering, based primarily on the recommendation from the JBS2 and National Institute for Health and Clinical Excellence (NICE) Cardiovascular Guidance on Statins (figure 7). The algorithm uses scientific rationale from the STELLAR[31] and VYVA[30] trials (figure 9) to calculate accepted benchmark options, based on simvastatin 40 mg being widely regarded as the most cost-effective first-line treatment for all high-risk patients, as recommended by NICE.

Who to treat

Primary adviser: Dr Terry McCormack

The JBS2 guidelines have placed greater emphasis on the identification and appropriate treatment of people not only with clinical evidence of atherosclerotic disease, but also apparently healthy individuals with a high total CVD risk of ≥20% over 10 years (equivalent to a 15% CHD risk) (see table 1).[3] From the age of 40, all patients should be considered for a CVD risk assessment based on the prediction charts outlined in figure 8. Primary care is responsible for the identification, risk assessment and management of apparently healthy individuals (<40 years) with a family history of premature atherosclerotic disease.[3]

Additional traits which need to be factored into the final risk CVD assessments include: Indian subcontinent origin, which increases the risk by 1.5 times; a family history of premature CVD, and especially CHD (men <55 years and women <65 years) in a first-degree relative, which increases the risk by about 1.3; and hypertriglyceridaemia (>1.7 mmol/L) which increases the risk by a factor of 1.3.[3] Risk increases with age and therefore risk tables are biased towards elderly patients. To correct this, the new JBS2 tables are based on just three ages; 49, 59 and 69 years. This is intended to bring younger patients into the treatment zone. However, a final decision about using drug therapy will also be influenced by other factors, not included in the risk estimation model, such as co-existent non-vascular disease and life expectancy.[3]

In people with an acute coronary syndrome, cerebral infarction or transient ischaemic attack, a statin should, for practical reasons, be prescribed during the inpatient stay. For people with cerebral atherosclerotic disease a statin is indicated to reduce the risk of a further major cardiovascular event.[3]

A multidisciplinary approach

Primary adviser: Ms Jan Procter-King

There can be no doubt that better quality preventive care will result in fewer CVD events and a reduction in premature morbidity and mortality in patients aged less than 65 years. At the same time, the millions of patients who would now be eligible for assessment and treatment, as a result of the aspirational JBS2 guidelines, will put greater pressure on already stretched primary resources. The NICE guidance suggests that if all patients fulfilling the JBS2 criteria for high risk are treated, about 3.3 million patients will be eligible for statin therapy – this equates to more than 300 patients on the average practice list of about 6,000 patients.[32] Fortunately, the GMS Contract has provided primary care with additional resources to implement best practice policies. Equally, the impact of practice-based commissioning (PBC) will hopefully provide strong financial incentives for practices to consider the commissioning of the most appropriate health services to meet the longer-term health needs of their populations.

The future management of atherosclerotic disease will be increasingly protocol-driven and managed by primary care nurses, community pharmacists and the broader team. Improving the quality of practice data to identify and prioritise all adults >40 years and younger adults (<40 years) with a family history of premature atherosclerotic disease is the first step in the effective management of this group.

It is likely that nurses will not only have a key role in lifestyle interventions (encouraging patients to stop smoking, modify their diet and alcohol intake, exercise and lose weight), but also in the prescribing of lipid-lowering treatments according to agreed protocols.

Treating to target

Primary adviser: Dr Marc Evans

The JBS2 guidelines state that the priority for the management of patients with hyperlipidaemia or dyslipidaemia is the optimal control of total and LDL-C to targets of <4.0 mmol/L and <2.0 mmol/L, respectively, or a 25% reduction in total cholesterol and a 30% reduction in LDL-C, whichever is the lower absolute value[3] (see calculator, figure 10). Statins are the recommended first-line treatment for all high-risk people with established atherosclerotic disease, diabetes mellitus (type 1 or type 2) or total CVD risk of ≥20% over 10 years (equivalent to a 15% CHD risk).[3]

The National Service Framework (NSF) targets state that in individuals with CHD, other occlusive arterial disease or at high risk of CHD, total cholesterol should be <5.0 mmol/L or by a reduction of 30%, whichever is greater and LDL-C should be <3.0 mmol/L or a reduction by 30%, whichever is greater.[33] These guidelines are widely accepted as suitable targets for the general population. However, it is broadly thought that for high-risk patients, as identified by the criteria laid out in the JBS2 guidelines, the standard of care should be the lower values of <4.0 mmol/L for total cholesterol and <2.0 mmol/L for LDL-C.

Based on NICE assessments of the most cost-effective treatment, simvastatin 40 mg is widely regarded as the most appropriate first-line treatment for all high-risk patients. The Scandinavian Simvastatin Survival Study (4S) and Heart Protection Study (HPS) have shown that simvastatin 40 mg is an effective and well tolerated drug, reducing initial LDL cholesterol by more than 30%.[18,34,35]

Treatment should be reviewed four to six weeks after statin therapy has been initiated or changed.[3] Alternatives to be considered in patients who tolerate statin therapy poorly include other lipid-lowering therapies such as a cholesterol absorption inhibitor, fibrates, nicotinic acid or anion exchange resins. In situations where the patient does not reach the required target on simvastatin 40 mg, first consider whether the patient is taking

the medication correctly. Depending on how far the patient is from the target levels, alternatives to consider, at this stage, include increasing the simvastatin dose to 80 mg, adding ezetimibe (which further lowers LDL-C by around 20–25%)[3,36] or switching to a more efficacious statin. Compared with simvastatin 40 mg, atorvastatin 40–80 mg produces a further 10–15% reduction in LDL-C[37] while rosuvastatin 40 mg produces a further 16% reduction in LDL-C and 12% reduction in total cholesterol. As a guide, patients with a total cholesterol value of >5.0 mmol/L and/or an LDL-C >2.5 mmol/L are greater than 20% from the JBS2 targets of total and LDL-C of <4.0 mmol/L and <2.0 mmol/L, respectively.

While clinical trials show that switching statins is an effective strategy to improve lipid goal achievement,[38] a retrospective cohort study of new statin users found that switching statins substantially reduces the likelihood that patients will be compliant and remain on treatment long enough to obtain the full benefit of statin treatment.[39] For this reason, special care should be given to patients who change drugs to ensure appropriate compliance.

There are advantages and disadvantages to up-titrating the statin dose of either simvastatin 40 mg or atorvastatin 40 mg to the maximum 80 mg dose. As a general rule, the doubling of the statin dose will reduce LDL-C by a further 6%[26] but increased diligence will be required to monitor the patient for adverse effects, which will occur with greater frequency at the higher dose.[40]

The alternative is to consider a 'dual control' strategy combining 20, 40 or 80 mg of simvastatin with ezetimibe 10 mg (ezetimibe/simvastatin). The >50% LDL-C reduction achieved with the usual (lowest) dose of simvastatin 20 mg and ezetimibe 10 mg is similar to the LDL-C reduction with atorvastatin 80 mg (figure 6b). The advantage of combining statins with ezetimibe means that a lower dose of statin can be used. While adding ezetimibe to a statin offers a large reduction in LDL-C, adding a fibrate or nicotinic acid to a statin may be indicated in patients with low HDL-C or hypertriglyceridaemia.[41]

Key messages

- In line with latest guidance from the US, the standard of care now recommended by the JBS2 for high-risk patients is new lower targets of <4.0 mmol/L for total cholesterol and <2.0 mmol/L for LDL-C or a 25% reduction in total cholesterol and a 30% reduction in LDL-C, (whichever is the lower absolute value). These targets should be considered particularly relevant for those patients at high-risk of CHD (see section on 'Who to treat' for clarification of high-risk patients)
- According to the latest QOF guidance for 2006, a target for total cholesterol of <5.0 mmol/L should be considered the 'audit target' below which to aim all eligible CHD, CVD and diabetes mellitus patients
- CVD prevention should focus equally on those with established atherosclerotic disease, diabetes and apparently healthy individuals with a high CVD risk (>20% absolute risk over 10 years), irrespective of their starting level of total cholesterol
- Advances in statin therapy and the availability of new low-dose combination treatment with the cholesterol absorption inhibitor, ezetimibe, have made the delivery of new lower targets more achievable

Conflict of Interest Statements

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EZETROL®▼
(ezetimibe)
ABRIDGED PRODUCT INFORMATION

Refer to Summary of Product Characteristics (SPC) before Prescribing

Information about adverse event reporting can be found at www.yellowcard.gov.uk. Adverse events should also be reported to MSD-SP Ltd (tel: 01992 467272).

PRESENTATION

10 mg Tablet containing 10 mg of ezetimibe.

USES

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 dose. 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. *Skeletal muscle:* In post-marketing experience with 'Ezetrol', myopathy and rhabdomyolysis have been reported. Most patients who developed rhabdomyolysis were taking a statin concomitantly with 'Ezetrol'. However, rhabdomyolysis has been reported very rarely with 'Ezetrol' monotherapy and very rarely with the addition of 'Ezetrol' to other agents known to be associated with increased risk of rhabdomyolysis. If myopathy is suspected based on muscle symptoms or is confirmed by a creatinine phosphokinase (CPK) level >10 times the ULN, immediately discontinue 'Ezetrol', any statin, and any of these other agents. Advise all patients starting therapy with 'Ezetrol' of the risk of myopathy and to report promptly any unexplained muscle pain, tenderness or weakness. *Hepatic insufficiency:* Not recommended in patients with moderate or severe hepatic insufficiency due to the unknown effects of the increased exposure to 'Ezetrol'. *Fibrates:* The safety and efficacy of co-administration have not been established. There is a possible risk of cholelithiasis and gall-bladder disease in patients receiving fenofibrate and 'Ezetrol'. If suspected, conduct gall-bladder investigations and discontinue co-administration. *Ciclosporin:* Exercise caution when initiating 'Ezetrol' in patients taking ciclosporin and monitor ciclosporin concentrations. *Warfarin, another coumarin anticoagulant or fluindione:* Monitor the International Normalised Ratio (INR) if taken together with 'Ezetrol'. *Excipient:* 'Ezetrol' tablets contain lactose: do not use in patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption.

Interactions (studies have only been performed in adults): Colestyramine: Concomitant colestyramine administration decreased the mean AUC of total 'Ezetrol' approximately 55%. The incremental low density lipoprotein cholesterol (LDL C) reduction due to adding 'Ezetrol' to colestyramine may be lessened by this interaction. *Statins:* No clinically significant pharmacokinetic interactions were seen upon co-administration with atorvastatin, simvastatin, pravastatin, lovastatin, fluvastatin, or rosuvastatin.

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

Refer to SPC for complete information on side effects

Clinical studies

In clinical studies where 'Ezetrol' was administered alone or with a statin, 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=1,691) or co-administered with a statin (n=1,675), or with fenofibrate (n=185):

'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.

'Ezetrol' co-administered with fenofibrate:

Gastro-intestinal disorders: abdominal pain.

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.

In clinical trials, CPK >10 X ULN was reported for 4 of 1,674 (0.2%) patients administered 'Ezetrol' alone vs 1 of 786 (0.1%) patients administered placebo, and for 1 of 917 (0.1%) patients co-administered 'Ezetrol' and a statin vs 4 of 929 (0.4%) patients administered a statin alone. There was no excess of myopathy or rhabdomyolysis associated with 'Ezetrol' compared with the relevant control arm (placebo or statin alone).

Post-marketing experience

The following additional adverse reactions have been reported in post-marketing experience: [Rare (≥1/10,000, <1,000 or Very rare (<1/10,000)]

Blood and lymphatic system disorders: thrombocytopenia (very rare). *Immune system disorders:* hypersensitivity including rash (rare), urticaria (rare), anaphylaxis (very rare) and angioedema (very rare). *Gastro-intestinal disorders:* nausea (rare); pancreatitis (very rare). *Hepatobiliary disorders:* hepatitis (rare); cholelithiasis (very rare); cholecystitis (very rare). *Musculoskeletal and connective tissue disorders:* arthralgia (rare); myalgia (rare); myopathy/rhabdomyolysis (very rare). *Laboratory values:* increased transminases (rare); increased CPK (rare).

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

POM Date of review of prescribing information: December 2006

® denotes registered trademark of MSP Singapore Company, LLC

INEGY®▼
ezetimibe/simvastatin
ABRIDGED PRODUCT INFORMATION

Refer to Summary of Product Characteristics (SPC) before prescribing.

Information about adverse event reporting can be found at www.yellowcard.gov.uk. Adverse events should also be reported to MSD-SP Ltd (tel: 01992 467272).

PRESENTATION

Tablets containing 10 mg ezetimibe and 20, 40 or 80 mg of simvastatin.

USES

As adjunctive therapy to diet in: *Hypercholesterolaemia:* in primary (heterozygous familial and non-familial) hypercholesterolaemia or mixed hyperlipidaemia where use is appropriate:

- patients not appropriately controlled with a statin alone
- patients already treated with a statin and ezetimibe.

INEGY contains ezetimibe and simvastatin. Simvastatin (20-40 mg) has been shown to reduce the frequency of cardiovascular events. Studies to demonstrate the efficacy of INEGY or ezetimibe in the prevention of complications of atherosclerosis have not been completed. *Homozygous Familial Hypercholesterolaemia (HoFH):* Patients may also receive adjunctive treatments (e.g., low-density lipoprotein [LDL] apheresis).

DOSAGE AND ADMINISTRATION

For oral administration, with or without food. Put patients on an appropriate lipid-lowering diet and continue during treatment. *Hypercholesterolaemia:* The dosage range is 10/10 mg/day* through 10/80 mg/day in the evening. The typical dose is 10/20 mg/day or 10/40 mg/day given as a single dose in the evening. The 10/80 mg dose is only recommended in patients with severe hypercholesterolaemia and high risk for cardiovascular complications. Consider the patient's low-density lipoprotein cholesterol (LDL-C) level, coronary heart disease risk status, and response to current cholesterol-lowering therapy when starting therapy or adjusting the dose. Individualise the dose based on the known efficacy of the various dose strengths of INEGY and the response to the current cholesterol-lowering therapy. Make any adjustments at intervals of not less than 4 weeks. *Homozygous Familial Hypercholesterolaemia:* The recommended dosage is 10/40 mg/day or 10/80 mg/day in the evening. May be used as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis). *Coadministration with other medicines: Bile acid sequestrants:* dosing should occur either ≥2 hours before or ≥4 hours after administration of a bile acid sequestrant. *Amiodarone or verapamil:* the dose should not exceed 10/20 mg/day. *Ciclosporin or lipid-lowering doses (≥1 g/day) of niacin:* the dose should not exceed 10/10 mg/day*. *Diltiazem:* do not exceed 10/40 mg unless clinical benefit outweighs increased risk of myopathy and rhabdomyolysis. *Use in elderly:* no dosage adjustment required. *Use in children and adolescents:* not recommended. *Use in hepatic impairment:* no dosage adjustment required in 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. *Use in renal impairment:* no dosage adjustment required in moderate renal insufficiency. If treatment in patients with severe renal insufficiency (creatinine clearance ≤30 ml/min) is deemed necessary, implement dosages above 10/10 mg/day* cautiously.

CONTRA-INDICATIONS

Hypersensitivity to ezetimibe, simvastatin, or to any of the excipients. Pregnancy and lactation. Active liver disease or unexplained persistent elevations in serum transaminases. Concomitant administration of potent CYP3A4 inhibitors (e.g., itraconazole, ketoconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors and nefazodone).

PRECAUTIONS

Myopathy/Rhabdomyolysis: In post-marketing experience with ezetimibe, cases of myopathy and rhabdomyolysis have been reported. Most patients who developed rhabdomyolysis were taking a statin concomitantly with ezetimibe. However, rhabdomyolysis has been reported very rarely with ezetimibe monotherapy and very rarely with the addition of ezetimibe to other agents known to be associated with increased risk of rhabdomyolysis. Simvastatin, like other HMG-CoA reductase inhibitors, occasionally causes myopathy manifested as muscle pain, tenderness or weakness with creatine kinase (CK) above 10 X the upper limit of normal (ULN). Myopathy sometimes takes the form of rhabdomyolysis with or without acute renal failure secondary to myoglobinuria, and very rare fatalities have occurred. The risk of myopathy/rhabdomyolysis is dose related for simvastatin. *CK measurement:* CK should not be measured following strenuous exercise or in the presence of any plausible alternative cause of CK increase. If CK levels are significantly elevated at baseline (>5 X ULN), measure levels again within 5 to 7 days. *Before treatment:* Advise all patients starting therapy, or in whom the dose is being increased, of the risk of myopathy and to report promptly any unexplained muscle pain, tenderness or weakness. Exercise caution in patients with pre-disposing factors for rhabdomyolysis. Measure CK level before starting treatment in the following: elderly (age >70 years); renal impairment; uncontrolled hypothyroidism; personal or familial history of hereditary muscular disorders; previous history of muscular toxicity with a statin or fibrate; alcohol abuse. In these situations, clinical monitoring is recommended. If a patient has previously experienced a muscle disorder on a fibrate or a statin, initiate treatment with caution. If CK levels are significantly elevated at baseline (>5 X ULN), treatment should not be started. *Whilst on treatment:* If muscle pain, weakness or cramps occur measure CK levels and stop treatment if found to be significantly elevated (>5 X ULN). If muscular symptoms are severe even if CK levels are <5 X ULN, consider discontinuation. Discontinue if myopathy is suspected for any other reason. If symptoms resolve and CK levels return to normal, then re-introduction of INEGY or another statin-containing product may be considered at the lowest dose and with close monitoring. Stop therapy temporarily a few days prior to elective major surgery and when any major medical or surgical condition supervenes. *Measures to reduce the risk of myopathy caused by interactions:* The risk of myopathy and rhabdomyolysis is significantly increased by concomitant use with potent inhibitors of CYP3A4 (such as itraconazole, ketoconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, nefazodone, whose concomitant use is contra-indicated), as well as ciclosporin, danazol and gemfibrozil. If treatment with itraconazole, ketoconazole, erythromycin, clarithromycin or telithromycin is unavoidable, suspend therapy with INEGY during the course of treatment. The risk of myopathy and rhabdomyolysis is also increased by concomitant use of other fibrates, lipid-lowering doses (≥1 g/day) of niacin or by concomitant use of amiodarone or verapamil with higher doses of INEGY. There is also a slight increase in risk when diltiazem is used with the 10/80 mg dose. Concomitant intake with grapefruit juice should be avoided. Do not exceed 10/10 mg* daily in patients receiving concomitant medication with ciclosporin, danazol or lipid-lowering doses (≥1 g/day) of niacin. Weigh the benefits of the combined use with ciclosporin, danazol or niacin carefully against the potential risks of these combinations. Monitor ciclosporin concentrations in patients receiving INEGY and ciclosporin. The combined use of INEGY at doses higher than 10/20 mg daily with amiodarone or verapamil should be avoided unless the clinical benefit outweighs the increased risk of myopathy. *Liver enzymes:* Perform liver function tests before treatment and thereafter when clinically indicated. Patients titrated to the 10/80 mg dose should receive an additional test prior to titration, 3 months after titration to the 10/80 mg dose, and periodically thereafter (e.g., semi-annually) for the first year of treatment. Pay special attention to patients who develop elevated serum transaminase levels. Use cautiously in patients who consume substantial quantities of alcohol. *Hepatic insufficiency:* Not recommended in patients with moderate or severe hepatic insufficiency. *Other interactions: Cholestyramine:* Concomitant cholestyramine administration decreased the mean AUC of total ezetimibe approximately 55%. The incremental low-density lipoprotein cholesterol (LDL-C) reduction due to adding INEGY to cholestyramine may be lessened by this interaction. *Warfarin and other coumarin anticoagulants:* Very rare cases of elevated INR have been reported. Prothrombin time should be determined before starting INEGY and frequently enough to ensure that no significant alteration of prothrombin time occurs. *Fibrates:* concomitant use not recommended.

*The 10/10 mg tablet is not marketed in the UK. This dose can be met by co-administering 10 mg of each of ezetimibe and simvastatin.

SIDE EFFECTS: Refer to SPC for complete information on side effects.

Clinical Studies: The frequencies of adverse events are ranked according to the following: *Very common (≥1/10), Common (≥1/100, < 1/10), Uncommon (≥1/1000), < 1/100), Rare (≥ 1/10,000, <1/1000), Very rare (<1/10,000) including isolated reports.* INEGY: *Nervous system disorders:* Common: headache. *Gastro-intestinal disorders:* Common: flatulence. *Musculoskeletal, connective tissue, and bone disorders:* Common: myalgia: *Laboratory values:* The incidence of clinically important elevations in serum transaminases (ALT and/or AST ≥3 X ULN, consecutive) was 1.7% for patients treated with INEGY. Clinically important elevations of CK (≥10 X ULN) were seen in 0.2% of the patients treated with INEGY. *Post-marketing experience:* Adverse reactions reported for INEGY are consistent with those previously reported with ezetimibe and/or simvastatin. *In addition to the above, other side effects reported with one of the individual components may be potential undesirable effects with INEGY. Ezetimibe: Blood and lymphatic system disorders:* Very rare: thrombocytopaenia. *Gastro-intestinal disorders:* Common: abdominal pain, diarrhoea. Rare: nausea. Very rare: pancreatitis. *Hepato-biliary disorders:* Rare; hepatitis. Very rare: cholelelithiasis, cholecystitis. *Skin and subcutaneous tissue disorders:* Rare: hypersensitivity reactions, including rash, urticaria and very rarely, angioedema. *Musculoskeletal, connective tissue disorders:* Rare: arthralgia. Very rare: myopathy/rhabdomyolysis. *General disorders and administration site conditions:* Common: fatigue. *Laboratory values:* Rare: increased transaminases, increased CK. *Simvastatin: Blood and lymphatic system disorders:* Rare: anaemia. *Nervous system disorders:* Rare: dizziness, paraesthesia, peripheral neuropathy. *Gastro-intestinal disorders:* Rare: constipation, abdominal pain, dyspepsia, diarrhoea, nausea, vomiting, pancreatitis. *Hepato-biliary disorders:* Rare: hepatitis/jaundice. *Skin and subcutaneous tissue disorders: Rare: rash, pruritus, alopecia. Musculoskeletal, connective tissue and bone disorders:* Rare: myopathy, rhabdomyolysis, muscle cramps. *General disorders and administration site conditions:* Rare: aesthenia. A hypersensitivity syndrome has been reported rarely which included some of the following features: angioedema, lupus-like syndrome, polymyalgia rheumatica, dermatomyositis, vasculitis, thrombocytopenia, eosinophilia, red blood cell sedimentation rate increased, arthritis and arthralgia, urticaria, photosensitivity reaction, pyrexia, flushing, dyspnoea and malaise. *Laboratory values:* Rare: increases in γ-glutamyl transpeptidase, elevated alkaline phosphatase.

PACKAGE QUANTITIES AND BASIC NHS COST

28 Tablets 10/20 mg: £33.42
28 Tablets 10/40 mg: £38.98
28 Tablets 10/80 mg: £41.21

Marketing Authorisation numbers

10/20 mg: PL 19945/0008
10/40 mg: PL 19945/0009
10/80 mg: PL 19945/0010

Marketing Authorisation holder

MSD-SP Limited, Hertford Road, Hoddesdon, Hertfordshire EN11 9BU, UK

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