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The clinical and cost-effectiveness of intensive versus standard lipid lowering with statins in the prevention of cardiovascular events amongst patients with acute coronary syndromes: a systematic review

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The clinical and cost-effectiveness of intensive versus standard lipid lowering with statins in the prevention of cardiovascular events amongst patients with acute coronary syndromes: a systematic review

A WEST MIDLANDS HEALTH TECHNOLOGY ASSESSMENT COLLABORATION REPORT

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WEST MIDLANDS HEALTH TECHNOLOGY ASSESSMENT COLLABORATION (WMHTAC)

The West Midlands Health Technology Assessment Collaboration (WMHTAC) produces rapid systematic reviews about the effectiveness of healthcare interventions and technologies, in response to requests from West Midlands Health Authorities or the HTA programme. Reviews usually take 3-6 months and aim to give a timely and accurate analysis of the quality, strength and direction of the available evidence, generating an economic analysis (where possible a cost-utility analysis) of the intervention.

CONTRIBUTIONS OF AUTHORS:

Wendy Greenheld – Main reviewer: wrote protocol; undertook searches; undertook data inclusion/exclusion, data extraction and data analysis for systematic review of effectiveness; wrote summary, background and effectiveness sections.

Jayne Wilson – Second reviewer: advised on protocol; provided an independent assessment of data inclusion/exclusion and checked data extracted for systematic review of effectiveness; read and commented on the final draft.

Sue Bayliss – Information specialist: advised on search strategies.

Chris Hyde – Senior reviewer: advised on protocol; undertook data inclusion/exclusion, quality assessment and analysis for systematic review of economic evaluations; wrote economic analysis section; read and commented on the final draft.

CONFLICTS OF INTEREST:

None

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West Midlands Regional Evaluation Panel

Recommendation

Supported. Quality of Evidence: Level 1 – at least one properly designed randomised controlled trial

Anticipated expiry date:

2011

ABBREVIATIONS

ACC	American College of Cardiology
ACS	Acute coronary syndrome
AMI	Acute myocardial infarction
BCS	British Cardiac Society
CABG	Coronary artery bypass graft
CHD	Coronary heart disease
CI	Confidence interval
CRP	C-reactive protein
CVE	Cerebrovascular event
DM	Diabetes mellitus
DRG	Diagnosis-related group
ECG	Electrocardiogram
ESC	European Society of Cardiology
HF	Heart failure
HR	Hazard ratio
HDL-C	High-density lipoprotein cholesterol
HMG CoA reductase	3-hydroxy-3-methylglutaryl coenzyme A reductase
ICER	Incremental cost-effectiveness ratio
ITT	Intention to treat
LDL-C	Low-density lipoprotein cholesterol
Lp-PLA_2	Lipoprotein-associated phospholipase A_2
MI	Myocardial infarction
MINAP	Myocardial Infarction National Audit Project
NCEP	National Cholesterol Education Programme
NICE	National Institute for Health and Clinical Excellence
NNT	Number needed to treat
NSF	National Service Framework
NSTEMI	Non-ST-segment elevation myocardial infarction
PCI	Percutaneous coronary intervention
QALY	Quality-adjusted life-year
RCT	Randomised controlled trial
RR	Relative risk
STA	Single Technology Appraisal
STEMI	ST-segment elevation myocardial infarction
UAP	Unstable angina pectoris
WHO	World Health Organisation

DEFINITIONS

Units of measurement for clinical data on lipids: To-date there is no international uniformity regarding the units of measurement used in the reporting of clinical data on lipids. In Europe lipid levels (total cholesterol, LDL-C, HDL-C and triglycerides) are measured in mmol/l (the SI unit) whereas the conventional unit in the USA is mg/dl. The main studies identified in this report and US guidelines (Adult Treatment Panel III of the National Cholesterol Education Programme (NCEP)) use the US unit of measurement (mg/dl) whereas the UK guidelines use the SI unit (mmol/l). To convert total cholesterol, LDL-C and HDL-C from US units to SI units, or vice versa, a conversion factor of 0.0259 is required (the conversion factor for triglycerides is 0.0113):

- to convert from US to SI units multiply by the conversion factor
- to convert from SI to US units divide by the conversion factor

EXECUTIVE SUMMARY

Background

The efficacy of statins in reducing low-density lipoprotein cholesterol (LDL-C), cardiovascular events and total mortality is well-established and underpins current international guidelines which recommend an LDL-C level of <100mg/dl (2.6mmol/l) for patients with established coronary heart disease (CHD). Current Department of Health guidance recommends patients with established CHD should receive statins and dietary advice to lower total serum cholesterol concentrations to either <5mmol/l (193mg/dl) or by 25%, whichever is greater, and LDL-C to either <3mmol/l (116mg/dl) or by 30%, again whichever is greater. There is less consensus on the added benefits and risks from more intensive LDL-C lowering to levels substantially below 100mg/dl (2.6mmol/l). However the results of recent studies have led the Adult Treatment Panel III of the National Cholesterol Education Programme (NCEP) to introduce a more aggressive, but optional, LDL-C goal of <70mg/dl (1.8mmol/l) for patients at very high risk of CHD, even if baseline LDL-C levels are <100mg/dl (2.6mmol/l). Following an acute coronary syndrome (ACS) event the risk of further cardiovascular occurrences is especially high and growing evidence on the effectiveness of statins, in improving endothelial function, decreasing platelet activity and reducing vascular inflammation has fuelled the hypothesis that an early, intensive approach may be beneficial.

Aim

To review the clinical and cost-effectiveness of the early administration (within 14 days of an ACS index event) of high-dose statins, aimed at reducing LDL-C to levels <70mg/dl (1.8mmol/l), in comparison with standard statin therapy aimed at reducing LDL-C to levels <100mg/dl (2.6mmol/l) in the treatment of patients at high cardiovascular risk following an ACS.

Methods

For the systematic review of effectiveness the bibliographic databases of the Cochrane Library (CENTRAL), MEDLINE and EMBASE were searched up to July 2007, without language restriction. Supplementary hand searches of the included

studies' citation lists were undertaken along with searches of the research registers of ongoing trials (The National Research Register, Current Controlled Trials *meta*Register and ISRCTN database, and ClinicalTrials.gov) in October 2007. Finally enquiries were made to pharmaceutical companies and experts in the field. Included were randomised controlled trials (RCTs) that compared the clinical effectiveness of any high-dose/potency statin, initiated within 14 days of an ACS index event, aimed at reducing LDL-C levels to <70mg/dl (1.8mmol/l) with standard statin therapy, also initiated within 14 days of an ACS index event, aimed at reducing LDL-C levels to <100mg/dl (2.6mmol/l). The main outcomes sought were reductions in death from all causes, death from cardiovascular causes and cardiovascular events/procedures. For the economic analysis a systematic review of existing evaluations of the costs, quality of life and cost-effectiveness of lipid lowering amongst patients with CHD was undertaken. As for effectiveness the particular focus was on intensive lipid lowering in patients with ACS. MEDLINE, EMBASE, NHSEED and OHE HEED were searched up to June 2007 and enquiries made to pharmaceutical companies and experts in the field.

Results

Number and quality of studies and direction of evidence

The effectiveness review included two RCTs: Colivicchi et al's trial (n=81), and the PROVE IT-TIMI 22 trial (n=4,162). Both trials were well conducted adopting appropriate randomisation procedures and methods of analysis. Both compared high-dose atorvastatin (80mg/day) with standard lipid lowering therapy aimed at meeting an LDL-C target of <100mg/dl (2.6mmol/l). In summary evidence from both trials seemed to strongly support the effectiveness of early intensive lipid lowering with high-dose atorvastatin for high risk ACS patients. The main weight of evidence was provided by the larger PROVE IT-TIMI 22 trial (n=4,162). The median LDL-C levels achieved during follow-up in the PROVE IT-TIMI 22 trial were 62mg/dl (1.6mmol/l) in the high-dose (atorvastatin 80mg/day) group and 95mg/dl (2.5mmol/l) in the standard-dose (pravastatin 40mg/day) group. Kaplan-Meier event rates for the trial's primary endpoint of death or a major cardiovascular event at two years were 22.4% in the atorvastatin group and 26.3% in the pravastatin group. This represented a 16% (95%CI: 5-26%, p=0.005) reduction in the hazard ratio for death

or a major cardiovascular event in the atorvastatin group. A non-significant trend favouring high-dose atorvastatin emerged at 30 days and was consistent over the course of the trial. Intensive lipid lowering with atorvastatin also had a consistently beneficial effect on the trial's secondary endpoints. At two years there were statistically significant reductions in the risk of recurrent unstable angina (29%, p=0.02) and the need for revascularisation (14%, p=0.04), and non-significant reductions in the rates of death from any cause (28%, p=0.07) and death or myocardial infarction (18%, p=0.06). Stroke rates between the groups did not differ significantly.

Costs and efficiency

The review of economic evaluations included one cost-effectiveness study of intensive vs. moderate lipid lowering for ACS patients. A further relevant ongoing cost-effectiveness analysis was also identified[§]. The rationale for the economic model (Markov) included was to assess the cost-effectiveness of high-dose statin therapy in comparison with standard statin therapy using a life-time time horizon. The Markov model was well reported but, given its complexity, it was impossible to convey all its features in a journal article. A working copy of the model was requested but to-date has not been received. Access may have provided the opportunity to explore its working and evaluate the impact of using UK specific data as the model draws upon data from US sources and reports costs in US dollars (2005 prices). However, with the proviso that the only information is that in the journal article, the model appears to be of good quality. Its structure is plausible and includes most of the health states one would expect to be represented in order to capture the benefits which might arise from high as opposed to standard lipid lowering strategies. In general the cost-effectiveness of high-dose relative to standard-dose statins appears to be supported for ACS. The main challenge is the generalisability of the results to the UK given that the costs are derived from the US health-care system. However, if this is thought to be acceptable, the results of the cost-effectiveness modelling indicate that intensive lipid lowering with high-dose

[§] Details made available after the report's completion were tabled at the Regional Evaluation Panel meeting on 25th February 2008, but did not change the initial conclusion, and indeed strengthened it (a critical appraisal of the analysis is included as an addendum).

statins is highly likely to be cost-effective at the drug price differentials and willingness to pay thresholds operating in the NHS. For a drug price differential of 1.0 GBP/day (c 2.0 USD/day) the model suggests an ICER of 21,300 USD/QALY, or approximately 10,650 GBP/QALY.

Conclusion

For ACS patients the early use of high-dose/potency statins significantly reduces the risk of death or a major cardiovascular event in comparison with standard lipid lowering regimens. Overall, modelling of the cost-effectiveness of high-dose relative to standard-dose statins appears to support the use of high-dose statins for ACS patients. If we accept that the model's results, derived from the US health-care system, are generalisable to the UK, intensive lipid lowering with high-dose statins seems highly likely to be cost-effective at drug price differentials and willingness to pay thresholds likely to be operating in the NHS.

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1 AIM OF THE REVIEW

The aim of the review was to assess the clinical and cost-effectiveness of intensive versus moderate lipid lowering with statins in the prevention of cardiovascular events amongst patients at high cardiovascular risk following an acute coronary syndrome (ACS) event. It sought to compare the early administration (within 14 days of an ACS index event) of high-dose/high potency statins, aimed at reducing low-density lipoprotein cholesterol (LDL-C) to levels <70mg/dl (1.8mmol/l), with standard statin therapy (a low to moderate dose/potency initially with dosage adjustments up to the maximum if required) aimed at reducing LDL-C to levels <100mg/dl (2.6mmol/l).

2 BACKGROUND

The efficacy of statins in reducing LDL-C, cardiovascular events and total mortality is well-established[1-5] and underpins current international guidelines[6,7] which recommend an LDL-C level of <100mg/dl (2.6mmol/l) for patients with established coronary heart disease (CHD). Current UK Department of Health guidance recommends patients with established CHD should receive statins and dietary advice to lower total serum cholesterol concentrations to either <5mmol/l (193mg/dl) or by 25%, whichever is greater, and LDL-C to either <3mmol/l (116mg/dl) or by 30%, again whichever is greater.[8] There is less consensus on the added benefits and risks from more aggressive LDL-C lowering to levels substantially below 100mg/dl (2.6mmol/l). However the results of recent studies[9-13] have led the US Adult Treatment Panel III of the National Cholesterol Education Programme (NCEP)[14] to introduce a more aggressive, but optional, LDL-C goal of <70mg/dl (1.8mmol/l) for patients at very high risk of CHD, even if baseline LDL-C levels are <100mg/dl (2.6mmol/l). Following an ACS event the risk of further cardiovascular occurrences is especially high and growing evidence on the effectiveness of statins (even at low doses), in improving endothelial function, decreasing platelet activity and reducing vascular inflammation has fuelled the hypothesis that an early intensive approach may be beneficial.[15-17]

2.1 Description of underlying health problem

2.1.1 Epidemiology

CHD is a preventable disease that kills more than 110,000 people in England every year. More than 1.4 million people suffer from angina and 275,000 people have a myocardial infarction (MI) annually. CHD is the biggest cause of death in the country.[18] Prevalence of treated CHD rises with age. It has been estimated that 4.2% of men and 3.2% of women in England and Wales have treated CHD however this figure rises from 0.01% of men and women under 35 years of age to >20% of men and >16% of women aged 75 years and over.[19]

2.1.2 Acute coronary syndrome (ACS)

The term ‘acute coronary syndrome’ encompasses a range of thrombotic coronary artery diseases that includes unstable angina, non-ST-segment elevation myocardial infarction (NSTEMI) and ST-segment elevation myocardial infarction (STEMI). The unification of these conditions under a single term reflects the understanding that they are caused by a similar sequence of events characterised by erosion, fissuring or rupture of a pre-existing atherosclerotic plaque, leading to thrombosis (clotting) within the coronary arteries and impaired blood supply to the myocardium (heart muscle). The clinical spectrum of ACS results from the varying degree of coronary artery occlusion.[20]

2.1.2.1 Atherosclerotic plaque formation

Most people have some evidence of atherosclerotic plaque formation however, as a result of lifestyle and/or genetics, this process is more pronounced in some individuals. An atherosclerotic plaque is characterised by a lipid rich core with one side embedded within the coronary intima and the other side, the luminal surface, covered by a fibrous cap. This fibrous cap is a dense extracellular matrix of collagen, elastin and proteoglycans and its integrity is essential for the maintenance of plaque stability. The fibrous cap is most vulnerable at its shoulder, where it meets the normal vessel intima. It is at this site where a combination of enzymatic processes and inflammation begin to degrade the stability of the plaque. The susceptible

plaque will erode, fissure and ultimately rupture, providing a site for platelet adhesion. As platelets begin to gather, they are further activated by the binding of vonWillibrand factor and the expression of glycoprotein IIb/IIIa, resulting in platelet aggregation. Thrombosis will continue, eventually leading to coronary vessel occlusion.[20,21]

2.1.2.2 Symptoms of ACS

The symptoms of ACS are due to myocardial ischaemia, resulting from an imbalance between the supply and demand for myocardial oxygen. Myocardial ischaemia most often develops as a result of reduced blood supply, due to atherosclerotic plaques, to a portion of the myocardium. The plaques initially allow sufficient blood flow to match myocardial demand. When myocardial demand increases these areas of narrowing may become clinically significant and precipitate angina. Angina that is produced by exercise, eating and/or stress and subsequently relieved with rest is called chronic stable angina. Over time, the plaques may thicken and rupture, exposing a thrombogenic surface upon which platelets aggregate and thrombi form. The patient may note a change in the symptoms of cardiac ischaemia with changes in the severity or duration of symptoms. This condition is referred as unstable angina. The result of persistent ischaemia is MI. Patients who have symptoms of acute myocardial ischaemia and are tested by an electrocardiogram (ECG) may or may not have an ST-segment elevation. Complete occlusion of a coronary artery causes an ST-segment elevation and partial occlusion an ST-segment depression. If untreated most patients who have ST-segment elevation will ultimately develop a Q-wave acute myocardial infarction (AMI). However the aim of modern treatment with thrombolysis, or ideally primary angioplasty, is to open the artery and prevent full thickness infarction/Q-waves developing. Patients who have ischaemic discomfort without an ST-segment elevation are having either unstable angina, or a non-ST-segment elevation myocardial infarction that usually leads to a non-Q-wave MI.[20,21]

2.1.2.3 Diagnosis of ACS

The main diagnostic categories of ACS, unstable angina and MI, are defined by the serum concentration of cardiac enzymes and markers. The cardiac markers, troponin T and troponin I, are very sensitive to myocardial injury and damage. Minimal damage can be detected, allowing the identification of 'micro-infarcts' where there is an elevation in the troponin concentration without a significant rise in creatine kinase or other cardiac enzymes.[22] The use of troponin measurement has led to a blurring of the distinction between unstable angina and MI. The European Society of Cardiology (ESC)[23] and American College of Cardiology (ACC)[24] state that any elevation of a tropinin or the creatine kinase MB (muscle, brain) isoenzyme is evidence of myocardial necrosis and that the patient should be classified as having a MI. The British Cardiac Society (BCS) definition has three categories for ACS, with a threshold of serum troponin concentration above which clinical MI is diagnosed.[25] Patients with a troponin concentration below this threshold but above the reference range are designated as having an ACS with evidence of myocyte necrosis. This is similar to the previous World Health Organisation (WHO) definition of MI.[26] However most UK cardiology units are now adopting the ESC/ACC definition and labelling creatine kinase negative/troponin positive cases as MI's (personal correspondence with Dr Russell Davis, Consultant Cardiologist at Sandwell & West Birmingham Hospitals NHS Trust).

Table 1 Current definitions and prognosis of ACS according to troponin T concentration

	12 hr serum troponin T concentration (µg/l)		
	<0.01	**≥0.01 and <1.0**	**≥1.0**
BCS definition	ACS with unstable angina	ACS with myocyte necrosis	ACS with clinical myocardial infarction
ESC/ACC definition	unstable angina	myocardial infarction	myocardial infarction
WHO definition	unstable angina	unstable angina	myocardial infarction
30-day mortality[27]	4.5%	10.4%	12.9%
6-month mortality[27]	8.6%	18.7%	19.2%

From: Scottish Intercollegiate Guidelines Network. SIGN 93. Acute coronary syndromes. A national clinical guideline. February 2007[22]

2.1.2.4 Prognosis in ACS

Patients with ACS continue to have a poor outcome despite advances in modern therapies (see Table 1).[27] Of those admitted with a presumed ACS, 36% are ultimately diagnosed with MI. The 30-day and six-month mortality for patients with ACS is especially high amongst those with elevated troponin concentrations but is also elevated in those patients with unstable angina (troponin negative). The presence of ST-segment deviation is a stronger predictor of an adverse outcome than elevations in troponin concentrations.[22]

2.1.2.5 Treatment of ACS

Initial management

If an ECG confirms changes suggestive of MI (ST-segment elevations in specific leads, a new left bundle branch block or a true posterior MI pattern), thrombolysis may be administered or primary coronary angioplasty may be performed. In the former, medication is injected that stimulates fibrinolysis, destroying blood clots obstructing the coronary arteries. In the latter, a catheter is passed up a large artery to identify blockages in the coronary arteries, and balloon angioplasty and possibly stenting is performed. Additional first-line treatments generally include anti-

ischaemic agents (IV nitroglycerin, beta-blockers), antiplatelet agents (aspirin, clopidogrel) and antithrombins (heparin).[28]

If an ECG does not show typical changes, the term 'non-ST-segment elevation ACS' is applied. The patient may still have suffered a NSTEMI. The accepted management for unstable angina and NSTEMI is treatment with aspirin, heparin and clopidogrel, with intravenous glyceryl trinitrate and opioids if pain persists.[29]

Secondary prevention of cardiovascular events following an ACS

Treatment aimed at preventing future cardiovascular events may include aspirin, beta-blockers, ACE inhibitors, calcium channel blockers, diuretics and statins. Other classes of lipid lowering drugs (fibrates, bile acid sequestrants, cholesterol absorption inhibitors, nicotinic acid, omega-3 fatty acids) may be considered in addition to a statin if the total cholesterol and LDL-C targets have not been achieved, or if other lipid parameters such HDL-C or triglycerides need to be treated.[30]

2.2 Statins

Statins competitively inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase, an enzyme involved in cholesterol synthesis. Inhibition of HMG CoA reductase lowers LDL-C levels by slowing down the production of cholesterol in the liver and increasing the liver's ability to remove the LDL-C already in the blood. Statins are more effective than other lipid regulating drugs in lowering LDL-C but less effective than the fibrates in reducing triglyceride concentrations.[31] However statins reduce cardiovascular disease events and total mortality irrespective of initial cholesterol concentrations.[9]

As they affect the liver statins are contra-indicated in active liver disease. They are also contra-indicated in pregnancy and during breast feeding.

Side-effects of statins include reversible myositis and rhabdomyolisis (a rare but significant side-effect). If myopathy is suspected and creatine kinase is markedly

elevated (more than five times upper limit of normal), or muscular symptoms are severe, treatment should be discontinued. Other side-effects are headache, altered liver-function tests (rarely hepatitis), parasthesia, and gastro-intestinal effects including abdominal pain, flatulence, constipation, diarrhoea, nausea and vomiting. Rash and hypersensitivity reactions (including angioedema and anaphylaxis) have also been reported rarely.[31]

Five statins are currently authorised for use in the UK: atorvastatin, fluvastatin, pravastatin, rosuvastatin and simvastatin. Amongst the different drugs within the class there is considerable variation in terms of potency in reducing LDL-C (see Table 2). Dose for dose, there is roughly a hierarchy in LDL-C reducing efficacy: rosuvastatin, atorvastatin, simvastatin, pravastatin, fluvastatin, in declining order. Across-dose analyses have shown that rosuvastatin 10-80mg reduces LDL-C by a mean of 8.2% more than atorvastatin 10-80mg, 12-18% more than simvastatin 10-80mg, and 26% more than pravastatin 10-40mg (all $p<0.001$).[32]

Table 2 Statins: the drug types (and doses/potencies) available in the class

Statin	Doses available	Maximum dose	What dose constitutes a high potency?	What dose constitutes a low to moderate potency?
Atorvastatin	10, 20, 40 & 80mg tablets	80mg	40-80mg	10-20mg
Fluvastatin	20 & 40mg capsules & 80mg tablets	80mg	n/a	All (20 & 40 very low)
Pravastatin	10, 20 & 40mg tablets	40mg	n/a	All (10 & 20 very low)
Rosuvastatin	5, 10, 20 & 40mg tablets	40mg	10-40mg	5mg
Simvastatin	10, 20, 40 & 80mg tablets	80mg	Possibly 80mg	10-20mg low 40mg standard dose

From: personal correspondence with Dr Russell Davis, Consultant Cardiologist at Sandwell & West Birmingham Hospitals NHS Trust

2.2.1 Licensing indications relevant to UK practice

Atorvastatin

Atorvastatin (Pfizer Ltd) is a synthetic statin. It is licensed as an adjunct to diet for patients with primary hypercholesterolaemia, heterozygous familial hypercholesterolaemia, homozygous familial hypercholesterolaemia or combined (mixed) hyperlipidaemia, when response to diet and appropriate measures is inadequate, and for the prevention of cardiovascular events in patients with type 2 diabetes and at least one additional risk factor for cardiovascular disease. Atorvastatin is available as 10mg, 20mg, 40mg and 80mg tablets. The usual starting dose is 10mg/day, which may be increased at intervals of at least four weeks. The maximum dose is 80mg/day.[31]

Fluvastatin

Fluvastatin (Novartis Pharmaceuticals UK Ltd) is a synthetic statin. It is licensed as an adjunct to diet in patients with primary hypercholesterolaemia or combined (mixed) hyperlipidaemia, to slow the progression of coronary atherosclerosis in patients with primary hypercholesterolaemia and concomitant CHD who have not responded adequately to dietary control, and for the prevention of coronary events after percutaneous coronary intervention. Fluvastatin is available in two formulations: an immediate release formulation available as 20mg and 40mg capsules, and an extended release (XL) formulation available as 80mg tablets. The usual starting dose is 20-40mg/day adjusted at intervals of at least four weeks up to 80mg/day. For patients who have undergone percutaneous coronary intervention the dosage is 80mg/day.[31]

Pravastatin

Pravastatin (Bristol-Myers Squibb Pharmaceuticals Ltd) is a natural statin found in fungi. It is licensed as an adjunct to diet for primary hypercholesterolaemia or combined (mixed) hyperlipidaemia in patients who have not responded adequately to dietary control, as an adjunct to diet to prevent cardiovascular events in patients with hypercholesterolaemia, for the prevention of cardiovascular events in patients with previous MI or unstable angina, and for the reduction of hyperlipidaemia in

patients receiving immunosuppressive therapy following solid organ transplantation. Pravastatin is available as 10mg, 20mg and 40mg tablets. The recommended starting dose for hypercholesterolaemia is 10-40mg/day, adjusted at intervals of not less than four weeks. A dosage of 40mg/day is recommended for the prevention of cardiovascular events. For patients with post-transplantation hyperlipidaemia the recommended starting dose is 20mg/day increased if necessary to 40mg/day (under close medical supervision).[31]

Rosuvastatin

Rosuvastatin (AstraZeneca UK Ltd) is a synthetic statin. It is licensed for the treatment of primary hypercholesterolaemia, mixed dyslipidaemia, or homozygous familial hypercholesterolaemia in patients who have not responded adequately to diet or other appropriate measures. Rosuvastatin is available as 5mg, 10mg, 20mg and 40mg tablets. The recommended starting dose is 5-10mg/day adjusted if necessary at intervals of at least four weeks to 20mg/day and increased after a further four weeks to 40mg/day only in severe hypercholesterolaemia with high cardiovascular risk and under specialist supervision. The maximum 40mg dose is contraindicated for patients of Asian origin.[31]

Simvastatin

Simvastatin (Merck Sharp & Dohme Ltd) is a semi-synthetic statin based on Lovastatin. It is licensed for the treatment of primary hypercholesterolaemia, homozygous familial hypercholesterolaemia or combined (mixed) hyperlipidaemia in patients who have not responded adequately to diet and other appropriate measures, and the prevention of cardiovascular events in patients with atherosclerotic cardiovascular disease or diabetes mellitus. Simvastatin is available as 10mg, 20mg, 40mg and 80mg tablets. The recommended starting dose is 10-20mg/day for primary hypercholesterolaemia, 40mg/day or 80mg daily in three divided doses (with largest dose at night) for homozygous familial hypercholesterolaemia, and 20-40mg/day for the prevention of cardiovascular events with dose titrations up to a maximum of 80mg/day at intervals not less than four weeks if needed.[31]

2.2.2 Costs

Atorvastatin

The acquisition cost of atorvastatin under the brand name Lipitor (Pfizer Ltd) is £18.03 for 28 x 10mg tablets, £24.64 for 28 x 20mg tablets, £28.21 for 28 x 40mg tablets, and £28.21 for 28 x 80mg tablets (excluding VAT).[31]

Fluvastatin

The acquisition cost of fluvastatin under the brand names Lescol and Lescol XL (Novartis Pharmaceuticals UK Ltd) is £15.26 for 28 x 20mg capsules, £15.26 for 28 x 40mg capsules, and £19.20 for 28 x 80mg tablets (excluding VAT).[31]

Pravastatin

The acquisition cost of pravastatin under the brand name Lipostat (Bristol-Myers Squibb Pharmaceuticals Ltd) is £15.05 for 28 x 10mg tablets, £27.61 for 28 x 20mg tablets and 27.61 for 28 x 40mg tablets. The acquisition cost of non-proprietary Pravastatin is £3.11 for 28 x 10mg tablets, £4.13 for 28 x 20mg tablets, and £6.34 for 28 x 40mg tablets.[31]

Rosuvastatin

The acquisition cost of rosuvastatin under the brand name Crestor (AstraZeneca UK Ltd) is £18.03 for 28 x 5mg tablets, £18.03 for 28 x 10mg tablets, £26.02 for 28 x 20mg tablets, and £29.69 for 28 x 40mg tablets.[31]

Simvastatin

The acquisition cost of simvastatin under the brand name Zocor (Merck Sharp & Dohme Ltd) is £18.03 for 28 x 10mg tablets, £29.69 for 28 x 20mg tablets, £29.69 for 28 x 40mg tablets, and £29.69 for 28 x 80mg tablets. The acquisition cost of non-proprietary Simvastatin is £1.83 for 28 x 10mg tablets, £2.18 for 28 x 20mg tablets, £3.80 for 28 x 40mg tablets, £12.91 for 28 x 80mg tablets.[31]

2.3 Current service provision

Clinical practice regarding the provision of lipid lowering with statins following an ACS is governed by current National Service Framework (NSF)[8] and National Institute for Health and Clinical Excellence (NICE)[33] guidelines. NSF guidance[8] on total cholesterol and LDL-C targets recommends patients with established CHD should receive statins and dietary advice to lower serum cholesterol concentrations to either <5mmol/l (193mg/dl) or by 25%, whichever is greater, and LDL-C to either <3mmol/l (116mg/dl) or by 30%, again whichever is greater. Focusing on drug choice NICE guidance,[33] issued in January 2006 (due for review in December 2007), states that, when the decision has been made to initiate a statin, therapy should usually start with a drug at a low acquisition cost (taking into account required daily dose and product price per dose).

Most patients, therefore, currently receive simvastatin 40mg/day. This is given at night and started on day one when a diagnosis of ACS is confirmed. If not reaching the recommended target, patients receive a more potent statin (atorvastatin or rosuvastatin), or have ezetimibe added. Nicotinic acid is used rarely by lipidologists for patients with persistently low HDL-C. Similarly fibrates are used rarely by cardiologists (personal correspondence with Dr Russell Davis, Consultant Cardiologist at Sandwell & West Birmingham Hospitals NHS Trust).

Data from the National Audit of Myocardial Infarction Project (MINAP) for 2006/7 indicate, on average, 96% of patients in England are discharged from hospital on statins following a MI.[34]

2.4 Description of new intervention

The new intervention aims to reduce LDL-C to levels substantially below present targets for patients hospitalised following an ACS. For patients in whom statin therapy is not contra-indicated, early, intensive lipid lowering with a high-dose/potency statin (see Table 2) aimed at lowering LDL-C to levels <70mg/dl (1.8mmol/l) is proposed.

3 EFFECTIVENESS

3.1 Methods for reviewing effectiveness

3.1.1 Search strategy

A systematic search was undertaken for any completed and ongoing RCTs comparing the effectiveness of intensive versus moderate lipid lowering with statins for patients with an ACS. The following sources were searched:

- Bibliographic databases: Cochrane Library (CENTRAL), MEDLINE, and EMBASE. Details of the search strategies used are provided in appendix 1. Searches were conducted up to July 2007. No language restrictions were employed.
- Research registers of ongoing trials: The National Research Register, Current Controlled Trials *meta*Register and ISRCTN database, and ClinicalTrials.gov. Searches were undertaken in October 2007.
- Citation lists of included studies.
- Contact with experts: Dr R Davis, Consultant Cardiologist at Sandwell & West Birmingham Hospitals NHS Trust.
- Contact with manufacturers of the five statins currently licensed for use in the UK. Details of the pharmaceutical companies approached are provided in appendix 1.

3.1.2 Inclusion and exclusion criteria

Inclusion criteria

The following criteria were used to determine a study's inclusion in the review:

Population

Patients aged ≥ 18 years, hospitalised with one of the following ACS events: unstable angina, NSTEMI and STEMI.

Intervention

Any high-dose/potency statin initiated within 14 days of an index event, aimed at lowering LDL-C levels to <70mg/dl (1.8mmol/l). Any co-intervention was accepted.

Comparator

Any low to moderate-dose/potency statin (with dosage adjustments up to the maximum recommended dose if required) initiated within 14 days of an index event, aimed at lowering LDL-C levels to <100mg/dl (2.6mmol/l). Any co-intervention was accepted.

Outcomes

- Death from all causes
- Death from cardiovascular causes
- Cardiovascular events/procedures:
    - Myocardial infarction or re-infarction
    - Cardiac arrest with resuscitation
    - Recurrent myocardial ischaemia requiring hospitalisation
    - Coronary revascularisation procedures (percutaneous transluminal angioplasty or coronary artery bypass graft)
    - Stroke (any stroke, hemorrhagic or non-hemorrhagic, fatal or non-fatal)
    - Composite outcomes
- Adverse events
- Any other valuable trial information reported

Study design

Completed and ongoing RCTs.

Exclusion criteria

Any study that assessed patients for whom statin therapy was contraindicated i.e. patients with active liver disease (or persistently abnormal liver function tests), patients with acute porphyria, pregnant women, and breast feeding women.

3.1.3 Making inclusion/exclusion decisions

Two reviewers (WG and JW) independently assessed papers eligible for inclusion/exclusion by examining the titles and, where available, abstracts. Disagreements were resolved by discussion and consultation with a third party (CH). Full copies of relevant, or potentially relevant, references were obtained for detailed examination. Final inclusion/exclusion decisions were again made independently by two reviewers (WG and JW) prior to detailed scrutiny of the results and study quality assessment.

The main author (T R Pederson) of the IDEAL trial[35] was contacted for further information. The IDEAL trial[35] randomised 8,888 patients with a history of AMI to either high-dose atorvastatin (80mg/day) or standard-dose simvastatin (20mg/day). The study was conducted at 190 ambulatory cardiology care and specialist practices in northern Europe. An examination of the patients' baseline characteristics indicated the majority were recruited > two months after a MI, taking the time taken to initiate lipid lowering therapy well beyond our criteria of up to 14 days after an index event. However it was stated that a sizable number of patients (n=999) experienced a MI ≤ two months before entering the trial. We therefore contacted the main author (T R Pederson) to see if this group included patients starting treatment within 14 days of a MI but were advised only eight patients met our criteria. In view of the paucity of relevant data we decided to exclude the trial.

Of the two trials included in the review[13,36] one, the Colivicchi trial,[36] did not fully meet our inclusion criteria as it compared high-dose atorvastatin (80mg) with standard care, aimed at lowering LDL-C levels to <100mg/dl (2.6mmol/l), rather than a low to moderate-dose statin. However, as 34 of the 41 patients (83%) in the control group received various statins, the decision was taken to include it. The time taken to initiate lipid lowering medication was also outside our criteria, of up to14 days after an index event, but only very marginally (mean time to initiate therapy 12 ± 4 days). All other parameters fulfilled our criteria.

3.1.4 Data extraction strategy

Data was extracted by WG using a pre-defined form (see appendix 2) and checked by JW. For studies with multiple publications it was planned to report the data extracted as a single study and in the case of reported discrepancies use the most recent publication. Eleven of the included papers related to the PROVE IT-TIMI 22 trial.[13] However as the individual papers addressed different aspects of the trial and drew upon different subsets of the main trial population[13] the results were reported separately. In the case of the major publication for the trial[13] the authors were contacted for additional information (the figures for the 95% confidence intervals (CIs) for the hazard ratios (HRs) at different points in the trial for the primary end point, and the 95% CIs for the HRs for the secondary endpoints and individual components of the primary endpoint).

3.1.5 Quality assessment strategy

Two reviewers (WG and JW) independently assessed the methodological quality of the selected studies using the checklist based on Verhagen et al's quality assessment criteria[37] which formed part of the data extraction form. Disagreements were resolved by discussion.

3.1.6 Data handling and synthesis

The studies were tabulated and summarised naratively. Meta-analysis was ruled out in view of the heterogeneity observed between the two included studies in terms of their populations (unstable angina pectoris or non-Q-wave acute myocardial infarction in the Colivicchi trial[36] versus unstable angina, NSTEMI or STEMI in the PROVE IT-TIMI 22 trial[13]) and comparators (standard care in the Colivicchi trial[36] versus pravastatin (40mg/day) in the PROVE IT-TIMI 22 trial[13]).

3.2 Results

3.2.1 Number of studies identified

Potentially relevant citations, and their abstracts, identified from searches of the electronic databases were assessed individually (n=6,405). Citations not meeting the review's inclusion criteria were excluded (n=6,353). The full papers for 52 studies were retrieved for more detailed assessment. After evaluation of the full texts, a further 40 papers were excluded. Twelve papers were included in the review, relating to two RCTs.

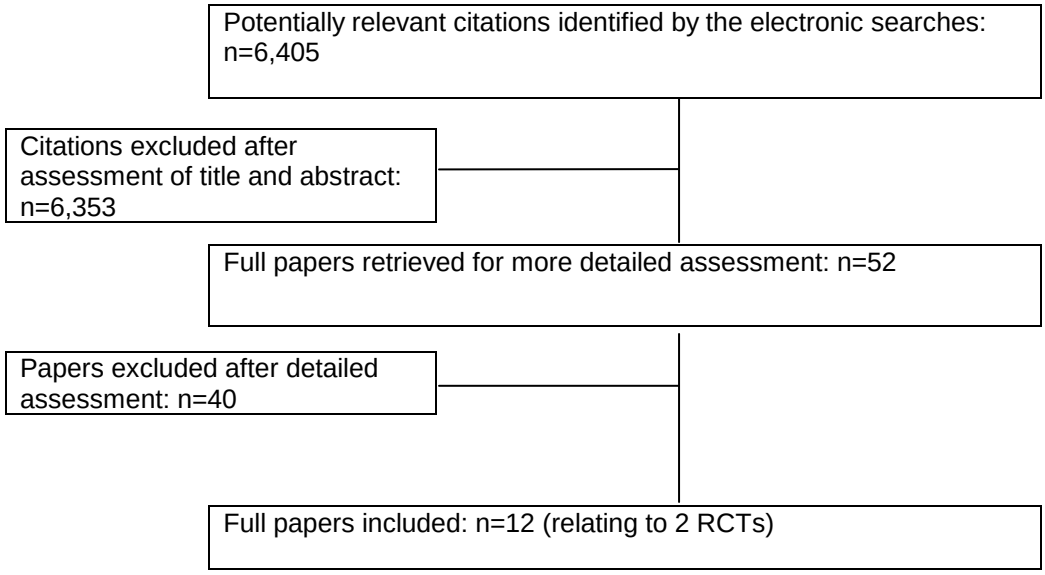

Figure 1 Flow diagram of the study selection process

3.2.2 Number and type of studies included

Two RCTs were included in the review. The full references for these studies, and the identified papers related to them, are provided in appendix 3.

3.2.3 Number and type of studies excluded with reasons

As noted in section 3.2.1 a substantial number of studies identified by the electronic searches did not meet the inclusion criteria and were excluded in the initial assessment of titles and abstracts. It is not practical to give details of all these studies. Therefore only details of the studies excluded following examination of the full paper are provided, along with the reason for their exclusion, in appendix 4.

3.2.4 Summary of quality of studies

An assessment of the quality of the studies relating to each intervention, using a checklist based on Verhagen et al's quality assessment criteria[37] is provided in appendix 5. Both RCTs were well conducted adopting appropriate randomisation procedures and methods of analysis (intention to treat (ITT)). The large (n=4,162) PROVE IT-TIMI 22 trial was a double-blind RCT however it was unclear whether or not the outcome assessors were blinded to treatment. The design of the smaller (n=81) Colivicchi trial did not permit blinding of the patients and care providers, however the trial's outcome assessors were blinded to treatment allocation. Knowledge, by any party, of the patient's treatment allocation introduces a possible source of bias. However, given the hard clinical endpoints examined in the trials, the chance of this would seem to be very small.

3.2.5 Summary of results

As noted in section 3.1.3 the Colivicchi trial[36] did not fully meet our inclusion criteria as it used standard care as a comparator. However, as 34 of the 41 patients (83%) in the control group received low to moderate-dose statins, the decision was taken to include it. The Colivicchi trial[36] was the earliest trial we identified to assess the effects of early intensive lipid lowering with statins following ACS events (restricted here to unstable angina or non-Q-wave acute myocardial infarction) in reducing ischaemic recurrences.

The main study identified was the PROVE IT-TIMI 22 trial.[13] This large (n=4,162) multicentre RCT primarily aimed to compare pravastatin with atorvastatin with the goal of determining whether lowering LDL-C with pravastatin (40mg/day) to a level of approximately 100mg/dl (2.6mmol/l) provided a clinical benefit similar to LDL-C lowering with atorvastatin (80mg/day) to a much lower level of approximately 70mg/dl (1.8mmol/l). The PROVE IT-TIMI 22 trial fully met our inclusion criteria and assessed patients hospitalised for the full spectrum of ACS events (unstable angina, NSTEMI and STEMI). Along with the major publication for this study[13] and an initial paper outlining the trial design[38] we identified nine further papers we felt merited inclusion[39-47] Our outline of these papers centres on the following themes: additional

important clinical endpoints,[39] subgroup analyses,[40,41] non-lipid lowering anti-inflammatory effects of statins,[42-45] early and late effects of high-dose statins,[46]and the safety and efficacy of achieving very low LDL-C levels with intensive statin therapy.[47] The main characteristics of the included trials are provided below.

3.2.5.1 The Colivicchi trial

Methods:

This open label, prospective RCT with parallel groups[36] assessed the effectiveness of the addition of high-dose atorvastatin (80mg/day) to conventional treatment early after either unstable angina pectoris (UAP) or non-Q-wave AMI in the reduction of ischaemic recurrences.

Population:

Eighty one patients with either UAP or non-Q-wave AMI consecutively admitted to the S. Filippo Neri Hospital, Rome, Italy between January 1999 and July 2001.** Before enrolment, all patients were receiving maximal conventional therapy (nitrates, calcium antagonists and β blockers) including ≥2 medications at maximal tolerated doses. At discharge from hospital, patients were randomised to receive conventional medical treatment (comparator: n=41) or conventional medical treatment plus 80mg/day atorvastatin (intervention: n=40). The mean time from hospital admission to discharge and randomisation was 12 ± 4 days.

Inclusion criteria: angiographic evidence of severe and diffuse coronary artery disease that was not amenable to direct revascularisation by coronary artery bypass grafting or percutaneous transluminal coronary angioplasty, as determined by a cardiac surgeon and an interventional cardiologist during the index admission; objective evidence of symptomatic reversible myocardial ischaemia (≥ 0.1 mV ST-segment depression on the electrocardiogram) at a low exercise workload (<4 METs) while receiving medical treatment (≥ 2 antianginal medications at maximal

** We have checked the generalisability of the study population and its applicability to middle-aged/elderly populations in the developed world seems reasonable.

tolerated doses) as assessed by treadmill ergometry (Bruce's protocol) before discharge; and left ventricular ejection fraction >35%.

Exclusion criteria: the presence of congestive heart failure; the need for continuous use of intravenous antianginal medications; and the presence of any major concurrent illness.

Intervention:

Conventional medical treatment (maximal combination therapy) plus atovastatin 80mg/day. Atorvastatin was added to medical treatment at discharge and no other lipid lowering treatment was allowed.

Comparator:

Maximal tolerated combination therapy plus lipid lowering therapy aimed at attaining LDL-C levels <100mg/dl (2.6mmol/l). For patients requiring statin treatment to reach the LDL-C goal during the study, atorvastatin was started at the initial dose of 20mg/day. Patients already receiving other statins or lipid lowering drugs before inclusion were allowed to continue their treatment after randomisation, but the dosage was titrated to reach LDL-C levels <100mg/dl (2.6mmol/l). In the control group, 34 of 41 patients (83%) received various statins (12 (29%) received atorvastatin (mean dose 18 ± 4 mg/day), 14 (34%) received simvastatin (mean dose 19 ± 2 mg/day), and eight (19%) received pravastatin (mean dose 37 ± 7 mg/day)). Four of the 41 patients (10%) were treated with fibrates.

Outcomes sought:

Composite primary endpoint: Cardiac death, nonfatal AMI or recurrent symptomatic myocardial ischaemia with objective evidence (electrocardiographic, echocardiographic, or scintigraphic) requiring emergency hospitalisation during the follow-up period.

Secondary endpoints: The occurrence of any of the primary endpoint components.

Analysis:

The primary analysis of all outcomes was by ITT analysis. Also an on-treatment analysis of the primary endpoint was performed. Recurrence of ischaemic events in the two treatment arms was tested using the odds ratio of the two-binomial proportion analysis. The cumulative risk of recurrence of ischaemic events within each group was estimated by means of the Kaplan-Meier method. Survival curves for the two different treatment groups were then formally compared using the log-rank test. Mean ± SD was calculated for continuous variables, and frequencies were measured for categorical variables. Differences between groups were analysed by un-paired Student's *t* test for continuous variables and the chi-square test for categorical variables; a *p* value of <0.05 was considered significant.

Results:

Clinical monitoring for ischaemic events for 12 months after randomisation was planned with efficacy and safety analyses every six months during the study. The power calculation predicted a sample size of 46 per group to give an α level of 0.05 and a test power of 0.80. Sample size calculation was based on an expected 70%/year recurrence rate of ischaemic events in the conventional treatment arm and 50%/year recurrence rate in the atorvastatin arm. Enrolment commenced in January 1999 and the fifth formal interim analysis was performed in August 2001 when 81 patients had been enrolled and follow-up data was available in all cases. As this interim analysis showed a significant effect in favour of atorvastatin the decision was made to terminate enrolment and follow-up. All patients were followed up for ≥60 days after randomisation. For all included patients, formal study participation ended if any primary endpoint component occurred.

In the ITT analysis, a primary endpoint event occurred in nine of 40 patients (22%; three deaths, four nonfatal AMI, and two emergency admissions for symptomatic myocardial ischaemia) in the atorvastatin arm, and in 19 of 41 patients (46%; four deaths, seven nonfatal MI, and eight emergency admissions for symptomatic myocardial ischaemia) in the conventional treatment arm. The difference was found to be significant (odds ratio: 0.33, 95% CI: 0.12-0.88, p=0.025). No patients were lost to follow-up. During follow-up, one patient in the atorvastatin arm was not

assessable by on-treatment analysis as he discontinued statin treatment due to intolerable side-effects. Therefore 80 patients were included in the on-treatment analysis which produced similar results to the ITT analysis (odds ratio: 0.29, 95% CI: 0.13-0.80, p=0.015). Overall a 24% absolute reduction in the primary combined endpoint was noted. Treatment of five patients was required to prevent one cardiac ischaemic recurrence (see Table 3). Intensive lipid lowering therapy was associated with a lower incidence of the primary combined endpoint within four weeks of treatment. Statistical significance was reached after six weeks of therapy, and the Kaplan-Meier actuarial curves describing event-free survival continued to diverge up to the eighth month of the study (p=0.024). There were no significant differences in the occurrence of each primary endpoint component between the study arms.

Table 3 Odds ratio for composite primary endpoint event in high-dose statin vs. conventional treatment groups at the end of follow-up (≥60 days)

Primary endpoint	Odds Ratio (95% CI)	Event Rates		NNT[a]
		Atorvastatin (high-dose statin)	Conventional treatment	
Cardiac death, nonfatal MI or recurrent symptomatic myocardial ischemia requiring emergency hospitalisation	0.33 (0.12 – 0.88)	22%	46%	5

[a] NNT (number needed to treat) calculated by reviewer

LDL-C levels: Decreases in both groups were seen at follow-up, but levels were constantly lower in the atorvastatin arm (p<0.0001). However, despite treatment with lipid lowering drugs, in six of 41 patients assigned to the control arm LDL-C levels exceeded 100 mg/dl (2.6mmol/l).

Adverse events: In one patient atorvastatin was withdrawn after two months of treatment following the appearance of persistent muscle pain associated with a significant increase in total serum creatine kinase (two times the upper limit of normal). Both muscle pain and biochemical abnormalities resolved after discontinuation of the drug. No other major adverse effects were noted.

3.2.5.2 The PROVE IT-TIMI 22 trial

3.2.5.2.1 The major publication

Methods:

This double blind, multicentre RCT with parallel groups[13] compared the effectiveness of aggressive lipid lowering using atorvastatin (80mg/day) with standard lipid lowering using pravastatin (40mg/day) for patients hospitalised for an ACS, in reducing death (from any cause), and cardiovascular events and procedures. The trial was designed to establish the non-inferiority of pravastatin as compared with atorvastatin with respect to the time to an endpoint event.

Population:

4,162 patients hospitalised for ACS enrolled at 349 sites in eight countries (Australia, Canada, France, Germany, Italy, Spain, UK & USA).[††]

Inclusion criteria: men and women at least 18 years old; hospitalised for an ACS (AMI with or without ECG evidence of ST-segment elevation or high-risk unstable angina) in the preceding ten days (median time to randomisation: seven days); patients had to be in a stable condition and were to be enrolled after a percutaneous revascularisation procedure if one was planned; patients had to have a total cholesterol level of ≤ 240mg/dl (6.2mmol/l) measured at the local hospital within the first 24 hours after the onset of the ACS or up to six months earlier if no sample had been obtained during the first 24 hours; patients who were receiving long-term lipid lowering therapy at the time of their index ACS had to have a total cholesterol level of ≤ 200mg/dl (5.2mmol/l) at the time of screening in the local hospital.

Exclusion criteria: patients with a coexisting condition that shortened expected survival to < two years; current statin therapy at a dose of 80mg/day; current lipid lowering therapy with fibric acid derivatives or niacin that could not be discontinued before randomisation; patients who had received drugs that are strong inhibitors of cytochrome P-4503A4 within the month before randomisation or were likely to

[††] We have checked the generalisability of the study population and its applicability to middle-aged/elderly populations in the developed world seems reasonable.

require such treatment during the study period (as atorvastatin is metabolised by this pathway); patients who had undergone percutaneous coronary intervention within the previous six months (other than for the qualifying event) or coronary-artery bypass surgery within the previous two months or were scheduled to undergo bypass surgery in response to an index event; factors that might prolong the QT-interval; obstructive hepatobiliary disease or other serious hepatic disease; unexplained elevation in the creatine kinase level that was more than three times the upper limit of normal and that was not related to MI, or a creatinine level of more than 2.0 mg/dl (176.8µmol/l).

Intervention:

Standard medical and interventional treatment for ACS plus atorvastatin (80mg/day) initiated within ten days of an index event, aimed at lowering LDL-C to a level of approximately 70mg/dl (1.8mmol/l).

Comparator:

Standard medical and interventional treatment for ACS plus pravastatin (40mg/day) initiated within ten days of an index event, aimed at lowering LDL-C to a level of approximately 100mg/dl (2.6mmol/l), with pravastatin dose increases (in a blinded fashion) if LDL-C was >125mg/dl (3.2mmol/l).

N.B. Patients were also randomly assigned to receive (with the use of a two-by-two factorial design) a ten-day course of the antibiotic gatifloxacin or placebo every month during the trial. The results of this component of the trial, which aimed to examine the role of chlymadia pneumoniae infection in cardiovascular disease by evaluating the effectiveness of the antibiotic gatifloxacin in reducing cardiovascular events, are not reported here.

Outcomes sought:

<u>Composite primary endpoint</u>: Death from any cause, MI, documented unstable angina requiring rehospitalisation, revascularisation (with either coronary artery bypass grafting or percutaneous coronary intervention) occurring ≤ 30 days after randomisation, and stroke.

N.B. MI was defined by the presence of symptoms suggestive of ischaemia or infarction, with either ECG evidence (new Q-waves in two or more leads) or cardiac-marker evidence of infarction, according to the standard TIMI and American College of Cardiology definition.[48,49] Unstable angina was defined as ischaemic discomfort at rest for at least ten minutes prompting revascularisation, combined with one of the following: ST-segment or T-wave changes, cardiac–marker elevations that were above the upper limit of normal but did not meet the criteria for MI, or a second episode of ischaemic chest discomfort lasting more than ten minutes that was distinct from the episode that had prompted hospitalisation.

Secondary endpoints: (1) Risk of death from CHD, nonfatal MI, or revascularisation if performed ≤ 30 days after randomisation. (2) The risk of death from CHD or nonfatal MI. (3) The risk of the individual components of the primary endpoint.

Analysis:

Although the trial was designed as a time-to-event study, the definition of non-inferiority was arrived at through a consideration of two-year event rates. Based on the assumptions of a two-year event rate of 22% in the atorvastatin group and equal efficacy between the two treatments it was determined that a sample size of 2,000 patients per group would give the study a statistical power of 87%, and this power would be preserved if follow-up continued until 925 events occurred. All efficacy analyses were based on the ITT principle. Estimates of the HRs and associated 95% CIs comparing pravastatin with atorvastatin were obtained with the use of the Cox proportional-hazards model, with randomised treatment as the covariate and stratification according to the receipt of gatifloxacin or placebo. Using the two-by-two factorial design, a preliminary test for interaction was conducted but none found. For the primary endpoint, the interaction *p* value was 0.90 and the HRs comparing pravastatin with atorvastatin were almost identical for the gatifloxacin and placebo groups. When it was determined that non-inferiority was not demonstrated the subsequent assessment of superiority was carried out using two-sided confidence intervals.

Results:

Patients were recruited from November 2000 to December 2001. The trial continued until 925 events had been reported to the co-ordinating centre, after which time all patients were requested to return for a final study visit (in August or September 2003). Follow-up lasted from 18 to 36 months (mean 24 months). Eight patients (0.2%) were lost to follow-up.

Kaplan-Meier event rates for the primary endpoint at two years were 22.4% in the high-dose atorvastatin group and 26.3% in the standard-dose pravastatin group representing a 16% (95%CI: 5-26%, p=0.005) reduction in the HR for death or a major cardiovascular event in the atorvastatin group. The benefit of atorvastatin (80mg/day) in comparison with pravastatin (40mg/day) emerged as early as 30 days and was consistent over time (see Table 4).

Table 4 Hazard ratios for a composite primary endpoint event in high vs. standard-dose statin groups at different time intervals

Censoring Time	Hazard Ratio (95% CI)	Risk Reduction	Event Rates		NNT[a]
			Atorvastatin (high dose)	Pravastatin (standard dose)	
30 days	0.83 (0.54 – 1.28)	17%	1.9%	2.2%	334
90 days	0.82 (0.65 – 1.03)	18%	6.3%	7.7%	72
180 days	0.86 (0.72 – 1.02)	14%	12.2%	14.1%	53
End of follow-up (mean 24months)	0.84 (0.74 – 0.95)	16%	22.4%	26.3%	26

[a]NNT (number needed to treat) calculated by reviewer

Cannon et al[13] reported that the risk of the secondary endpoint of death due to CHD, MI, or revascularisation was reduced by 14% in the atorvastatin group (p=0.029), with a two-year event rate of 19.7% in comparison with 22.3% in the pravastatin group. Furthermore the authors[13] stated the risk of death, MI or urgent revascularisation was reduced by 25% in the atorvastatin group (p<0.001).

Overall a consistent pattern of benefit favouring high-dose atorvastatin was seen amongst the individual components of the primary endpoint. There were significant reductions in the need for revascularisation (14%, p=0.04) and in the risk of recurrent unstable angina (29%, p=0.02), and non-significant reductions in the rates of death from any cause (28%, p=0.07), and death or MI (18%, p=0.06). Stroke rates were low and did not differ significantly between the groups (see Table 5).

Table 5 Hazard ratios for a secondary endpoint event and individual components of the primary endpoint in high vs. standard-dose statin groups

End Point	Hazard Ratio (95% CI)	Risk Reduction	2-Year Event Rates		NNT[a]
			Atorvastatin (high dose)	Pravastatin (standard dose)	
Death from any cause	0.72 (0.50 – 1.03)	28%	2.2%	3.2%	100
Death from CHD	0.70 (0.41 – 1.22)	30%	1.1%	1.4%	334
Death from other causes	0.73 (0.45 – 1.19)	27%	1.2%	1.8%	167
MI	0.87 (0.69 -1.10)	13%	6.6%	7.4%	125
Death or MI	0.82 (0.67 – 1.0)	18%	8.3%	10.0%	59
Death from CHD or MI	0.84 (0.68 – 1.05)	16%	7.2%	8.3%	91
Revascularisation	0.86 (0.74 – 0.99)	14%	16.3%	18.8%	40
MI, revascularisation, or death from CHD	0.86 (0.75 – 0.99)	14%	19.7%	22.3%	39
Unstable angina requiring hospitalisation	0.71 (0.53 – 0.95)	29%	3.8%	5.1%	77
Stroke	1.09 (0.59 - 2.04)	-9%	1.0%	1.0%	N/A

[a]NNT (number needed to treat) calculated by reviewer

Lipid profile: The median LDL-C levels achieved during follow-up were 62mg/dl (1.6mmol/l), interquartile range 50-79mg/dl (1.3-2.1mmol/l) in the atorvastatin group; and 95mg/dl (2.5mmol/l) interquartile range 79-113mg/dl (2.1-2.9mmol/l) in the

pravastatin group (p<0.001). The median HDL-C levels rose by 6.5% in the atorvastatin group and 8.1% in the pravastatin group (p<0.001).

C-reactive protein: Median C-reactive protein levels fell from 12.3mg/l in each group at baseline to 1.3mg/l in the atorvastatin group and 2.1mg/l in the pravastatin group (p<0.001).

Adverse events: The discontinuation of treatment rates due to an adverse event, the patient's preference or other reasons were 22.8% in the atorvastatin group and 21.4% in the pravastatin group at one year (p=0.30), and 33% in the atorvastatin group and 30.4% in the pravastatin group at two years (p=0.11). The percentages of patients who had elevations in alanine aminotransferase levels that were more than three times the upper limit of normal were 3.3% in the atorvastin group and 1.1% in the pravastatin group (p<0.001). Study medication was discontinued due to a report of myalgias or muscle aches or elevations in creatine kinase levels in 3.3% of the atorvastatin treated patients and 2.7% of the pravastatin treated patients (p=0.23). There were no cases of rhabdomyolysis in either group.

3.2.5.2.2 Additional important clinical endpoints

Hospitalisation for heart failure

One paper[39] sought to compare the relationship between intensive statin therapy and the risk of heart failure (HF) after an ACS. The primary efficacy outcome for the analysis was the time from randomisation to the first occurrence of hospitalisation for congestive HF that occurred 30 days or longer after randomisation. An ITT analysis of all 4,162 patients enrolled in the trial was undertaken. Kaplan-Meier event rates at two years were 1.6% in the atorvastatin group and 3.1% in the pravastatin group representing a 45% (95%CI: 0.35-0.85, p=0.008) reduction in the HR for hospitalisation for HF (see Table 6).

Table 6 Hazard ratio for hospitalisation for heart failure in high vs. standard-dose statin groups

End Point	Hazard Ratio (95% CI)	Risk Reduction	2-Year Event Rates		NNT[a]
			Atorvastatin (high dose)	Pravastatin (standard dose)	
Hospitalisation for congestive HF ≥ 30 days after randomisation	0.55 (0.35 - 0.85)	45%	1.6%	3.1%	67

[a]NNT (number needed to treat) calculated by reviewer

3.2.5.2.3 Subgroup analyses

Two papers assessed clinical outcomes for high-risk subgroups.[40,41]

Patients with diabetes and ACS

One paper[40] sought to examine the impact of lipid lowering with statins after an ACS for patients with diabetes mellitus (DM). In a pre-specified subgroup analysis using the main trial data (n=4,162) the outcomes of the patients with DM (n=978) were compared against those without DM (3,184). ITT analyses were undertaken. In addition to the composite primary endpoint (see section 3.2.5.2.1) a triple endpoint of acute cardiac events (death, MI or unstable angina requiring rehospitalisation) was assessed. Overall patients with DM had more clinical events than those without DM at two years. The Kaplan-Meier event rate of the primary endpoint for patients with DM was 28.4% with atorvastatin and 31.8% with pravastatin. Although underpowered to reach statistical significance the direction of change favoured atorvastatin (HR: 0.88, p=0.62). In the larger non-diabetic subgroup the primary endpoint was significantly reduced by intensive therapy (20.6% with atorvastatin and 24.7% with pravastatin). The interaction term between DM status and intensive statin therapy was not significant (p=0.62) suggesting the benefit of intensive therapy did not differ significantly in patients with and without DM. The Kaplan-Meier event rate for the triple endpoint of intensive vs. standard therapy was 21.1% vs. 26.6% (p=0.03) in patients with DM, and 14% vs.18% (p=0.002) in those without DM (see Table 7). With intensive therapy the number of events prevented per 1000 patients with DM was 55 compared with 40 events prevented per 1000 patients without DM.

Table 7 Hazard ratio for acute cardiac events[a] in high vs. standard-dose statin groups for patients with and without diabetes

Sub-group	Hazard Ratio (95% CI)	Risk Reduction	2-Year Event Rates		NNT[b]
			Atorvastatin (high dose)	Pravastatin (standard dose)	
Diabetes (n=978)	0.75 (0.58 - 0.97)	25%	21.1%	26.6%	19
No Diabetes (n=3184)	0.76 (0.64 - 0.90)	24%	14%	18%	25

[a]Death, MI and unstable angina requiring rehospitalisation

[b]NNT calculated by reviewer

Elderly patients with ACS

One paper[41] sought to examine the efficacy and safety of the achievement of the NCEP goal[14] of LDL-C <70mg/dl in elderly patients with ACS. The relationship between LDL-C at 30 days after an ACS event and subsequent clinical outcomes was compared amongst elderly patients (aged ≥ 70 years) vs. younger counterparts, using the composite endpoint of death, MI or unstable angina requiring rehospitalisation. Patients (n=378) who experienced one of the clinical endpoints prior to day 30 were excluded from the analysis as this could have impacted on their lipid profile and the likelihood of a further cardiac event. A greater proportion of patients in both age groups achieved the NCEP goals at 30 days on atorvastatin vs. pravastatin (elderly patients: 74.6% vs. 27.7%, p<0.001; younger patients: 72.1% vs. 20.5%, p<0.001). Amongst the 634 elderly patients the achievement of an LDL-C level of <70mg/dl was associated with an 8% absolute and 40% relative lower risk of events (HR: 0.60, 95%CI: 0.41-0.87, p=0.008) vs. corresponding benefits of 2.3% and 26% in the 3,150 younger patients (HR: 0.74, 95%CI: 0.59-0.94, p=0.013), see Table 8. The estimated number of events preventable (from Kaplan-Meier rates) amongst the elderly by the achievement of these goals was 80 events at 2 years for every 1000 patients at goal vs. those not at goal, compared with 23 events potentially prevented in younger patients. The incidence of major side-effects amongst the elderly was similar to that in younger patients and did not differ with the intensity of the statin regimen.

Table 8 Relationship between LDL-C at 30 days and subsequent risk of acute cardiac events[a] for elderly and younger patients

Sub-group	Hazard Ratio (95% CI)	Risk Reduction	2-Year Event Rates		NNT[b]
			LDL-C at 30 days < 70mg/dl	LDL-C at 30 days ≥ 70mg/dl	
Elderly ≥ 70 years (n=634)	0.60 (0.41 – 0.87)	40%	13.5%	21.5%	13
Younger < 70 years (n=3,150)	0.74 (0.59 – 0.94)	26%	8.1%	10.4%	44

[a]Death, MI and unstable angina requiring rehospitalisation

[b]NNT calculated by reviewer

3.2.5.2.4 Non-lipid lowering anti-inflammatory effects of statins

Four papers examined the impact of the non-lipid lowering, anti-inflammatory effects of statins on clinical outcomes: the 'pleiotropic' properties[‡‡] of statins.[42-45]

An examination of the relationship between LDL-C and C-reactive protein (CRP) levels achieved after treatment with atorvastatin (80mg/day) or pravastatin (40mg/day) showed that although patients achieving LDL-C levels of <70mg/dl had fewer clinical events (recurrent MI or death from coronary causes) than those with higher LDL-C levels (2.7 vs. 4.0 events per 100 person-years, p=0.008), this difference was almost mirrored in those with CRP levels <2mg/l and LDL-C levels ≥70mg/dl (2.8 vs. 3.9 events per 100 person-years, p=0.006). Reductions in CRP levels were seen to have a consistently beneficial effect independent of LDL-C levels achieved, with the lowest rate of recurrent events (1.9 per 100 person-years) seen in patients with LDL-D levels <70mg/dl and CRP levels <1mg/l.[42]

An examination of the relationship between LDL-C, CRP and cerebrovascular events (CVE) indicated whilst the lipid profiles of patients with and without a CVE were similar, those with a CVE had higher CRP levels than those without a CVE at 30 days (2.7 vs. 1.9mg/l, p=0.012) and four months (2.4 vs. 1.7mg/l, p=0.005).[43]

[‡‡] Pleiotropic means having multiple effects. Most of the benefits of statins are attributed to their inhibition of cholesterol biosynthesis. However statins may exert cholesterol-independent or pleiotropic effects by improving endothelial function, enhancing plaque stability, decreasing inflammation and inhibiting the thrombogenic response.

An examination of the relative efficacy of atorvastatin vs. pravastatin in achieving the dual goals of LDL-C <70mg/dl (1.8mmol/l) and CRP <2mg/l indicated although atorvastatin was superior to pravastatin, neither agent brought the majority of patients below thresholds needed to maximise benefit.[44]

Finally an examination of lipoprotein-associated phospholipase A_2 (Lp-PLA_2) activity, an enzyme thought to have an inflammatory role, indicated that at 30 days follow-up Lp-PLA_2 was significantly lowered with high-dose statin therapy and was associated with an increased risk of cardiovascular events independent of CRP and LDL-C levels.[45]

3.2.5.2.5 Early and late effects of high-dose statins

One paper[46] aimed to determine the time-frame during which the benefits associated with intensive statin therapy after an ACS occurred. It assessed possible benefits soon after an ACS and for more stable patients. A composite triple endpoint of death, MI or rehospitalisation for recurrent ACS was determined for the atorvastatin and pravastatin groups at 30 days. This composite triple endpoint was also assessed in stable patients from six months to the end of the study, after censoring for clinical events before six months. At 30 days the composite endpoint occurred in 3% of patients receiving atorvastatin vs. 4.2% of patients receiving pravastatin representing a 28% risk reduction (HR: 0.72, 95%CI: 0.52-0.99, p=0.046). From six months after an ACS to the end of the study atorvastatin was associated with a composite event rate of 9.6% vs.13.1 in the pravastatin group representing a 28% risk reduction (HR:0.72, 95%CI: 0.58-0.89, p=0.003), see Table 9.

Table 9 Hazard ratios for a composite triple endpoint event[a] in high vs. standard-dose statin groups during an early and later time frame

Time-frame after ACS index event	Hazard Ratio (95% CI)	Risk Reduction	Event Rates		NNT[b]
			Atorvastatin (high dose)	Pravastatin (standard dose)	
Early: up to 30 days	0.72 (0.52 – 0.99)	28%	3%	4.2%	84
Later: from 6 months to end of study	0.72 (0.58 – 0.89)	28%	9.6%	13.1%	29

[a]Death, MI or rehospitalisation for recurrent ACS
[b]NNT (number needed to treat) calculated by reviewer

3.2.5.2.6 Safety and efficacy of achieving very low LDL-C levels with intensive statin therapy

One paper[47] sought to evaluate the safety and efficacy of achieving very low LDL-C levels with intensive statin therapy. Patients treated with atorvastatin (n=1,825) were divided by four-month LDL-C values into groups: >100mg/dl, >80 to 100mg/dl, >60 to 80mg/dl, >40 to 60mg/dl, and <40mg/dl. Those with lower LDL-C levels were more often male, older, diabetic, and had lower baseline LDL-C levels. They had prior statin therapy and fewer prior MIs. There were no significant differences in safety parameters, including muscle, liver, or retinal abnormalities, intracranial haemorrhage, or death, in the very low LDL-C groups. The <40mg/dl and 40 to 60mg/dl groups had fewer major cardiac events (death, MI, stroke, recurrent ischemia and revascularisation).

3.2.6 Discussion and conclusion of effectiveness evaluations

Extensive searches identified only two RCTs[13,36] that compared the effectiveness of the early initiation (within 14 days of an ACS index event) of intensive vs. standard lipid lowering with statins in preventing further cardiovascular events following an ACS. The 14-day cut-off point was set to take account of the high event risk in the early stages after ACS during which time it has been hypothesised the role of statins in modulating plaque vulnerability may be beneficial,[15-17] and reflect current clinical practice to initiate standard-dose statins when the diagnosis of ACS is confirmed and continue treatment upon discharge from hospital (see section 2.3).

Our search results contrasted with those of other recent publications[50,51] comparing high-dose with standard-dose statin therapy, which identified four large RCTs[13,35,52,53] as a result of the broader study selection criteria adopted (particularly in respect of time taken to initiate treatment).

Cannon et al's[50] meta-analysis included RCTs of intensive vs. standard-dose statins that enrolled >1000 patients with either stable CHD or ACS. Of the four trials identified two, the TNT[53] and IDEAL[35] trials, involved patients with stable CHD (and therefore did not meet our population (ACS patients) and intervention (high dose statins initiated within 14 days of an index event) inclusion criteria) and two, the PROVE IT-TIMI 22[13] and A to Z[52] trials, involved patients with ACS. Of the two trials identified by Cannon et al[50] assessing ACS patients only one, PROVE IT-TIMI 22,[13] met our inclusion criteria. The A to Z trial (phase Z)[52] compared early intensive (40mg/day simvastatin for one month followed by 80mg/day simvastatin) with delayed conservative lipid lowering (placebo for four months followed by 20mg/day simvastatin) and therefore did not meet our intervention and comparator inclusion criteria (high vs. moderate-dose statins initiated within 14 days of an index event). However whilst the design of the A to Z trial did not adequately reflect our research question, and the trial failed to achieve its pre-specified primary endpoint, its main results were not dissimilar at two-years from the PROVE IT-TIMI 22 trial,[13] see Table 10.

Table 10 Hazard ratios for the main effectiveness parameters in the A to Z and PROVE IT-TIMI 22 trials at two years in high vs. standard-dose statin groups

Endpoint	Hazard Ratio (95% CI)	
	A to Z	PROVE IT-TIMI 22
Composite primary endpoint[a]	0.89 (0.76 – 1.04)	0.84 (0.74 – 0.95)
Death from any cause	0.79 (0.61 – 1.02)	0.72 (0.50 -1.03)
MI	0.96 (0.77 – 1.21)	0.87 (0.69 – 1.10)
Stroke	0.79 (0.48 – 1.30)	1.09 (0.59 – 2.04)
Rehospitalisation[b]	0.99 (0.76 – 1.31)	0.71 (0.53 – 0.95)
Revascularisation	0.93 (0.73 – 1.20)	0.86 (0.74 – 0.99)

[a] The primary endpoint in the A to Z trial was a composite of cardiovascular death, nonfatal MI, readmission for ACS and stroke; in PROVE IT-TIMI 22 it was a composite of death from any cause, MI, unstable angina requiring rehospitalisation, revascularisation and stroke.
[b] Rehospitalisation referred to admission for ACS in the A to Z trial; and an episode of unstable angina requiring admission in the PROVE IT-TIMI 22 trial.

The effectiveness data from the RCTs[13,35,52,53] identified in Cannon et al's[50] meta-analysis were also used to inform Chan et al's[51] cost-effectiveness model of intensive vs. moderate lipid lowering in two clinical scenarios: ACS and stable coronary artery disease. Chan et al's[51] study assessing the incremental benefit and cost-effectiveness of high-dose statin therapy in high risk patients with coronary artery disease was the only relevant paper identified in our systematic review of economic evaluations (see section 4.2.1). Accordingly our conclusions regarding the likely cost-effectiveness of the early initiation of high vs. standard-dose statins for ACS patients rest on our appraisal of Chan et al's[51] model (see section 4.2.2).

The main results of the two trials identified in our effectiveness review are summarised in Table 11. Of these the large (n=4,162) PROVE IT-TIMI 22 trial[13] provides the main weight of evidence.

Table 11 Summary of the main results of the Colivicchi and PROVE IT-TIMI 22 trials

Results	Colivicchi[36] (n=81)	PROVE IT-TIMI 22[13] (n=4,162)
Trial population	Patients with unstable angina pectoris or non-Q-wave acute myocardial infarction.	Patients with either acute myocardial infarction (with or without electrocardiographic evidence of ST-segment elevation) or high-risk unstable angina.
Intervention	Standard medical treatment (maximal combination therapy) plus atovastatin 80mg/day. Atorvastatin was added to medical treatment at discharge and no other lipid-lowering treatment was allowed. The mean time from hospital admission to discharge and randomisation was 12 ± 4 days.	Standard medical and interventional treatment for ACS plus atorvastatin (80mg/day) aimed at lowering LDL-C to a level of approximately 70mg/dl. Patients were randomised ≤ 10 days after hospital admission (mean 7 days).
Comparator	Maximal tolerated combination therapy plus lipid-lowering therapy aimed at attaining LDL-C levels <100mg/dl. 34 of 41 patients (83%) received various statins.	Standard medical and interventional treatment for ACS plus pravastatin (40mg/day), aimed at lowering LDL-C to a level of approximately 100mg/dl (with pravastatin dose increases (in a blinded fashion) if LDL-C was >125mg/dl).
Composite primary endpoint	Cardiac death, nonfatal MI or recurrent symptomatic myocardial ischemia requiring emergency hospitalisation	Death from any cause, myocardial infarction, documented unstable angina requiring rehospitalisation, revascularisation (with either coronary artery bypass grafting or percutaneous coronary intervention) occurring ≤ 30 days after randomisation, and stroke.
Clinical outcomes	Although monitoring was planned for 12 months, the trial was terminated early due to the significant effect seen in favour of atorvastatin at an interim analysis. Follow-up was ≥ 60 days for all patients. A primary endpoint event occurred in nine of 40 patients (22%) in the atorvastatin arm, and in 19 of 41 patients (46%) in the conventional treatment arm. ITT analysis, odds ratio: 0.29 (95% CI: 0.13-0.80, p=0.15). Overall a 24% absolute reduction was noted (NNT: 5).	Event rates for the primary endpoint at two years were 22.4% in the atorvastatin group and 26.3% in the pravastatin group representing a 16% (95%CI: 5-26%, p=0.005) reduction in the HR for the atorvastatin group. Overall a 3.9% absolute reduction was noted (NNT: 26).
LDL-C levels at follow-up	LDL-C levels decreased in both groups, but levels were constantly lower in the atorvastatin arm (p<0.0001). Despite treatment with lipid-lowering drugs, in 6 of 41 patients assigned to the control arm LDL-C levels exceeded 100mg/dl.	Median LDL-C levels were 62mg/dl (interquartile range 50-79mg/dl) in the atorvastatin group and 95mg/dl (interquartile range 79-113mg/dl) in the pravastatin group (p<0.001).

Adverse events	Atorvastatin withdrawn following the appearance of persistent muscle pain associated with a significant increase in total serum creatine kinase (n=1).	Treatment was discontinued in 22.8% in the atorvastatin group and 21.4% in the pravastatin group at one year (p=0.30), and 30.4% in the atorvastatin group and 33% in the pravastatin group at two years (p=0.11). Elevations in alanine aminotransferase levels were seen in 3.3% in the atorvastin group and 1.1% in the pravastatin group (p<0.001). Medication was discontinued due to a report of myalgias or muscle aches or elevations in creatine kinase levels in 3.3% of the atorvastatin treated patients and 2.7% of the pravastatin treated patients (p=0.23). There were no cases of rhabdomyolysis in either group.

The results reported in the Colivicchi[36] and PROVE IT-TIMI 22[13] trials indicate early aggressive lipid lowering with high-dose atorvastation (80mg/day) provides significantly greater protection against the composite outcome of death or major cardiovascular events than standard regimens for patients with ACS.

A comparison of the two trials indicates a quite substantial difference in the magnitude of effect reported (24% absolute reduction (NNT: 5) in Colivicchi vs. 3.9% absolute reduction (NNT: 26) in PROVE IT-TIMI 22). A likely explanation for the high event rate (46%) observed in the control arm of Colivicchi et al's trial[36] is the play of chance given the study's small sample size (n=81). However an examination of the main parameters summarised in Table 11 also highlights heterogeneity between the two trials in terms of their populations (the Colivicchi trial assesses patients at low to moderately high risk whereas the PROVE IT-TIMI 22 trial assesses the full clinical spectrum of ACS patients) and composite primary endpoints (the Colivicchi trial assesses cardiac death, nonfatal MI or recurrent symptomatic myocardial ischemia requiring emergency hospitalisation whereas the PROVE IT-TIMI 22 trial assesses death from any cause, MI, documented unstable angina requiring rehospitalisation, revascularisation and stroke) which may account for some of the observed disparity in the levels of effectiveness reported.

Both trials[13,36] compared the addition of high-dose atorvastatin (80mg/day) with lipid lowering therapy aimed at meeting the NCEP Adult Treatment Panel III

recommendation of LDL-C <100mg/dl for patients with established CHD or CHD risk equivalents,[6] that was in place at the time of their design. In both trials[13,36] intensive or moderate lipid lowering therapy was an adjunct to standard medical and interventional treatment for ACS. This is an important proviso as lipid lowering is only one of a number of equally important elements in the effective, initial and long term, management of ACS patients (see section 2.1.2.5). Both trials[13,36] noted significantly lower LDL-C levels amongst patients receiving high-dose atorvastatin lending weight to the premise that reductions in LDL-C levels correlate with reductions in the number of cardiovascular recurrences.

Finally both trials[13,36] reported a similar adverse event profile. No cases of rhabdomyolysis were reported in either trial. Discontinuation of treatment following reports of myalgias, muscle aches or elevations in creatine kinase were similar amongst the two treatment arms in the larger PROVE IT-TIMI 22 trial. In the Colivicchi trial only one patient (receiving atorvastatin 80mg/day) withdrew as a result of persistent muscle pain associated with a significant increase in creatine kinase. However the percentages of patients in the PROVE IT-TIMI 22 trial who had elevations in alanine aminotransferase levels that were more than three times the upper limit of normal were significantly higher in the atorvastatin group.

An examination of the later analyses of the PROVE IT-TIMI 22 trial data indicates high-dose atorvastatin is equally effective in reducing acute cardiac events amongst the higher risk subgroups of elderly patients with ACS,[41] and diabetic patients with ACS[40] (see section 3.2.5.2.3). Trial data[39] (see section 3.2.5.2.2) also highlights a significantly reduced rate of hospitalisation for HF amongst patients treated with atorvastatin (80mg/day) vs. pravastatin (40mg/day). PROVE IT- TIMI 22 trial data[13,46] indicates the benefit of atorvastatin (80mg/day) in comparison with pravastatin (40mg/day) begins to emerge within 30 days of an ACS event (possibly due to its greater anti-inflammatory effect at this critical time (see section 3.2.5.2.4)) and remains consistent over the trial's duration (see Table 4). Thus lending support to the initiation of high-dose statin therapy before discharge from hospital and the continuation of intensive therapy in the longer term.

In summary evidence, principally from the PROVE IT-TIMI 22 trial,[13] seems to strongly confirm the effectiveness of early intensive lipid lowering with high-dose atorvastatin for high risk ACS patients. The PROVE IT-TIMI 22 trial Kaplan-Meier event rates for the composite primary endpoint at two years were 22.4% in the atorvastatin group and 26.3% in the pravastatin group representing a 16% (95%CI: 5-26%, p=0.005) reduction in the hazard ratio for death or a major cardiovascular event in the atorvastatin group. Intensive therapy with atorvastatin (80mg/day) was seen to have a consistently beneficial effect on cardiac events, including a 29% (p=0.02) reduction in the risk of recurrent unstable angina and a 14% (p=0.04) reduction in the need for revascularisation. Furthermore the reduction in the rate of death from any cause approached statistical significance (HR: 0.72, 95%CI: 0.50-1.03, p=0.07) as did the reduction in the rate of death or MI (HR: 0.82,95%CI: 0.67-1.0, p=0.06), see Table 5.

Trial evidence on the effectiveness of the early initiation (within 14 days or an index event) of intensive lipid lowering for ACS patients has, to-date, focused exclusively on atorvastatin (80mg/day) as a high-dose agent. These results may possibly be extrapolated to inform an assessment of the effectiveness of other high-dose statins, for example simvastatin (80mg/day). However to permit a definitive judgement on the equivalence or non-equivalence of other high-dose statins with atorvastatin (80mg/day) a well conducted RCT would appear to be a high National Health Service priority.

4 ECONOMIC ANALYSIS

4.1 Methods for economic analysis

The main approach adopted was a systematic review of existing evaluations of costs, quality of life and cost-effectiveness of lipid lowering in CHD. As for effectiveness the particular focus was on early intensive lipid lowering in patients with ACS. MEDLINE, EMBASE, NHSEED and OHE HEED were searched up to June 2007 by WG (details of the search strategies used are provided in appendix 6). Additionally the manufacturers of the five statins currently licensed for use in the UK were contacted for details of any cost-effectiveness studies or economic models (see appendix 6). All further stages of the review (inclusion/exclusion, quality assessment and analysis) were conducted by a single reviewer (CH). The frame-work for quality assessment and analysis was the same as that suggested for Single Technology Appraisals (STAs) by the National Institute for Health and Clinical Excellence (NICE).[54]

4.2 Results of systematic review of economic evaluations

4.2.1 Quantity of studies

One thousand three hundred and fifty citations were identified by the searches. Most of these were excluded on the basis of clear irrelevance from information in the title and abstract. Thirty four studies were retrieved in full for detailed assessment. The disposition of these studies was as follows:

- One cost-effectiveness model of intensive vs. moderate lipid lowering in ACS
- Ten cost-effectiveness models of intensive/moderate lipid lowering vs. no lipid lowering in ACS
- Nine cost-effectiveness models of lipid lowering in ischemic heart disease where the cost-effectiveness of high degrees of lipid lowering in high risk populations could be considered
- Fourteen studies which did not consider cost-effectiveness

All but one study, Chan et al,[51] were effectively excluded. A further potentially directly relevant on-going study was also identified. Full details of the study by Ward et al[55] were received after the completion of the report, but were available in time for the REP panel meeting itself. A critical appraisal and summary were presented at the meeting, and are attached to this report as an addendum.

4.2.2 Appraisal of Chan et al's economic model

The rationale for this economic model[51] was to compare the cost-effectiveness of high-dose vs. conventional-dose statin therapy. The authors constructed a Markov model in TreeAge Pro to assess this in two clinical scenarios, firstly ACS and secondly stable coronary artery disease. High-dose statin therapy was represented by atorvastatin 80mg and conventional-dose statin therapy by simvastatin 20mg. The effect of high-dose and conventional-dose statin therapy was compared in hypothetical cohorts of 60 year old patients considering the impact on all cause mortality, myocardial infarction, stroke, rehospitalisation and revascularisation. Effectiveness data were principally drawn from RCTs comparing high-dose and standard-dose statins, specifically the PROVE IT-TIMI 22[13] and A to Z[52] trials in the case of ACS. Chan et al's inclusion of the A to Z trial reflects a broader study selection criteria than that adopted in the effectiveness review which excluded this trial, given its focus on the initiation high vs. moderate-dose statins within 14 days of an ACS index event. Cost data were taken from recognised sources of cost data in the United States as 2005 US dollars. Because of flux in drug cost data, the cost of drugs was considered in terms of the difference between the high-dose and standard-dose regimens and a cost-effectiveness ratio calculated for each level of difference in price e.g. 0.5 $/day difference; 1.0 $/day difference; 1.5 $/day difference etc. The cost-effectiveness ratio used was the incremental cost per quality-adjusted life-year (QALY).

4.2.2.1 Model structure

The model was a Markov model with a cycle length of one year. The outline, redrawn from the paper, is given in figure 2.

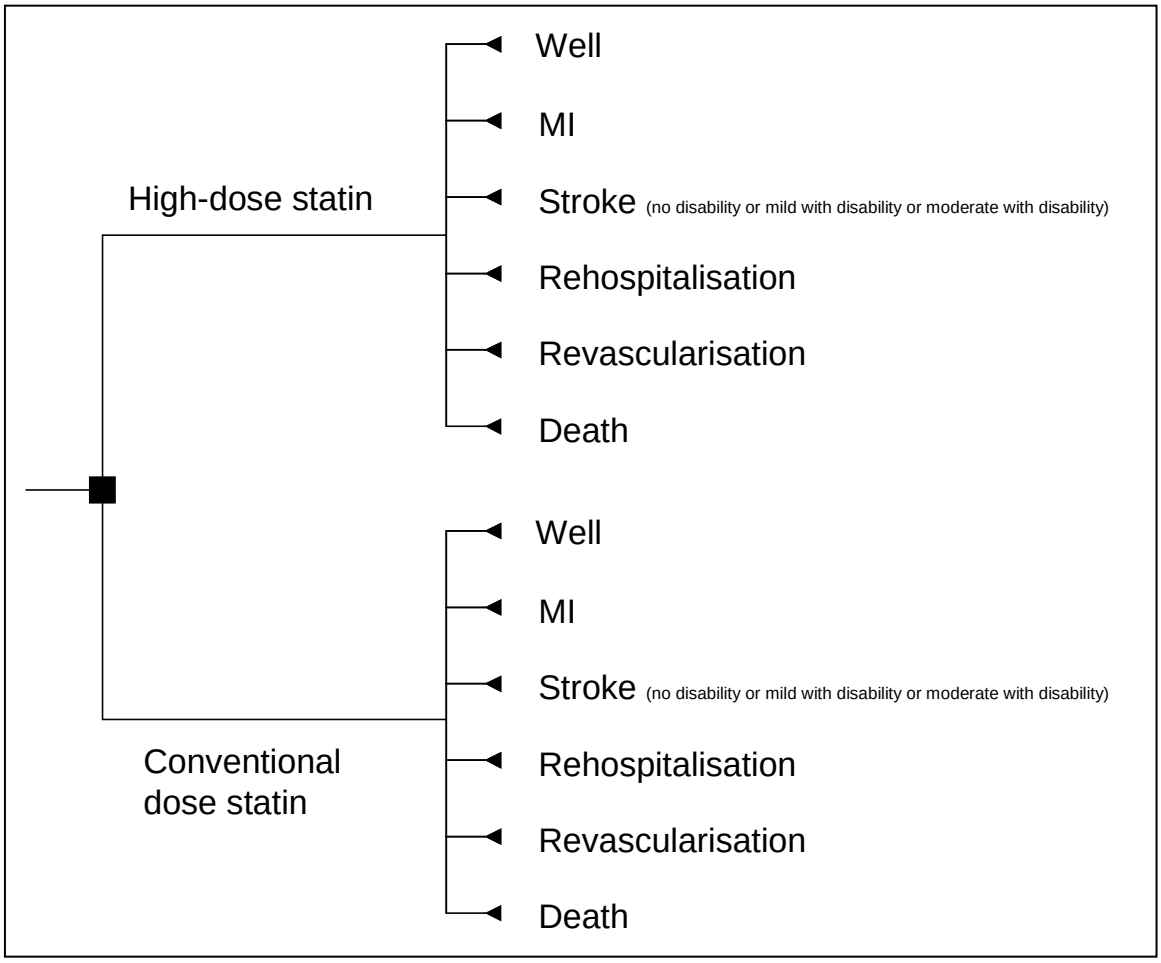

Figure 2 Simplified schematic of the Markov model

The diagram indicates that at the beginning of each cycle in the model hypothetical patients enter each of the six states in proportion to probabilities derived from effectiveness research. This will differ according to whether high or conventional-dose statins are given and in this way the difference between the two treatments is captured in the model. The six states in this model are the outcomes of interest, "being well", having an MI or stroke, being hospitalised, requiring a revascularisation procedure or death. In the model stroke is further sub-divided into stroke with no resulting disability, mild stroke with disability and moderate stroke with disability.
For the model of stable coronary artery disease the transition probabilities for each year are the same over each year that the Markov model runs. For the ACS model, different probabilities are used in the first two years to reflect the possibility that the response to lipid lowering and the relative importance of the outcomes will probably vary.

The perspective of the model was stated to be societal and the setting was community/hospital in the United States. Discounting (presumed to be for both costs and benefits) was applied at 3% per annum and the costs were expressed in 2005 US dollars.

4.2.2.2 Data sources

These are clearly displayed in table 1 of the paper. The effectiveness and base-line risk estimates are derived from published RCTs, and include information about uncertainty. The parameters for ACS are reproduced in the table below:

Table 12 Effectiveness parameters used in ACS model by Chan et al

Parameter	High vs standard-dose statins Relative risk (range)	Standard lipid lowering Event rates %/y (range)
Death from any cause	0.76 (0.62 – 0.94)	2.32 (1.74 – 2.90)
MI	0.92 (0.78 - 1.07)	3.55 (2.66 – 4.44)
Stroke	0.89 (0.66 - 1.31)	0.63 (0.47 – 0.79)
Rehospitalisation	0.84 (0.61 – 1.18)	2.4 (1.8 – 3.0)
Revascularisation	0.88 (0.79 – 0.99)	5.82 (4.37 – 7.28)

Similarly the parameters for costs and utilities and their ranges are also clearly displayed and are reproduced in the tables below:

Table 13 Cost parameters used in ACS model by Chan et al

Parameter		Point estimate	Range
Death		9300	0 - 18400
MI	Uncomplicated DRG 122 (80%)	5040	3780 - 6300
	Complicated DRG 121 (20%)	8050	6040 - 10060
Stroke (initial)	No disability (29%)	6400	4800 - 8000
	Mild disability (41%)	8000	6000 - 10000
	Mod/severe disability (30%)	12900	9700 - 16100
Stroke (follow-up costs per year)	No disability (29%)	0	0
	Mild disability (41%)	2700	2000 - 3400
	Mod/severe disability (30%)	10000	5000 - 20000
Rehospitalisation DRG 143		2800	2100 - 3500
Re-vascularisation	PCI DRG 111 (70%)	12200	9150 - 15250
	CABG DRG 107 (30%)	26700	20000 - 33400
Note: All costs in US $ 2005 DRG = Diagnosis-related group PCI = Percutaneous coronary intervention CABG = Coronary artery bypass graft			

Table 14 Utility values used in model by Chan et al

Health state		Point estimate	Range
Well		0.974	0.877 to 1.0
Death		0	N/A
MI		0.9	0.81 to 1.0
Stroke	No disability (29%)	Presumed to be same as “well”	
	Mild disability (41%)	0.76	0.60 – 1.0
	Mod/severe disability (30%)	0.39	0 – 1.0
Rehospitalisation		Reduced by 0.5 for 7 days	None given
Re-vascularisation	PCI (70%)	Reduced by 0.5 for 7 days	None given
	CABG (30%)	Reduced by 0.5 for 28 days	None given
Note: Utility of 0 represents worst imaginable health state; 1.0 represents perfect health			

4.2.2.3 Analysis

The model indicated was constructed and run on TreeAge Pro. Extensive sensitivity analyses appear to have been conducted, starting with one-way sensitivity analyses exploring the impact of variation in parameters within the ranges indicated in the parameter tables. This was extended to two-way sensitivity analyses incorporating the two factors emerging as being most important in the one-way sensitivity analyses (modelled efficacy of high-dose statins beyond clinical trial duration and the difference in cost between high and conventional-dose statins). Finally a probabilistic

sensitivity analysis was conducted using 10,000 simulations to consider simultaneous variation in all the parameters in the model.

4.2.2.4 Critique of model

The model is well reported but even with this, given the model's complexity, it is impossible to convey all its features in a journal article. A working copy of the model has been requested but has not, as yet, been received. If this can be obtained there would be greater opportunity to explore its working and to evaluate the impact of using UK specific data.

However, with the proviso that the only information is that in the journal article, the model appears to be of good quality. The model structure is plausible and includes most of the health states that one would expect to be represented in order to capture the benefits which might arise from high as opposed to conventional lipid lowering strategies. More critically there is no health state which captures the side-effects of lipid lowering, but nor too is there a state which captures changes in frequency and severity of angina which might arise from more intensive lipid lowering. There is always a trade-off between fidelity (representing exactly what happens to a patient) and concentrating on the most important health states to make the model manageable. The trade-off in this model appears to be reasonable.

The parameters used also appear to be derived from credible sources. The uncertainty around the parameters is clearly represented and again appears reasonable. The effectiveness parameters used show some differences from the results indicated in the review of effectiveness, reflecting the fact that they draw upon effectiveness data from an additional RCT, the A to Z trial,[52] excluded from the effectiveness review as it did not meet the intervention and comparator inclusion criteria (high vs. moderate-dose statins initiated within 14 days of an index event). However, with the exception of the difference in relative risk (RR) for stroke, the differences between the point estimates used in model and those in the RCTs included in the effectiveness review will lead to a more conservative estimate of overall effectiveness in the model. High drop-out rates with statin therapy are an

important concern, but the model takes imperfect compliance into account because estimates of effect based on ITT analyses are used. An obvious problem with respect to applying the cost-effectiveness results to the NHS is that the costs are derived from the US health-care system. However, debatably the nature of the health care system and the care pathways for this disease are sufficiently similar that general conclusions may be robust provided the level of the US costs are felt to be similar to UK costs, taking into account the exchange rate which for the purpose of this report might be judged to be between 1.5 to 2.0 US$ to 1.0 GBP. Running the model with UK costs would be ideal and might still be feasible if a working copy of the Chan et al model were to be obtained.

The analysis itself also appears to have been well performed if the procedures described have been correctly implemented. The range of sensitivity analyses described is particularly thorough.

4.2.2.5 Results, focusing on use in acute coronary syndrome

In general the cost-effectiveness of high-dose relative to standard-dose statins appears to be supported for ACS. This is not the case for their use in stable coronary artery disease which is not considered in further detail because it is not the focus for this report.

The specific results for ACS obtained from the model were:

QALYs

Intensive statin therapy	13.589
Conventional statin therapy	13.237
Incremental QALYs	0.352

This yielded the following cost per QALY at the following given levels of difference in price per day between high and standard-dose statin regimens (read from Figure 3a in published paper, bar value for 3.5 USD):

- 1.0 USD/day 5,700 USD/QALY
- 2.0 USD/day 21,300 USD/QALY
- 3.0 USD/day 36,900 USD/QALY
- 3.5 USD/day 44,000 USD/QALY

These results were sensitive to many parameters, particularly assumptions about the persistence of benefit after 5 years. If the benefit was reduced to 50% the incremental cost-effectiveness ratios (ICERs) given above would change to (read from Figure 3a in published paper, bar value for 3.5 USD):

- 1.0 USD/day 14,200 USD/QALY
- 2.0 USD/day 29,800 USD/QALY
- 3.0 USD/day 45,400 USD/QALY
- 3.5 USD/day 52,600 USD/QALY

The result of the probabilistic sensitivity analysis, taking variation of all parameters into account, is presented in the cost-effectiveness acceptability curves in Figure 4 of the paper. This indicates that the probability of high-dose statins being cost-effective at a willingness to pay of 45,000 USD (c 30,000 GBP at an exchange rate of 1.5 USD = 1.0 GBP) is close to 100%.

4.3 Discussion and conclusion of economic evaluations

The main findings are that of the Chan et al economic model[51] described above. Although there were other potentially relevant economic evaluations identified in the systematic review, no others were directly relevant to the issue in question, the cost-effectiveness of intensive vs. moderate lipid lowering with statins in acute coronary syndromes. The Chan et al model[51] appears well conducted with the proviso that it can only be judged on the detail reported. The main challenge is the generalisability of the results to the UK given that the costs are in USD. However, if this is thought to be acceptable, the results of the cost-effectiveness modelling indicate that aggressive lipid lowering with high-dose statins is highly likely to be cost-effective at drug price differentials and willingness to pay thresholds likely to be operating in the

NHS. Thus for a drug price differential of 1.0 GBP/day (c 2.0 USD/day) the Chan et al model[51] suggests an ICER of 21,300 USD/QALY, or approximately 10,650 GBP/QALY.

There is true uncertainty about this estimate, some of which is considered in Chan et al's model[51] which suggests that the estimate of cost-effectiveness is robust to changes in the large number of variables they explore. Some uncertainty however relates to an inability, which is often the case with published health economic models, to fully examine how the model works. It is possible that this source of uncertainty may yet be reduced if the working model does become available. Alternative models corroborating the findings of the Chan et al model[51] would be also reassuring, but the only similar model we have been able to identify is currently in the process of publication. Again if this model were to become fully available, uncertainty may be reduced.

In consequence, at the current point in time, a policy decision on the likely cost-effectiveness of the early use of high-dose statins in ACS rests on a judgement about the reliability and applicability of the findings by Chan et al.[51]

5 CONCLUSIONS

For ACS patients the early use of high-dose/potency statins significantly reduces the risk of death or a major cardiovascular event in comparison with standard lipid lowering regimens. Overall, modelling of the cost-effectiveness of high-dose relative to standard-dose statins appears to support the use of high-dose statins for ACS patients. If we accept that the model's results, derived from the US health-care system, are generalisable to the UK, aggressive lipid lowering with high-dose statins seems highly likely to be cost-effective at drug price differentials and willingness to pay thresholds likely to be operating in the NHS.[§§] Trial evidence on the effectiveness of the early initiation (within 14 days of an index event) of aggressive lipid lowering for ACS patients has, to-date, focused exclusively on atorvastatin (80mg/day) as a high-dose agent. These results may possibly be extrapolated to inform an assessment of the effectiveness of other high-dose statins, for example simvastatin (80mg/day). However, if a definitive judgement on the equivalence or non-equivalence of other high-dose statins with atorvastatin (80mg/day) is required, a well conducted RCT would appear to be a high National Health Service priority.

[§§] The results of the additional health economic model received after the completion of the report, but presented to the Regional Evaluation Panel as per the paper attached in the Addendum to this report, reinforced the initial conclusions.

6 ADDENDUM – TABLED AT REP MEETING 25/2/08

Appraisal of Ward et al's economic model[55]

Introduction

In the original report only one published cost-effectiveness analysis addressing the question of interest was identified. A further analysis was identified as in progress. This analysis by ScHARR at the University of Sheffield[55] has now been made available in the public domain and the following is a critical appraisal and summary of its key findings.

General overview

The objective of the model was, "To determine if the strategy for treating ACS patients with intensive dose statin compared with standard dose statin can be considered cost-effective and to what extent these results are influenced by the age of the patient at the start of treatment." A Markov model with life-time time horizon was used to achieve this. Intensive statin therapy was represented by atorvastatin 80mg and standard statin therapy by simvastatin 20mg. The health states captured in the model were unstable angina, MI, stroke, fatal CHD, fatal stroke or non vascular death. Effectiveness estimates were derived from a meta-analysis of four large RCTs[13,35,52,53] and cost and utility estimates from other reviews of published literature. The cost year was GBP 2006 and the ICER expressed as cost per QALY. The economic analysis was conducted from the perspective of the UK NHS.

Model structure

The model was a further development of an existing Markov model from the same research group comparing the effects of normal dose statin therapy with no statin therapy, to which a further comparison of high versus normal dose statin therapy was added. The cycle length of the model was one year, patients leaving the model at death or 100 years of age. The patients enter the model after experiencing a new qualifying event, which are new unstable angina, new acute myocardial infarction and new non fatal stroke. In subsequent cycles patients in the model can move to one of the following states:

- Unstable angina
- MI
- Stroke
- Fatal CHD
- Fatal stroke
- Non vascular death

Entry into any one of the last three states means that the patient exits the model. Moves following entry into one of the first three states could be to either “post unstable angina”, “post MI” and “post stroke” respectively where there are no further events of interest, or to any of the other health states. The exception is reversion to new unstable angina which cannot occur. Moves from the “post unstable angina”, “post MI” and “post stroke” are either to remain in that state, or to move to new MI, new stroke, fatal CHD, fatal stroke and non vascular death. Again moving to new unstable angina is not permitted in the model.

The states in the model and the possible movements between these are summarised in figure 1 of the paper illustrating the patient pathway. There may however be omission of lines indicating potential transitions to new stroke from new unstable angina and post unstable angina.

The numbers of patients moving between states in the model are determined by transition probabilites which are in turn derived from evidence on effectiveness. The probabilities of dying from other causes are derived from life tables from the UK Government Actuary Dept. The costs and utilities associated with each state are also derived from published evidence described in detail in the next section.

Data sources

These are clearly displayed in Table 2 of the paper. The effectiveness estimates are derived from published RCTs, and include information about uncertainty. The parameters for acute coronary syndrome are reproduced in the table below:

Effectiveness parameters used in model by Ward S et al with particular reference to high versus normal dose statin comparison	
Parameter	**High vs standard RR (range)**
Death from any cause	0.76 (0.62 – 0.94)
MI	0.92 (0.78 -1.07)
Stroke	0.89 (0.66 -1.31)
Rehospitalisation	Not a parameter in this model
Revascularisation	Not a parameter in this model

The values of the parameters are identical to those used by Chan et al[51] and are based on the same two RCTs, A to Z[52] and PROVE IT-TIMI 22.[13]

The parameters for costs and utilities and their ranges are clearly displayed and are again reproduced in the tables below. The costs were expressed in 2006 GBP. For the categories which were clearly comparable in nature (MI and stroke) costs were larger than those of Chan et al[51] even taking into account potential variation in exchange rates.

Cost parameters used in model by Ward S et al		
Parameter	**Point estimate**	**Range**
Standard dose statin (20mg simvastatin)	24.25	
High dose statin (80mg atorvastatin)	367.74	
Monitoring for intensive dose (Y1)	58.88	
Monitoring for intensive dose (Y2+)	29.44	
Unstable angina	477	358 - 596
Unstable angina (post event)	201	151 - 121
MI	4934	3701 - 6168
MI (post event)	201	151 - 121
Fatal CHD	1261	946 - 1576
Stroke	8070	6053 - 10088
Stroke (post event)	2169	1627 - 2711
Fatal stroke	7425	5569 - 9281
Note: All costs in GB £2006		
Utility values used in model by Ward S et al		
Health state	**Point estimate**	**Range**
Unstable angina (Y1)	0.77	0.65 to 0.89
Unstable angina (subsequent)	0.72	0.85 to 0.97*
MI (Y1)	0.65	0.76 to 0.87*
MI (subsequent)	0.71	0.84 to 0.96*
Stroke (Y1)	0.53	0.63 to 0.72*
Stroke (subsequent)	0.59	0.69 to 0.80*
Note: Utility of 0 represents worst imaginable health state; 1.0 represents perfect health * Probable mistranscription. Lower limit of range probably point estimate and vice versa		

The utilities appear lower than those used by Chan et al.[51] However, this is partly because the ranges appear to have been mis-transcribed as the point estimate falls outside the range and is more likely to be the lower limit of the range.

Analysis

The base-case was derived using 10,000 Monte Carlo simulations. Further the impact of varying key parameters within their specific ranges was examined by holding the parameter value constant and sampling from all other parameter distributions simultaneously, again using 10,000 Monte Carlo simulations. In this way sensitivity to variation in key model parameters was varied. Discounting of both costs and benefits was applied at 3.5% per annum.

Critique of model

This is a generally well reported model developed from a previous version which has received wide scrutiny. It fulfils most of the criteria demanded by quality checklists for economic models such as those suggested by Philips et al.[56] The rationale for the structure of the model is well described as are the sources of the parameters, which seem to have been identified in a systematic manner. In the analysis, considerable effort has been made to make explicit uncertainty.

The most obvious potential area for criticism concerns the simplification of the range of outcomes which might be influenced by high-dose statins in acute coronary syndromes. Relative to the model by Chan et al,[51] Ward et al[55] do not include states which capture new operations and procedures, such as revascularisation, and readmissions. This is discussed by the model authors who note that their cost-estimates for non-fatal MI included revascularisation costs in a proportion of patients. In the appraisal the greater costs associated with MI and stroke in Ward et al[55] relative to Chan et al[51] were also noted by way of corroborating this. So it may be that Ward et al do capture the potential to reduce procedure costs even though they do not have a state for this in their model.

Ward et al[55] like Chan et al[51] do not have states which capture adverse events associated with high-dose statins. Ward et al argue that the generally minor nature of these means that the impact of the on the ICER is likely to be small.

One of the referees commenting on the West Midlands report, reflecting on the Chan et al model,[51] also felt that an absence of states representing chronic heart

failure, a frequent long-term consequence of ischaemic heart disease, may lead to underestimation of benefit arising from high-dose statins.

Results, focusing on use in acute coronary syndrome

In general the cost-effectiveness of high-dose relative to standard-dose statins appears to be generally supported for acute coronary syndromes.

Base-case results in Ward S et al Average values for a cohort of 1000 males aged 60 years (using 10,000 MonteCarlo simulations)		
	Standard dose statin	High dose statin
Number of MIs	258	222
Number of strokes	120	100
Number of fatal CHD	340	327
Number of fatal stroke	85	82
Total number of events	802	731
Discounted life-years	12041	12317
Discounted QALYs	7362	7534
Total cost (lifetime)	£10,902,000	£15,000,000
Incremental QALYs	172	
Incremental costs	£4,098,141	
Incremental cost per QALY	£23,779	

The probabilistic sensitivity analysis suggests a probability of being cost-effective at a threshold of £20,000 of 43% and at a threshold of £30,000 of 68%.

The sensitivity analyses suggested that the ICER does vary depending on plausible variation on some of the parameters. In particular the ICER fell to £14,205 per QALY in a male cohort aged 70 and increased to £37,822 in a male cohort aged 50 years. The results also appear to be sensitive to assumptions about the size of effect of high-dose statins on mortality.

Results, comparing Ward et al with Chan et al

Both studies provide support for the use of high-dose statins relative to normal doses in acute coronary syndromes based on cost-effectiveness. The second study by Ward et al, appears much more cautious in its support. There are not marked differences between the models particularly in terms of the model quality as based on reported characteristics. We did note some differences, although the degree to which they might be responsible for the observed difference in ICER is unclear:

- The model by Ward et al[55] does not allow reversion to unstable angina. However, it is likely that this is probably true for Chan et al[51] too.
- The model by Ward et al deals differently with the challenge that patients with ACS initially have higher rates of disease, but later these fall as the patient stabilises and effectively becomes a patient with stable CHD. Ward et al[55] integrate this change into the model; Chan et al[51] have two separate versions of the model, with the ACS version operating for the first two years and the stable CHD version for subsequent years.
- Costs associated with MI and stroke are much higher in Ward et al.[55]
- Ward et al[55] do not include revascularisation and rehospitalisation as health states, although they feel this is compensated for by the higher costs allocated for MI, see above, allowing for a proportion of patients to have revascularisation procedures.

On balance, it seems most likely that Chan et al[51] represents a slightly over optimistic view of cost-effectiveness and Ward et al[55] a slightly pessimistic view. However, an issue relating to both models is their use of the combined results of PROVE IT-TIMI 22[13] and A to Z[52] as a basis for their estimate of the effectiveness of high-dose statins. Earlier in the West Midlands report however, we forward an argument that A to Z[52] may not provide an accurate estimate of the size of effect of the early initiation of high-dose relative to standard-dose statins. If accepted and estimates of effectiveness were based on PROVE IT-TIMI 22[13] alone in both models, estimates of cost-effectiveness would be improved in both cases. Not including benefits specifically associated with avoiding heart failure in the longer term may be a further possible cause of underestimation of cost-effectiveness in both models.

7 APPENDICES

Appendix 1 Search strategies for effectiveness studies

Bibliographic databases searched:

Database: Ovid MEDLINE (R) <1950 to 2007 June Week 3>
Search strategy:

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1 acute coronary syndrome$.mp.
2 unstable angina$.mp. or exp Angina, Unstable/
3 angina$.mp.
4 myocardial infarction$.mp. or exp Myocardial Infarction/
5 acute myocardial infarction$.mp.
6 non-Q-wave myocardial infarction$.mp.
7 Q-wave myocardial infarction$.mp.
8 non-ST-segment elevation myocardial infarction$.mp.
9 ST-segment elevation myocardial infarction$. mp.
10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11 exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/ or statin$.mp.
12 atorvastatin.mp.
13 fluvastatin.mp.
14 pravastatin.mp. or exp Pravastatin/
15 rosuvastatin.mp.
16 simvastatin.mp. or exp Simvastatin/
17 cerivastatin.mp.
18 lovastatin.mp. or exp Lovastatin/
19 hydroxymethylglutaryl-Coa-reductase inhibitor$.mp. or exp Hydroxymethylglutaryl CoA Reductase Inhibitors/
20 hydroxymethylglutaryl-Coa-reductase$.mp. or exp Hydroxymethylglutaryl CoA Reductases/
21 antilipaemic agent$.mp.
22 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21
23 10 and 22
24 randomized controlled trial.pt.
25 controlled clinical trial.pt.
26 randomized controlled trials.sh.
27 random allocation.sh.
28 double blind method.sh.
29 single blind method.sh.
30 or/24-29
31 (animals not human).sh.
32 30 not 31
33 clinical trial.pt.
34 exp clinical trials/
35 (clin$ adj25 trial$).ti,ab.
36 ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)). ti,ab.
37 placebo$.ti,ab.
38 random$.ti,ab.
39 placebos.sh.
40 research design.sh.
41 or/33-40
42 41 not 31
43 42 not 32
44 comparative study.sh.
45 exp evaluation studies/
46 follow up studies.sh.

47 prospective studies.sh.
48 (control$ or prospectiv$ or volunteer$).ti,ab.
49 or/44-48
50 49 not 31
51 49 not (32 or 43)
52 32 or 43 or 51
53 23 and 52

Database: EMBASE <1996 to 2007 Week 26>
Search strategy:
---
1 acute coronary syndrome$.mp.
2 unstable angina$.mp.
3 angina$.mp.
4 myocardial infarction$.mp. or exp Heart Infarction/
5 acute myocardial infarction$.mp. or exp Acute Heart Infarction/
6 non-Q-wave myocardial infarction$.mp.
7 Q-wave myocardial infarction$.mp.
8 non-ST-segment elevation myocardial infarction$.mp.
9 exp ST Segment Elevation/ or ST-segment elevation myocardial infarction$. mp.
10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11 statin$.mp. or exp STATIN/
12 atorvastatin.mp. or exp ATORVASTATIN/
13 fluvastatin.mp.
14 pravastatin.mp. or exp PRAVASTATIN/
15 rosuvastatin.mp. or exp ROSUVASTATIN/
16 simvastatin.mp. or exp SIMVASTATIN/
17 cerivastatin.mp. or exp CERIVASTATIN
18 lovastatin.mp.
19 hydroxymethylglutaryl-Coa-reductase inhibitors$.mp. or exp Hydroxymethylglutaryl Coenzyme a Reductase Inhibitor/
20 hydroxymethylglutaryl-Coa-reductase$.mp. or exp Hydroxymethylglutaryl Coenzyme a Reductase/
21 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
22 10 and 21
23 randomized controlled trial/
24 exp clinical trial/
25 exp controlled study/
26 double blind procedure/
27 randomization/
28 placebo/
29 single blind procedure/
30 (control$ adj (trial$ or stud$ or evaluation$ or experiment$)).mp.
31 ((singl$ or doubl$ or trebl$ or tripl$) adj5 (blind$ or mask$)).mp.
32 (placebo$ or matched communities or matched schools or matched populations).mp.
33 (comparison group$ or control group$).mp.
34 (clinical trial$ or random$).mp.
35 quasiexperimental or quasi experimental or pseudo experimental). mp.
36 matched pairs.mp.
37 or/23-36
38 22 and 37

Database: Cochrane Library (Wiley) 2007, Issue 2
Search strategy:

#1 “acute coronary syndrome*”
#2 “unstable angina*”
#3 “myocardial infarction*”
#4 MeSH descriptor **Myocardial Infarction** explode all trees
#5 angina*

#6 "acute myocardial infarction*"
#7 "non-Q-wave myocardial infarction*"
#8 "Q-wave myocardial infarction*"
#9 "non-ST-segment elevation myocardial infarction*"
#10 "ST-segment elevation myocardial infarction*"
#11 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10)
#12 MeSH descriptor **Hydroxymethylglutaryl-CoA Reductase Inhibitors** explode all trees
#13 statin*
#14 atorvastatin
#15 fluvastatin
#16 MeSH descriptor **Pravastatin** explode all trees
#17 pravastatin
#18 rosuvastatin
#19 MeSH descriptor **Simvastatin** explode all trees
#20 simvastatin
#21 cerivastatin
#22 MeSH descriptor **Lovastatin** explode all trees
#23 lovastatin
#24 "hydroxymethylglutaryl-Coa-reductase*"
#25 "antilipaemic agent*"
#26 (#12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25)
#28 (#11 AND #26)

Drug companies contacted:

The following manufacturers of the five statins currently licensed for use in the UK were contacted for details of any ongoing trails or unpublished studies:

Atovastatin: Pfizer Ltd, Walton Oaks, Dorking Road, Tadworth, Surrey, KT20 7NS

Fluvastatin: Novartis Pharmaceuticals UK Ltd, Frimley, Camberley, Surrey, GU16 7SR

Pravastatin: Bristol-Myers Squibb Pharmaceuticals Ltd, Uxbridge Business Park, Sanderson Road, Uxbridge, Middlesex, UB8 1DH

Rosuvastatin: AstraZeneca UK Ltd, Horizon Place, 600 Capability Green, Luton, Bedfordshire, LU1 3LU

Simvastatin: Merck Sharp & Dohme Ltd, Hertford Road, Hoddesdon, Hertfordshire, EN11 9BU

Appendix 2 Data extraction form

Intensive versus moderate lipid lowering with statins in the prevention of cardiovascular events amongst patients with acute coronary syndromes

Reference ID	
Data extracted by	
Extraction date	

Paper details

First author	
Title	
Journal	
Year, volume and Page numbers	
Full text article or abstract?	
Country	
Funding	
Related papers	
Other comments	

Intensive vs. moderate lipid lowering with statins for patients with acute coronary syndromes

Aim of study

Trial information

Number of patients randomised	
Duration of intervention	
Duration of follow-up	
Total length of trial	
Trial start date	
Trial completion date	
Frequency of data collection	

Population

Inclusion criteria	
Exclusion criteria	

Baseline characteristics of the study groups		
Variable	**Intervention (N=)**	**Control (N=)**
Age – years		
Male – no. (%)		
Female – no. (%)		
Current smoker – no. (%)		
Diabetes mellitus – no. (%)		
Metabolic syndrome – no. (%)		
Hypertension – no. (%)		
Previous MI - no. (%)		
Previous coronary bypass – no. (%)		
Previous coronary angioplasty- no. (%)		
Type of index event - no. (%)		
Unstable angina		
MI without ST-segment elevation		
MI with ST-segment elevation		
Lipid profile - mg/dl		
Total cholesterol		
LDL cholesterol		
HDL cholesterol		
Triglycerides		
Differences between the groups		
Other comments		

Intervention

Type of statin administered	
Statin dose administered	
Time taken to initiate statin therapy following an index event	
Target LDL-C level	

Comparator

Type of statin administered	
Statin dose administered	
Time taken to initiate statin therapy following an index event	
Target LDL-C level	

Co-interventions for an index event

Variable – no. (%)	**Intervention (N=)**	**Control (N=)**
Coronary artery bypass graft		
Percutaneous transluminal angioplasty		
Fibrinolysis		
Nitrates		
Beta-blockers		
Calcium channel blockers		
ACE inhibitors		
Heparin		
Glycoprotein IIb/IIIa inhibitors		
Aspirin		
Clopidogrel		
Other co-interventions		

Outcomes sought

Primary	
Secondary	

Analysis

	Comments
Statistical techniques used	

Results

Variable – no. (%)	**Intervention (N=)**	**Control (N=)**
Death from all causes		
Death from cardiovascular causes		
Cardiovascular events/procedures		
Myocardial infarction or re-infarction		
Cardiac arrest with resuscitation		
Recurrent myocardial ischemia requiring hospitalisation		
Coronary revascularisation procedures (coronary artery bypass graft or percutaneous transluminal angioplasty)		
Stroke (any stroke, hemorrhagic or non-hemorrhagic, fatal or non-fatal)		
Composite outcomes		
Other information reported		
Lipid profile		
Total cholesterol		
LDL-C cholesterol		
HDL-C cholesterol		
Triglycerides		

Define any terms that are unclear:

Adverse events		
Variable – no. (%)	**High dose group** **(N=)**	**Moderate dose group** **(N=)**
Total adverse events related to treatment		
Discontinuation due to treatment related adverse events		
Raised alanine aminotransferase levels (ALT)		
Raised aspartate aminotransferase levels (AST)		
Raised creatine kinase levels		
Myalgia		
Myopathy		
Rhabdomyolysis		
Other information reported		

Define any terms that are unclear:

Other comments

Study quality

	Yes	No	Unclear	Comments
1. Was the assignment to the treatment groups really random? Adequate approaches to sequence generation: • computer-generated random numbers • random numbers tables Inadequate approaches to sequence generation: • use of alternation, case record numbers, birth dates or week days				
2. Was the treatment allocation concealed? Adequate approaches to concealment of randomisation: • centralised or pharmacy-controlled randomisation • serially-numbered identical containers • on-site computer based system with a randomised sequence that is not readable until allocation • other approaches with robust methods to prevent foreknowledge of the allocation sequence to clinicians and patients Inadequate approaches to concealment of randomisation: • use of alternation, case record numbers, birth dates or week days • open random numbers lists • serially numbered envelopes				
3. Were the groups similar at baseline in terms of prognostic factors?				
4. Were the eligibility criteria specified?				
5. Were outcome assessors blinded to the treatment allocation?				
6. Was the care provider blinded?				
7. Was the patient blinded?				
8. Were the point estimates and measures of variability presented for the outcome measure?				
9. Did analyses include an intention to treat analysis?				

Appendix 3 Studies included in the review

*indicates the major publication for the study

Colivicchi 2002

*Colivicchi F, Guido V, Tubaro M, Ammirati F, Montefoschi N, Varveri A, Santini M. Effects of Atorvastatin 80mg Daily Early After Onset of Unstable Angina Pectoris or Non-Q-Wave Myocardial Infarction. *Am J Cardiolgy* 2002;**90**:872-4

PROVE IT-TIMI 22

*Cannon CP, Braunwald E, McCabe CH, Rader DJ, Rouleau JL, Belder R, Joyal SV, Hill KA, Pfeffer MA, Skene AM, Pravastatin or Atorvastatin Evaluation and Infection Therapy- Thrombolysis in Myocardial Infarction 22 Investigators. Intensive versus Moderate Lipid Lowering with Statins after Acute Coronary Syndromes. *N Engl J Med* 2004;**350**:1495-504

Cannon CP, McCabe CH, Belder R, Breen J, Braunwald E. Design of the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE IT)-TIMI 22 Trial. *Am J Cardiol* 2002;**89**:860-1

Ridker PM, Morrow DA, Rose LM, Rifai N, Cannon CP, Braunwald E. Relative Efficacy of Atorvastin 80mg and Pravastatin 40mg in Achieving the Dual Goals of Low-Density Liprotein Cholesterol <70mg/dl and C-Reactive Protein <2mg/l: An Analysis of the PROVE IT-TIMI 22 Trial. *J Am Coll. Cardiology* 2005;**45**:1644-8

Ray KK, Cannon CP, McCabe CH, Cairns R, Tonkin AM, Sacks FM, Jackson G, Braunwald E for the PROVE IT-TIMI 22 Investigators. Early and Late Benefits of High-Dose Atorvastatin in Patients With Acute Coronary Syndromes. *J Am Coll. Cardiology* 2005;**46**:1405-10

Wiviott SD, Cannon CP, Morrow DA, Ray KK, Pfeffer MA, Braunwald E for the PROVE IT-TIMI 22 Investigators. Can Low-Density Lipoprotein Be Too Low? The Safety and Efficacy of Achieving Very Low Low-Density Lipoprotein With Intensive Statin Therapy. *J Am Coll. Cardiology* 2005;**46**:1411-6

Ridker PM, Cannon CP, Morrow D, Rifai N, Rose LM, McCabe CH, Pfeffer MA, Braunwald E for the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) Investigators. C-Reactive Protein Levels and Outcomes after Statin Therapy. *N Engl J Med* 2005;**352**:20-8

Scirica BM, Morrow DA, Cannon CP, Ray KK, Sabatine MS, Jarolim P, Shui A, McCabe CH, Braunwald E for the PROVE IT-TIMI 22 Investigators. Intensive Statin Therapy and the Risk of Hospitalization for Heart Failure After an Acute Coronary Syndrome in the PROVE IT-TIMI 22 Study. *J Am Coll. Cardiology* 2006;**47**:2326-31

Mega JL, Morrow DA, Cannon CP, Murphy S, Cairns R, Ridker PM, Braunwald E. Cholesterol, C-reactive protein, and cerebrovascular events following intensive and moderate statin therapy. *J Thromb Thrombolysis* 2006;**22**:71-6

O'Donoghue M, Morrow DA, Sabatine MS, Murphy SA, McCabe CH, Cannon CP, Braunwald E. Lipoprotein-Associated Phospholipase A2 and Its Association With Cardiovascular Outcomes in Patients With Acute Coronary Syndromes in the PROVE IT-TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction) Trial. *Circulation* 2006;**113**:1745-52

Ray KK, Bach RG, Cannon CP, Cairns R, Kirtane AJ, Wiviott SD, McCabe CH, Braunwald E, Gibson M for the PROVE IT-TIMI 22 Investigators. Benefits of achieving the NCEP optional LDL-C goal among elderly patients with ACS. *European Heart Journal* 2006;**27:**2310-6

Ahmed S, Cannon CP, Murphy SA, Braunwald E. Acute coronary syndromes and diabetes: is intensive lipid lowering beneficial? Results of the PROVE IT-TIMI 22 trial. *European Heart Journal* 2006;**27**:2323-9

Appendix 4 Studies excluded from the review with reasons

(excluded after consultation of the full paper)

Study	**Reason for exclusion**
Arutiunov GP, Kartseva TP, Voevodina NI, Daiter II, Malanichev RV, Marfunina AA, et al. [Effects of aggressive therapy with simvastatin in patients with acute coronary syndrome and initially normal level of LDLP cholesterol on cardiovascular outcomes (LAOKOON). Pilot randomized trial]. [Russian]. *Ter Arkh* 2005;**77(9)**:53-60	Not high dose
Atorvastatin is more effective than pravastatin in preventing recurrent cardiac events. *Evidence-based Healthcare & Public Health* 2004;**8(5)**	Duplicate (PROVE IT trial abstract)
Blazing MA, de Lemos JA, Dyke CK, Califf RM, Bilheimer D, Braunwald E, et al. The A-to-Z Trial: Methods and rationale for a single trial investigating combined use of low-molecular-weight heparin with the glycoprotein IIb/IIIa inhibitor tirofiban and defining the efficacy of early aggressive simvastatin therapy. *Am Heart J* 2001;**142(2)**:211-7	Not high dose initially
Cannon CP, Braunwald E, McCabe CH, Hillegas WB, Alam GK. High dose atorvastatin was superior to standard dose pravastatin in reducing death or major CV events in acute coronary syndrome. *Evidence Based Medicine* 2004;**9(5)**	Duplicate (PROVE IT trial abstract)
Cannon CP, Steinberg BA, Murphy SA, Mega JL, Braunwald E. Meta-analysis of cardiovascular outcomes trials comparing intensive versus moderate statin therapy. *Journal of the American College of Cardiology* 2006;**48(3)**:438-45	Review
Comparison of intensive and moderate lipid lowering with statins after acute coronary syndromes. *Indian Heart J* 2004;**56(2)**	Duplicate (summary of PROVE IT trial)
Correia LC, Magalhaes LP, Santana O, Rocha MS, Passos LC, D'Oliveira A, Jr., et al. Effect of atorvastatin (80 mg) on recurrent ischemia in unstable angina pectoris or non-ST-elevation acute myocardial infarction. *Am J Cardiol* 2003;**91(11)**:1355-7	High dose vs. placebo
Dupuis J, Tardif JC, Rouleau JL, Ricci J, Arnold M, Lonn E, et al. Intensity of lipid lowering with statins and brachial artery vascular endothelium reactivity after acute coronary syndromes (from the BRAVER trial). *Am J Cardiol* 2005;**96(9)**:1207-13	Not relevant outcomes
Early initiation of statins following ACS does not improve outcomes. *Journal of Family Practice* 2006;**55(8)**:664	Review
Faergeman O. High-dose atorvastatin or normal-dose simvastatin in treatment of patients with coronary heart disease (IDEAL trial) - Secondary publication. *Ugeskr Laeger* 2006;. **168(18)**	Not ACS
Farmer JA, Farmer JA. Intensive versus moderate lipid lowering with statins in acute coronary syndromes. *Curr Atheroscler Rep* 2005;**7(2)**:85-6	Review
Fathi R, Haluska B, Short L, Marwick TH, Fathi R, Haluska B, et al. A randomized trial of aggressive lipid reduction for improvement of myocardial ischemia, symptom status, and vascular function in patients with coronary artery disease not amenable to intervention. *Am J Med* 2003;**114(6)**:445-53	Not ACS
Gaspardone A, Versaci F, Proietti I, Tomai F, Altamura L, Skossyreva O, et al. Effect of atorvastatin (80 mg) initiated at the time of coronary artery stent implantation on C-reactive protein and six-month clinical events. *Am J Cardiol* 2002; **90(7)**	Not ACS
Guyton JR. Benefit versus Risk in Statin Treatment. *Am J Cardiol* 2006;**97(Suppl 1)**:17	Review
Hennekens CH, Hollar D, Eidelman RS, Agatston AS. Update for primary healthcare providers: Recent statin trials and revised national cholesterol education program III guidelines. Medgenmed [Computer File]: *Medscape General Medicine* 2006;**8(1)**	Review

Study	Reason for exclusion
High-dose simvastatin fails to achieve primary end point in trial of ACS. *Formulary* 2004;**39(10)**	Not high dose initially
Hulten E, Jackson JL, Douglas K, George S, Villines TC. The effect of early, intensive statin therapy on acute coronary syndrome: a meta-analysis of randomized controlled trials. [Review] [44 refs]. *Archives of Internal Medicine* 2006;**166(17)**:1814-21	Review
Khush KK, Waters D, Khush KK, Waters D. Lessons from the PROVE-IT trial. Higher dose of potent statin better for high-risk patients. Cleve Clin J Med 2004;**71(8)**:609-16	Review
Knatterud GL, Campeau L. Benefit of aggressive lipid lowering in post CABG trial patients. *Cardiology Review* 2001;**18(11)**	Not ACS
Koren MJ, Koren MJ. Statin use in a "real-world" clinical setting: aggressive lipid lowering compared with usual care in the Aggressive Lipid-Lowering Initiation Abates New Cardiac Events (ALLIANCE) trial. Am J Med 2005;**118** (**Suppl 12A)**:16-21	Not ACS
Lu M, Can L, Kültürsay H, Payzin S, lu C. Early use of pravastatin in patients with acute myocardial infarction undergoing coronary angioplasty. *Acta cardiologica* 2002;**57**:295-302	Not high dose
McCormick LS, Black DM, Waters D, Brown WV, Pitt B, McCormick LS, et al. Rationale, design, and baseline characteristics of a trial comparing aggressive lipid lowering with Atorvastatin Versus Revascularization Treatments (AVERT). *Am J Cardiol* 1997 Nov;**80(9)**:1130-3.	Not ACS
Mizia-Stec K, Gasior Z, Zahorska-Markiewicz B, Janowska J, Mizia M, Pysz P, et al. High doses of simvastatin in ACS decrease serum PDGF levels without influencing immune activation. *Folia Cardiologica* 2006;**13(4)**:326-30	Not relevant outcomes
Mizia-Stec K, Gasior Z, Zahorska-Markiewicz B, Jastrzebska-Maj E, Gomulka S, Mizia M. High simvastatin doses in acute coronary syndromes and doppler indices of endothelial function in long-term observation. *Folia Cardiologica* 2004;**11(6)**	Not relevant outcomes
Nissen SE, Tuzcu EM, Schoenhagen P, Crowe T, Sasiela WJ, Tsai J, et al. Statin therapy, LDL cholesterol, C-reactive protein, and coronary artery disease.[see comment]. *N Engl J Med* 2005;**352(1)**:29-38	Not ACS
Olsson AG. Erratum: High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: The IDEAL study: A randomized controlled trial (Journal of the American Medical Association (November 16, 2005) 294 (2437-2445)). *JAMA* 2005; **294(24)**:28.	Not ACS
Pedersen TR, Faergeman O, Kastelein JJ, Olsson AG, Tikkanen MJ, Holme I, et al. Design and baseline characteristics of the Incremental Decrease in End Points through Aggressive Lipid Lowering study. *Am J Cardiol* 2004;**94(6)**:720-4	Not ACS
Pedersen TR, Faergeman O, Kastelein JJ, Olsson AG, Tikkanen MJ, Holme I, et al. High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial.[see comment]. *JAMA* 2005;**294(19)**:2437-45	Not ACS
Ray KK, Cannon CP, Cairns R, Morrow DA, Rifai N, Kirtane AJ, et al. Relationship between uncontrolled risk factors and C-reactive protein levels in patients receiving standard or intensive statin therapy for acute coronary syndromes in the PROVE IT-TIMI 22 trial. *J Am Coll Cardiol* 2005;**46(8)**:1417-24	Not relevant outcomes
Rouleau J, Rouleau J. Improved outcome after acute coronary syndromes with an intensive versus standard lipid-lowering regimen: results from the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) trial. Am J Med 2005 Dec;118 Suppl 12A:28-35	Review
Schwartz GG, Oliver MF, Ezekowitz MD, Ganz P, Waters D, Kane JP, et al. Rationale and design of the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) study that evaluates atorvastatin in unstable angina pectoris and in non-Q-wave acute myocardial infarction.[see comment]. *Am J Cardiol* 1998;**81(5)**:578-81	High dose vs. placebo

Study	**Reason for exclusion**
Schwartz GG, Olsson AG, Szarek M, Sasiela WJ, Schwartz GG, Olsson AG, et al. Relation of characteristics of metabolic syndrome to short-term prognosis and effects of intensive statin therapy after acute coronary syndrome: an analysis of the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) trial. *Diabetes Care* 2005;**28(10)**:2508-13	High dose vs. placebo
Shishehbor MH, Patel T, Bhatt DL. Using statins to treat inflammation in acute coronary syndromes: Are we there yet? *Cleveland Clinic Journal of Medicine* 2006;**73(8)**:760-6	Review
Silva M, Matthews ML, Jarvis C, Nolan NM, Belliveau P, Malloy M, et al. Meta-analysis of drug-induced adverse events associated with intensive-dose statin therapy. *Clinical Therapeutics* 2007;**29(2)**:253-60	Review
TNT - More evidence that 'lower is better' for LDL-C. British *Journal of Cardiology* 2005; **12(2)**	Not ACS
Waters DD, Guyton JR, Herrington DM, McGowan MP, Wenger NK, Shear C, et al. Treating to New Targets (TNT) Study: does lowering low-density lipoprotein cholesterol levels below currently recommended guidelines yield incremental clinical benefit? *Am J Cardiol* 2004;**93(2)**:154-8	Not ACS
Waters DD. Safety of high-dose atorvastatin therapy. Am J Cardiol 2005;**96(Suppl 5)**	Review
Wiviott SD, de Lemos JA, Cannon CP, Blazing M, Murphy SA, McCabe CH, et al. A tale of two trials: a comparison of the post-acute coronary syndrome lipid-lowering trials A to Z and PROVE IT-TIMI 22.[see comment]. *Circulation* 2006;**113(11)**:1406-14	Review
Yang J, Li XP, Zhao SP, Li J, Li JD, Xie XM, et al. [The effect of early fluvastatin therapy on inflammatory factors in acute coronary syndrome]. Zhonghua nei ke za zhi [*Chinese journal of internal medicine*] 2005;**44**:184-7	Not high dose

Appendix 5 Quality assessment of the included studies

	Colivicchi 2002	PROVE IT-TIMI 22
1. Was the assignment to the treatment groups really random?	Yes- a computer-generated randomisation list was used to assign patients to the study arms	Yes- a central randomisation system was used that involved a permuted block design in which assignment was stratified according centre
2. Was the treatment allocation concealed?	No	Yes
3. Were the groups similar at baseline in terms of prognostic factors?	Yes	Yes- the two groups of patients were well matched with the exception of a history of peripheral arterial disease which was more common in the pravastatin group (p=0.03)
4. Were the eligibility criteria specified?	Yes	Yes
5. Were outcome assessors blinded to the treatment allocation?	Yes	Unclear
6. Was the care provider blinded?	No	Yes
7. Was the patient blinded?	No	Yes
8. Were the point estimates and measures of variability presented for the outcome measure?	Yes	Yes
9. Did analyses include an intention to treat analysis?	Yes	Yes

Appendix 6 Search strategies for economic evaluation, modelling and quality of life

Bibliographic databases searched:

Database: Ovid MEDLINE(R) <1950 to June Week 2 2007>
Search strategy (economic evaluation):
----

1 acute coronary syndrome$.mp.
2 unstable angina$.mp. or exp Angina, Unstable/
3 angina$.mp.
4 myocardial infarction$.mp. or exp Myocardial Infarction/
5 acute myocardial infarction$.mp.
6 non-Q-wave myocardial infarction$.mp.
7 Q-wave myocardial infarction$.mp.
8 non-ST-segment elevation myocardial infarction$.mp.
9 ST-segment elevation myocardial infarction$.mp.
10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11 exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/ or statin$.mp.
12 atorvastatin.mp.
13 fluvastatin.mp.
14 pravastatin.mp. or exp Pravastatin/
15 rosuvastatin.mp.
16 simvastatin.mp. or exp Simvastatin/
17 cerivastatin.mp.
18 lovastatin.mp. or exp Lovastatin/
19 hydroxymethylglutaryl-Coa-reductase inhibitor$.mp. or exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/
20 hydroxymethylglutaryl-Coa-reductase$.mp. or exp Hydroxymethylglutaryl CoA Reductases/
21 antilipaemic agent$.mp.
22 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21
23 10 and 22
24 economics/
25 exp "costs and cost analysis"/
26 cost of illness/
27 exp health care costs/
28 economic value of life/
29 exp economics medical/
30 exp economics hospital/
31 economics pharmaceutical/
32 exp "fees and charges"/
33 (econom$ or cost or costs or costly or costing or price or pricing or pharmacoeconomic$).tw.
34 (expenditure$ not energy).tw.
35 (value adj1 money).tw.
36 budget$.tw.
37 or/24-36
38 23 and 37
39 from 38 keep 1-156

Database: EMBASE <1980 to 2007 Week 25>
Search strategy (economic evaluation):
----

1 acute coronary syndrome$.mp.
2 unstable angina$.mp.
3 angina$.mp.
4 myocardial infarction$.mp. or exp Heart Infarction/
5 acute myocardial infarction$.mp. or exp Acute Heart Infarction/
6 non-Q-wave myocardial infarction$.mp.
7 Q-wave myocardial infarction$.mp.

8 non-ST-segment elevation myocardial infarction$.mp.
9 exp St Segment Elevation/ or ST-segment elevation myocardial infarction$.mp.
10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11 statin$.mp. or exp STATIN/
12 atorvastatin.mp. or exp ATORVASTATIN/
13 fluvastatin.mp.
14 pravastatin.mp. or exp PRAVASTATIN/
15 rosuvastatin.mp. or exp ROSUVASTATIN/
16 simvastatin.mp. or exp SIMVASTATIN/
17 cerivastatin.mp. or exp CERIVASTATIN/
18 lovastatin.mp.
19 hydroxymethylglutaryl-Coa-reductase inhibitor$.mp. or exp Hydroxymethylglutaryl Coenzyme a Reductase Inhibitor/
20 hydroxymethylglutaryl-Coa-reductase$.mp. or exp Hydroxymethylglutaryl Coenzyme a Reductase/
21 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
22 10 and 21
23 cost benefit analysis/
24 cost effectiveness analysis/
25 cost minimization analysis/
26 cost utility analysis/
27 economic evaluation/
28 (cost or costs or costed or costly or costing).tw.
29 (economic$ or pharmacoeconomic$ or price$ or pricing).tw.
30 (technology adj assessment$).tw.
31 or/23-30
32 22 and 31
33 from 32 keep 1-542

Database: Ovid MEDLINE(R) <1950 to June Week 2 2007>
Search strategy (modelling):
----

1 acute coronary syndrome$.mp.
2 unstable angina$.mp. or exp Angina, Unstable/
3 angina$.mp.
4 myocardial infarction$.mp. or exp Myocardial Infarction/
5 acute myocardial infarction$.mp.
6 non-Q-wave myocardial infarction$.mp.
7 Q-wave myocardial infarction$.mp.
8 non-ST-segment elevation myocardial infarction$.mp.
9 ST-segment elevation myocardial infarction$.mp.
10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11 exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/ or statin$.mp.
12 atorvastatin.mp.
13 fluvastatin.mp.
14 pravastatin.mp. or exp Pravastatin/
15 rosuvastatin.mp.
16 simvastatin.mp. or exp Simvastatin/
17 cerivastatin.mp.
18 lovastatin.mp. or exp Lovastatin/
19 hydroxymethylglutaryl-Coa-reductase inhibitor$.mp. or exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/
20 hydroxymethylglutaryl-Coa-reductase$.mp. or exp Hydroxymethylglutaryl CoA Reductases/
21 antilipaemic agent$.mp.
22 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21
23 10 and 22
24 decision support techniques/
25 markov.mp.
26 exp models economic/
27 decision analysis.mp.
28 cost benefit analysis/
29 economic model$.mp.

30 monte carlo method$.mp.
31 monte carlo.mp.
32 exp decision theory/
33 (decision$ adj2 (tree$ or analy$ or model$)).mp.
34 or/24-33
35 23 and 34
36 from 35 keep 1-75

Database: EMBASE <1980 to 2007 Week 25>
Search strategy (modelling):
---
1 acute coronary syndrome$.mp.
2 unstable angina$.mp.
3 angina$.mp.
4 myocardial infarction$.mp. or exp Heart Infarction/
5 acute myocardial infarction$.mp. or exp Acute Heart Infarction/
6 non-Q-wave myocardial infarction$.mp.
7 Q-wave myocardial infarction$.mp.
8 non-ST-segment elevation myocardial infarction$.mp.
9 exp St Segment Elevation/ or ST-segment elevation myocardial infarction$.mp.
10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11 statin$.mp. or exp STATIN/
12 atorvastatin.mp. or exp ATORVASTATIN/
13 fluvastatin.mp.
14 pravastatin.mp. or exp PRAVASTATIN/
15 rosuvastatin.mp. or exp ROSUVASTATIN/
16 simvastatin.mp. or exp SIMVASTATIN/
17 cerivastatin.mp. or exp CERIVASTATIN/
18 lovastatin.mp.
19 hydroxymethylglutaryl-Coa-reductase inhibitor$.mp. or exp Hydroxymethylglutaryl Coenzyme a Reductase Inhibitor/
20 hydroxymethylglutaryl-Coa-reductase$.mp. or exp Hydroxymethylglutaryl Coenzyme a Reductase/
21 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
22 10 and 21
23 decision support techniques/
24 markov.mp.
25 exp models economic/
26 decision analysis.mp.
27 cost benefit analysis/
28 economic model$.mp.
29 monte carlo.mp.
30 exp decision theory/
31 (decision$ adj2 (tree$ or analys$ or model$)).mp.
32 or/23-31
33 22 and 32
34 from 33 keep 1-131

Database: Ovid MEDLINE(R) <1950 to June Week 2 2007>
Search strategy (quality of life):
---
1 acute coronary syndrome$.mp.
2 unstable angina$.mp. or exp Angina, Unstable/
3 angina$.mp.
4 myocardial infarction$.mp. or exp Myocardial Infarction/
5 acute myocardial infarction$.mp.
6 non-Q-wave myocardial infarction$.mp.
7 Q-wave myocardial infarction$.mp.
8 non-ST-segment elevation myocardial infarction$.mp.
9 ST-segment elevation myocardial infarction$.mp.

10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11 exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/ or statin$.mp.
12 atorvastatin.mp.
13 fluvastatin.mp.
14 pravastatin.mp. or exp Pravastatin/
15 rosuvastatin.mp.
16 simvastatin.mp. or exp Simvastatin/
17 cerivastatin.mp.
18 lovastatin.mp. or exp Lovastatin/
19 hydroxymethylglutaryl-Coa-reductase inhibitor$.mp. or exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/
20 hydroxymethylglutaryl-Coa-reductase$.mp. or exp Hydroxymethylglutaryl CoA Reductases/
21 antilipaemic agent$.mp.
22 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21
23 10 and 22
24 quality of life/
25 life style/
26 health status/
27 health status indicators/
28 value of life/
29 quality adjusted life.mp.
30 or/24-29
31 23 and 30
32 from 31 keep 1-80

Database: EMBASE <1980 to 2007 Week 25>
Search strategy (quality of life):
----

1 acute coronary syndrome$.mp.
2 unstable angina$.mp.
3 angina$.mp.
4 myocardial infarction$.mp. or exp Heart Infarction/
5 acute myocardial infarction$.mp. or exp Acute Heart Infarction/
6 non-Q-wave myocardial infarction$.mp.
7 Q-wave myocardial infarction$.mp.
8 non-ST-segment elevation myocardial infarction$.mp.
9 exp St Segment Elevation/ or ST-segment elevation myocardial infarction$.mp.
10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11 statin$.mp. or exp STATIN/
12 atorvastatin.mp. or exp ATORVASTATIN/
13 fluvastatin.mp.
14 pravastatin.mp. or exp PRAVASTATIN/
15 rosuvastatin.mp. or exp ROSUVASTATIN/
16 simvastatin.mp. or exp SIMVASTATIN/
17 cerivastatin.mp. or exp CERIVASTATIN/
18 lovastatin.mp.
19 hydroxymethylglutaryl-Coa-reductase inhibitor$.mp. or exp Hydroxymethylglutaryl Coenzyme a Reductase Inhibitor/
20 hydroxymethylglutaryl-Coa-reductase$.mp. or exp Hydroxymethylglutaryl Coenzyme a Reductase/
21 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
22 10 and 21
23 quality of life/
24 quality adjusted life year/
25 health status/
26 health status indicator$.mp.
27 or/23-26
28 22 and 27
29 from 28 keep 1-260

Database: Cochrane Library (Wiley) 2007, Issue 2 (NHS EED)
Search strategy:

#1	"acute coronary syndrome*"
#2	"unstable angina*"
#3	"myocardial infarction*"
#4	MeSH descriptor **Myocardial Infarction** explode all trees
#5	angina*
#6	"acute myocardial infarction*"
#7	"non-Q-wave myocardial infarction*"
#8	"Q-wave myocardial infarction*"
#9	"non-ST-segment elevation myocardial infarction*"
#10	"ST-segment elevation myocardial infarction*"
#11	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10)
#12	MeSH descriptor **Hydroxymethylglutaryl-CoA Reductase Inhibitors** explode all trees
#13	statin*
#14	atorvastatin
#15	fluvastatin
#16	MeSH descriptor **Pravastatin** explode all trees
#17	pravastatin
#18	rosuvastatin
#19	MeSH descriptor **Simvastatin** explode all trees
#20	simvastatin
#21	cerivastatin
#22	MeSH descriptor **Lovastatin** explode all trees
#23	lovastatin
#24	"hydroxymethylglutaryl-Coa-reductase inhibitor*"
#25	"antilipaemic agent*"
#26	(#12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25)
#27	(#11 AND #26)

OHE HEED June 2007

Search terms used: statin,* atorvastatin, fluvastatin, pravastatin, rosuvastatin and simvastatin.

Drug companies contacted:

The following manufacturers of the five statins currently licensed for use in the UK were contacted for details of any cost-effectiveness studies or economic models:

Atovastatin: Pfizer Ltd, Walton Oaks, Dorking Road, Tadworth, Surrey, KT20 7NS

Fluvastatin: Novartis Pharmaceuticals UK Ltd, Frimley, Camberley, Surrey, GU16 7SR

Pravastatin: Bristol-Myers Squibb Pharmaceuticals Ltd, Uxbridge Business Park, Sanderson Road, Uxbridge, Middlesex, UB8 1DH

Rosuvastatin: AstraZeneca UK Ltd, Horizon Place, 600 Capability Green, Luton, Bedfordshire, LU1 3LU
Simvastatin: Merck Sharp & Dohme Ltd, Hertford Road, Hoddesdon, Hertfordshire, EN11 9BU

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2 Sacks FM, Pfeffer MA, Moye LA, Rouleau JL, Rutherford JD, Cole TG, *et al*. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. *N Engl J Med* 1996; **335**(14):1001-1009.

3 Scandanavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994; **344**(8934):1383-1389.

4 Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, Macfarlane PW, *et al*. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. *N Engl J Med* 1995; **333**(20):1301-1307.

5 The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. *N Engl J Med* 1998; **339**(19):1349-1357.

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URL:http://www.doh.gov.uk/nsf/coronary.htm [Accessed 20th September 2007]

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13 Cannon CP, Braunwald E, McCabe CH, Rader DJ, Rouleau JL, Belder R, *et al*. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med* 2004; **350**(15):1495-1504.

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15 Sposito AC, Chapman MJ. Statin therapy in acute coronary syndromes: mechanistic insight into clinical benefit. *Arterioscler Thromb Vasc Biol* 2002; **22**(10):1524-1534.

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