Statin safety in perspective – maximising the risk:benefit

MARC EVANS

Abstract

Statins are prescribed worldwide for patients with coronary heart disease (CHD) and also for those at risk of developing atherosclerotic vascular disease. They represent a valuable treatment option for managing lipid levels. However, the well-publicised withdrawal of cerivastatin (Baycol®, Bayer) in 2001 led to concern and much subsequent discussion over the safety of statins. This review looks at the evidence in relation to the benefits and risks of statins and demonstrates that the benefits of statins far outweigh the risks.

Key words: statins, cholesterol, LDL-cholesterol, coronary heart disease, guidelines.

Br J Cardiol 2004;**11**:449–54

Marc Evans

Introduction

In order to establish the optimum way of treating patients with statins, both the benefits and risks associated with statins across the dose range should be evaluated. This review assesses the efficacy, safety and tolerability of marketed statins to give a practical overview on maximising the risk:benefit of the use of this class of drug.

Benefits of statins

Cholesterol: current evidence and guidelines

Guideline recommendations are useful benchmarks for evidence-based practice, applied in the context of clinical judgement. They may not always reflect the most up-to-date evidence, however, since they are published intermittently.

Despite the clear epidemiological association between cholesterol and cardiovascular risk, many individuals who develop vascular disease do not have particularly elevated cholesterol levels. The evidence that incrementally lower cholesterol is better in terms of cardiovascular disease risk comes both from epidemiological studies and randomised clinical trials. Epidemiological evidence supporting the notion that lower low-density lipoprotein cholesterol (LDL-C) levels are associated with lower coronary heart disease (CHD) risk comes from studies of men in rural China, where participants in the lowest quartile of LDL-C (< 3.0 mmol/L) had coronary event rates 75% lower than those in the highest quartile.[1] Further evidence in support of this notion comes from the Seven Countries study, initiated in the 1960s, which assessed the relationship between serum cholesterol and CHD on both an intra- and inter-population basis,[2] as well as prospective longitudinal studies such as PROCAM (Prospective Cardiovascular Munster Study) and the Framingham study.[3,4]

Every major clinical end point trial of lipid lowering therapy[5] has demonstrated that lower LDL-C levels are associated with a reduced atherosclerotic disease burden. Analysis of the relationship between LDL-C levels and major coronary events in studies such as 4S (Scandinavian Simvastatin Survival Study) after only one year of treatment suggests that event rates are lower for each lower tertile of LDL-C, while event rates may be reduced for each increasing tertile of LDL-C reduction.[6] Such observations suggest that there may be no threshold for LDL-C reduction beyond which additional cardiovascular benefit may not be achieved. Indeed, O'Keefe has suggested that the optimum LDL-C levels should be in the range of 1.3–1.8 mmol/L – the typical level of our hunter-gatherer forefathers where there was no evidence of atherosclerosis, even in individuals living to their seventh or eighth decade of life.[7]

Guidelines are indeed recommending lower and lower LDL-C

Llandough Hospital, Penlan Road, Penarth, CF64 2XX.
Marc Evans, Consultant Diabetologist
Correspondence to: Dr M Evans
(email: marc.evans2@ntlworld.com)

Table 1. Guidelines are taking LDL-C targets lower

Guideline	Year published	LDL-C target (mmol/L)	TC target (mmol/L)
JBS	1998	< 3.0	< 5.0
EAS	1998	< 3.0	< 5.0
NSF for CHD	2000	< 3.0 & 30% reduction	< 5.0 and 25% reduction
EAS	2003	< 2.5 in high risk	< 4.5 in high risk
BHS IV	2004	< 2.0 in high risk	< 4.0 in high risk
European guidelines	2004	< 3.0 in non-high risk < 2.5 in high risk, CVD and diabetes	< 5.0 in non-high risk < 4.5 in high risk, CVD and diabetes
NCEP ATP III	2004	< 1.8 in very high risk < 2.6 in moderately high risk and 30–40% reduction	Not specified in 2004 update

Key: JBS = Joint British Societies; EAS = European Atherosclerosis Society; NSF for CHD = National Service Framework for Coronary Heart Disease; BHS IV = British Hypertension Society guidelines for hypertension management 2004; NCEP ATP III = National Cholesterol Education Program Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III); LDL-C = low-density lipoprotein cholesterol; TC = total cholesterol; CVD = cardiovascular disease

targets (table 1), although the target of 5 mmol/L in the General Medical Services (GMS) Contract is somewhat less stringent than all other new recommendations.

However, current guidelines base recommendations about initiation of cholesterol lowering therapy primarily on an estimated risk of coronary events alone. HPS (the Heart Protection Study)[8] demonstrated a reduction in CHD events and also in ischaemic strokes and peripheral revascularisations. In this study, the chief determinants of absolute risk were the type of pre-existing vascular disease, the presence or absence of type 2 diabetes or some combination of these conditions, with significant reductions in relative risk produced by statin therapy irrespective of pre-treatment LDL-C levels.[8] Such a concept is further supported by data from the recent CARDS trial (Collaborative Atorvastatin Diabetes Study). This demonstrated that statin therapy resulted in a significant reduction of cardiovascular events in patients with type 2 diabetes plus one other cardiovascular risk factor, who had pre-treatment cholesterol levels at or near to currently accepted target levels.[9]

Based on such observations, it seems logical to initiate statin therapy based on a global cardiovascular risk assessment rather than simple pre-treatment cholesterol levels. It is apparent that current guidelines may lead to substantial under-treatment in some individuals as targets are set at less stringent levels than those achieved in many recent statin therapy clinical trials.[10-12] Furthermore, there is a growing body of evidence that has yet to be taken into account by current guidelines to suggest that the lower the LDL-C, the better. The result of studies, such as PROVE-IT (Pravastatin or Atorvastatin Evaluation and Infection Therapy – Thrombolysis in Myocardial Infarction)[11] and REVERSAL (Regressing Atherosclerosis with Aggressive Lipid Lowering),[12] demonstrate that there is continuing risk reduction with LDL-C levels as low as 1.6 mmol/L.

However, LDL-C alone does not represent the entire atherogenic lipid profile. Indeed, data from studies such as MR FIT (Multiple Risk Factor Intervention Trial),[13] PROCAM[3] and the Strong Heart Study[14] suggest that non-high-density lipoprotein cholesterol (non HDL-C) levels are key lipid predictors of CHD risk, since this fraction accounts for all atherogenic lipoproteins, including LDL-C, very low-density lipoprotein cholesterol (VLDL-C), intermediate-density lipoprotein cholesterol (IDL-C), lipoprotein (a) cholesterol and chylomicrons. HDL-C, however, exhibits numerous vascular protective properties, including anti-oxidant properties and anti-inflammatory effects, as well as facilitating reverse cholesterol ester transport and demonstrating plaque stabilising properties. Indeed, a 1% increase in HDL-C is associated with a 2–3% decrease in CHD risk, while a 1% decrease in LDL-C is associated with a 1% decrease in CHD risk.[15]

Statins in clinical practice

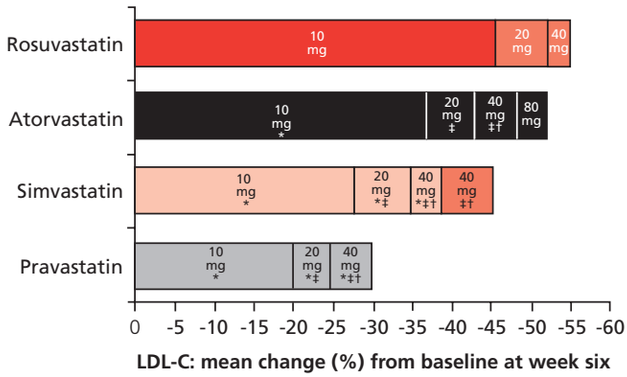
Based on the concept that treatment guidelines stipulate ever lower targets for LDL-C combined with the growing evidence supporting the notion that lower is better, practicing clinicians face the problem of how best to achieve optimal cholesterol reduction. The options available include using higher doses of traditional statins, the use of newer, more efficacious statins, and combining moderate or high-dose statin with an agent that acts in a complementary fashion (bile acid sequestrant, niacin or cholesterol absorption blocker). Rosuvastatin, launched in March 2003, is a potent, hydrophilic enantiomeric statin producing reductions in LDL-C of 46% at the 10 mg start dose.[10] Ezetimibe, also launched in early 2003, is a selective cholesterol absorption inhibitor with action at the intestinal epithelium producing reduction of LDL-C of up to 20% at the therapeutic dose of 10 mg once daily.[16]

Statins, however, remain the mainstay of cholesterol lowering-therapy, exerting a therapeutic effect through inhibiting the activity of 3-hydroxy-methylglutaryl coenzyme A (3-HMG-CoA) reductase, the enzyme involved in the rate-limiting step in cholesterol biosynthesis, resulting in a secondary increase in hepatocyte LDL-receptor expression, thus facilitating plasma cholesterol clearance.

Statins – efficacy

Several studies have demonstrated that statins may differ in their lipid modifying properties. The largest such study, the STELLAR[10] (Statin Therapies for Elevated Lipid Levels compared Across doses to Rosuvastatin) study, compared rosuvastatin, atorvastatin, simvastatin and pravastatin across licensed doses for reducing LDL-C and other lipid parameters in patients (n=2,431) with hypercholesterolaemia (LDL-C ≥ 160 and < 250 mg/dL [≥ 4.14 and < 6.47 mmol/L respectively]; triglycerides < 400 mg/dL [< 4.52 mmol/L]). It found that after six weeks of treatment, rosuvastatin

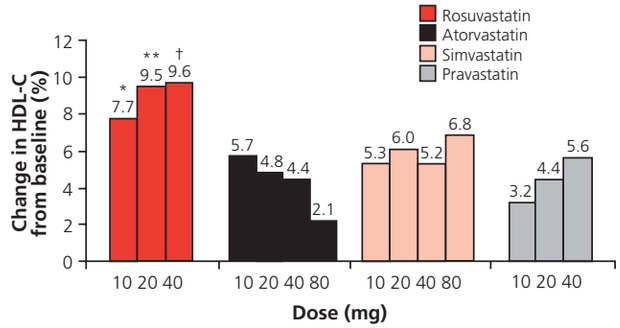
Figure 1. LDL-C reduction across statin dose ranges in the STELLAR study



Key: LDL-C = low-density lipoprotein cholesterol; STELLAR = Statin Therapies for Elevated Lipid Levels compared Across doses to Rosuvastatin; *p=<0.002 *vs.* rosuvastatin 10 mg; ‡ p=<0.002 *vs.* rosuvastatin 20 mg; † p=<0.002 *vs.* rosuvastatin 40 mg

Adapted from Jones PH *et al.*[10]

Figure 2. Change in HDL-C across statin dose ranges in the STELLAR study



Key: HDL-C = high-density lipoprotein cholesterol; *p=<0.002 *vs.* pravastatin 10 mg; ** p=<0.002 *vs.* atorvastatin 20, 40, 80 mg; simvastatin 40 mg; pravastatin 20, 40 mg; † p=<0.002 *vs.* atorvastatin 40 mg, 80 mg; simvastatin 40 mg; pravastatin 40 mg

Observed data in ITT population

Adapted from Jones PH *et al.*[10]

resulted in significantly greater LDL-C reductions dose for dose compared with other statins (figure 1).[10]

In addition, the STELLAR study showed that rosuvastatin 10 mg to 40 mg raised HDL-C by 7.7–9.6% compared with 5.7–2.1%, 5.2–6.8% and 3.2–5.6% for atorvastatin 10–80 mg, simvastatin 10–80 mg and pravastatin 10–40 mg, respectively (figure 2). Importantly, this effect was maintained across the dose range.[10]

Risks of statins

Safety of statins

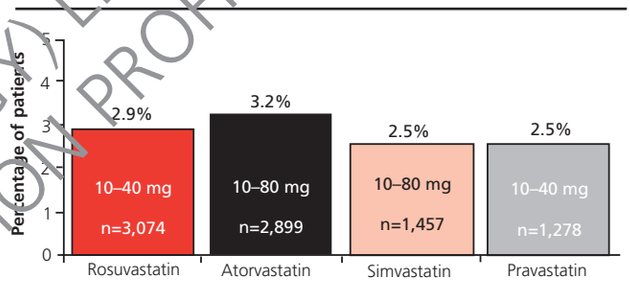
Overall, the statin class of drugs has a good safety profile and is well tolerated. The withdrawal of cerivastatin, however, led to questions regarding the safety of statins and, as with all drugs, the safety profile of statins must be evaluated relative to their clinical benefits.

The overall adverse event rate associated with statin therapy is low, with the most common side effects reported being headaches, gastrointestinal disturbance and myalgia.[17] Based on data from the rosuvastatin pre-registration clinical trial package, which reviewed the key currently available statins in the UK (simvastatin, atorvastatin, pravastatin, and rosuvastatin), statins have equivalent adverse event withdrawal rates of approximately 3% (figure 3).[18]

However, as with most drugs, statins exhibit a dose-related adverse events (AEs) profile.[18] One of the most common side effects associated with statin therapy relates to muscle toxicity and myopathy. It is important to appreciate that there is a distinct classification of muscle AE, ranging from mild myopathy to frank rhabdomyolysis. Furthermore, rhabdomyolysis and myositis have a strict clinical definition (table 2).[19]

The total reported incidence of statin-associated myotoxicity

Figure 3. Adverse event withdrawal rates of statins



Adapted from Brewer HB[19]

ranges from between 1–7%[19] and is a function of dose rather than LDL-C reduction.[18] This dose-related effect has been demonstrated across the statin class (figure 4)[18] and was further supported in the A to Z trial which demonstrated higher rates of side effects with simvastatin 80 mg.[20]

Myalgia is the most common side effect with statins while rhabdomyolysis and myositis, the most serious of muscle AEs, account for less than 0.1% of all statin-related AEs, with comparable reporting rates across currently available statins.[21] Cerivastatin was a lipophilic enantiomeric agent with a dual excretory pathway (2C8 and 3A4). The pre-marketing data showed increased rates of myotoxicity, particularly at higher doses, while the post-marketing data revealed the incidence of myotoxicity was greater than ten times that of other statins. The majority of cases of rhabdomyolysis occurred with the 0.8 mg dose and there was a particularly high incidence associated with the use of cerivastatin in combination with gemfibrozil.

Table 2. Classification of muscular adverse events

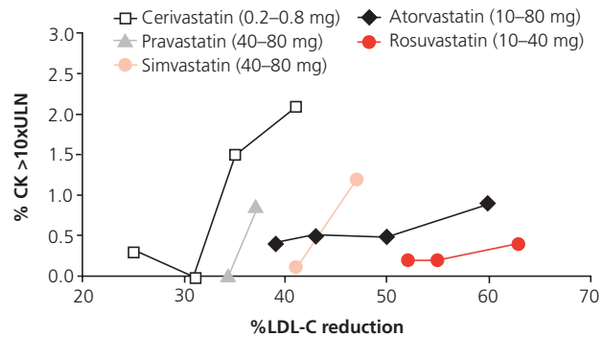
Myalgia
- Diffuse muscle discomfort
- Proximal muscles most often involved
- Creatine kinase (CK) levels may be normal or slightly elevated
- Completely reversible
- Most common feature of statin myotoxicity
- Dose related

Myopathy
- Muscle pain with elevated CK levels (> 10 X upper limit of normal)
- Predominantly effects upper limb proximal muscles
- Characteristic muscle fibre necrosis and electromyography appearances
- Dose related

Myositis
- Occurs with or without elevated CK levels
- Characterised by muscle weakness
- Biopsy – variation in muscle fibre size with associated inflammatory cell infiltrate
- Dose related phenomenon

Rhabdomyolysis
- Characterised by muscle destruction – release of myoglobin, muscle pain, swelling and CK levels
- Myoglobin may cause acute renal failure and by inhibiting nitric oxide metabolism may cause vasoconstriction and tissue ischaemia
- Inherited muscle enzyme defects present in ~ 25% of cases
- Can be fatal

Figure 4. Myopathy in association with statins is dose-related



Key: CK = creatine kinase; ULN = upper limits of normal; LDL-C = low-density lipoprotein cholesterol

Adapted from Brewer HB[19]

Table 3. Reported rates of fatal rhabdomyolysis per statin[23]

Statin	Number of fatal rhabdomyolysis cases	Number of prescriptions (10^6)	Number of cases/10^6 prescriptions
Cerivastatin	31	9.8	3.16
Lovastatin	19	99	0.19
Simvastatin	14	116	0.12
Atorvastatin	6	140	0.04
Pravastatin	3	81	0.04
Fluvastatin	0	37	-
TOTAL	73	484	3.55

Note: Rosuvastatin had in excess of 10 million prescriptions with no cases of fatal rhabdomyolysis at the time of this publication

The frequency of rhabdomyolysis reported with the currently available statins is less than one in 100,000 and is comparable for simvastatin, atorvastatin, rosuvastatin, pravastatin, fluvastatin and lovastatin.[21,22] Deaths due to rhabdomyolysis are very rare (<1:1,000,000.) The reported rate of deaths due to rhabdomyolysis as a function of cerivastatin therapy were many fold greater than seen with other agents (table 3). Indeed, Staffa reported that after 9.8 million prescriptions in the US there were 31 cases of fatal rhabdomyolysis reported.[23] Since the withdrawal of cerivastatin, rosuvastatin has been launched and, to date, there have been in excess of 10 million prescriptions with no fatal cases of rhabdomyolysis reported (AstraZeneca, data on file).

In summary, whilst rhabdomyolysis may be serious and life-threatening, it is very rare in relation to currently available statin therapy. When it does occur, it is most commonly in the context of predisposing risk factors, such as trauma, major surgery, hypothyroidism, liver failure, renal failure and concomitant drug therapy such as amiodarone.[18]

Statins and the kidney

Mild proteinuria has recently been identified in patients treated with all statin therapy,[24] although this is generally transient and reversible. Furthermore, the finding of mild proteinuria is not predictive of any acute or progressive change in renal function or suggestive that statin therapy is associated with deteriorating renal function. In fact, statin therapy, potentially through improvements in vascular function, has been shown to improve glomerular filtration rates.[24]

The excreted urine proteins appear to be mainly low molecular weight proteins, indicating a specific effect on proximal tubular protein reabsorption. In recent *in vitro* studies, various statins decreased protein reabsorption in an opossum kidney cell line derived from proximal tubules[25] and human tubular kidney cells.[26] This effect was associated with inhibition of 3-HMG CoA reductase and was reversed by adding mevalonate (the product of 3-HMG-CoA reductase) and geranylgeranyl pyrophosphate (a mevalonate product involved in protein prenylation), suggesting a potential pharmacologic mechanism for the tubular proteinuria seen with statin therapy.[26]

Statin therapy - risk:benefit assessment

The majority of LDL-C lowering effects associated with statin therapy occur with the starting dose, whilst the doubling of

Key messages: practical advice on the use of statins

- The use of a statin should be determined by the overall coronary heart disease (CHD) risk rather than baseline cholesterol
- Patients with type 2 diabetes represent a CHD equivalent and should receive statin therapy
- Optimise risk:benefit profile of statins by using the lowest dose of the most efficacious agent
- In patients not reaching target, titrate statin as required to maximum tolerated dose (consider specialist referral if appropriate)
- If target levels are still unattained consider adding a therapy with a complementary mode of action e.g. ezetimibe
- To minimise risk of myotoxic adverse events, assess any potential contributing factors e.g. trauma, major surgery, hypothyroidism, liver failure, renal failure and concomitant drug therapy

dosage only results in 6–9% further cholesterol reduction. Increased doses are valuable in more difficult to treat patients and very high-risk groups (e.g. familial hypercholesterolaemia) and may result in relatively small additional effects. Adverse events related to statin therapy, although relatively infrequent, exhibit a clear dose-response relationship. Thus, in order to optimise the risk:benefit profile associated with statin therapy, the most prudent approach would be to use a low dose of the most efficacious agent, hence optimising the therapeutic benefit whilst minimising the potential for adverse events.

Conflict of interest

ME has received research support from AstraZeneca and Glaxo-SmithKline.

References

1. Chen Z, Peto R, Collins R *et al*. Serum cholesterol concentration and coronary heart disease in a population with low cholesterol levels. *BMJ* 1991;**303**:276-82.
2. Verschuuren WM, Jacobs DR, Bloemberg BP *et al*. Serum total cholesterol and long-term coronary heart disease mortality in different culture: twenty five year follow up of the seven countries study. *JAMA* 1995; **274**:131-6.
3. Assmann G, Cullen P, Schulte H. The Munster Heart Study (PROCAM): results of follow up at 8 years. *Eur Heart J* 1998;**19**(suppl A):A2-A11.
4. Wilson PW, Anderson KM, Castelli WP. Twelve year incidence of CHD in middle aged adults during the era of hypertensive therapy. The Framingham Offspring Study. *Am J Med* 1991;**90**:276-82.
5. Brady A, Betteridge J. Cholesterol reduction correlates with reduction in CHD Events. *Br J Cardiol* 2003;**10**:218-19.
6. Scandinavian Simvastatin Survival Study. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease. *Lancet* 1994; **344**:1383-9.
7. O'Keefe JH, Jr, Cordain L, Harris WH, Moe RM, Vogel R. Optimal low density lipoprotein is 50-70mg/dl – lower is better and physiologically normal. *J Am Coll Cardiol* 2004;**43**(11):2142-6.
8. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20536 high risk individuals: a randomised placebo controlled trial. Heart Protection Study Collaborative Group. *Lancet* 2002;**360**:7-22.
9. Colhoun HM, Betteridge DJ, Durrington PN *et al*. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet* 2004;**364**:641-2.
10. Jones PH, Davidson MH, Stein EA *et al*. for the STELLAR study group. Comparison of the Efficacy and Safety of Rosuvastatin Versus Atorvastatin, Simvastatin and Pravastatin Across Doses (STELLAR Trial). *Am J Cardiol* 2003;**92**:152-60.
11. 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.
12. Nissen S. REVERSAL: A prospective, randomized, double blind, multi-center study comparing the effects of atorvastatin vs. pravastatin on the progress of coronary atherosclerotic lesions as measured by intravascular ultrasound. Late breaking clinical trials. American Heart Asssociation Scientific Sessions 2003, Orlando, Florida, USA.
13. Klag MJ, Whelton PK, Randall BL *et al*. Blood pressure and end stage renal disease in men. *N Engl J Med* 1996;**334**:13-18.
14. Resnick HE, Jones K, Ruotolo G *et al*. Insulin resistance, the metabolic syndrome and risk of incident cardiovascular disease in nondiabetic American Indians: The Strong Heart Study. *Diabetes Care* 2003;**26**:861-7.
15. Expert Panel on Detection Evaluation and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education Programme (NCEP) Expert Panel on Detection Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 2001;**285**:2486-97.
16. Bays HE, Moore PB, Drehobl MA *et al*. Effectiveness and tolerability of ezetimibe in patients with primary hypercholesterolemia: pooled analysis of two phase II studies. *Clin Ther* 2001;**23**:1209-30.
17. Evans M, Rees A, Roberts A. The future direction of cholesterol lowering therapy. *Curr Opin Lipidol* 2002;**13**:663-9.
18. Brewer HB. Benefit-risk assessment of rosuvastatin 10 to 40 milligrams. *Am J Cardiol* 2003;**92**(suppl 1):23K-29K.
19. Evans M, Rees A. Effects of HMG-CoA reductase inhibitors on skeletal muscle: are all statins the same? *Drug Saf* 2002;**25**:649-63.
20. de Lemos JA, Blazing MA, Wiviott SD *et al*. Early intensive vs a delayed conservative simvastatin strategy in patients with acute coronary syndromes – phase Z of The A to Z trial. *JAMA* 2004;**292**:1307-16.
21. Food and Drug Administration (FDA) Adverse Events Reporting (AER) Database: AstraZeneca data on file (September 2004).
22. Shepherd J, Hunninghake DB, Stein EA *et al*. Safety of rosuvastatin. *Am J Cardiol* 2004;**94**:882-8.
23. Staffa JA, Chang J, Green L. Cerivastatin and reports of fatal rhabdomyolysis. *N Engl J Med* 2002;**346**:539-40.
24. Vidt DG, Cressman MD, Harris S, Pears JS, Hutchinson HG. Rosuvastatin-induced arrest in progression of renal disease. *Cardiology* 2004;**102**:52-60.
25. Sidaway JE, Davidson RG, McTaggart F *et al*. Inhibitors of 3-hydroxy-3-methylglutaryl-CoA reductase reduce receptor-mediated endocytosis in opossum kidney cells. *J Am Soc Nephrol* 2004;**15**;2258-65.
26. Verhulst A, D'Haese PC, De Broe ME. Inhibitors of HMG-CoA reductase reduce receptor-mediated endocytosis in human kidney proximal tubular cells. *J Am Soc Nephrol* 2004;**15**:2249-57.