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Review

Monthly Focus: Cardiovascular, Renal, Endocrine & Metabolic

Pharmacotherapy for dyslipidaemia – current therapies and future agents

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Current lipid-altering agents that lower low density lipoprotein cholesterol (LDL-C) primarily through increased hepatic LDL receptor activity include statins, bile acid sequestrants/resins and cholesterol absorption inhibitors such as ezetimibe, plant stanols/sterols, polyphenols, as well as nutraceuticals such as oat bran, psyllium and soy proteins; those currently in development include newer statins, phytostanol analogues, squalene synthase inhibitors, bile acid transport inhibitors and SREBP cleavage-activating protein (SCAP) activating ligands. Other current agents that affect lipid metabolism include nicotinic acid (niacin), acipimox, high-dose fish oils, antioxidants and policosanol, whilst those in development include microsomal triglyceride transfer protein (MTP) inhibitors, acylcoenzyme A: cholesterol acyltransferase (ACAT) inhibitors, gemcabene, lifibrol, pantothenic acid analogues, nicotinic acid-receptor agonists, anti-inflammatory agents (such as Lp-PLA$_2$ antagonists and AGI-1067) and functional oils. Current agents that affect nuclear receptors include PPAR-α and -γ agonists, while in development are newer PPAR-α, -γ and -δ agonists, as well as dual PPAR-α/γ and 'pan' PPAR-α/γ/δ agonists. Liver X receptor (LXR), farnesoid X receptor (FXR) and sterol-regulatory element binding protein (SREBP) are also nuclear receptor targets of investigational agents. Agents in development also may affect high density lipoprotein cholesterol (HDL-C) blood levels or flux and include cholesteryl ester transfer protein (CETP) inhibitors (such as torcetrapib), CETP vaccines, various HDL 'therapies' and upregulators of ATP-binding cassette transporter (ABC) A1, lecithin cholesterol acyltransferase (LCAT) and scavenger receptor class B Type 1 (SRB1), as well as synthetic apolipoprotein (Apo)E-related peptides. Fixed-dose combination lipid-altering drugs are currently available such as extended-release niacin/lovastatin, whilst atorvastatin/amlodipine, ezetimibe/simvastatin, atorvastatin/CETP inhibitor, statin/PPAR agonist, extended-release niacin/simvastatin and pravastatin/aspirin are under development. Finally, current and future lipid-altering drugs may include anti-obesity agents which could favourably affect lipid levels.

Keywords: ABC A1, ACAT, acipimox, adiposopathy, AGI-1067, CETP, cholesterol, CRP, ezetimibe, FM-VP4, FXR, gemcabene, HDL-C, implitapide, JUPITER, large unilamellar vesicles, LCAT, LDL-C, lifibrol, lipid, Lp-PLA$_2$, LXR, MTP, niacin, PAF-AH, pantethine, pantothenic acid, phytostanol, PPAR, RXR, squalene synthase, SRB1, SREBP, stanol, sterol, torcetrapib, triglyceride

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1. Background

Atherosclerosis is by far the single most important pathological process in the development of coronary heart disease (CHD), which is the single most common cause of morbidity and mortality in both men and women in developed nations

Table 1. Lipid-altering efficacy of common lipid-altering agents [3].

Lipid-altering agent	Change in LDL-C (%)	Change in triglyeride (%)	Change in HDL-C (%)
Statins	↓ 18 – 55	↓ 7 – 30	↑ 5 – 15
Nicotinic acid (niacin)	↓ 5 – 25	↓ 20 – 50	↑ 15 – 35
Fibric acids (fibrates)	↓ 5 – 20*	↓ 20 – 50	↑ 10 – 20
Ezetimibe	↓ 17 – 22	↓ 4 - 11	↑ 2 – 5
Bile acid sequestrants	↓ 15 – 30	No change to increased	↑ 3 – 5
Fish oils[†]	No change to increased	↓ 20 – 50	No change to increased
Phytosterols/phytostanols	↓ 10 – 15	No change to decreased	No change to increased

*Fibrates may increase LDL-C blood levels in some patients with hypertriglyceridaemia. [†]The lipid-altering effects of fish oil listed are with administration of ~ 5 – 9 g of omega-3 fatty acids per day.
HDL-C: High density lipoprotein-cholesterol; LDL-C: Low density lipoprotein-cholesterol.

[30]]. Atherosclerosis is a complex disease with multiple risk factors. It has been reported that 80 – 90% of patients who develop significant CHD and > 95% of patients who experience fatal CHD have major atherosclerotic risk factors, such as cigarette smoking, diabetes mellitus, hypertension and dyslipidaemia [1] – all of which are modifiable through lifestyle, diet or therapeutic measures.

With regard to treatment of dyslipidaemia, numerous well-controlled outcome studies of lipid-altering drug monotherapy in > 50,000 subjects have consistently demonstrated a relative CHD risk reduction (compared to placebo) of only ~ 20 – 40% after ~ 3 – 6 years of therapy [2]. Thus, the majority of patients observed in monotherapy trials of lipid-altering drugs have not had their CHD 'prevented'. This suggests that further absolute and relative CHD risk will only be achieved through extending the duration of lipid-altering therapy, achieving more aggressive lipid treatment goals and treating multiple lipid parameters. It may also be reasonable to conclude that the best way to further reduce CHD risk is to aggressively correct the abnormality or abnormalities which contribute most to the atherosclerotic process in the individual patient. This may occur through monotherapy, or perhaps through a multifactorial approach with the use of a variety of anti-atherogenic agents whose mechanisms of actions differ, and whose treatment targets may result in additive and/or complementary benefits.

Towards reaching these goals, authoritative bodies such as the National Cholesterol Education Program, Adult Treatment Panel III (NCEP ATP III) have established guidelines with the primary focus being the achievement of low density lipoprotein cholesterol (LDL-C) treatment targets, which is based upon a vast amount of data largely derived from evidenced-based outcomes trials [3]. Thus, a reduction in LDL-C blood levels remains the primary target of most current lipid-altering drugs (Table 1). However, emerging data has suggested that improvements in other lipoprotein parameters might also be beneficial. This has prompted the NCEP ATP III to include additional treatment targets, such as non-high density lipoprotein cholesterol (non-HDL-C) blood levels in patients with hypertriglyceridaemia. Other experts have also suggested that the evidence is compelling enough to recommend HDL-C blood levels as a specific treatment target [2,4]. Finally, the NCEP ATP III has recognised a number of emerging CHD risk factors, such as inflammatory markers and lipoprotein particle size, that may have prognostic and potential therapeutic implications.

2. Current agents that predominantly increase LDL/ApoB – E receptor activity

2.1 Agents that impair cholesterol synthesis (statins)

The origins of cholesterol in LDL-C are from predominantly three sources: peripheral cholesterol synthesis; hepatic cholesterol synthesis; and intestinal cholesterol absorption (Figure 1). The relative contribution of each is likely to be the result of genetic predisposition, dietary factors, physical exercise, lifestyle habits, drug therapy and a complex interplay of enzymatic up- and downregulation [5]. However, irrespective of the origin of cholesterol, the liver is the major regulating organ of circulating LDL-C, mainly through the up- and downregulation of hepatic LDL receptors (Figure 1).

Lipid-altering agents which impair liver cholesterol synthesis, as illustrated by statins, lower LDL-C blood levels through the secondary upregulation and increased activity of hepatic LDL receptors. At therapeutic doses, blood levels of all statins are measurable in the peripheral circulation. Thus, various other non-hepatic tissues which synthesise cholesterol and which possess LDL receptors on their cellular membranes, are also exposed to statins to some extent. However, the principal therapeutic target of statins is the liver. Thus, the vast majority of clearance of circulating LDL-C is specifically through hepatic LDL receptors.

A reduction in the exposure of arterial endothelia to circulating LDL-C reduces the potential for LDL receptor independent cholesterol diffusion across the arterial endothelia and thus, reduces potential cholesterol uptake by subendothelial macrophages. Reduction in macrophage foam-cell creation reduces the subsequent creation of atherosclerotic plaques and inflammatory response (Figure 2), thus reducing

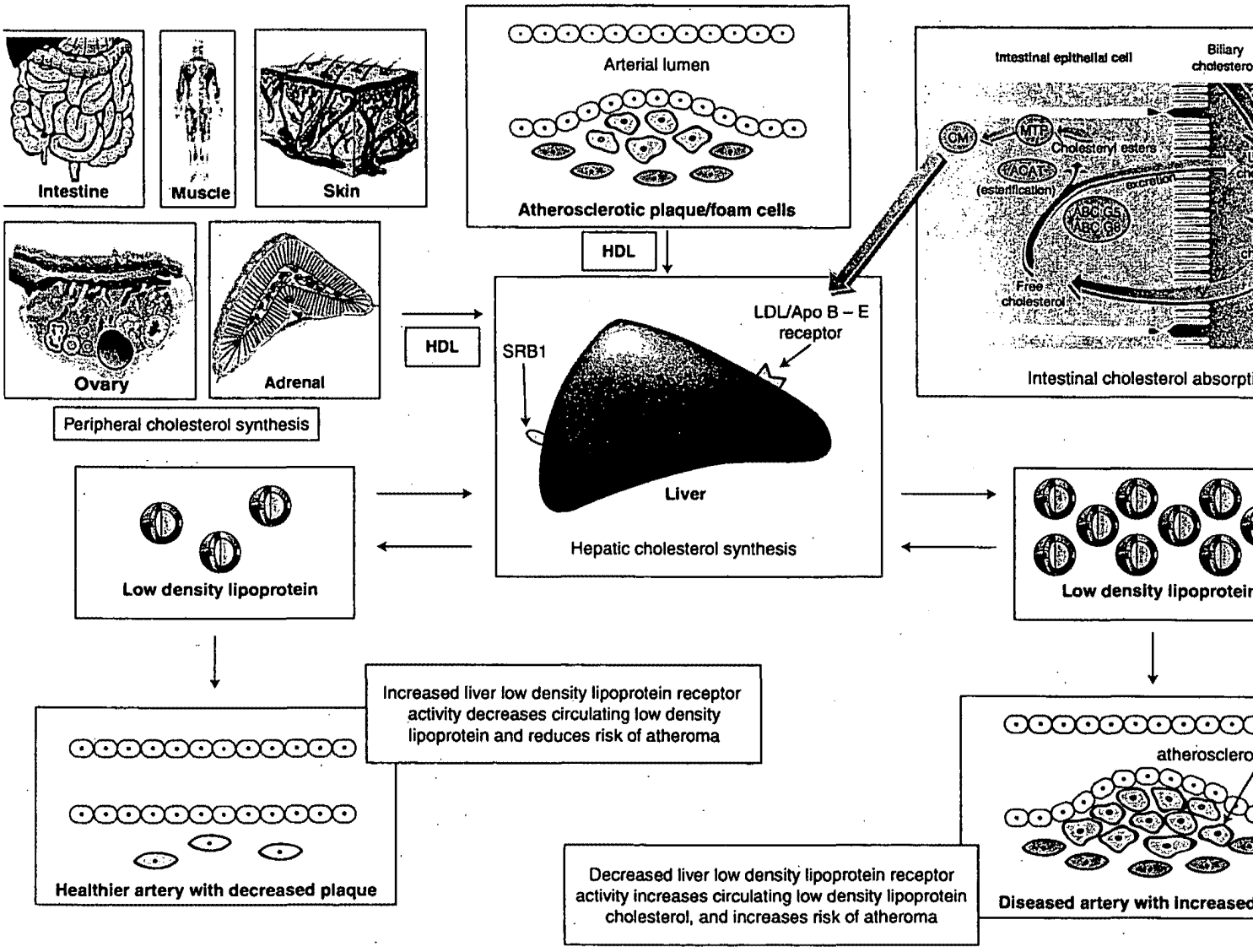

Figure 1. A simplified figure of cholesterol origins of LDL-C. Cholesterol may be derived from peripheral and liver synthesis, or intestinal cholesterol al hepatic LDL-C receptor activity (through interventions such as diet and therapeutic agents) may increase clearance of circulating LDL-C, reduce LDL-C levels, redu formation, and thus reduce CHD risk. A decrease in hepatic LDL-C receptor activity may increase circulating LDL-C levels, increase the risk of LDL-C diffusion inflammatory cell activity with formation of an atheroma or atherosclerotic plaque, and thus increase CHD risk. Adapted from [22].

ABC: ATP-binding cassette; ACAT: Acyl-coenzyme A cholesterol acyltransferase; CM: Chylomicrons; HDL: High-density lipoprotein; LDL-R: Low-density lipoprotein receptor;

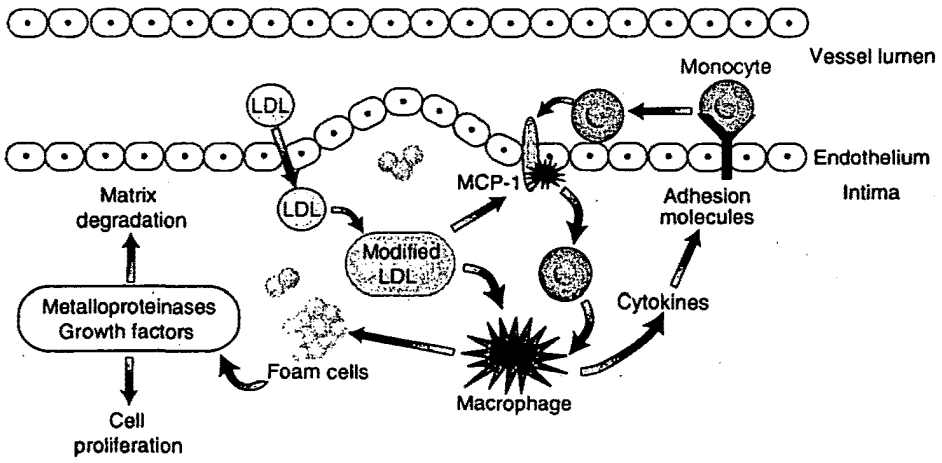

Figure 2. Inflammatory processes involved in atherosclerotic lesions. Monocytes attach to the endothelium through adhesion molecules, and then may migrate into the subendothelium (intima) through stimulation by MCP-1. During this migration, monocytes become activated into macrophages that undergo cell division, produce cytokines, and express scavenger receptors which internalise modified LDL-C resulting in foam cell formation. Macrophages and foam cells may also produce growth factors that may promote cell proliferation and metalloproteinases that may promote cell matrix degradation. Adapted from [307].
LDL: Low-density lipoprotein; MCP-1: Monocyte chemoattractant protein-1.

Box 1. Examples of potential adverse effects and potential drug interactions of statins.

Potential adverse effects

- Myalgias with/without elevations in muscle enzymes
- Elevations in creatine kinase (CK) blood levels with or without myalgias
- Myopathy (defined as muscle symptoms and CK elevations > 10 times the upper limits of normal)
- Rhabdomyolysis
- Elevations in liver transaminase blood levels
- Gastritis

Potential drug interactions

- Simvastatin, atorvastatin and lovastatin are metabolised by the hepatic cytochrome P450 (CYP) 3A4 enzyme system, and may have drug interactions if taken with drugs that are inhibitors (competitive or otherwise) of this same CYP 3A4 enzyme system, such as cyclosporin, macrolide antibiotics, protease inhibitors, nefazodone and azole antifungal agents
- Pravastatin does not undergo significant metabolism through the CYP mixed oxidase system. This results in less potential for drug interactions with drugs that are inducers or inhibitors of the CYP enzyme system. However, pravastatin blood levels may increase when taken concurrently with cyclosporin
- It is sometimes recommended that some statins be administered in lower doses when used concomitantly with amiodarone, verapamil, cyclosporin, fibrates, or niacin. However, the use of statin in combination with the extended-release niacin formulation (as high as niacin 2000 mg and lovastatin 40 mg/day) has been shown to be as safe with regard to liver and muscle enzyme elevation as higher doses of statin alone (such as atorvastatin 40 mg and simvastatin 40 mg) [88]
- Fluvastatin blood levels decrease with rifampin. Fluvastatin blood levels increase with glyburide, phenytoin, cimetidine, ranitidine, and omeprazole. Fluvastatin is at least partially metabolised through the CYP 2C9 enzyme system and has the potential to have drug interactions with other drugs that interact with this same enzyme system
- Some statins have been suggested to interact with digoxin, and increase the clotting time in patients treated with warfarin
- In general, the use of statins with fibrates has been shown to reduce clearance, and increase circulating levels of all statins (except perhaps fluvastatin), increasing the risk of myopathy and possibly rhabdomyolysis. This appears to be particularly true when statins are used in combination with gemfibrozil [87,220,221]
- Rosuvastatin does not undergo metabolism through the CYP 3A4 enzyme system to a clinically significant extent, resulting in less potential drug interactions than with statins that are significantly metabolised through this enzyme system (such as atorvastatin, simvastatin and lovastatin). Rosuvastatin is not extensively metabolised at all, with only 10% recovered as metabolite formed through CYP 2C9. Rosuvastatin absorption may be decreased with concurrent antacids, which does not occur if antacids are taken ≥ 2 h after rosuvastatin. As with other statins, rosuvastatin blood levels may increase when taken concurrently with cyclosporin

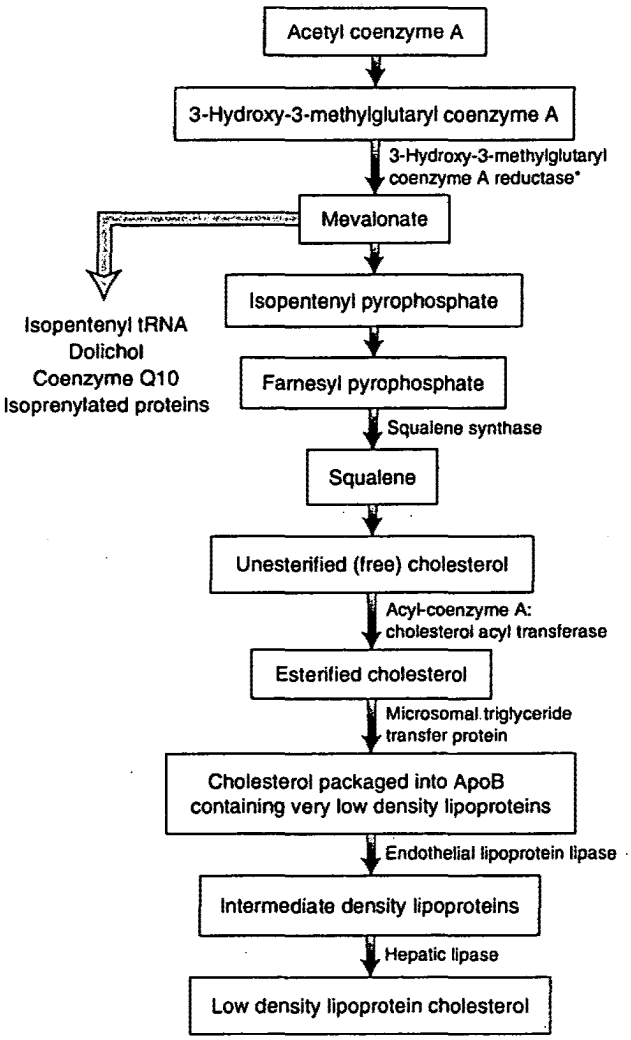

Figure 3. Simplified schematic of cholesterol synthesis and hepatic ApoB – containing lipoprotein assembly [219]. Animal data suggests that marked inhibition of mevalonate production might occasionally result in elevated liver enzymes, myopathy, and inhibition of renal tubular reabsorption of protein. *Rate limiting step in cholesterol biosynthesis.
Coenzyme A = Ubiquinone 10.

the potential for plaque rupture, which might otherwise manifest as myocardial infarction, peripheral arterial occlusion or stroke. In this way, the reduction of circulating LDL-C reduces CHD event risk.

Statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors; HMG CoA reductase inhibitors) inhibit the rate limiting step of cholesterol synthesis where HMG CoA is converted to mevalonate (Figure 3). In general, statins are both efficacious and well-tolerated in reducing LDL-C blood levels (Table 1). It is the lipid-altering effects of statins, primarily the reduction in LDL-C blood levels, that are thought to account for their benefits in reducing atherosclerosis (such as improved endothelial function and plaque stabilisation) that lead to a reduction in CHD. Statins may also have other favourable effects that may be independent of modification of blood lipids. However, while these 'pleiotropic' effects are of enormous scientific interest, they have yet to be proven to be of definitive clinical relevance [6].

Therapeutically, statins have been shown in large, well-controlled trials to safely lower LDL-C blood levels by > 50% [7], reduce CHD morbidity [8-13] and reduce overall mortality in clinical outcomes trials [14]. Due to their proven safety and efficacy, statins are currently the most prescribed lipid-altering drug (Box 1).

The most recently approved statin, rosuvastatin, has been shown to have greater LDL-C blood level lowering effects compared both on a mg/mg basis, and across its entire dose range than all other approved statins (Table 2) [7,15]. (Rosuvastatin has not, as yet, proven to have beneficial CHD outcomes, as has been the case with all statins upon initial approval). Potential efficacy benefits above that of other previously approved statins include increased efficacy in LDL-C lowering. Another potential benefit is that rosuvastatin may result in higher HDL-C blood levels at its higher doses [2] compared to atorvastatin at its higher doses [7,15]. (Atorvastatin demonstrates an attenuated HDL raising effect as the dose is increased to the 80 mg dose; however, the actual clinical outcomes implications of this finding have not been established [91]).

Rosuvastatin is not metabolised through the cytochrome P450 (CYP) 3A4 enzyme system to a clinically significant extent [16,17], resulting in less potential drug interactions than with statins that are significantly metabolised through this enzyme system (such as atorvastatin, simvastatin and lovastatin). In fact, rosuvastatin is not extensively metabolised at all, with only 10% recovered as metabolite, which is formed through CYP 2C9. Consequently, clinically significant drug interactions do not occur when used with concomitant drugs metabolised through CYP 3A4 such as erythromycin and the azole antifungal agents. Although warfarin plasma concentrations may not be altered, the International Normalised Ratio (INR) may be increased by coadministration with rosuvastatin and therefore, should be frequently monitored both before and after initiation or change of dose of rosuvastatin. When taken together with antacids, rosuvastatin levels may be decreased, although this does not occur if these two agents are taken 2 h apart. Oestrogens and progestin levels may be increased, whilst digoxin levels are unaffected by rosuvastatin. As with other statins, the administration of cyclosporin and gemfibrozil may increase rosuvastatin concentrations. Although neither rosuvastatin nor fenofibrate levels are altered by concomitant administration, reports of increased risk of myopathy and rhabdomyolysis with other statins used with fibrates have led to the recommendation that the use of fenofibrate plus rosuvastatin combination therapy should only occur if the potential benefits outweigh the potential risks. The combination therapy of rosuvastatin and gemfibrozil generally should be avoided [17]. Rosuvastatin is marketed at 5 – 40 mg doses. The incidence of creatinine kinase elevations > 10 times the upper

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