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Review

Expert Opinion

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3. Existing drug treatments
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5. Current research goals
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Cardiovascular & Renal

New lipid-lowering agents

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Lipid-lowering is established as a proven intervention to reduce atherosclerosis and its complications. This article summarises imminent developments in lipid-lowering therapy, including new statins and cholesterol absorption inhibitors currently undergoing investigation for licensing. It also discusses other therapeutic targets such as squalene synthase, microsomal transfer protein (MTP), acyl-cholesterol acyl transferase (ACAT), cholesterol ester transfer protein (CETP), peroxosimal proliferator activating receptors (PPARs) and lipoprotein (a) (LP(a)), for which compounds have been developed and have at least reached trials in animal models. Lipid-lowering drugs are likely to prove a fast-developing area for novel treatments, as possible synergies exist between new and established compounds for the treatment of atherosclerosis.

Keywords: cholesterol, HDL, LDL, management, therapy

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1. Background

The progression of atherosclerosis, which is responsible for coronary heart disease, stroke, carotid and femoral artery stenosis (peripheral vascular disease), is associated with multiple cardiovascular risk factors, including hyperlipidaemia. The interaction of risk factors is complex (Figure 1) and synergistic. While the role of low density lipoprotein cholesterol (LDL-C) is well-established in both epidemiological and interventional studies, the case for raising high density lipoprotein cholesterol (HDL-C) is strong, with some evidence for benefit with HDL-raising therapies in selected groups.

2. Medical need

The well-established role of hyperlipidaemia in atherosclerosis has led to numerous intervention studies with diet, various pharmaceuticals and even surgery (ileal bypass), which have shown a consistent relationship of a 1% reduction in LDL-C with a 1% reduction in cardiovascular events [1] (Table 1). This concept has been slightly extended to include data suggesting that a 1% increase in HDL-C is associated with a 3% reduction in cardiovascular events. The data on triglycerides is more difficult to interpret given the close inter-relationship between triglyceride and HDL-C levels. Other lipoprotein fractions, including triglyceride-rich remnants and lipoprotein (a) (Lp(a)), have also been associated with atherosclerosis, although there are few direct intervention studies on these parameters.

3. Existing drug treatments

Data on the clinical evidence base for the currently available classes of lipid modulating drugs are shown in Table 1.

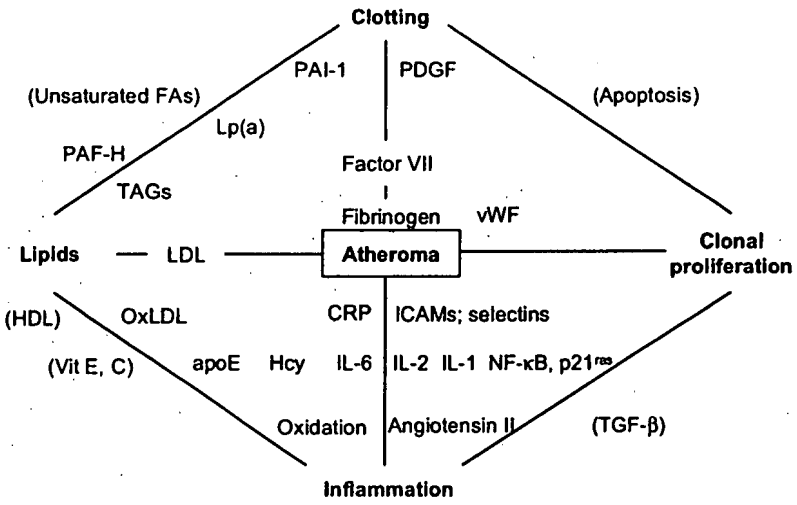

Figure 1. A schematic placing of biochemical risk factors and protective factors (in brackets) and their interactions in causing or protecting against atheroma.

apoE: Apolipoprotein E; CRP: C-reactive protein; FA: Fatty acid; Hcy: Homocysteine; HDL: High density lipoprotein; ICAM: Intercellular adhesion molecule; IL: Interleukin; LDL: Low density lipoprotein; Lp(a): Lipoprotein (a); NF- κB: Nuclear factor kappaB; OxLDL: Oxidised LDL-cholesterol; p21 [ras]: Ras oncogene product; PAF-H: Platelet activating factor hydrolase; PAI-1: Plasminogen activator inhibitor-1; PDGF: Platelet-derived growth factor; TAG: Triacylglycerol; TGF-β: Transforming growth factor-beta; vWF: von Willebrand factor.

Table 1. Summary of major end point trials.

Primary	Treatment	Number		Starting		Reduction		Events		
		Men	*Women*	*LDL (mmol/l)*	*TG (mmol/l)*	*LDL (%)*	*TG (%)*	*PTCA/ CABG*	*MI*	*Death*
LRC	Cholestyramine	10,627	-	5.3	1.70	8	+3	-	25	20
WHO	Clofibrate	3806	-	~ 5	-	(9)	-	-	19	19
HHS	Gemfibrozil	4081	-	5.37	2.01	11	35	-	34	37
VA-HIT	Gemfibrozil	2531	-	2.90	1.81	0	25	9	22	22
4S	Simvastatin	3617	827	4.87	1.51	35	10	37	34	42
CARE	Pravastatin	3583	576	3.60	1.00	28	14	27	27	24
LIPID	Pravastatin	7498	1516	3.89	1.56	25	11	20	29	22
WOSCOPS	Pravastatin	6595	-	5.00	1.70	26	12	37	31	32
AF/TexCAPS	Lovastatin	5608	997	3.89	1.78	25	15	33	40	N/A
Post-CABG	Lovastatin ± cholestyramine	1243	108	3.98	1.76	14/38	-	29	12.5	10
HPS	Simvastatin	15,454	5082	3.5	2.0	31	23	24	26	13
GREACE	Atorvastatin	1256	344	4.65	2.08	46	31	51	59*	43

*Non-fatal

NB Lovastatin is not licensed in the UK.

Conversion factors mmol/l → md/dl cholesterol x 38.61; triglycerides x 88.5.

4S: Scandinavian Simvastatin Survival Study [82]; AF/TexCAPS: Air Force Texas Coronary Atherosclerosis Prevention Study [86]; CABG: Coronary artery bypass graft; CARE: Cholesterol and Recurrent Events [83]; GREACE: The Greek Atorvastatin and Coronary-heart disease Evaluation [88]; HDL: High density lipoprotein; HHS: Helsinki Heart Study [81]; HPS: Heart Protection Study (2 x 2 design with antioxidants) [14]; LDL: Low density lipoprotein; LIPID: Long-term Intervention with Pravastatin in Ischaemic Disease [84]; LRC: Lipid Research Clinics Primary PreventionTrial [34,79]; MI: Myocardial infarction; Post-CABG: Post-Coronary Artery Bypass Graft Study (2 x 2 design with coumarin) [87]; PTCA: Percutaneous transluminal coronary angioplasty; TG: Triglycerides; VA-HIT: Veterans Affairs HDL-Intervention Trial [53]; WHO: WHO clofibrate study [80]; WOSCOPS: West of Scotland Coronary Prevention Study [85].

3.1 Statins

Statins are originally fungally derived compounds that competitively inhibit the rate-limiting enzyme hydroxyl-methyl-glutaryl-CoA reductase (HMG-CoA-R) (Figure 2). They are effective and safe drugs that can produce a maximum LDL reduction of ~ 70%, with parallel reductions in triglyceride and a modest rise in HDL [2]. The reduction in intrahepatic cholesterol synthesis results in upregulation of LDL-receptors and a fall in plasma cholesterol. Their main disadvantage is that dose titration by doubling only results in a 5 – 7% extra reduction in LDL, but at the expense of increasing side effects. Statins have anti-inflammatory and cell cycle actions through reduction of isoprenoid intermediates of cholesterol synthesis. The clinical evidence for the use of statins in both secondary and primary prevention of coronary heart disease is overwhelming [3,4].

3.2 Fibrates

Fibrates are an established drug class that act as nuclear agonists at the peroxisomal proliferator activating receptor alpha (PPAR-α) element, regulating expression of apolipoprotein A1 and A2 (principal components of HDL), lipoprotein lipase, apolipoprotein C-III (associated with triglyceride-rich remnant particles), acute phase proteins including fibrinogen and C-reactive protein, and clotting factors (plasminogen activator inhibitor 1) among many other genes. Their chief actions are to lower triglycerides and raise HDL-C [5,6]. There is evidence that fibrates reduce cardiovascular events in patients with low HDL and elevated triglycerides, but effects observed in trials in patients with raised LDL are generally negative.

3.3 Bile acid sequestrants

Bile acid sequestrants reduce cholesterol absorption by sequestering bile acids and preventing opsonisation of lipid-rich particles in the gut by bile acids. This limits uptake of cholesterol associated with bile acids. The reduction in hepatic portal vein cholesterol results in upregulation of hepatic LDL-receptors and a reduction in plasma cholesterol. They can raise triglycerides, have minimal effects on HDL and are additive to the action of statins. Their main limitation is a high side effect rate caused by the presence of colonic bile acids resulting in bloating, nausea and diarrhoea.

3.4 Nicotinic acid

Nicotinic acid acts by reducing the synthesis of very low-density lipoprotein (VLDL) in the liver. The exact mechanism of action is unclear, but does involve interference with fatty acid esterification involved in assembly of VLDL prior to the action of microsomal transfer protein (MTP) [7-9]. Although well-established as efficacious in clinical trials, its use has been limited by a prostaglandin E2-induced flushing most commonly seen with fast-release preparations and hepatotoxicity associated with slow release preparations [10]. However, new medium-speed release preparations (e.g., extended-release niacin, Niaspan®; KOS Pharmaceuticals Inc.) show better side effect profiles and retard the progression of atherosclerosis in human coronary arteries and are also capable of being coformulated with statins [10-12].

4. Therapeutic class review and rationale for novel therapies

Not all patients tolerate the currently available drugs, with side effects requiring discontinuation of therapy being seen in ~ 5% of patients in clinical practice receiving statins or fibrates and 30% in the case of bile acid sequestrants. Also, while treatment with currently available statins achieves the LDL target of 3 mmol/l in ~ 90% of cases at maximum dose, evidence from the Post-Coronary Artery Bypass Graft (Post-CABG) study [13], reinforced by the recently published Heart Protection Study [14], suggests that LDL targets will need to be reset to lower values of around 2 mmol/l. The emphasis on LDL and HDL also neglects other lipoprotein fractions, for example, Lp(a), which are associated with increased cardiovascular risk, but whose levels are little affected by currently available therapies [15]. Thus, new lipid-lowering agents are required to address the issues of increased efficacy, other risk factors and improved tolerability.

5. Current research goals

There are many compounds in development; these can be divided into groups based on their principal mechanism of action (Table 2).

5.1 Therapies to reduce LDL-cholesterol

5.1.1 New statins

There are five agents available at present, with simvastatin and atorvastatin the most potent, which all inhibit HMG-CoA-R. These drugs can achieve a maximum LDL reduction of 45 – 50% in large-scale studies, although smaller studies have shown reductions up to 61 and 56% in small populations or at supra-maximal doses, respectively. Like all statins, these agents show a 6 – 7% increment in LDL reduction for each doubling of dose above clinical initiation levels. Thus, the availability of newer compounds with a wider therapeutic range may result in more powerful statins becoming available [16]. Two agents are in the process of being licensed or in development: rosuvastatin (Crestor®, ZD4522; AstraZeneca) and pitavastatin (NK-104; Laboratoires Negma, Novartis), of which the first was licensed in 2003. Rosuvastatin is a long half-life (19 h) statin that has been shown to reduce LDL by 57% at 40 mg, with a reasonable safety profile in initial studies [17-19]. At this dose, it dose not show any fall in HDL as is occasionally seen with atorvastatin [20], but instead a 14% increase. Rosuvastatin does not cause the degree of myalgia and side effects that were observed in trials of simvastatin at 120 mg, despite achieving a superior LDL reduction [21]. Although there are

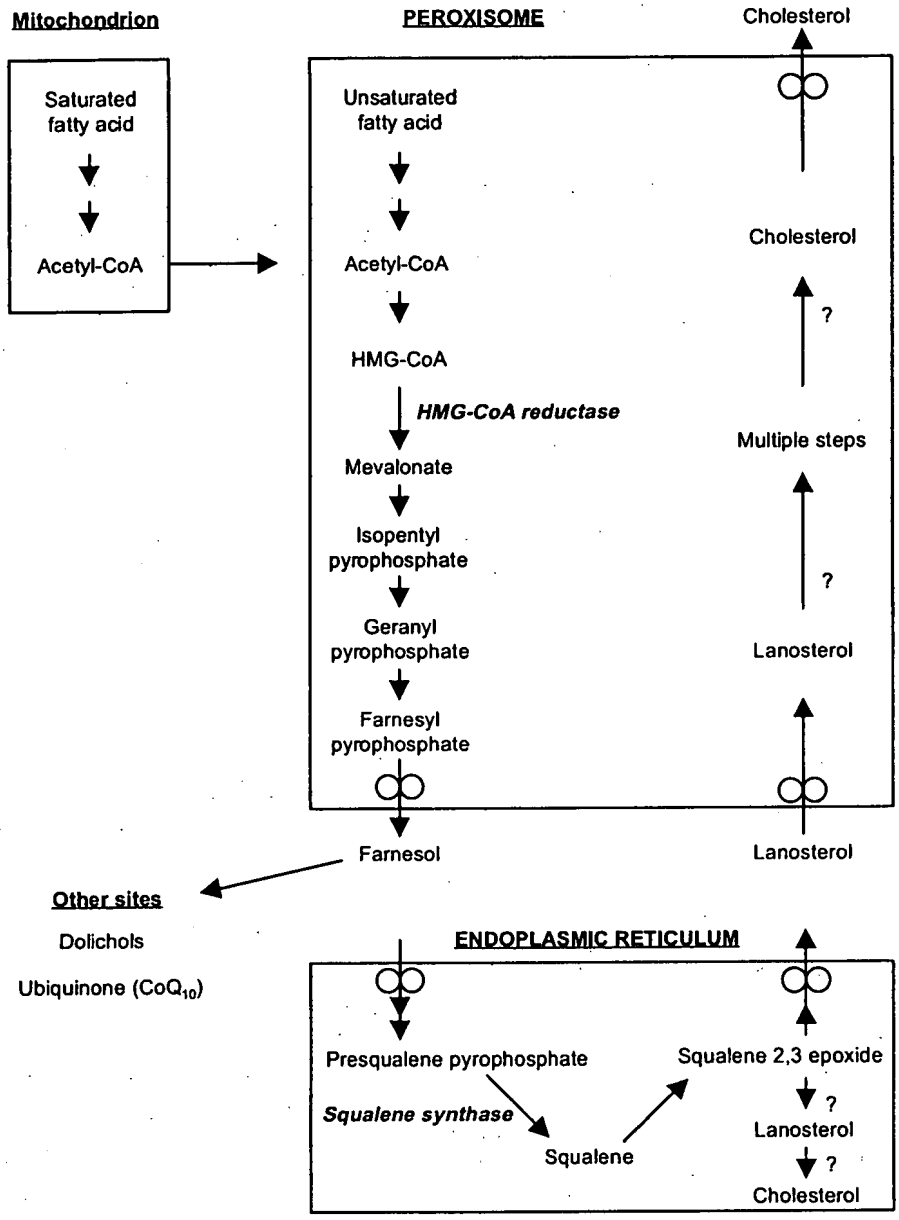

Figure 2. Compartmentation and simplified biochemistry of cholesterol synthesis. Drug targets are shown in bold italics.

anecdotal reports of rhabdomyolysis at the highest (80 mg) dose of rosuvastatin in clinical trials, even at 40 mg it delivers more LDL reduction than the currently available top doses of simvastatin and atorvastatin. Initial studies with rosuvastatin suggest that it shares the benefits of other statins on endothelial function [19]. One curious side effect of rosuvastatin that has yet to be fully explored is a transient tubular proteinuria that was noted in patients with normal renal function. There is little data as yet in patients with nephrotic syndrome or diabetic nephropathy. Pitavastatin also has been shown to be effective at reducing LDL by > 30% at a dose of 8 mg, but no data as yet exists on higher doses of this agent [22].

5.1.2 *Squalene synthase inhibitors*

While the early and final stages of cholesterol synthesis occur in peroxisomes, one of the limiting stages of cholesterol synthesis occurs in the endoplasmic reticulum (ER) and is catalysed by squalene synthase (Figure 2). Inhibition of squalene synthase is likely to lead to a reduction in cholesterol synthesis without affecting synthesis of compounds derived from geranyl pyrophosphate, including dolichols and ubiquinone (co-enzyme Q_{10}), or affecting the control of protein function through farnesylation [23,24]. The mechanism of myalgia associated with statin therapy may be associated with depletion of mitochondrial ubiquinone levels [25].

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