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New lipid-modifying therapies

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Lipid abnormalities are central among the risk factors for the development of cardiovascular disease and their correction remains a major target for the medical community. Inhibitors of 3-hydroxy-3-methyl glutaryl coenzyme A reductase (statins) are the most widely prescribed and best tolerated of the currently available lipid-modifying therapies. Newer agents in this class (e.g., rosuvastatin) have proven to be more effective at lowering levels of low-density lipoprotein cholesterol. New formulations of drugs such as nicotinic acid, which improve treatment regimens and reduce unpleasant side effects, may result in improved patient compliance with this therapy. The development of novel drugs such as cholesterol absorption inhibitors (e.g., ezetimibe) and acyl-coenzyme A cholesterol acyltransferase inhibitors (e.g., avasimibe) will provide clinicians with therapeutic options that exploit different pathways to those currently being utilised. By combining these agents with statins, greater improvements in the lipid profile than those seen to date could be produced. In addition, advances in our understanding of the pathophysiology of dyslipidaemia have enabled other novel therapeutic targets to be identified and studies with experimental drugs underscore the potential of these approaches.

Keywords: cardiovascular disease, cholesterol absorption, combination therapy, low-density lipoprotein, statin

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1. Introduction

Epidemiological and prospective studies have identified a variety of risk factors for the development of atherosclerotic cardiovascular disease. Of these, elevated levels of low-density lipoprotein cholesterol (LDL-C) and reduced levels of high-density lipoprotein cholesterol (HDL-C) are among the most notable [1,2]. Hypertriglyceridaemia is also associated with an increased risk of atherosclerotic disease, although to a lesser extent than LDL-C [1]. In addition to plasma lipid levels, which represent targets for current and new drugs, increasing the resistance of LDL particles to oxidation and modifying the kinetics of circulating lipoproteins might become new targets of therapy in the near future. Together with drugs affecting lipid metabolism, new compounds that act directly on the atherosclerotic process (e.g., metalloproteinase inhibitors, acyl-CoA cholesterol acyltransferase [ACAT] inhibitors) are being developed. Novel therapies with a multiplicity of targets may help develop a 'chemotherapy approach' to the prevention and treatment of atherosclerotic lesions in humans.

Several classes of therapy are currently available for the pharmacological treatment of lipid abnormalities, including fish oils, fibric acid derivatives (fibrates), nicotinic acid, bile acid sequestrants and inhibitors of 3-hydroxy-3-methyl glutaryl coenzyme A (HMG-CoA) reductase, also known as statins. Of these, statins are the most widely prescribed because they are well-tolerated and very effective at lowering LDL-C [3]. Despite improvements in treatments for lipid abnormalities, control of dyslipidaemia remains inadequate; a recent European survey of risk factor management in patients with established coronary heart disease (CHD) revealed that only half of those receiving lipid-lowering therapy had attained their total cholesterol goal

[4]. Although clinicians can help to reduce the number of undertreated patients through better use of current treatments, additional therapies are required in order to optimise prevention and treatment of cardiovascular disease. This review examines new advances in lipid-modifying therapies, including improvements in currently available treatments and the development of agents targeting novel therapeutic pathways. The development of drugs that directly interfere with the formation of atherosclerotic plaques will not be described.

2. Agents that predominantly decrease plasma levels of low-density lipoprotein cholesterol

2.1 New statins

Statins act by competitively inhibiting HMG-CoA reductase, the enzyme that catalyses the rate-limiting step in cholesterol biosynthesis [3]. This results in a reduction in hepatocyte cholesterol concentration, stimulating increased expression of hepatic LDL receptors (LDL-Rs), which clear LDL-C from the circulation. While this effect is considered the primary mechanism of LDL-C lowering, it has also been suggested that statins can inhibit the synthesis of some lipoproteins, since they can lower LDL-C in patients without functional LDL-Rs [3]. Several landmark clinical trials with statins have demonstrated their efficacy in lowering LDL-C as well as their benefits in reducing CHD and total mortality [5-9]. Large intervention trials are now underway to test whether larger reduction in LDL-C yields greater benefit. In patients with hypercholesterolaemia, currently available agents can lower LDL-C by 24 – 60%, reduce triglyceride levels by 10 – 29% and modestly increase HDL-C levels by 6 – 12% [10].

In addition to their ability to lower LDL-C, it is generally recognised that statins have cholesterol-independent or 'pleiotropic' effects. Inhibition of mevalonate synthesis by HMG-CoA reductase can also prevent the production of isoprenoid intermediates that may modulate cellular events through the post-transcriptional modification of G proteins [11]. The inhibition of these isoprenoids may be responsible for the ability of statins to modulate inflammation and thrombogenesis, improve endothelial function and stabilise atherosclerotic plaque [11]. While the clinical importance of these pleiotropic effects is not easily established, since they are difficult to differentiate from the benefits of lipid lowering, it may be that they contribute to the ability of statins to reduce cardiovascular events.

In general, statin monotherapy is well-tolerated and adverse events are rare [3]. The most serious adverse effect associated with statin treatment is myopathy and rhabdomyolysis may develop if the condition is not recognised and treatment is discontinued. The withdrawal of cerivastatin from clinical use has heightened awareness of these effects, although there is now extensive data available to indicate that the increased incidence of rhabdomyolysis with cerivastatin was specific to that agent [12]. Several factors can influence whether a statin may induce an adverse event. For example, it has been suggested that the lipophilicity of a statin determines whether it can enter into muscular tissues and induce myopathy [13]. Hydrophilic statins require an active uptake mechanism to enter into the liver and they do not easily penetrate into peripheral tissues [14,15]. Therefore, hydrophilic statins may be less likely to provoke an adverse event than lipophilic agents. Indeed, there is evidence to suggest that pravastatin, a hydrophilic agent, may be less myotoxic than more lipophilic statins [13]. Drug interactions are another mechanism by which adverse effects can occur, often as a result of shared metabolic pathways. The cytochrome P450 3A4 isoenzyme metabolises the greatest number of drugs in humans and, therefore, statins utilising this pathway may have a higher potential for adverse drug interactions [16].

Newer agents in the statin class include rosuvastatin, recently approved for use in Europe over the dose range 10 – 40 mg, and pitavastatin, currently in development. In hypercholesterolaemic patients, rosuvastatin has been shown to reduce LDL-C by up to 63% [17]. Data from comparative studies have shown that rosuvastatin is more effective than atorvastatin, simvastatin and pravastatin at reducing LDL-C, as well as raising HDL-C [18-20]. In patients with primary hypercholesterolaemia, LDL-C levels were reduced by 47% with rosuvastatin 10 mg/day compared with 36% for atorvastatin 10 mg/day [20]. In similar studies, rosuvastatin 10 mg/day lowered LDL-C by 48%, compared with 36% for simvastatin 20 mg/day [19] and 27% for pravastatin 20 mg/day [18]. In addition, greater efficacy of rosuvastatin compared with atorvastatin has been demonstrated in patients with heterozygous familial hypercholesterolaemia [21], and rosuvastatin also significantly reduces LDL-C in patients with homozygous familial hypercholesterolaemia [22]. Clinical trials with rosuvastatin indicate that it is well-tolerated [23], possibly because it is relatively hydrophilic and does not undergo significant metabolism, being predominantly excreted unchanged [15].

Pitavastatin is also effective at lowering LDL-C levels [24]. A randomised trial comparing pitavastatin (2 mg/day) and pravastatin (10 mg/day) in 240 patients showed a decrease in LDL-C of 37.6 and 18.4%, respectively [25]. These results confirmed initial data in Japanese subjects with primary hypercholesterolaemia showing that pitavastatin 2 mg/day is more effective at reducing LDL-C levels than pravastatin 10 mg/day (-38 versus -18%) [26] (Table 1). Furthermore, in a trial in diabetic patients, pitavastatin treatment reduced LDL-C by 36.1%, together with a significant reduction of triglycerides (28.7%) and remnant particles (30.9%) [33]. Pitavastatin is a relatively lipophilic agent with an octanol/phosphate buffer partition coefficient similar to that of atorvastatin and is only minimally metabolised by cytochrome P450 enzymes [34].

2.2 New formulations of current treatments

Although niacin decreases triglyceride levels and raises HDL-C in addition to lowering LDL-C, new formulations of this compound will be discussed in the section on drugs affecting LDL-C levels. The lipid-modifying effects of niacin have

Table 1. Summary of clinical data for new lipid-modifying agents.

Treatment	Mechanism of action	Dose	N	Therapy duration (wks)	% Change from baseline			Ref.
					LDL-C	HDL-C	TG	
Monotherapy								
Avasimibe	ACAT inhibitor	50 – 500 mg	130	8	NS	NS	-23[‡]	[27]
JTT-705	CETP inhibitor	300 – 900 mg	198	4	-7.7	+34.5	NS	[28]
Colesevelam hydrochloride	Bile acid sequestrant	3.75 g	137	6	-19.1	+11.2[§]	NS	[29]
Ezetimibe	Specific cholesterol absorption inhibitor	10 mg	615*	12	-17.7[¶]	+1[¶]	-1.7[**]	[30]
Rosuvastatin	HMG-CoA reductase inhibitor	10 – 40 mg	206	6	-63[‡‡]	+14[‡]	-35[‡]	[17]
Pitavastatin	HMG-CoA reductase inhibitor	2 mg	125	12	-38	+4.2	-23	[26]
Combination therapy								
Extended-release niacin/ lovastatin		500/10 – 2000/40 mg	600	16	-47	+30	-42	[31]
Colesevelam hydrochloride/ lovastatin		2.3 g/10 mg	135	4	-34[‡‡]	NS	NS	[32]

*n = 606 for change in LDL-C from baseline. [‡]p < 0.05 versus placebo. [§]p = 0.006 versus placebo. [¶]p < 0.01 versus placebo. [**]p < 0.09 versus placebo. [‡‡]p < 0.0001 versus placebo.

ACAT: Acyl-CoA cholesterol acyltransferase; CETP: Cholesteryl ester transfer protein; HDL-C: High-density lipoprotein cholesterol; HMG-CoA: Hydroxy-methylglutaryl coenzyme A; LDL-C: Low-density lipoprotein cholesterol; NS: No significant change from baseline; TG: Triglyceride.

been known for almost 50 years and its primary mechanism of action is a reduction in the hepatic production of triglyceride-rich lipoproteins as a result of the mobilisation of free fatty acids from peripheral tissues [35]. The benefits of niacin treatment have been confirmed in a major outcome-based clinical trial. A 5-year follow up of the Coronary Drug Project, a large secondary prevention study conducted in 8341 patients, reported that niacin (3 g/day) effectively reduced total cholesterol (9.9% from baseline) and triglycerides (26.1% from baseline) [36]. Niacin treatment was also associated with significant reductions in non-fatal myocardial infarction (MI) and death from CHD and cerebrovascular disease when compared with placebo (14 and 26%, respectively; $p < 0.005$) [36]. Further evidence that niacin reduces CHD events came from the Familial Atherosclerosis Treatment Study (FATS), a small trial demonstrating that niacin and a bile acid sequestrant in combination were at least as effective as lovastatin combined with a bile acid sequestrant at reducing clinical events and angiographic disease progression in coronary arteries [37].

Immediate-release niacin is associated with frequent dosing and cutaneous flushing, contributing to poor patient compliance [38]. In addition, potentially serious side effects such as deterioration of glycaemic control and increased glycosylation of haemoglobin in diabetic patients have also been reported [39]. Consequently, new extended-release preparations of niacin have been developed that are designed to be more acceptable to patients. Studies indicate that extended-release formulations of niacin are generally well-tolerated and essentially equivalent to immediate-release niacin with respect to efficacy in increasing HDL-C and reducing triglycerides [40-42].

It has recently been suggested that, since niacin and statins modify lipid levels and reduce the risk of CHD by different mechanisms, their use in combination may have an additive effect at reducing coronary events [43]. When used in combination with a statin, extended-release formulations of niacin have also been shown to be effective in improving lipid parameters [44]. A combination of lovastatin and extended-release niacin is available in the US and interim data from a study of 818 patients with dyslipidaemia have shown that 16 weeks of treatment with the combination (daily dose range: 500 mg niacin/10 mg lovastatin to 2000 mg niacin/40 mg lovastatin) reduced LDL-C by 47% from baseline and favourably modified HDL-C and triglyceride levels [31] (Table 1). Flushing, a common side effect of niacin treatment, was reported in 7% of patients receiving the combination, who subsequently withdrew from the study. In the HDL-Atherosclerosis Treatment Study (HATS), a 3-year, double-blind trial, the combination of simvastatin and niacin was found to significantly regress proximal coronary stenoses compared with placebo, in parallel with substantial changes in LDL-C (-42%) and HDL-C (+26%) [45].

2.3 Squalene synthase inhibitors

The enzyme squalene synthase plays an important role in the cholesterol biosynthetic pathway. In monkeys, ER-27856, the tripivaloyloxymethyl ester prodrug of ER-28448, lowered cholesterol levels more potently than pravastatin, simvastatin and

atorvastatin [46]. In addition, this compound has interesting triglyceride-lowering effects both in homozygote and heterozygote animal models of familial hypercholesterolaemia [47]. This effect was also found with a similar inhibitor, YM-53601, in hamsters and is explained by a LDL-R-independent mechanism [47,48]. A new inhibitor of squalene synthase (CJ-15,183) has been identified in the fermentation broth of the fungus *Aspergillus aculateus* [49]. However, no data are currently available regarding the clinical efficacy of this agent.

2.4 Microsomal transfer protein inhibitors

Microsomal transfer protein (MTP) facilitates the translocation of apolipoprotein B (apoB) and its assembly with triglyceride and cholesterol within the hepatic cells. Absence of this protein in the genetic disorder called abetalipoproteinaemia is associated with almost undetectable levels of very-low-density lipoprotein (VLDL) and LDL in plasma. Patients also present with a neurological disorder due to abnormal vitamin E transport and fat malabsorption and steatosis. Genetic manipulation of mice to knockout the MTP gene can decrease plasma apoB levels by 95% and increase the secretion rate of apoB particles by 74%. Thus, the potency of MTP inhibition to decrease atherogenic lipoprotein concentrations must be balanced against potential adverse effects due to inhibition of intestinal fat absorption and hepatic lipid secretion. MTP inhibitors have been shown to decrease LDL-C and VLDL-C in a human liver cell line consequent to inhibition of apoB secretion [50]. However, the development of these compounds has been hampered due to side effects, mainly diarrhoea and steatosis with a high incidence of liver enzyme increase. A series of benzimidazole-based analogues of the BMS-201038 have been recently described [51]. Incorporation of an unsubstituted benzimidazole moiety in place of a piperidine group led to increases in potency, both in a cellular assay of apoB secretion and especially in animal models of cholesterol lowering. The most potent compound in this series, 3g (BMS-212122), was significantly more effective than BMS-201038 in reducing plasma lipids (cholesterol, VLDL/LDL, triglyceride) in both hamsters and cynomolgus monkeys [51].

2.5 Inhibitors of bile acid absorption from the intestine

The bile acid sequestrants (resins), which have been in clinical use for several decades, act by binding bile acids in the intestine, thereby disrupting their reabsorption and lowering intrahepatic cholesterol levels. A subsequent increase in the synthesis of LDL-Rs leads to a reduction in the level of plasma LDL-C. Despite being effective at reducing cholesterol levels, bile acid sequestrants are associated with undesirable side effects and, consequently, patient compliance is poor [52]. The development of new bile acid sequestrants may help to reduce the side-effect problems associated with resins. One such bile acid sequestrant is colesevelam hydrochloride, a non-absorbed, polymeric cholesterol-lowering agent that was recently launched in the US. In a placebo-controlled study, colesevelam 3.75 g/day was reported to lower LDL-C levels by 19.1% and increase HDL-C by 8.1% compared with baseline [29] (Table 1). Constipation, a common effect with the older resins, was not apparent with colesevelam treatment in this study. The higher potency of the drug might be explained by the greater binding affinity for glycocholic acid [53]. The efficacy and tolerability of colesevelam used in combination with a statin has also been demonstrated (Table 1). For example, additional reductions in LDL-C of 8 – 16% above that produced by statins alone have been reported with combination therapy. Furthermore, the overall incidence of adverse effects with colesevelam alone and in combination with statins was similar to that observed with placebo [32,54,55].

Reabsorption of bile acids from the intestine is mediated by the ileal Na^+/bile acid cotransporter (IBAT) and inhibition of this transporter would be expected to produce pharmacological effects similar to those of bile acid sequestrants. Several compounds have been reported to inhibit IBAT *in vivo*. One of these compounds, the novel IBAT inhibitor S-8921, has shown promising cholesterol-lowering capabilities in preclinical studies [56-58]. Treatment of heterozygous Watanabe heritable hyperlipidaemic rabbits with S-8921 reduced plasma cholesterol levels by 29 – 37% [58]. In the same study, treatment with S-8921 inhibited the accumulation of cholesterol in the aortic arch and reduced the severity of coronary atherosclerosis [58].

2.6 Inhibitors of cholesterol absorption from the intestine

Plasma cholesterol levels are influenced not only by *de novo* biosynthesis but also by the absorption of dietary and biliary cholesterol from the intestine and the removal of cholesterol from the blood [59]. Interrupting the absorption of cholesterol has therefore become an important target for lowering serum cholesterol levels. Since the 1950s, it has been recognised that plant sterols and stanols (produced by hydrogenating sterols) can reduce serum cholesterol. As a result of structural similarities with cholesterol, plant sterols and stanols can compete for the limited space available in mixed micelles, the packages in the intestinal lumen that deliver lipids for absorption into mucosal cells and thereby inhibit the absorption of cholesterol from the intestine. Esterified plant sterols or stanols can be incorporated into foods and several products enriched with plant sterol and stanol esters have become available, such as margarine and yoghurt.

Studies have consistently demonstrated that 1.6 – 2.5 g/day of plant sterols reduced LDL-C levels by 10 – 15%. A recent analysis of 14 randomised trials of dietary sterols and stanols reported that 2 g of plant sterols or stanols added to an average daily portion of margarine can reduce LDL-C by 0.33 – 0.54 mmol/l [60]. Interestingly, the efficacy of plant sterols appears to be additive to or even synergistic with, other lipid-modifying agents [61].

Recent evidence supports the presence of a specific transporter that facilitates the movement of cholesterol from bile acid micelles into the brush border membranes of enterocytes [62]. This pathway for cholesterol transport has been exploited as a therapeutic target with the development of ezetimibe, an azetidinone derivative. Ezetimibe is a selective inhibitor of cholesterol absorption that reduces the delivery of cholesterol to the liver and thereby promotes the synthesis of LDL-Rs, resulting in a reduction of plasma LDL-C [30,63]. Pooled data from Phase II studies have shown that 22% of patients receiving ezetimibe 10 mg/day achieved reductions in plasma LDL-C of > 25% [30]. Recent Phase III study results indicate that ezetimibe 10 mg/day lowers LDL-C by ~ 17% in patients with primary hypercholesterolaemia and has favourable effects on other lipid parameters [63] (Table 1). Several studies have also demonstrated additive lipid-lowering effects of ezetimibe when combined with statin therapy [64-67]. Indeed, additional reductions in LDL-C of 12 – 14% have been reported in hypercholesterolaemic patients receiving ezetimibe in combination with atorvastatin [67], lovastatin [65], pravastatin [66] or simvastatin [64] compared with individuals treated with statin monotherapy. Addition of ezetimibe to ongoing open-label statin therapy has also been shown to reduce LDL-C levels by a further 21% compared with statin monotherapy in patients with primary hypercholesterolaemia [68]. Interestingly, ezetimibe in combination with atorvastatin or simvastatin, was recently shown to decrease LDL-C in patients with the homozygous form of familial hypercholesterolaemia [69].

2.7 Sterol regulatory element-binding protein cleavage-activating protein ligands

LDL-R pathway is a key component in the maintenance of cholesterol homeostasis, and upregulation of LDL-R expression is a new therapeutic target for reducing LDL-C. Regulation of LDL-R expression by cholesterol involves the sterol regulatory element-binding protein (SREBP) transcription factors as well as SREBP cleavage-activating protein (SCAP). A new class of drugs that act directly on SCAP has been identified [70]. These drugs upregulate the expression of LDL-R even when the cells are loaded with sterols. The magnitude of the upregulation of the LDL-R is greater than that obtained with statins. Such results represent a promising approach for decreasing both VLDL and LDL levels.

3. Drugs that affect intracellular metabolism of lipid

3.1 Inhibitors of acyl-CoA cholesterol acyltransferase

An important process in the pathogenesis of atherosclerosis is the accumulation of cholesteryl ester (CE) in macrophages and smooth muscle cells of the arterial wall. The ACAT enzyme, which is responsible for the esterification and therefore the storage of cholesterol, is central to this process. Limiting the esterification of cholesterol by inhibiting ACAT may prevent its storage by macrophages and therefore inhibit the formation of arterial plaques. Several potentially useful agents have been identified.

Avasimibe is an ACAT inhibitor that is currently in early clinical development. It has been shown to reduce atherosclerotic lesion size in a cholesterol-fed rabbit model [71]. Furthermore, by limiting macrophage accumulation and reducing the expression of matrix metalloproteinases (MMPs), enzymes involved in vascular matrix remodelling, avasimibe could potentially stabilise atherosclerotic lesions and prevent plaque rupture [71]. The availability of clinical data are currently limited, but a placebo-controlled study in 130 men and women with combined hyperlipidaemia and hypoalphalipoproteinaemia has produced some promising results (Table 1) [27]. Dose-independent reductions in total triglycerides and VLDL of 23 and 30%, respectively ($p < 0.05$ versus placebo), have been reported with avasimibe (dose range 50 – 500 mg/day). However, total cholesterol, LDL-C and HDL-C remained unchanged from baseline following avasimibe treatment.

Other ACAT inhibitors have been identified, including NTE-122 and F 12511 [72,73]. Preclinical studies have shown that NTE-122 reduces serum and hepatic cholesterol levels in cholesterol-fed rabbits and rats [72] and that F 12511 is capable of reducing serum cholesterol levels in rabbits with endogenous hypercholesterolaemia [73]. Furthermore, a combination of F 12511 and atorvastatin reduced plasma total cholesterol and apoB-100-containing lipoproteins in this model to a greater extent than either agent alone [73].

4. High-density lipoprotein as a new target for therapeutic intervention

Although elevated plasma LDL-C levels have been the traditional focus of the medical community, epidemiological data have shown that low levels of HDL-C can also play an important role in the development of cardiovascular disease [74]. As previously discussed, several of the currently established agents, including niacin, fibrates and statins, are effective at increasing HDL-C. In the Veterans Affairs High-density lipoprotein cholesterol Intervention Trial (VA-HIT), gemfibrozil treatment was shown to increase HDL-C and reduce the relative risk of CHD death and non-fatal MI by 22% in patients with low HDL-C and LDL-C levels [75]. Nevertheless, it remains uncertain whether the increase in HDL-C observed with the other lipid-modifying compounds translates into a substantial decrease in cardiovascular morbidity and mortality. The increasing prevalence of the so-called plurimetabolic syndrome is associated with an increased prevalence of low HDL-C in the population. Thus, HDL-C as a target for intervention represents one of the most challenging issues in the field, with a huge potential benefit but also a need to prove the concept that increasing HDL-C is indeed beneficial.

It has been suggested that the protective effects of HDL-C are exerted through a number of mechanisms, including the promotion of reverse cholesterol transport and pleiotropic effects. The rate of reverse cholesterol transport is probably

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