Curr Cardiol Rep (2014) 16:506
DOI 10.1007/s11886-014-0506-3

Emerging Therapeutic Approaches to Treat Dyslipidemia

David Preiss · Chris J. Packard

Published online: 3 June 2014

Abstract Statins are safe, efficacious and the cornerstone of cardiovascular disease prevention strategies. A number of add-on therapies with complementary actions on the plasma lipid profile have been tested in large scale trials to see if they give incremental benefit. In particular, the 'HDL hypothesis' – that raising this lipoprotein will promote reverse cholesterol transport and reduce cardiovascular risk – has been examined using drugs such as dalcetrapib and niacin. So far, results have been negative, and this has raised questions over the nature of the association of HDL with atherosclerosis, and whether statins reduce cardiovascular risk through multiple mechanisms. There is still an unmet clinical need especially in those patients who cannot tolerate statins and those with severe hyperlipidemia, and so new therapeutic approaches have been developed. These show significant promise in terms of LDL-cholesterol lowering but significant challenges include cost, route of administration (subcutaneous injection) and side effects. Testing in major outcome trials will be required to demonstrate their clinical utility.

Keywords Cardiovascular disease · Dyslipidemia · Hypercholesterolemia · LDL-cholesterol · Antisense oligonucleotide therapy · Microsomal transfer protein inhibition · PCSK9 inhibition · CETP inhibition

This article is part of the Topical Collection on *Lipid Abnormalities and Cardiovascular Prevention*

D. Preiss (✉)
BHF Glasgow Cardiovascular Research Centre, University of Glasgow, Glasgow G12 8TA, UK
e-mail: david.preiss@glasgow.ac.uk

C. J. Packard
Glasgow Clinical Research Facility, Western Infirmary, NHS Greater Glasgow and Clyde, Tennent Building, Church Street, Western Infirmary, Glasgow G11 6NT, UK
e-mail: chris.j.packard@gmail.com

Introduction

Cardiovascular disease remains a major cause of morbidity and mortality in both the developing and developed world with management of key risk factors and treatment of affected individuals consuming substantial fractions of national health care budgets. Of the various strategies available to reduce cardiovascular risk, lipid modifying therapy has been one of the most intensively investigated and most successful [1, 2]. In randomized clinical trials, statin therapy has led to substantial reductions in a range of cardiovascular outcomes including myocardial infarction, stroke and revascularization in almost all populations in which it has been tested. With many statins now available off-patent, this powerful class of agents can be employed widely in cardiovascular disease prevention not only in wealthy nations but worldwide.

However, challenges remain. Despite the ability to generate impressive reductions in low density lipoprotein (LDL)-cholesterol with statin therapy, control blood pressure with a plethora of agents plus facilitate cessation of smoking, a modifiable residuum of cardiovascular disease risk persists and additional therapies are needed to achieve the best possible benefit for patients. Further, when treating individuals at high cardiovascular risk or with significant hyperlipidemia, clinicians are regularly confronted with patients who are unable to tolerate the prescribed medication due to side-effects or who require combination therapy.

The purpose of this brief review is to describe novel lipid-modifying drugs which have recently been considered for regulatory approval or which are in various stages of clinical development. The agents are discussed in four categories depending on the lipoprotein class most impacted by treatment (LDL-cholesterol modification, high density lipoprotein [HDL]-cholesterol modification, triglyceride modification, lipoprotein(a) modification), although it is recognized that many drugs have multiple actions throughout the lipoprotein spectrum.

Novel LDL-Modifying Therapies

The strong, consistent epidemiological link between plasma cholesterol levels and cardiovascular risk has long been recognized [3], and has prompted over the last 40 years the development of a variety of clinically useful drugs (fibrates, bile acid sequestrants, niacin, statins, ezetimibe) and other therapeutic approaches (plasmapheresis, ileal bypass surgery) that are able to lower circulating cholesterol concentrations from about 15 % (fibrates) to more than 50 % (potent statins). Many of these therapeutic manoeuvres have been tested in clinical trials and have yielded favourable results. From meta-analyses of statin trials, the dogma has emerged that a 1.0 mmol/L decrease in LDL-cholesterol is associated with a reduction of approximately 22 % [2] in major cardiovascular outcomes - fatal and non-fatal - in medium and high cardiovascular risk patients, in men and women, and in those with and without diabetes. Serious side effects of statin therapy are few [4–6] and comfortably outweighed by the benefits derived from treatment. However, 10-20 % of patients prescribed statins report side-effects, usually muscle related, that are dose-limiting leading to sub-optimal therapy or discontinuation of the medication.

The greatest impact on LDL-cholesterol is seen at the starting dose of a statin and ranges from 20 % reduction on 10 mg of pravastatin to a 45 % decrease on 10 mg of rosuvastatin [7]. When this is considered insufficient for optimal therapy, the usual next step is to up-titrate the drug by doubling the dose. However, it is now well recognized that this step (doubling of any statin dose) provides only an additional 6 % lowering in LDL-cholesterol. Further therapeutic challenges are encountered in the case of patients with homozygous or severe heterozygous familial hypercholesterolemia (FH) who may respond poorly to even high dose statin therapy due to the underlying defect in LDL-receptor expression, or start from such an elevated baseline LDL-cholesterol concentration that combination therapy is required. Until recently, additional powerful cholesterol lowering agents have not been available.

Novel therapies for lowering LDL-cholesterol are discussed below and Fig. 1 presents schematically the mechanisms of action of four new drug classes. By way of background it is helpful to consider the metabolism of apolipoprotein B100 (apo B100)-containing lipoproteins (very low density lipoprotein [VLDL], intermediate density lipoprotein [IDL], and LDL). Apo B100 is the main protein in VLDL. It is a large structural protein that is incorporated into the newly synthesized lipoprotein within the liver and remains with the particle throughout its lifetime in the circulation. VLDL assembly takes place in the endoplasmic reticulum (ER) where microsomal triglyceride transfer protein (MTP), which forms a dimer with protein disulfide isomerase (PDI), transfers lipid (triglyceride, phospholipid, cholesterol ester) to the growing apo B100 polypeptide chain and so helps build the nascent lipoprotein particle. Once fully lipidated, VLDL is released into the circulation where its core triglyceride is progressively removed under the action of lipases, to yield first IDL and then LDL.

In the circulation there is rapid exchange of triglyceride and cholesteryl ester between the apo B100-containing lipoproteins and HDL that is facilitated by cholesteryl-ester transfer protein (CETP). The action of this protein increases the cholesteryl ester content of apo B100-containing lipoproteins and reduces the amount of this lipid in HDL. LDL particles which have a half-life in the circulation of about three days are usually removed by LDL receptors, most of which are expressed by the liver. If this pathway is saturated or inefficient then LDL is taken up by tissues including the arterial wall in a LDL receptor-independent process.

Microsomal Transfer Protein inhibition

As noted above, ribosomal translation and insertion of the nascent apo B100 polypeptide chain into the ER allows VLDL assembly to begin and particle lipids are added via the agency of the MTP/PDI dimer complex. When MTP is inhibited, lipid movement into the ER ceases and there is redirection of the nascent apo B100 into the cytosol where it is subject to degradation by the proteasome. As a result VLDL production is reduced, and VLDL and LDL levels in the circulation fall. A number of MTP inhibitors were taken into clinical development but most were discontinued due to concerns over the appearance or aggravation of hepatic steatosis. However, Cuchel and Rader [8] continued to pursue MTP inhibition as a therapeutic strategy and attempted to balance the VLDL/LDL lowering effect against the propensity to accumulate liver fat. They have been successful in determining a dosing schedule with lomitapide that offers a useful lipid-lowering effect with only modest changes in liver lipid content. The drug is delivered as a daily oral capsule.

Recent Clinical Trials

A small number of clinical studies with MTP inhibitors have been conducted in patients with both dyslipidemia and homozygous FH over the last six years [8–10]. The results of the studies in homozygous FH are summarized in Table 1. In an additional study in patients with hypercholesterolemia, the MTP inhibitor AEGR-733 was given orally at increasing doses for 12 weeks in combination with ezetimibe at which point LDL-C was reduced by 26 % compared to ezetimibe monotherapy [9].

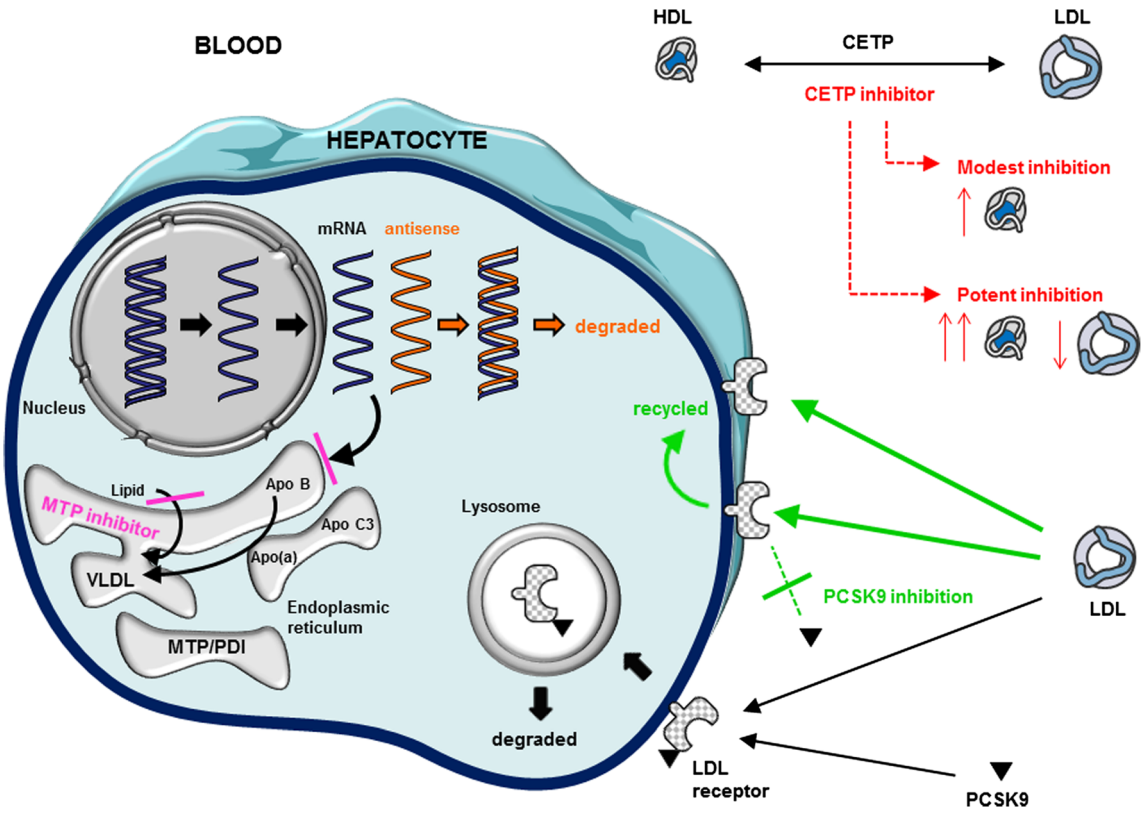

Fig. 1 Schematic diagram of mechanisms by which novel therapies modify LDL, HDL and triglycerides in the liver and the circulation. *Footnote*: With antisense oligonucleotides, mRNA of the protein of interest (apo B100, apo C3, Lp(a)) is hybridized and degraded in the cytosol with resultant reduction in the intended production of the protein of interest in the endoplasmic reticulum (*highlighted in orange*); MTP inhibition reduces entry of lipid and nascent apolipoprotein B into the endoplasmic reticulum lumen, with resultant fall in circulating VLDL and LDL (*highlighted in pink*); PCSK9 inhibition reduces levels of circulating PCSK9 with the result that more LDL-receptors are recycled after accepting LDL-cholesterol (*highlighted in green*); potent inhibition on the plasma protein CETP results in a marked increase in HDL and a fall in LDL while modest inhibition results in a smaller rise in HDL (*highlighted in red*)

Side-Effects

MTP inhibitors have notable hepatic effects with increases in ALT and intracellular fat. Hepatic fat content has been shown to increase multiple-fold based on magnetic resonance spectroscopy (MRS) analysis. In one trial of 29 patients with homozygous FH, it rose from 1 to 8 % of liver volume [10], and then fell during the wash-out phase after active treatment showing that it is a reversible phenomenon.

Status

In 2013, both the Food and Drug Administration (FDA) and European Medicines Agency (EMA) gave marketing authorization for the use of lomitapide in patients with homozygous FH.

Antisense Apolipoprotein B100 Oligonucleotide Therapy

An alternative approach to reducing VLDL production in the liver is to inhibit the synthesis of apo B100 itself. Antisense oligonucleotide (ASO) technology provides this opportunity. The agent acts by hybridizing to apo B100 mRNA within the cytosol and rendering it ineffectual as a template for protein translation. The consequent reduction in apo B100 production impacts directly on VLDL assembly and, as with MTP inhibitors, leads to a fall in circulating levels of VLDL and LDL. The ASO to apo B100 is given by subcutaneous injection, typically on a weekly basis.

Recent Clinical Trials

Mipomersen (an ASO directed at the mRNA for apo B100) has been tested in a variety of patient populations including those with dyslipidemia (from mild to severe) [11–15], those who are classed as statin intolerant [16], and homozygous and heterozygous FH [17–19]. Reductions in LDL-cholesterol have been impressive. The results of early clinical trials conducted in patients with homozygous and heterozygous familial FH, the condition in which mipomersen is most likely to be used in future, are summarized in Table 1.

Table 1 Results of lipid-modifying effects of MTP inhibitors and apo B100 antisense oligonucleotides in trials of patients with familial hypercholesterolemia

Trial	Participants	Background therapy	Intervention	Control	Duration	N	Change in LDL-C	Change in Lp(a)*
Microsomal triglyceride transfer protein inhibition								
Cuchel et al. [8]	Homozygous FH	All lipid-lowering therapy (including apheresis) stopped 4 weeks before study	MTP inhibitor BMS-201038 oral (each dose taken for 7 days, then uptitrated): a) 0.03 mg/kg/d b) 0.1 mg/kg/d c) 0.3 mg/kg/d d) 1.0 mg/kg/d	No control arm	4 weeks	6	Compared to baseline after each week of relevant dose†: a) -4 % b) -7 % c) -25 % d) -51 % respectively	No clinically significant changes
Cuchel et al. (HoFH Lomitapide Study) [10]	Homozygous FH	Baseline lipid-lowering therapy maintained	MTP inhibitor, lomitapide oral: Up to maximum dose of 60 mg/d (median dose 40 mg/d)	No control arm	26 weeks	29	Compared to baseline at 26 weeks: -50 %	Compared to baseline at 26 weeks: -15 %
Antisense oligonucleotide apolipoprotein B therapy								
Raal et al. [17]	Homozygous FH	Maximum tolerated lipid-lowering drug	Mipomersen sc 200 mg every week	Placebo sc	26 weeks	51	Compared to placebo: -21 %	Compared to placebo: -23 %
Akdim et al. [18]	Heterozygous FH	Conventional therapy	Mipomersen sc: a) 50 mg/wk b) 100 mg/wk c) 200 mg/wk d) 300 mg/wk	Placebo sc	6 weeks	44	Compared to placebo: a) -13 % b) -11 % c) -21 % d) -34 % respectively	Compared to placebo: a) 0 % b) -12 % c) -14 % d) -21 % respectively
Stein E et al. [19]	Heterozygous FH, coronary artery disease and≥LDL-C 100 mg/dL	On maximal tolerated statin therapy	Mipomersen sc 200 mg every week	Placebo sc	26 weeks	124	Compared to placebo: -32 %	Compared to placebo: -21 %

†by preparative ultra-centrifugation

FH: familial hypercholesterolemia; sc: subcutaneous injection; LDL-C: LDL-cholesterol; MTP: microsomal triglyceride transfer protein; Lp(a): lipoprotein (a)

Side-Effects

Two particular issues are worthy of attention. First, local reactions at injection sites have proven problematic with pain, swelling and skin discoloration. It remains unclear if this apparent immune reaction may reflect a more generalized reaction with potential autoimmunity and treatment resistance over longer periods of therapy. Secondly, elevations in ALT are commonly observed. Studies using magnetic resonance spectroscopy initially suggested that fat accumulation in the liver was limited though more recent investigations have indicated that it may approach levels of 6-15 % of liver volume [15, 19], with a reduction after withdrawal of therapy. The clinical importance of this finding (as with lomitapide) is unclear with some comparing it to the liver fat accumulation that occurs in abetalipoproteinemia, apparently without clinical consequences [20]. There may also be a modest increase in risk of developing flu-like symptoms.

Status

In January 2013, the FDA approved the use of mipomersen for the treatment of patients with homozygous FH. However, in late 2012 the EMA rejected an application for use of the drug in patients with either homozygous or severe heterozygous FH.

Proprotein Convertase Subtilisin/Kexin Type 9 Inhibition

There has been great interest in the potential exploitation of proprotein convertase subtilisin/kexin type 9 (PCSK9)-based therapies since genetic polymorphism studies over the last decade demonstrated that gain-of-function PCSK9 mutations were apparently linked to increased cardiovascular risk [21] while loss-of-function mutations had the opposite effect [22, 23]. PCSK9, an enzyme produced in the liver, has an intracellular action on LDL receptors (i.e. within hepatocytes) but its most important role appears to be as a circulating regulator of LDL receptor activity throughout the body. It binds to LDL-receptors on cell surfaces and directs the receptor, once it is internalized, towards lysosomal degradation rather than recycling to the cell membrane. The net effect of PCSK9 is to alter the abundance of LDL receptors in cells and so impact on plasma LDL levels. Given the clear demonstration that statin therapy yields cardiovascular benefit as a result of increasing expression of LDL-receptors with a consequent reduction in circulating LDL-cholesterol, there has been enthusiastic pursuit of various approaches to PCSK9 inhibition since it appears to operate by a linked mechanism. These approaches include the use of monoclonal antibodies directed against PCSK9, and ASO-based PCSK9 synthesis inhibitors [24]. At present, the former approach has been the most productive and agents in clinical development have yielded promising results [25••, 26–32]. PCSK9 monoclonal antibody preparations are given as subcutaneous injections, typically every 2-4 weeks.

Recent Trial Results

The first published data describing the clinical utility of PCSK9 inhibition with monoclonal antibodies became available in 2012 [25••]. Subsequently, a combination of single ascending dose and multiple ascending dose studies of PCSK9 monoclonal antibodies established the apparently safe and substantial dose-dependent LDL-cholesterol lowering capabilities of these agents, and also revealed that maximum efficacy was reached when all circulating PCSK9 had been bound. Table 1 summarizes the impressive phase 2 trial data from two leading monoclonal antibody programs. Notably, LDL-cholesterol is lowered to a similar extent regardless of concomitant statin therapy.

Side-Effects

Few side-effects have been commonly reported in the trials apart from mild injection site reactions.

Status

As yet, no PCSK9 inhibitors have been authorized for clinical use. Cost of therapy will be a major determinant of its future use outside of those with genetic dyslipidemias.

Cholesteryl-Ester Transfer Protein Inhibition

The predominant effect of CETP inhibition is to increase HDL, as described in the following section. While modest inhibition of CETP appears to have little effect on apo B100-containing lipoproteins [33•], potent CETP inhibition can substantially reduce the concentration of LDL-cholesterol [34–36]. Preliminary lipid turnover studies of potent CETP inhibition suggest that this LDL-lowering effect probably reflects either increased LDL-receptor expression or increased affinity of LDL for the LDL-receptor but further studies are required to fully explain this action of the drugs.

Recent trial results (including LDL-cholesterol effects), side-effects and drug status are described below.

Novel HDL-Modifying Therapies

HDL is believed to be responsible for the process of ‘reverse cholesterol transport’. In this pathway, disk-shaped nascent HDL in the circulation accepts cholesterol from cells (including cholesterol-laden foam cells) and, following esterification via the agency of lecithin-cholesterol acyltransferase, the lipid

migrates to the core of the particle and larger, spherical HDL are generated. These mature particles can be taken up by the liver via a number of mechanisms and in this way cholesterol is delivered to the only organ that can secrete it in bulk. This transport system is thought to be the principal route by which the body excretes cholesterol. As noted above, CETP facilitates the transfer of neutral lipid (cholesteryl ester and triglyceride) between lipoproteins, and a further possible pathway of return to the liver is for cholesteryl ester to be transferred to apo B-containing lipoproteins – chylomicron/VLDL remnants, IDL and LDL - which are taken up by LDL receptors on hepatocytes.

In epidemiological studies HDL-cholesterol is powerfully inversely associated with cardiovascular risk [37], albeit with an apparent flattening of this relationship at HDL-cholesterol levels above about 60 mg/dL. The consistency of this association, and the scientific plausibility of the 'HDL hypothesis' - that increasing HDL levels reduces cardiovascular risk - has led to the development of a variety of HDL-cholesterol raising therapies. However, many of the agents which increase HDL also have effects on other lipoproteins and in major outcome trials it has been problematic to ascribe any reduction in cardiovascular risk to a change in HDL per se. Further, compared to the substantial impact on cardiovascular risk of LDL lowering, the magnitude of benefit attributable (even tentatively) to HDL raising has been limited and in some cases absent. Fibrate monotherapy trials conducted in the 1980s and 1990s suggested a role for these agents in the treatment of high risk patients with low HDL-cholesterol [38, 39] but the magnitude of the HDL rise was small and, with the advent of statins, the incremental clinical benefit of adding a fibrate appears to be limited also. For example, in the ACCORD-Lipid trial in which fenofibrate was given on top of statin therapy, there was no additional cardiovascular risk reduction [40]. Proponents of fibrate therapy contend that these drugs are most usefully employed in patients with a syndrome of raised triglyceride and low HDL, and in subgroup analyses of patients with this lipid profile in both ACCORD-Lipid [40] and FIELD [41] there was a suggestion of worthwhile cardiovascular benefit. In addition, the potential use of fibrate therapy to reduce retinopathy complications in diabetes is promising and marketing authorization is being pursued for this indication. Based on early studies there was hope that niacin, which in most patient groups had a superior HDL raising effect compared to fibrates, would prove to be effective adjunct lipid-lowering therapy to statins. However, two recent clinical trials (AIM-HIGH and HPS2-THRIVE) have indicated a lack of further benefit from this combination compared to statin alone, and in HPS2-THRIVE, there were significant adverse effects of niacin/laropiprant (laropiprant is an anti-flushing agent) therapy [42•, 43].

The recent disappointing results for niacin, fenofibrate and CETP inhibitors in outcome trials have led to a major debate on the supposed benefits of therapies that raise HDL. It is clear that HDL-cholesterol is itself a simplistic measure of HDL structure, function and potential anti-atherogenic properties. The lipoprotein class is structurally highly heterogeneous and has a variety of functional roles including (but not limited to) reverse cholesterol transport, glucose homeostasis, anti-inflammatory and anti-hemostatic effects and carriage of micro RNA. A commonly expressed view is that specific HDL subfractions may be the key drivers of any cardiovascular benefit and that novel HDL-based therapies must be directed to the correct, as yet unidentified, target to see a reduction in risk of coronary heart disease [44].

Cholesteryl-Ester Transfer Protein Inhibition

Nature's clinical trials - Mendelian randomization studies - suggest a causal link between CETP gene variation and cardiovascular risk, with patients carrying a CETP reducing variant showing higher HDL-cholesterol and a reduced incidence of myocardial infarction [45]. The potency of pharmacological inhibition of CETP determines not only the extent to which a drug in this class raises HDL-cholesterol but also the amount of LDL-cholesterol lowering. The clinical relevance of CETP inhibitor-induced elevation in HDL-cholesterol and reduction in LDL-cholesterol (which is accompanied by a fall in apo B100 and hence particle number) remains uncertain. The effects of CETP inhibitors on circulating lipoproteins are shown in Fig. 1.

Recent Trial Results

The first major endpoint study of CETP inhibition, ILLUMINATE, in which oral torcetrapib therapy was investigated in 15,067 patients at high cardiovascular risk, was terminated early due to the finding of increased adverse outcomes despite potent effects on the plasma levels of both HDL-cholesterol (72 % increase) and LDL-cholesterol (25 % decrease) [34]. The second major trial, Dal-OUTCOMES, studied the effect of a modest strength oral CETP inhibitor, dalcetrapib, on 15,871 subjects who had had a recent acute coronary event [33•]. The trial showed no cardiovascular benefit despite a 30-40 % increase in HDL-cholesterol. Interestingly, Dal-OUTCOMES was as close as we have come to a 'pure' HDL raising trial since the drug has almost no impact on LDL-cholesterol and plasma triglyceride levels. Further large cardiovascular outcomes trials have been launched namely ACCELERATE for evacetrapib (which achieves ~80 % increase in HDL-C and ~10 % reduction in LDL-C [35]) and HPS3-REVEAL for anacetrapib (which achieves ~140 % increase in HDL-C and ~40 % reduction in LDL-C [36]). Both of these agents like dalcetrapib appear to lack the adverse blood pressure-raising effect of their predecessor, torcetrapib.

Side-Effects

Following the failure of torcetrapib in ILLUMINATE, further investigation of this specific drug confirmed an off-target effect of increased aldosterone production which led to higher blood pressure and drove the increased risk in cardiovascular events.

Status

No CETP inhibitor yet carries marketing approval.

Dual Peroxisome Proliferator-Activated Receptor α/γ Agonists

The glitazars are dual agonists for the peroxisome proliferator-activated receptor (PPAR) class of nuclear receptors with most specificity for the α and γ PPAR sub-types. Glitazar induced activation of these receptors leads to variations in the transcription of a number of related genes. As may be expected, the agents share lipid-modifying and glucose-lowering properties with PPAR α (fibrate) and PPAR γ (thiazolidinediones) agonists. Within the PPAR field, great excitement has been generated by the apparent ability of fenofibrate to improve microvascular outcomes such as retinopathy [46, 47]. While this appears to reflect a local ocular action rather than any systemic or lipid-related effect [48], the ability of dual PPAR agonists to provide retinal benefits is of interest. Muraglitazar and tesaglitazar development programs were discontinued in 2006. Other glitazars currently or recently under investigation include aleglitazar and saroglitazar.

Recent Trial Results

A major program of research into aleglitazar was stopped in 2013. This was based on a finding of futility in the ALECARDIO trial [49] (currently unpublished) in which aleglitazar was compared to placebo to investigate its effect on cardiovascular morbidity and mortality in patients with type 2 diabetes mellitus and recent acute coronary syndrome.

Side-Effects

Additional concerns arose in the ALECARDIO trial of aleglitazar. Part of the rationale to discontinue this trial along with the larger AlePREVENT trial was driven by concern over an increase in fractures and heart failure – both side effects were previously observed in thiazolidinedione trials [50, 51] – plus, unexpectedly, gastro-intestinal hemorrhage.

Status

Saroglitazar is approved for the treatment of diabetic dyslipidemia and hypertriglyceridemia in India though cardiovascular benefit has not yet been studied or demonstrated in any major trial.

Novel Triglyceride-Modifying Therapies

Therapies to reduce plasma triglyceride levels are generally used in an effort to decrease risk of either cardiovascular disease or pancreatitis. There is an intriguing discordancy of the link between triglycerides and cardiovascular disease in epidemiological surveys and genetic (Mendelian randomization) investigations. On the one hand, it is observed that inclusion of triglyceride levels has little impact on prediction of cardiovascular disease when other major classical risk factors including HDL-cholesterol are taken into account [37]. On the other, single nucleotide polymorphism studies of genes that regulate triglycerides suggest that triglyceride-mediated pathways may indeed be causally implicated in the development of cardiovascular disease [52••]. No high-quality data exist to demonstrate the ability of an agent to reduce triglyceride-driven pancreatitis and this may be impossible to examine in an adequately powered classical clinical trial. However, it is noteworthy that statins have been shown to reduce all-cause pancreatitis in trial participants with normal or modestly elevated triglyceride levels [53].

All of the agents discussed in the preceding sections lower circulating triglyceride levels to a greater or lesser extent and these are not discussed any further in this section.

Antisense Apolipoprotein C3 Oligonucleotide Therapy

Apolipoprotein C3 (apo C3) is a component of VLDL which inhibits the function of lipoprotein lipase and may promote VLDL assembly [54]. In individuals with genetically determined lower apo C3 levels, favourable lipid profiles (lower triglycerides and LDL-cholesterol, higher HDL-cholesterol), improved longevity and reduced coronary calcium score have been observed [55]. The technology applied for ASO apo C3 therapy is much the same as described above for apo B100 in that the drug, an oligonucleotide, hybridizes with apo C3 mRNA, thereby reducing translation to apo C3 and reducing incorporation into VLDL.

Recent Trial Results

In a recently published phase 1 trial of an apo C3 ASO (ISIS 304801), dose- and time-dependent reductions were observed

for apo C3 (up to 80 %) and circulating triglycerides (up to 50 %) [56].

Side-Effects

Injection site reactions have been the most-reported side-effect.

Status

This novel agent is not yet licensed for clinical use. ISIS 304801 will shortly enter phase 3 studies in patients with familial chylomicronemia syndrome (lipoprotein lipase [LPL] deficiency) and severe non-LPL deficiency hypertriglyceridemia.

Lipoprotein Lipase Gene Therapy

LPL deficiency is a rare condition which exposes homozygous individuals to severe hypertriglyceridemia and recurrent acute pancreatitis [57]. Alipogene tiparvovec is a LPL (S447X) gene variant in an adeno-associated viral vector of serotype 1 which is delivered to patients by multiple intramuscular injections under spinal anesthesia [58].

Recent Trial Results

In an uncontrolled trial of 14 LPL deficient patients who had previously developed acute pancreatitis, triglyceride levels were reduced by 40 % 3-12 weeks after treatment but had returned to baseline triglyceride levels by 26 weeks despite demonstration of ongoing LPL activity in the skeletal muscle [59]. Over 26 weeks, two patients experienced acute pancreatitis after therapy suggesting a benefit based on comparison of event rates prior to and after therapy.

Side-Effects

Due to the small number of subjects treated thus far, it is not possible to conclusively link reported adverse events to LPL gene therapy with the exception of discomfort and bruising due to the number of intramuscular injections.

Status

Alipogene tiparvovec was approved for clinical use by the EMA in 2012. It has been specifically developed for treating those with homozygous lipoprotein lipase deficiency and not for those with mutations in other genes related to LPL function such as apo C2 and apo A5. It is licensed as a single treatment (of multiple injections), based on weight, and is given with immunosuppression until 12 weeks after administration.

Lipoprotein(a)-Modifying Therapies

Lipoprotein(a) or Lp(a) is a lipoprotein that comprises a LDL particle in which a variable length apolipoprotein(a) is covalently bound via a disulphide linkage to the apo B100. Circulating Lp(a) levels are largely genetically determined, and epidemiological data have demonstrated that Lp(a) is an independent cardiovascular risk factor [60]. Mendelian randomization studies support this contention and indicate that Lp(a) may be causally implicated in the development of cardiovascular disease [61]. The latter recent observations have prompted renewed interest in the effects of lipid-modifying therapies on Lp(a). Statin therapy has little effect on plasma levels of this lipoprotein leading to the supposition that Lp(a) is not removed from the circulation by the LDL-receptor but by other, as yet unidentified, mechanisms.

Some of the agents discussed above in addition to their main modes of action also have the ability to reduce circulating Lp(a), namely antisense apo B100 oligonucleotide therapy, MTP inhibitors, PCSK9 inhibitors and CETP inhibitors, typically by 10-30 %. It has also been known for some time that niacin has an Lp(a) lowering effect. These actions are summarized in Tables 1 and 2. Lp(a) is formed in the extracellular space of hepatocytes as LDL particles are co-secreted with apo(a) polypeptide chains [62]. The rate of formation depends on both components being present, and it is likely that agents that reduce LDL secretion (such as ASO to apo B100 and MTP inhibitors) limit the amount of LDL available, and thereby Lp(a). It is more difficult to understand how CETP and PCSK9 inhibitors reduce Lp(a). Possibly, PCSK9 inhibitors increase the abundance of LDL receptors on hepatocyte cell surfaces which promotes the rapid uptake of newly secreted LDL and hence reduces the potential for Lp(a) formation.

Antisense Apolipoprotein(a) Oligonucleotide Therapy

The same strategy for reduction in production of specific proteins applied to apo B100 and apo C3 is also being applied to apolipoprotein(a) with ASO technology which aims to reduce Lp(a). Phase 1 studies are underway in healthy volunteers and results are awaited.

Conclusions and Future Developments

Statins are safe and effective and occupy the centre ground in cardiovascular prevention strategies. Newly developed and existing drugs have been tested as add-on therapy and, while the desired changes in plasma lipids have been achieved, there has been no demonstrable incremental benefit. This is a matter of concern for the future for pharmaceutical companies and the research community. The question arises as to whether statins are so effective (through LDL lowering and other pleiotropic

Table 2 Results of lipid-modifying effects of monoclonal antibodies against PCSK9 in phase 2 trials

Trial	Participants	Background therapy	Intervention	Control	Duration	N	Change in LDL-C*	Change in HDL-C*	Change in Lp(a)*
McKenney et al. [26]	LDL-C ≥100 mg/dL	Atorvastatin 10-40 mg/d	REGN727 sc: a) 50 mg, 100 mg or 150 mg every 2 weeks b) 200 mg or 300 mg every 4 weeks	Placebo sc	12 weeks	183	At 12 weeks: a) -35 %, -59 %, -67 % b) -38 %, -43 %, respectively	At 12 weeks: a) +8 %, +5 %, +7 % b) +7 %, +9 % respectively	At 12 weeks: a) -13 %, -26 %, -29 % b) -17, -8 % respectively
Stein et al. [27]	Heterozygous FH with LDL-C ≥100 mg/dL	On statin, with or without ezetimibe	REGN727 sc: a) 150 mg every 2 weeks b) 150 mg, 200 mg or 300 mg every 4 weeks	Placebo sc	12 weeks	77	At 12 weeks: a) -57 % b) -18 %, -21 %, -32 % respectively	At 12 weeks: a) +10 % b) +6 %, +4 %, +8 % respectively	At 12 weeks: a) -19 % b) -6 %, -4 %, -11 % respectively
Roth et al. [28]	LDL-C ≥100 mg/dL	Atorvastatin 10 mg/d	REGN727 sc: a) 150 mg every 2 weeks with atorvastatin 80 mg/d b) 150 mg every 2 weeks plus atorvastatin 10 mg/d	Placebo sc and atorvastatin increased to 80 mg/d	8 weeks	92	At 8 weeks: a) -56 % b) -49 % respectively	At 8 weeks: a) +9 % b) +6 % respectively	At 8 weeks: a) -28 % b) -32 % respectively
Raal et al. (RUTHERFORD) [29]	Heterozygous FH with LDL-C ≥100 mg/dL	On statin, with or without ezetimibe	AMG145: a) 350 mg every 4 weeks b) 420 mg every 4 weeks	Placebo sc	12 weeks	168	At 12 weeks†: a) -44 % b) -56 % respectively	At 12 weeks a) +8 % b) +7 % respectively	At 12 weeks: a) -23 % b) -32 % respectively
Sullivan et al. (GAUSS) [30]	Reported statin intolerance, LDL-C above NCEP threshold	16 % on statins at low dose	AMG145: a) 280 mg, 350 mg or 420 mg every 4 weeks b) 420 mg every 4 weeks plus ezetimibe 10 mg/d	Placebo sc and ezetimibe 10 mg/d	12 weeks	160	At 12 weeks†: a) -26 %, -28 %, -36 % b) -47 % respectively	At 12 weeks: a) +7 %, +7 %, +9 % b) +13 % respectively	At 12 weeks: a) -18 %, -12 %, -16 % b) -21 % respectively
Koren et al. (MENDEL) [31]	LDL-C 100 to 190 mg/dL at low cardiovascular risk	Not on statins	AMG145: a) 70 mg, 105 mg or 140 mg every 2 weeks b) 280 mg, 350 mg or 420 mg every 4 weeks	Placebo sc	12 weeks	406	At 12 weeks†: a) -37 %, -40 %, -47 % b) -44 %, -48 %, -53 % respectively	At 12 weeks: a) +4 %, +7 %, +10 % b) +3 %, +4 %, +6 % respectively	At 12 weeks: a) -11 %, -18 %, -29 % b) -22 %, -28 %, -29 % respectively
Giugliano et al. (LAPLACE-TIMI 57) [32]	LDL-C >85 mg/dL	On statin, with or without ezetimibe	AMG145: a) 70 mg, 105 mg or 140 mg every 2 weeks b) 280 mg, 350 mg or 420 mg every 4 weeks	Placebo sc	12 weeks	631	At 12 weeks†: a) -42 %, -60 %, -66 % b) -42 %, -50 %, -50 % respectively	At 12 weeks: a) +7 %, +7 %, +8 % b) +2 %, +6 %, +5 % respectively	Not reported

*compared to control arm, †by preparative ultra-centrifugation

FH: familial hypercholesterolemia, sc: subcutaneous injection, NCEP: National Cholesterol Education Program; LDL-C: LDL-cholesterol; HDL-C: HDL-cholesterol; Lp(a): lipoprotein(a)

actions) that other classes of agents may fail to exert further impact on atherogenic mechanisms, or whether the new drugs have been tested in the wrong populations of subjects receiving optimal treatment, or whether our understanding of the role of lipids (especially HDL) in cardiovascular disease is not as sound as we supposed.

New therapeutic approaches are needed for those who cannot tolerate statins and those with severe hyperlipidemia. We will learn soon if the addition of ezetimibe to statin therapy is beneficial when the results of the IMPROVE-IT trial are announced [63]. If positive, this study will raise hopes that at least some of the emerging treatment approaches described above will have clinical utility. The emphasis in recently released guidelines on evidential rather than goal-oriented prescribing leads to a judgement of each class of agents on its own merit, and focuses treatment on selected patient groups at highest cardiovascular risk [64].

Acknowledgment The Figure was generated using Servier Medical Art, provided by Servier, licensed under a Creative Commons Attribution 3.0 unported license (available at http://www.servier.com/Powerpoint-image-bank).

Compliance with Ethics Guidelines

Conflict of Interest David Preiss reports participating on an advisory board for Sanofi (outside the submitted work); and involvement in the planning and/or conduct of current trials of lipid modifying agents sponsored by Amgen and Pfizer.

Chris J. Packard reports receiving grants and personal fees from Roche, personal fees from MSD and personal fees from AstraZeneca, outside the submitted work.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Baigent C, Blackwell L, Emberson J, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet. 2010;376(9753):1670–81.
2. Baigent C, Keech A, Kearney PM, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet. 2005;366(9493):1267–78.
3. Kannel WB, Dawber TR, KAGAN A, Revotskie N, Stokes III J. Factors of risk in the development of coronary heart disease–six year follow-up experience. The Framingham Study. Ann Intern Med. 1961;55:33–50.
4. Link E, Parish S, Armitage J, et al. SLCO1B1 variants and statin-induced myopathy–a genomewide study. N Engl J Med. 2008;359(8):789–99.
5. Sattar N, Preiss D, Murray HM, et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. Lancet. 2010;375(9716):735–42.
6. Preiss D, Seshasai SR, Welsh P, et al. Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy: a meta-analysis. JAMA. 2011;305(24):2556–64.
7. Jones PH, Davidson MH, Stein EA, et al. Comparison of the efficacy and safety of rosuvastatin versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR* Trial). Am J Cardiol. 2003;92(2):152–60.
8. Cuchel M, Bloedon LT, Szapary PO, et al. Inhibition of microsomal triglyceride transfer protein in familial hypercholesterolemia. N Engl J Med. 2007;356(2):148–56.
9. Samaha FF, McKenney J, Bloedon LT, Sasiela WJ, Rader DJ. Inhibition of microsomal triglyceride transfer protein alone or with ezetimibe in patients with moderate hypercholesterolemia. Nat Clin Pract Cardiovasc Med. 2008;5(8):497–505.
10. Cuchel M, Meagher EA, du Toit TH, et al. Efficacy and safety of a microsomal triglyceride transfer protein inhibitor in patients with homozygous familial hypercholesterolaemia: a single-arm, open-label, phase 3 study. Lancet. 2013;381(9860):40–6.
11. Kastelein JJ, Wedel MK, Baker BF, et al. Potent reduction of apolipoprotein B and low-density lipoprotein cholesterol by short-term administration of an antisense inhibitor of apolipoprotein B. Circulation. 2006;114(16):1729–35.
12. Akdim F, Stroes ES, Sijbrands EJ, et al. Efficacy and safety of mipomersen, an antisense inhibitor of apolipoprotein B, in hypercholesterolemic subjects receiving stable statin therapy. J Am Coll Cardiol. 2010;55(15):1611–8.
13. Akdim F, Tribble DL, Flaim JD, et al. Efficacy of apolipoprotein B synthesis inhibition in subjects with mild-to-moderate hyperlipidaemia. Eur Heart J. 2011;32(21):2650–9.
14. McGowan MP, Tardif JC, Ceska R, et al. Randomized, placebo-controlled trial of mipomersen in patients with severe hypercholesterolemia receiving maximally tolerated lipid-lowering therapy. PLoS One. 2012;7(11):e49006.
15. Thomas GS, Cromwell WC, Ali S, Chin W, Flaim JD, Davidson M. Mipomersen, an Apolipoprotein B Synthesis Inhibitor, Reduces Atherogenic Lipoproteins in Patients with Severe Hypercholesterolemia at High Cardiovascular Risk: A Randomized, Double-Blind, Placebo-Controlled Trial. J Am Coll Cardiol 2013. doi:10.1016/j.jacc.2013.07.081.
16. Visser ME, Wagener G, Baker BF, et al. Mipomersen, an apolipoprotein B synthesis inhibitor, lowers low-density lipoprotein cholesterol in high-risk statin-intolerant patients: a randomized, double-blind, placebo-controlled trial. Eur Heart J. 2012;33(9):1142–9.
17. Raal FJ, Santos RD, Blom DJ, et al. Mipomersen, an apolipoprotein B synthesis inhibitor, for lowering of LDL cholesterol concentrations in patients with homozygous familial hypercholesterolaemia: a randomised, double-blind, placebo-controlled trial. Lancet. 2010;375(9719):998–1006.
18. Akdim F, Visser ME, Tribble DL, et al. Effect of mipomersen, an apolipoprotein B synthesis inhibitor, on low-density lipoprotein cholesterol in patients with familial hypercholesterolemia. Am J Cardiol. 2010;105(10):1413–9.
19. Stein EA, Dufour R, Gagne C, et al. Apolipoprotein B synthesis inhibition with mipomersen in heterozygous familial hypercholesterolemia: results of a randomized, double-blind, placebo-controlled trial to assess efficacy and safety as add-on therapy in patients with coronary artery disease. Circulation. 2012;126(19):2283–92.
20. Neely RD, Bassendine MF. Antisense technology to lower LDL cholesterol. Lancet. 2010;375(9719):959–61.

21. Abifadel M, Varret M, Rabes JP, et al. Mutations in PCSK9 cause autosomal dominant hypercholesterolemia. Nat Genet. 2003;34(2):154–6.
22. Cohen J, Pertsemlidis A, Kotowski IK, Graham R, Garcia CK, Hobbs HH. Low LDL cholesterol in individuals of African descent resulting from frequent nonsense mutations in PCSK9. Nat Genet. 2005;37(2):161–5.
23. Kotowski IK, Pertsemlidis A, Luke A, et al. A spectrum of PCSK9 alleles contributes to plasma levels of low-density lipoprotein cholesterol. Am J Hum Genet. 2006;78(3):410–22.
24. Lambert G, Sjouke B, Choque B, Kastelein JJ, Hovingh GK. The PCSK9 decade. J Lipid Res. 2012;53(12):2515–24.
25.•• Stein EA, Mellis S, Yancopoulos GD, et al. Effect of a monoclonal antibody to PCSK9 on LDL cholesterol. N Engl J Med. 2012;366(12):1108–18. *Of the various novel LDL-cholesterol lowering agents, inhibitors of PCSK9 appear the most promising. This trial contains the first published data describing the clinical utility of PCSK9 inhibition with monoclonal antibodies*.
26. McKenney JM, Koren MJ, Kereiakes DJ, Hanotin C, Ferrand AC, Stein EA. Safety and efficacy of a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 serine protease, SAR236553/REGN727, in patients with primary hypercholesterolemia receiving ongoing stable atorvastatin therapy. J Am Coll Cardiol. 2012;59(25):2344–53.
27. Stein EA, Gipe D, Bergeron J, et al. Effect of a monoclonal antibody to PCSK9, REGN727/SAR236553, to reduce low-density lipoprotein cholesterol in patients with heterozygous familial hypercholesterolaemia on stable statin dose with or without ezetimibe therapy: a phase 2 randomised controlled trial. Lancet. 2012;380(9836):29–36.
28. Roth EM, McKenney JM, Hanotin C, Asset G, Stein EA. Atorvastatin with or without an antibody to PCSK9 in primary hypercholesterolemia. N Engl J Med. 2012;367(20):1891–900.
29. Raal F, Scott R, Somaratne R, et al. Low-density lipoprotein cholesterol-lowering effects of AMG 145, a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 serine protease in patients with heterozygous familial hypercholesterolemia: the Reduction of LDL-C with PCSK9 Inhibition in Heterozygous Familial Hypercholesterolemia Disorder (RUTHERFORD) randomized trial. Circulation. 2012;126(20):2408–17.
30. Sullivan D, Olsson AG, Scott R, et al. Effect of a monoclonal antibody to PCSK9 on low-density lipoprotein cholesterol levels in statin-intolerant patients: the GAUSS randomized trial. JAMA. 2012;308(23):2497–506.
31. Koren MJ, Scott R, Kim JB, et al. Efficacy, safety, and tolerability of a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 as monotherapy in patients with hypercholesterolaemia (MENDEL): a randomised, double-blind, placebo-controlled, phase 2 study. Lancet. 2012;380(9858):1995–2006.
32. Giugliano RP, Desai NR, Kohli P, et al. Efficacy, safety, and tolerability of a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 in combination with a statin in patients with hypercholesterolaemia (LAPLACE-TIMI 57): a randomised, placebo-controlled, dose-ranging, phase 2 study. Lancet. 2012;380(9858):2007–17.
33.• Schwartz GG, Olsson AG, Abt M, et al. Effects of dalcetrapib in patients with a recent acute coronary syndrome. N Engl J Med. 2012;367(22):2089–99. *Dalcetrapib raises HDL-cholesterol effectively but has little effect on LDL-cholesterol and the results from this trial therefore represented an important examination of the 'HDL hypothesis'. Dalcetrapib had no effect on the risk of cardiovascular events*.
34. Barter PJ, Caulfield M, Eriksson M, et al. Effects of torcetrapib in patients at high risk for coronary events. N Engl J Med. 2007;357(21):2109–22.
35. Nicholls SJ, Brewer HB, Kastelein JJ, et al. Effects of the CETP inhibitor evacetrapib administered as monotherapy or in combination with statins on HDL and LDL cholesterol: a randomized controlled trial. JAMA. 2011;306(19):2099–109.
36. Cannon CP, Shah S, Dansky HM, et al. Safety of anacetrapib in patients with or at high risk for coronary heart disease. N Engl J Med. 2010;363(25):2406–15.
37. Di AE, Sarwar N, Perry P, et al. Major lipids, apolipoproteins, and risk of vascular disease. JAMA. 2009;302(18):1993–2000.
38. Frick MH, Elo O, Haapa K, et al. Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia. Safety of treatment, changes in risk factors, and incidence of coronary heart disease. N Engl J Med. 1987;317(20):1237–45.
39. Rubins HB, Robins SJ, Collins D, et al. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group N. Engl J Med. 1999;341(6):410–8.
40. Ginsberg HN, Elam MB, Lovato LC, et al. Effects of combination lipid therapy in type 2 diabetes mellitus. N Engl J Med. 2010;362(17):1563–74.
41. Keech A, Simes RJ, Barter P, et al. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. Lancet. 2005;366(9500):1849–61.
42.• Boden WE, Probstfield JL, Anderson T, et al. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. N Engl J Med. 2011;365(24):2255–67. *While niacin demonstrated some benefit in the Coronary Drug Project, evidence of benefit when added to a statin was sought in the AIM-HIGH trial. No benefit was demonstrated and similar results have been released from the larger HPS2-THRIVE study which also revealed an increase in many side-effects*.
43. University of Oxford CTSU. HPS2-THRIVE results. http://www.thrivestudy.org/, 2013.
44. Toth PP, Barter PJ, Rosenson RS, et al. High-density lipoproteins: a consensus statement from the National Lipid Association. J Clin Lipidol. 2013;7(5):484–525.
45. Ridker PM, Pare G, Parker AN, Zee RY, Miletich JP, Chasman DI. Polymorphism in the CETP gene region, HDL cholesterol, and risk of future myocardial infarction: Genomewide analysis among 18 245 initially healthy women from the Women's Genome Health Study. Circ Cardiovasc Genet. 2009;2(1):26–33.
46. Keech AC, Mitchell P, Summanen PA, et al. Effect of fenofibrate on the need for laser treatment for diabetic retinopathy (FIELD study): a randomised controlled trial. Lancet. 2007;370(9600):1687–97.
47. Chew EY, Ambrosius WT, Davis MD, et al. Effects of medical therapies on retinopathy progression in type 2 diabetes. N Engl J Med. 2010;363(3):233–44.
48. Chen Y, Hu Y, Lin M, et al. Therapeutic effects of PPARalpha agonists on diabetic retinopathy in type 1 diabetes models. Diabetes. 2013;62(1):261–72.
49. Lincoff AM, Tardif JC, Neal B, et al. Evaluation of the dual peroxisome proliferator-activated receptor alpha/gamma agonist aleglitazar to reduce cardiovascular events in patients with acute coronary syndrome and type 2 diabetes mellitus: rationale and design of the AleCardio trial. Am Heart J. 2013;166(3):429–34.
50. Kahn SE, Zinman B, Lachin JM, et al. Rosiglitazone-associated fractures in type 2 diabetes: an Analysis from A Diabetes Outcome Progression Trial (ADOPT). Diabetes Care. 2008;31(5):845–51.
51. Dormandy JA, Charbonnel B, Eckland DJ, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. Lancet. 2005;366(9493):1279–89.

52.•• Sarwar N, Sandhu MS, Ricketts SL, et al. Triglyceride-mediated pathways and coronary disease: collaborative analysis of 101 studies. Lancet. 2010;375(9726):1634–9. *In this large analysis, the authors studied genetic polymorphisms of the APOA5 gene to examine the possibility of a causal link between triglyceride-mediated pathways and cardiovascular disease. Triglyceride concentrations were 16% higher and coronary heart disease risk was 18% higher per C allele.*
53. Preiss D, Tikkanen MJ, Welsh P, et al. Lipid-modifying therapies and risk of pancreatitis: a meta-analysis. JAMA. 2012;308(8):804–11.
54. Sacks FM, Zheng C, Cohn JS. Complexities of plasma apolipoprotein C-III metabolism. J Lipid Res. 2011;52(6):1067–70.
55. Pollin TI, Damcott CM, Shen H, et al. A null mutation in human APOC3 confers a favorable plasma lipid profile and apparent cardioprotection. Science. 2008;322(5908):1702–5.
56. Graham MJ, Lee RG, Bell III TA, et al. Antisense oligonucleotide inhibition of apolipoprotein C-III reduces plasma triglycerides in rodents, nonhuman primates, and humans. Circ Res. 2013;112(11):1479–90.
57. Goldberg IJ, Merkel M. Lipoprotein lipase: physiology, biochemistry, and molecular biology. Front Biosci. 2001;6:D388–405.
58. Gaudet D. de WJ, Tremblay K et al. Review of the clinical development of alipogene tiparvovec gene therapy for lipoprotein lipase deficiency. Atheroscler Suppl. 2010;11(1):55–60.
59. Gaudet D, Methot J, Dery S, et al. Efficacy and long-term safety of alipogene tiparvovec (AAV1-LPLS447X) gene therapy for lipoprotein lipase deficiency: an open-label trial. Gene Ther. 2013;20(4):361–9.
60. Erqou S, Kaptoge S, Perry PL, et al. Lipoprotein(a) concentration and the risk of coronary heart disease, stroke, and nonvascular mortality. JAMA. 2009;302(4):412–23.
61. Clarke R, Peden JF, Hopewell JC, et al. Genetic variants associated with Lp(a) lipoprotein level and coronary disease. N Engl J Med. 2009;361(26):2518–28.
62. Trieu VN, McConathy WJ. A two-step model for lipoprotein(a) formation. J Biol Chem. 1995;270(26):15471–4.
63. Cannon CP, Giugliano RP, Blazing MA, et al. Rationale and design of IMPROVE-IT (IMProved Reduction of Outcomes: Vytorin Efficacy International Trial): comparison of ezetimbe/simvastatin versus simvastatin monotherapy on cardiovascular outcomes in patients with acute coronary syndromes. Am Heart J. 2008;156(5):826–32.
64. Stone NJ, Robinson J, Lichtenstein AH et al. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2013.