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Low-density lipoprotein cholesterol lowering therapies: what is on the horizon?

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LDL-C lowering therapies: What is on the horizon?

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Running head: Novel low density lipoprotein (LDL-C) therapies

Key words: low density lipoprotein (LDL-C), apolipoprotein B, cardiovascular disease, anti-sense oligonucleotides focused on apolipoprotein B, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, microsomal triglyceride transfer protein inhibitors

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Abstract:

Elevated low density lipoprotein cholesterol (LDL-C) levels are associated with an increased risk for cardiovascular disease (CVD). Statins have been the cornerstone of lipid therapy to lower LDL-C for the last two decades, but despite significant clinical efficacy in a majority of patients, a large residual risk remains for the development of initial or recurrent atherosclerotic cardiovascular disease. In addition, owing to side effects, a significant percentage of patients cannot tolerate any statin dose or a high enough statin dose. Thus, novel therapeutic agents are currently being developed to lower LDL-C levels further. This review will highlight these novel therapeutic agents including anti-sense oligonucleotides focused on apolipoprotein B, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors and microsomal triglyceride transfer protein inhibitors. For each therapeutic class, an overview of mechanism of action, pharmacokinetic data, and efficacy/safety evidence will be discussed.

Introduction:

Cardiovascular disease is the leading cause of death worldwide. There is compelling evidence from population-based studies and clinical trials that low density lipoprotein cholesterol (LDL-C) reduction is an effective strategy to reduce coronary heart disease (CHD) events andslow CHD (1). Statins are powerful LDL-C lowering agents that represent the therapy of choice for primary and secondary prevention of cardiovascular events (2, 3). Yet a significant proportion of patients remain at high risk. Some patients require larger reductions of LDL-C due to high baseline levels, such as those with familial hypercholesterolemia. Others develop adverse events and stop or discontinue current therapies (4-6). These issues demonstrate the need for additive or replacement therapy to statins, which work by inhibiting the first enzymatic reaction of endogenous cholesterol synthesis. This review will focus on new agents targeting other molecular pathways that can lower LDL-C.

Transport and fate of body cholesterol

Cholesterol originating from either de novo synthesis or from the diet is transported in blood by apolipoprotein (apo) B and apo A containing lipoproteins (Fig. 1). Apo A are associated with high density lipoproteins

(HDL). Lipid poor HDL are produced by the liver, the intestine or derived from chylomicrons. They take up free cholesterol from peripheral organs and macrophages and deliver it to the liver where it is excreted into the bile, an anti-atherogenic pathway known as the reverse cholesterol transport (7). Apo B and apo A1-containing lipoprotein pathways are interconnected by a set of enzyme activities that enable lipid exchange between particles. Cholesterol from nascent HDL is trans-esterified with phospholipid acyl chains by the enzyme lecithin:cholesterol acyltransferase (LCAT) into cholesteryl esters. Cholesteryl esters can be transferred to apo B containing lipoproteins such as very low-density lipoproteins (VLDL) or intermediary low density lipoproteins (IDL) in exchange for triglycerides (TGs) by the cholesteryl ester transfer protein (CETP) (8). Plasma phospholipid transfer protein (PLTP) is also associated with HDL and transfers phospholipids between lipoproteins, modulating their size and composition (8).

This review will focus on apoB-containing lipoproteins, represented by TG rich intestinal chylomicrons, and hepatic VLDL or VLDL-derived IDL and LDL (Fig. 1). Chylomicrons and VLDL bring fuel to peripheral organs as fatty acids and are progressively depleted of TGs by the action of lipases

(9). Thus, chylomicrons are converted into remnants and VLDL into IDL and LDL, enriched in cholesterol. LDL is removed too slowly from the circulation which allows it to exert proatherogenic properties; in particular it can be oxidized. Oxidized LDL is a source of cholesterol accumulation and foam cell formation in the artery wall.

Anti-sense oligonucleotides directed at apolipoprotein B

Disease states are often characterized by an abnormal protein or enzyme. There are many etiologies for hypercholesterolemia, one of which is an increase in the activity of the 3-hydroxy-3-methylglutaryl coenzyme A reductase enzyme causing increased cholesterol biosynthesis (2). As their name implies, the 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins), inhibit the rate limiting
enzyme for cholesterol biosynthesis. However, drugs created through antisense technology act differently from traditional enzyme or protein-targeting drugs. In antisense technology, the target gene is transcribed normally from DNA to mRNA, but the mRNA is then intercepted by an antisense oligonucleotide with which it undergoes a Watson-Crick type hybridization reaction so that the mRNA can no longer be translated into a protein (10). The antisense complex becomes a target for RNase H, an

enzyme that cleaves and destroys the mRNA-antisense oligonucleotide hybrid.

Mipomersen is a polynucleotide of 20 bases that is complementary in sequence to a segment of human Apo B-100 mRNA. It specifically binds to Apo B-100 mRNA, blocking the translation of the gene product (10-12). The inhibition of production of apo-B100 in the liver decreases levels of all apo B-containing lipoproteins, including very low-density lipoprotein (VLDL), LDL, and lipoprotein (a). Mipomersen is catabolized by endonucleases and exonucleases, which are ubiquitously expressed in all cells and tissues, and is excreted in the urine (13,14). It has no dependency on cytochrome P450 metabolism; consequently, there is little potential for interaction with statins, ezetimibe, bile acid binding resins, or other lipid lowering medications with which it might be used in combination.

Four phase 3 trials of mipomersen have been completed in the following patient populations: [1] homozygous FH, which occurs in 1 of 1,000,000 people (15); [2] heterozygous FH in patients with coronary artery disease (CAD) (16); [3] severe hypercholesterolemia [as defined later in this

section] (17); and [4] hypercholesterolemia in patients at high risk for CAD [as defined later in this section] (18).

These phase 3 trials were randomized, double blind, placebo-controlled, multicenter studies and in each the patients were already on stable doses of their maximally tolerated lipid-lowering therapies (15-18). Patients were administered weekly subcutaneous injections of placebo or 200 mg mipomersen for 26 weeks and were given the option to self-administer the drug. The primary efficacy end point was the percent change in LDL-C from baseline to week 28 (2 weeks after the last dose), and secondary end points included percent changes in apo B, total cholesterol, non-HDL-C, TG, lipoprotein (a) [Lp(a)], VLDL, Apo A1, HDL-C, and the LDL-C/HDL-C ratio.

Patients with homozygous FH and those with severe hypercholesterolemia achieved an average LDL-C reduction (above that achieved by maximum tolerated lipid-lowering therapies) of >100 mg/dL, representing 25% and 36% LDL-C reductions, respectively. Patients with heterozygous FH and CAD and those with hypercholesterolemia

and high risk of CAD achieved an average LDL-C reduction of 28% and 37% from baseline LDL-C respectively. Typically, the maximal steady-state LDL-C reduction was achieved at 12-16 weeks.

The most common adverse events leading to discontinuation with mipomersen treatment were mild-to-moderate injection site reactions and flu-like symptoms. Mipomersen has typically been shown to modestly increase hepatic fat (i.e., steatosis) in the range of 6%-12% (16,18,19). However, this effect was reversible after cessation of therapy and long-term extension studies have shown that in some patient's hepatic fat decreases over time with mipomersen use (20). Bilirubin indices, serum albumin and prothrombin times were not altered by mipomersen treatment, though 8% had an alanine aminotransferase level greater than three times the upper limit of normal on two consecutive occasions.

Mipomersen administration in conjunction with maximally tolerated statin therapy has shown great promise in phase III trials. The average LDL-C reduction exceeded 100mg/dl in patients with homozygous FH and severe hypercholesterolemia. An ongoing phase III clinical trial in Germany is evaluating the use of mipomersen in conjunction with LDL apheresis to

determine whether mipomersen will result in reduced apheresis time or frequency.

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors

The hepatic LDL receptor (LDLR) plays a central role in cholesterol homeostasis (21, 22). It is a large, complex protein with a binding domain for apo B. After apo B (as part of an apo B–containing lipoprotein) binds to LDLR, the receptor–apo B complex is internalized in a clarithrin-coated pit and enters the hepatocyte (23). Clarithrin then dissociates from LDLR, and the apo B particle undergoes lysosomal degradation, releasing cholesterol. The LDLR is recycled back to the surface of the hepatocyte, where it can again bind with apo B particles, enabling efficient clearance of LDL from the circulation. (Fig. 2)

PCSK9, a member of the proteinase K subfamily of subtilases, is a protease involved in regulating the level of circulating LDL-C through effects on LDLR. PCSK9 regulates the surface expression of LDLR by targeting them for lysosomal degradation. PCSK9 accelerates the

degradation of hepatic LDLR (24). Thus, sustained elevation of PCSK9 levels through gain of function variants would be associated with reductions in LDLR and increases in LDL-C. Conversely, inactivation of PCSK9 or reduction in PCSK9 levels would theoretically lead to reductions in LDL-C levels.

In the Atherosclerosis Risk in Communities Study (25), African Americans who had a loss-of-function PCSK9 mutation leading to 40-mg/dL lower LDL-C had a 90% reduction in coronary events in their middle years, from ages 40 to 55. White subjects who had another loss-of-function PCSK9 mutation, leading to 20-mg/dL lower LDL-C, had a 50% reduction in coronary events at the same ages.

Statins, bile acid sequestrants, and ezetimibe stimulate LDLR up regulation by decreasing the amount of cholesterol in the hepatocyte. This is a tightly regulated system. However, in a counter-regulatory action by the liver, statins also produce PCSK9 up-regulation (26). Thus, the potential reduction in LDL-C provided by some LDL-C–lowering drugs is limited by this compensatory increase in PCSK9.

The strategy of PCSK9 inhibition that has progressed farthest in clinical development is neutralization of PCSK9 with a selective monoclonal antibody. By neutralizing circulating PCSK9, monoclonal antibodies prevent PCSK9- mediated catabolism of LDLR, increase LDLR density on the surface of hepatocytes, and facilitate clearance of LDL and other atherogenic lipoproteins from the circulation (27).

Several monoclonal antibodies to PCSK9 are in clinical trial development. At the time of this publication, most of the published data has come from studies of REGN727/SAR236553 (REGN727**, Alirocumab**; Regeneron Pharmaceuticals, Inc. [Tarrytown, NY] and Sanofi-Aventis [Reston, VA]) and data from phase 3 trials of AMG 145**, Evolocumab** (Amgen, Washington, DC).

In the first phase 1 study of a PCSK9 monoclonal antibodies in humans, a group of healthy volunteers were administered either single-dose intravenous or subcutaneous REGN727 injections. In another phase 1 study, a group of patients with heterozygous familial hypercholesterolemia or non-familial hypercholesterolemia, who were following a modified diet, were administered multiple subcutaneous REGN727 injections on days 1,

29, and 43 (28). In these studies the administration of REGN727 led to profound effects on LDL-C concentration. Notably, a single dose in healthy volunteers led to 50%-70% reductions in LDL-C (Fig 3).

In a 12-week placebo-controlled study in which REGN727 was injected every 2 weeks (Q2W) or Q4W in patients with primary hypercholesterolemia (29), there was a 31% LDL-C reduction 2 weeks after the initial 50-mg dose that decreased further to a 40% change from baseline at 12 weeks (Fig 4). LDL-C levels after 12 weeks of 100- and 150-mg Q2W doses and 200- and 300-mg Q4W doses decreased by 64%, 72%, 43%, and 48%, respectively. These were the mean responses over time; however, the observed pattern was that upon injection of the PCSK9 monoclonal antibody there was a large decrease in LDL-C levels followed by a gradual rebound as the monoclonal antibodies were cleared from the circulation. In addition to reductions in LDL-C, TG decreased slightly (-8.4% with 300 mg), HDL-C increased (8.5% with 300 mg), and apo A1 levels increased at the greatest dose (4.2% with 300 mg). The incidence of adverse events was 45% in the group receiving placebo, 60% in the 50-mg Q2W, 65% in the 100-mg Q2W, 61% in the 150-mg Q2W, 67% in the 200-mg Q4W, and 47% in the 300-mg Q4W dosing groups (29). There were no

instances of elevated liver enzymes greater than 3 times the upper limit of normal (>3x ULN) or creatine kinase (>10x ULN) associated with administration of the PCSK9 antibody. Less than 1% of subjects reported muscle pain or weakness. Injection-site reactions occurred in the PCSK9 antibody groups but were generally mild and non-progressive.

A placebo-controlled statin combination study investigated the effects of 150 mg of REGN727 Q2W for 8 weeks plus 80 mg/d atorvastatin or a maintenance dose of 10 mg/d atorvastatin (Fig. 5). In the group receiving atorvastatin 80 mg/d plus placebo, there was a decrease in LDL-C of 17% compared with a 73% reduction in the group receiving atorvastatin 80 mg/d plus REGN727. With the REGN727 plus atorvastatin 10 mg/d combination, LDL-C was decreased by 66%.

REGN727 also significantly lowered apo B, non–HDL-C, Lp (a) and TG. Safety and tolerability results for the combination of atorvastatin plus REGN727 were also favorable (30).Three patients had elevated liver enzymes and none had significantly increased creatine kinase. One of the patients enrolled in the study developed leukocytoclastic vasculitis that resolved after treatment with prednisone. Injection site skin reactions were also rare and mild.

The Durable Effect of PCSK9 Antibody Compared with Placebo Study (DESCARTES) found that evolocumab administered monthly, either alone or in combination with a statin with or without ezetimibe (EZE), for 52 weeks lowered LDL-C by 57 percent in subjects with a range of cardiovascular risk (31). Based on screening LDL-C and NCEP-ATPIII risk, 901 subjects were randomized to one of four background lipid-lowering therapies (diet alone, atorvastatin 10 mg/d, atorvastatin 80 mg/d, atorvastatin 80 mg/d with EZE 10 mg/d). Subjects with LDL-C ≥ 75 mg/dL following lipid therapy lead-in (median baseline range 94–113 mg/dL) were randomized 2:1 to subcutaneous monthly evolocumab 420 mg or placebo. Results showed evolocumab reduced least squares mean (95 percent CI) LDL-C by 57 percent compared with placebo (P < 0.001) but responses varied, from 49 percent to 62 percent, among background therapies. LDL-C reduction at week 12 and week 52 were comparable (Fig 6).

Another phase 3 trial, MENDEL-2, evaluated evolocumab as a monotherapy in 614 randomized patients with heterozygous familial hypercholesterolemia (HeFH) not taking statins (32). Evolocumab biweekly (140 mg) or monthly (420 mg) rapidly and markedly lowered

LDL-C over 12 weeks compared with placebo or ezetimibe, reducing LDL-C from baseline, on average, by 55 to 57 percent more than placebo and 38 to 40 percent greater than ezetimibe ($P < 0.001$ for all comparisons).

A third clinical trial, RUTHERFORD-2 investigated the effect of PCSK9 inhibition with evolocumab on LDL-C levels in HeFH patients . The 12-week, multi-center trial randomized 331 patients 2:2:1:1 to evolocumab 140 mg subcutaneous biweekly: evolocumab 420 mg subcutaneous monthly: placebo subcutaneous biweekly: placebo subcutaneous monthly (33). Results showed that evolocumab administered either biweekly or monthly yielded significant reductions in LDL-C in HeFH patients on statins with or without ezetimibe. The mean reduction of LDL-C at week 12 was 61 percent in the 140 mg biweekly and 56 percent in the 420 mg monthly evolocumab dose groups, respectively. The mean reduction of LDL-C at the mean of weeks 10 and 12 was 61 percent in the 140 mg biweekly and 63 percent in the 420 mg monthly evolocumab dose groups, respectively. Thus, evolocumab 140 mg biweekly and 420 mg monthly dosing regimens were clinically equivalent.

Interestingly, a recent pooled analysis of data from 1,359 patients in four phase II trials assessed the effects of AMG145 (evolocumab) on Lp(a) levels (34), the relationships between Lp(a) and lowering of LDL-C and apo B, and finally the influence of background statin therapy. AMG145 treatment for 12 weeks resulted in significant mean dose-related reductions in Lp(a) of 29.5 % and 24.5 % with 140 mg and 420 mg every two and four weeks, respectively. Lipoprotein (a) reductions were significantly correlated with percentage reductions in LDL-C and apo B. Moreover, a trend toward a major reduction was observed in patients treated in combination with statins.

Finally, the TESLA study (Trial Evaluating PCSK9 Antibody in Subjects With LDL Receptor Abnormalities) was designed to evaluate the safety, tolerability and efficacy of AMG 145 in a particular setting of subjects with homozygous familial hypercholesterolemia (HoFH) in which it was unknown if PCSK9 inhibition would work (35). Eight HoFH patients with null or defective mutations in the LDL-receptor were recruited and treated with AMG145 (420 mg every four weeks for ⩾12 weeks, followed by every two weeks for an additional 12 weeks) .

After 12 weeks treatment, a 16.5 % LDL-C mean reduction from baseline was observed in the treated patients. However the patients who experienced significant reduction of LDL-C (up to 43.6 % from baseline) were carriers of defective mutations in the LDLR gene, while no significant changes from baseline were observed in HoFH patients carriers of null mutations (receptor negative patients).

A quarter century after approval of the first statin in 1987, reduction of LDL-C remains the best-validated goal of treatment in atherosclerosis. PCSK9 is poised to be a promising molecular target to reduce levels of LDL-C and other atherogenic lipoproteins below levels achievable with statins. The monoclonal antibody approach is expected to meet an important clinical need for LDL-C lowering in patients with statin intolerance, those who cannot achieve an adequate LDL-C level with existing therapy, refractory hypercholesterolemia, and those who may otherwise require LDL apheresis. It remains to be seen whether PCSK9 inhibition will assume a therapeutic role in atherosclerosis and this will depend upon the results of large cardiovascular outcomes trials.

Microsomal transfer protein inhibitors

The microsomal triglyceride transfer protein (MTP) is involved in the assembly and secretion of apo B-containing lipoproteins in the liver and intestine (36). Mutations in the gene encoding for MTP are the molecular basis of abetalipoproteinemia, a rare autosomal recessive disorder characterized by the absence of circulating apo B-containing lipoproteins of both hepatic and intestinal origins (37). The most prominent symptoms of abetalipoproteinemia are due to impaired absorption of dietary fat and predisposition to deficiency of fat-soluble vitamins, with progressive retinal and spinocerebellar degeneration caused by vitamin E deficiency. Following the discovery of the molecular cause of abetalipoprotein in the early 1990s (38, 39), MTP became a potential therapeutic target for the treatment of both hypercholesterolemia, as well as chylomicronemia.

MTP is responsible for transferring neutral lipids (mainly triglycerides) and phospholipids onto the assembling chylomicron and VLDL particles in the intestine and the liver, respectively (40, 41). In the absence of functional MTP, as seen in the condition of abetalipoproteinemia, apo B is not adequately lipidated in the endoplasmic reticulum and is targeted for proteosomal degradation (42). As a result, chylomicrons and VLDL are not effectively assembled or secreted into the circulation, accounting for the

absent apo B-containing lipoproteins in plasma. The discovery of the molecular basis of abetalipoproteinemia led directly to the concept that pharmacologic inhibition of MTP could be a strategy to reduce chylomicrons and LDL-C.

The only systemic MTP inhibitor that has continued to be developed beyond phase 2 clinical trials is lomitapide (formally BMS-201038 and AEGR-733). In a phase 2 double-blind placebo-controlled trial in moderately hypercholesterolemic subjects, lomitapide was dose-titrated and administered alone or in combination with ezetimibe (43). Lomitapide alone significantly reduced LDL-C and apo B (30 and 24%, respectively at 10 mg/day); combined therapy with ezetimibe was associated with a larger LDL-C decrease (46% at 10 mg/day of both lomitapide and ezetimibe). However, variable gastrointestinal side effects, transaminase elevations and hepatic fat increases were noted in this study.

Lomitapide was developed, in part, to treat homozygous familial hypercholesterolemia (hoFH), an autosomal dominant disorder due to impaired function of the LDLR. HoFH is characterized by markedly elevated LDL-C, often greater than 500 mg/dl, tendon xanthomas and markedly

premature and progressive atherosclerosis. Because of the impaired functionality of the LDLR, hoFH patients respond inadequately to conventional drug therapies that work through LDLR upregulation (44-47). A proof-of-concept study in six hoFH patients treated with lomitapide given as monotherapy in a dose-escalation regimen showed that doses of 0.3 and 1 mg/kg daily resulted in significant decreases in LDL-C, apo B and triglycerides, which at the higher dose were decreased by 51, 56, and 65%, respectively (48). The reduction in LDL-C levels was accompanied by a decrease in LDL-apo B production confirming that the mechanism by which MTP inhibition decreases LDL-C levels is by reducing the hepatic secretion of apoB-containing lipoproteins.

The magnitude of LDL-C reduction with lomitapide in hoFH was confirmed in a recently published multicenter phase III study in hoFH patients, in which lomitapide was dose-titrated up to a maximum of 60 mg/day on top of standard of care, including LDL apheresis (49). During the first 26 weeks (efficacy phase), lomitapide was gradually escalated and concomitant therapy remained unchanged. The median dose of lomitapide at the end of the efficacy phase was 40 mg/day. LDL-C, apo B and triglycerides were decreased by 50, 49 and 45%, respectively (Fig 7), at week 26 as

compared to baseline, and remained significantly reduced by 38, 43 and 31% at the end of the study, despite the changes in concomitant treatment that were allowed after week 26 (49). This trial confirmed that the efficacy of lomitapide is additive to that of other lipid-lowering treatments, including LDL apheresis, and is stable over time. The combined efficacy on LDL-C reduction in the phase III study allowed six patients undergoing apheresis to either stop or decrease the frequency of apheresis treatments.

In addition to a reduction in other apo B-containing lipoprotein parameters, lomitapide treatment was associated with a 15% reduction in Lp(a). The mechanism of this effect is not known, but it is interesting to note that mipomersen, which also reduces LDL-C levels via a decrease in production, decreases Lp(a) as well (15).

As expected, based on its mechanism, MTP inhibition with lomitapide is associated with the presence of gastrointestinal adverse events, including nausea, flatulence and diarrhea. Gastrointestinal adverse events were the most common reason for failure to tolerate a higher dose of lomitapide, causing three subjects to discontinue the study. Interestingly, these symptoms can be partially or completely controlled with a gradual dose-

escalation regimen, as well as adherence to a low-fat diet and dosing at times other than at meals (48, 49).

Based on its mechanism, MTP inhibition is also associated with an increase in liver fat content, which has historically been the major issue with this class of drugs. In the phase 2 study of lomitapide in hoFH patients, hepatic fat was measured by nuclear magnetic resonance spectroscopy at baseline and at the end of every 4-week dose escalation: in two of the six enrolled subjects, hepatic fat at the end of treatment was minimally increased (< 10%); in two others, hepatic fat was increased to 18–24%; and in the last two subjects, hepatic fat was increased more than 30% (48). Importantly, liver fat content and transaminase elevations were reversible with suspension of the drug (48).

During the phase 3 study in hoFH patients treated with lomitapide, liver fat content increased from1% at baseline to 8.6% at the end of the efficacy phase (week 26) during which the dose was titrated up to a maximum of 60 mg/day. Hepatic fat content then stabilized at this level for the rest of the study (8.3% at week 78). The changes in hepatic fat content were negatively correlated with the change in LDL-C levels (49). Approximately

one-third of the patients experienced an increase in alanine aminotranferase more than three times the upper limit of normal, and this was more common in subjects with greater increases in hepatic fat. Transaminase elevations were, however, generally transient and manageable with temporary dose reduction (49).

Lomitapide was approved in December 2012 for the treatment of hoFH. The 50 % reductions in LDL-C were considered to provide benefit that outweighed the increase in hepatic fat. Because of the risk of liver toxicity, lomitapide is available only through a restricted program called the JUXTAPID Risk Evaluation and Mitigation Strategy Program, which will require certification of all health care providers who prescribe it and pharmacies that dispense it. Combination with cytochrome P450 3A4 (CYP3A4) inhibitors increases exposure to lomitapide. Thus, lomitapide should not be used with strong and moderate CYP3A4 inhibitors, and dosage limitation (not exceeding 30 mg/d) is also required when administering concomitantly with weak CYP3A4 inhibitors.

CONCLUSIONS:

It has been close to 3 decades (IS THIS CORRECT???) since lovastatin (Mevacor) was approved to lower LDL-C. Since that time, statins have been shown to significantly reduce all forms of atherosclerotic disease, especially CHD and stroke. **But despite significant clinical efficacy in a majority of patients, a large residual risk remains for the development of initial or recurrent atherosclerotic cardiovascular disease. In addition, owing to side effects, a significant percentage of patients cannot tolerate any statin dose or a high enough statin dose. Clinical practice guidelines from the American Heart Association and American College of Cardiology (2) recommend at least a moderate to high intensity statin therapy for secondary prevention. There remains a large number of patients who are statin averse for whom there are limited alternatives for achieving significant LDL-C reductions (5).**

Thus, these newer classes of LDL-C lowering agents may hopefully fill an important clinical need for patients with statin intolerance, patients with high residual risk despite statin therapy, provide additive therapy in addition to statin therapy for patients with refractory hypercholesterolemia, and those who may otherwise require LDL apheresis.

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FIGURE LEGENDS

1. Figure 1: Overview of lipoprotein metabolism in humans.

2. Figure 2: Mechanism of PCSK9 inhibition with monoclonal antibodies. Reprinted with permission from Lambert et al.

3. Figure 3: Percent changes in LDL-C after increasing single doses of monoclonal antibody for PCSK9 (SAR236553/REGN 727) among healthy volunteers. Reprinted with permission from Stein et al.

4. Figure 4: Percent changes from baseline in LDL-C after 50-, 100-, 150-, 200-, and 300-mg doses of PCSK9 monoclonal antibody (SAR236553/REGN727) every 2 weeks for 12 weeks in patients with primary hypercholesterolemia. Reprinted with permission from McKenney et al.

5. Figure 5: Percent changes from baseline in LDL-C after 150 mg PCSK9 monoclonal antibody (SAR236553/REGN727) plus atorvastatin 10 or 80 mg/d for 8 weeks in patients with primary hypercholesterolemia. Reprinted with permission from Roth et al.

6. Figure 6: Percent reduction from baseline in LDL-C in the Evolocumab group as compared with the placebo group at weeks 12 and 52. Reprinted with permission from Blom et al.

7. Figure 7: Mean percent changes in LDL cholesterol, total cholesterol, and Apo B levels from baseline to week 26 (end of efficacy phase) in phase 3 homozygous FH trial. Data available at each time point is

expressed as mean (SD). Reprinted with permission from Cuchel & Meagher et al.

Figure 1

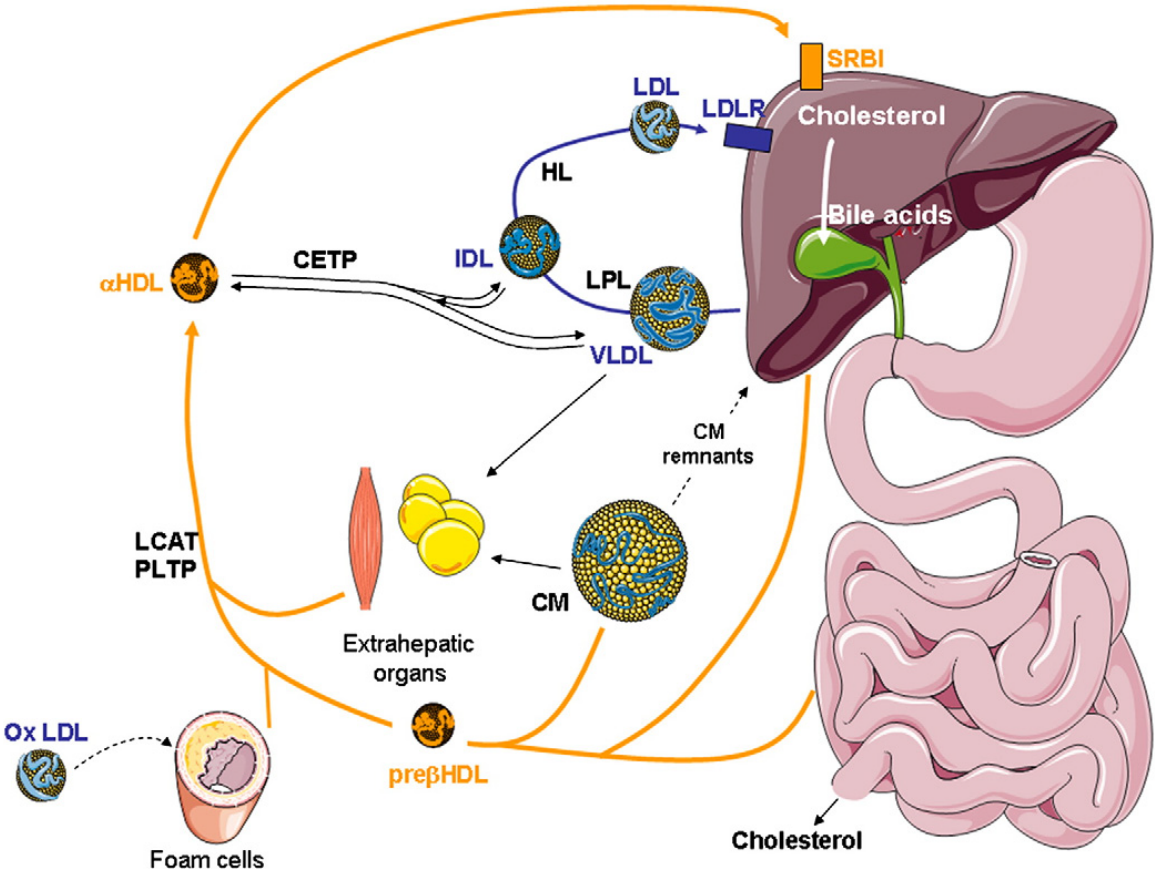

SRBI
LDL
LDLR
Cholesterol
HL
Bile acids
αHDL
CETP
IDL
LPL
VLDL
CM
remnants
LCAT
PLTP
Extrahepatic
organs
Ox LDL
preβHDL
Foam cells
Cholesterol

Figure 2

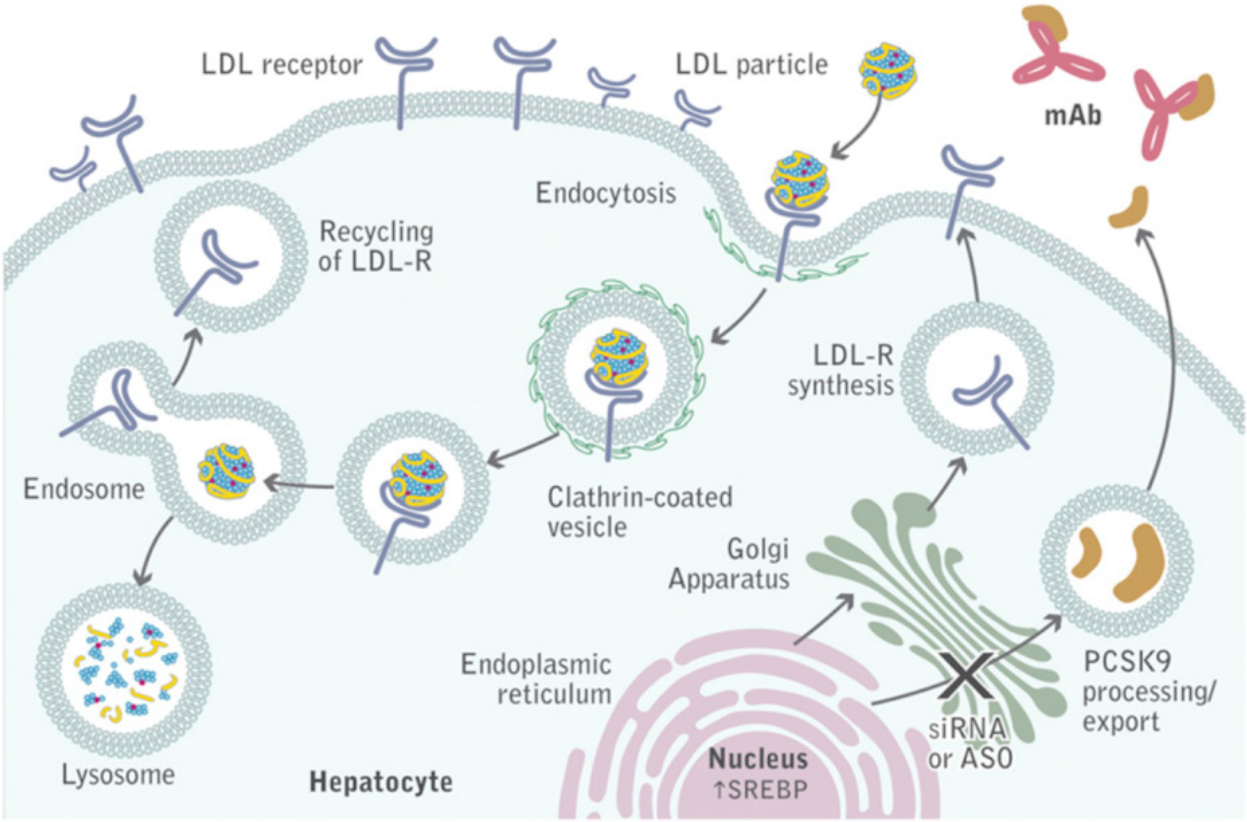
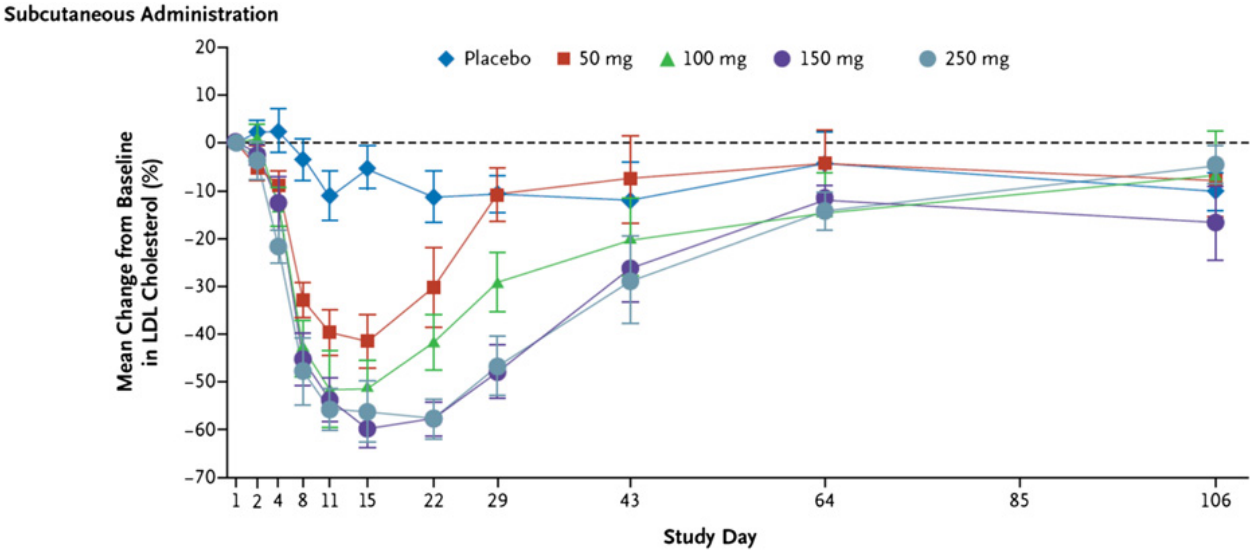

LDL receptor
LDL particle
mAb
Endocytosis
Recycling
of LDL-R
LDL-R
synthesis
Endosome
Clathrin-coated
vesicle
Golgi
Apparatus
Endoplasmic
reticulum
PCSK9
processing/
export
siRNA
or ASO
Nucleus
↑SREBP
Lysosome
Hepatocyte

Figure 3



No. at Risk

Placebo	8	8	8	8	8	8	8	8	7	7	7
50 mg	6	6	6	6	6	6	6	6	5	6	5
100 mg	6	6	6	6	5	6	6	6	5	6	6
150 mg	6	6	5	5	5	5	5	5	5	4	5
250 mg	6	6	6	6	6	6	6	6	6	6	6

Figure 4

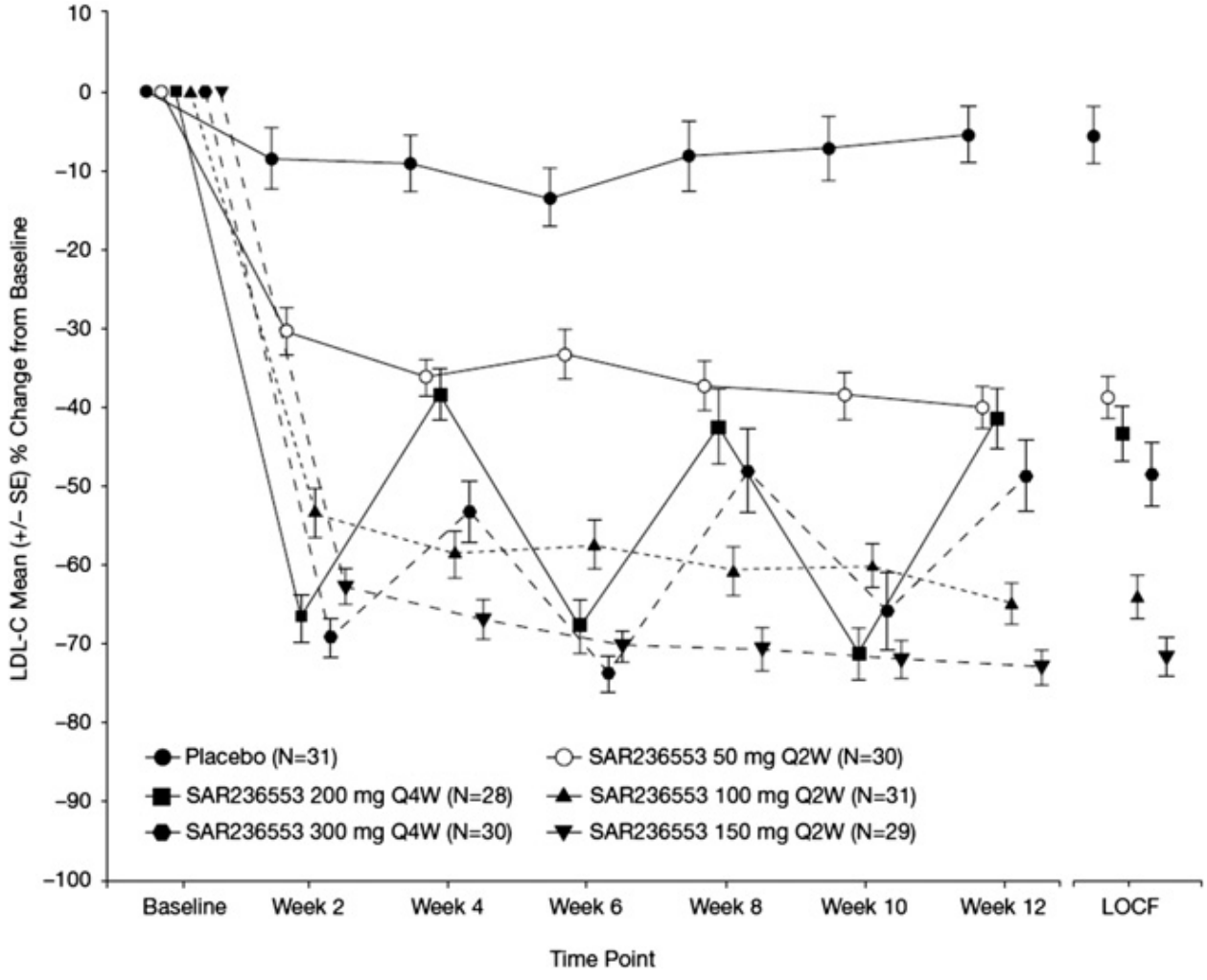

LDL-C Mean (+/− SE) % Change from Baseline
10
0
−10
−20
−30
−40
−50
−60
−70
−80
−90
−100
Placebo (N=31)
SAR236553 50 mg Q2W (N=30)
SAR236553 200 mg Q4W (N=28)
SAR236553 100 mg Q2W (N=31)
SAR236553 300 mg Q4W (N=30)
SAR236553 150 mg Q2W (N=29)
Baseline
Week 2
Week 4
Week 6
Week 8
Week 10
Week 12
LOCF
Time Point

Figure 5

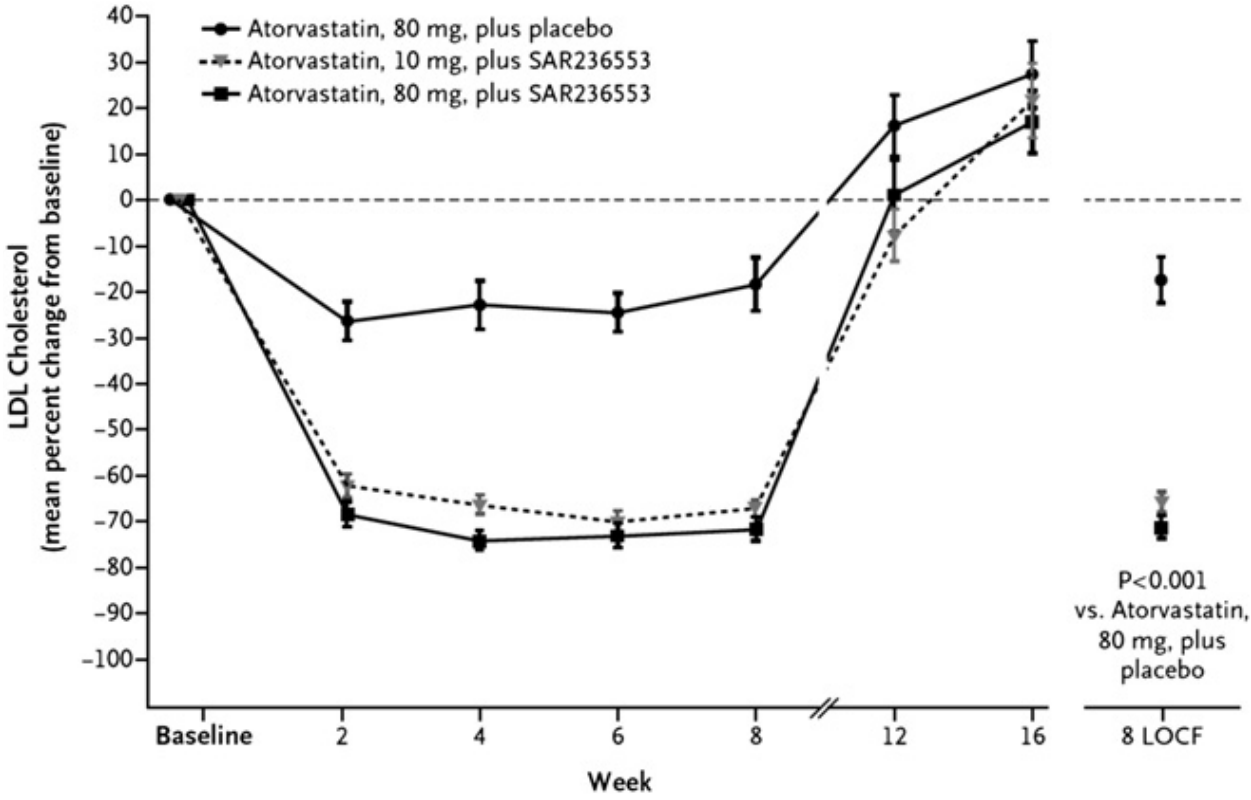

Atorvastatin, 80 mg, plus placebo
Atorvastatin, 10 mg, plus SAR236553
Atorvastatin, 80 mg, plus SAR236553
LDL Cholesterol
(mean percent change from baseline)
40
30
20
10
0
−10
−20
−30
−40
−50
−60
−70
−80
−90
−100
Baseline
2
4
6
8
12
16
Week
P<0.001
vs. Atorvastatin,
80 mg, plus
placebo
8 LOCF

Figure 6

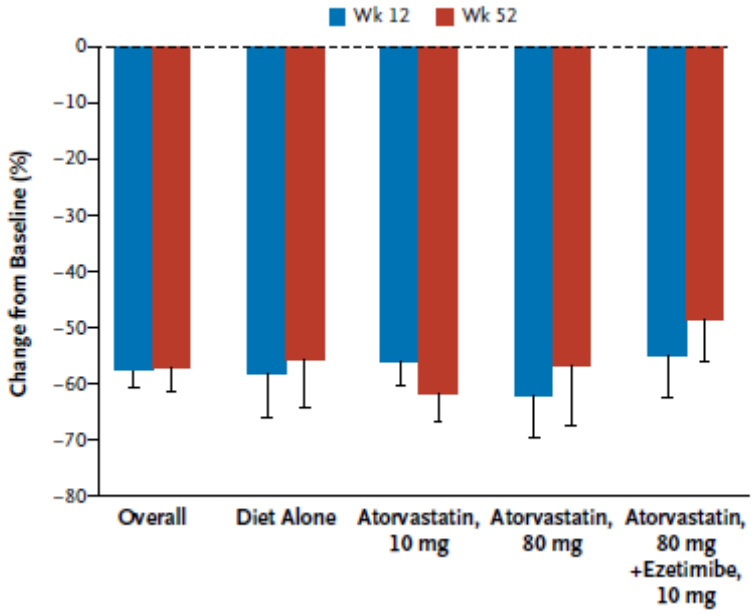
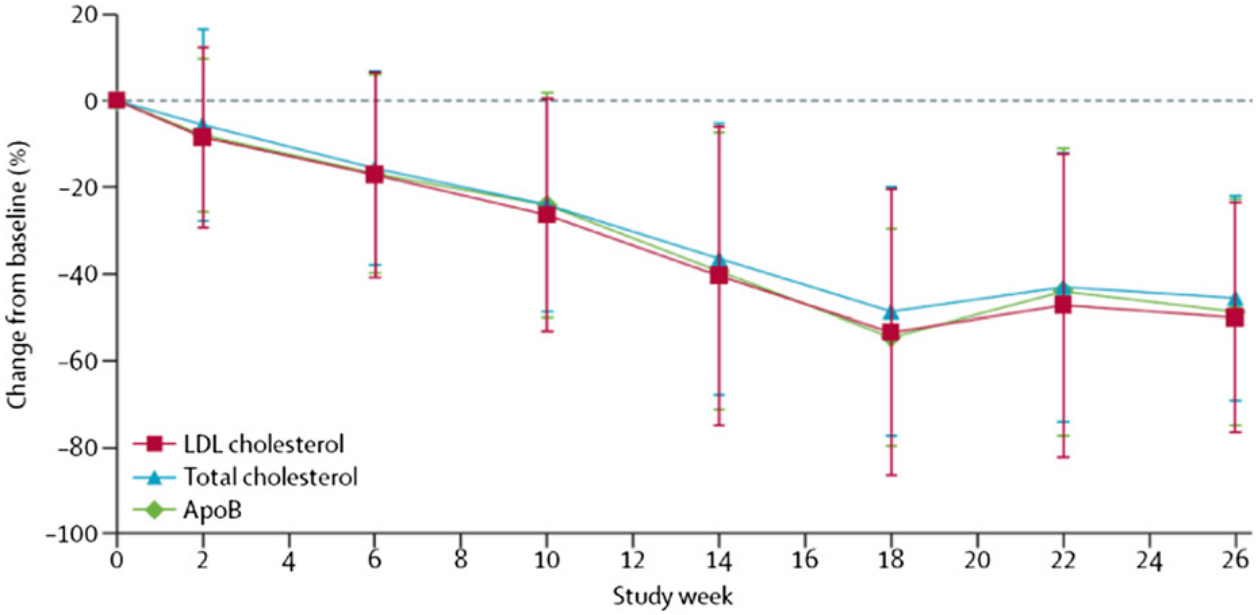

Wk 12
Wk 52
Change from Baseline (%)
0
−10
−20
−30
−40
−50
−60
−70
−80
Overall
Diet Alone
Atorvastatin, 10 mg
Atorvastatin, 80 mg
Atorvastatin, 80 mg +Ezetimibe, 10 mg

Figure 7


20
0
-20
-40
-60
-80
-100
Change from baseline (%)
LDL cholesterol
Total cholesterol
ApoB
0
2
4
6
8
10
12
14
16
18
20
22
24
26
Study week