Target Audience
This activity has been designed to meet the educational needs of cardiologists, interventional cardiologists, and other healthcare professionals involved in the care of patients with hypercholesterolemia.

Statement of Need/Program Overview
Given the prevalence of hypercholesterolemia in the United States, there is a clear need for cardiologists to understand the most current treatments for the disease. Cardiologists need to have full knowledge of the relationship between low-density lipoprotein cholesterol (LDL-C) levels and cardiovascular risk and treat patients accordingly. This can be accomplished by improving the identification of patients with coronary heart disease (CHD) and determining the most appropriate management strategies.

Many cardiologists continue to prescribe standard statin therapy, unaware of specific treatment options for patients with acute coronary syndromes or those unable to use statin therapy. Clearly, there is resistance among some cardiologists to administer newer therapies that can help treat hypercholesterolemia and further achieve, and even exceed, National Cholesterol Education Program (NCEP) treatment goals. Implementing emergent hypercholesterolemia therapies has increased significance since the use of statin therapy in CHD patients to current NCEP guideline goals only reduces cardiovascular events by about 35%; hence, 65% of patients remain subject to cardiovascular events. Thus, there is a need for clinicians to learn more about emerging therapies such as PCSK9 inhibition, which can be used alone and in combination as treatment for hypercholesterolemia.

Educational Objectives
After completing this activity, the participant should be better able to:
- Explain the relationship between LDL-C levels and cardiovascular risk, emphasizing the need to achieve at least current NCEP treatment guidelines
- Identify CHD and CHD-equivalent patients requiring treatment to achieve secondary modification goals
- Identify areas of resistance in achieving and exceeding NCEP treatment goals
- Review the role of PCSK9 inhibition as solo and combination therapy in clinical trials relative to LDL-C levels, safety, and efficacy

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Term of Offering
This activity was released on July 25, 2014 and is valid for 1 year. Requests for credit must be made no later than July 24, 2015.

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This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of Global Education Group (Global) and MRCME. Global is accredited by the ACCME to provide continuing medical education for physicians.

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System Requirements

PC	**MAC**
Microsoft Windows 2000 SE or above.	MAC OS 10.2.8
Flash Player Plugin (v7.0.1.9 or greater)	Flash Player Plugin (v7.0.1.9 or greater)
Internet Explorer (v5.5 or greater), or Firefox	Safari
Adobe Acrobat Reader*	Adobe Acrobat Reader*
	Internet Explorer is not supported on the MAC.

*Required to view printable (PDF) version of the lesson.

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Name of Faculty or Presenter	Reported Financial Relationship
Divya Ratan Verma, MD	Nothing to disclose
Eliot A. Brinton, MD, FAHA, FNLA	Consultant/Independent Contractor: Amgen, Sanofi, Aegerion, AstraZeneca, Genzyme, Kowa, Merck, Amarin, Arisaph, Lilly, Novartis (Takeda, Janssen), Atherotech Grant/Research Support: Health Diagnostic Laboratory Speaker's Bureau: Atherotech, Sanofi, Aegerion, Kowa, Genzyme, Amarin, AstraZeneca, Merck (Janssen, Takeda)

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Ashley Marostica, RN, MSN	Nothing to disclose
Amanda Glazar, PhD	Nothing to disclose
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Management of Hypercholesterolemia for Prevention of Atherosclerotic Cardiovascular Disease: Focus on the Potential Role of Recombinant Anti-PCSK9 Monoclonal Antibodies

Management of Hypercholesterolemia for Prevention of Atherosclerotic Cardiovascular Disease: Focus on the Potential Role of Recombinant Anti-PCSK9 Monoclonal Antibodies
Release date: July 25, 2014
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Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of death and disability in the United States and other developed nations, and is rising rapidly in the rest of the world. Low-density lipoprotein (LDL) is the major atherogenic particle in most patients at high risk for ASCVD events, and statin-based LDL-lowering treatment is the major focus of treatment for prevention of ASCVD. Despite this, an estimated 57 million US adults (25%) still have moderately elevated levels of LDL-cholesterol (LDL-C) $>$ 160 mg/dL, and many others have an LDL-C above the level considered appropriate for their high-risk status. Although statins are very effective for lowering LDL-C, and other classes of LDL-lowering medications are available, many patients still cannot achieve adequate LDL-lowering with maximal tolerated doses of US Food and Drug Administration–approved treatments. Thus, there is an unmet medical need for statin adjuncts in these patients, as well as for statin alternatives in statin-intolerant patients. A recently discovered human protein, proprotein convertase subtilisin/kexin type 9 (PCSK9), plays an important role in LDL metabolism by promoting degradation of the LDL receptor, and thus reducing clearance of LDL and increasing LDL-C levels. Accordingly, inhibition of PCSK9 activity has become an attractive target for drug development for lowering LDL-C, and human monoclonal antibodies against PCSK9, are now in late-stage clinical development. These antibodies are at least as effective as statins for LDL-C lowering (or more so), and their effects are additive to those of statins. To date, they have been well tolerated and apparently safe in clinical trials. Long-term randomized, controlled trials of their safety, tolerability, and ability to reduce ASCVD are now underway.

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KEY WORDS

Hypercholesterolemia • Atherosclerotic cardiovascular disease • PCSK9 • Low-density lipoprotein

Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of death and disability in the United States and developed nations, and is rising rapidly in other parts of the world. Atherosclerosis is caused primarily by dyslipidemia and other adverse factors that promote cholesterol deposition in the arterial intima.[1] An estimated 57 million (25.3%) US adults, aged ≥ 20 years, have plasma levels of low-density lipoprotein (LDL) cholesterol ≥ 160 mg/dL.[2]

Lipoprotein Biology

Cholesterol is an integral and necessary component of cell walls and is required for the synthesis of bile acids and steroid hormones. These essential functions are well maintained even at very low plasma LDL cholesterol levels and physiologic LDL cholesterol levels are probably no higher than 50 to 70 mg/dL.[3] Cholesterol, as well as triglycerides (TGs), are hydrophobic and thus require the micelle-like structure of lipoproteins for transport in plasma. Intestinal cholesterol and TGs (mainly of hepatobiliary origin in the case of cholesterol and virtually entirely of dietary origin in the case of TGs) are absorbed into the enterocytes of the small intestine where they are complexed with apolipoprotein (Apo) B-48 to form chylomicrons, for transport in thoracic lymph and then plasma. Chylomicrons transport TGs and small amounts of cholesterol to the body—primarily muscle, adipose tissue, and liver. Delivery of TGs is dependent on lipoprotein lipase, located in the vascular endothelium, which rapidly hydrolyzes the TGs in chylomicrons, creating smaller particles called chylomicron remnants. Chylomicron remnants are then taken up by various receptors (including in part by the LDL receptor [LDL-R]), primarily in the liver. In partial contrast, very-low density lipoproteins (VLDLs) are synthesized in the liver as TGs and small amounts of cholesterol are complexed with Apo B-100. As do chylomicrons, VLDL then carries TGs and cholesterol to the body, the former being delivered by hydrolysis of the TGs, similar to that of chylomicrons. Although a significant percentage of VLDL is taken up directly by the LDL-R in the liver before much TG hydrolysis occurs, most VLDL remains in the plasma; after more extensive hydrolysis, VLDL remnants, called intermediate-density lipoproteins (IDL), are created. Much of plasma IDL is cleared by the hepatic LDL-R, but much also undergoes further TG hydrolysis, becoming LDL, which has very little remaining TG and which is the major ligand of the LDL-R. Due to the much longer half-life (a few days) of LDL versus its precursors (and due to the relative lack of cholesterol in the core of high-density lipoprotein [HDL]), LDL normally carries the majority of circulating cholesterol.

... in conditions in which LDL-C is ≤ 50 mg/dL, such as with aggressive statin use, or in naturally occurring states such as hypobetalipoproteinemia, loss-of-function PCSK9 mutation, and hunter-gatherer populations, there is little or no ASCVD.

LDL Cholesterol Versus Atherosclerosis and ASCVD Risk

Although chylomicron remnants and all Apo B-100–containing lipoproteins are atherogenic, LDL appears to account for the vast majority of atherogenesis in most patients; as a result, the cholesterol content of LDL (plasma LDL cholesterol [LDL-C] levels) has been the major focus of treatment guidelines for prevention of ASCVD. In fact, in conditions in which LDL-C is ≤ 50 mg/dL, such as with aggressive statin use (Figure 1),[3-5] or in naturally occurring states such as hypobetalipoproteinemia,[6] loss-of-function proprotein convertase subtilisin/kexin type 9 (PCSK9) mutation,[7] and hunter-gatherer populations,[3] there is little or no ASCVD.

The Framingham Heart Study was an early epidemiologic study to quantitate the correlation between elevated total cholesterol and LDL-C with morbidity and mortality from ASCVD,[8] and many other subsequent studies have shown similar findings.[9,10] Of greater clinical importance, before the advent of statins, randomized clinical trials (RCTs) of several disparate types of LDL-C–lowering treatments over several decades have shown reduced ASCVD incidence.[11-13] The concordance of these earlier trials with statin RCTs strongly supports the LDL hypothesis that elevated LDL-C levels are causally related to the process of atherosclerosis and that treatment to lower LDL-C will decrease ASCVD events and mortality, proportional to the degree of LDL-C lowering. This relationship is seen most clearly in secondary

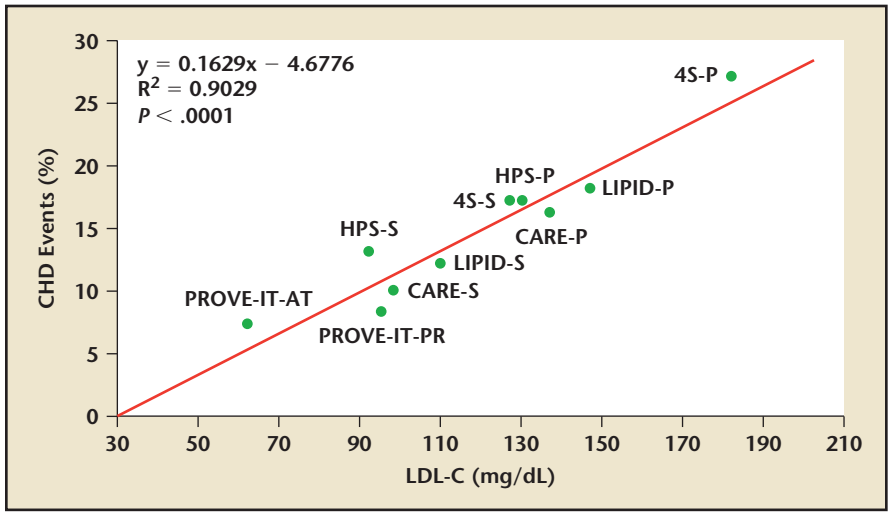

Figure 1. CHD event rates in statin secondary prevention trials were directly proportional to on-treatment LDL-C levels. Note that predicted event rate approaches zero at an LDL-C of 30 mg/dL. 4S, Scandinavian Simvastatin Survival Study; CARE, Cholesterol And Recurrent Events Trial; CHD, coronary heart disease; HPS, Heart Protection Study; LDL-C, low-density lipoprotein cholesterol; LIPID, Long-term Intervention with Pravastatin in Ischemic Disease Trial; PROVE-IT, Pravastatin or Atorvastatin Evolution and Infection Therapy trial. Reprinted with permission from O'Keefe JH Jr et al.[3]

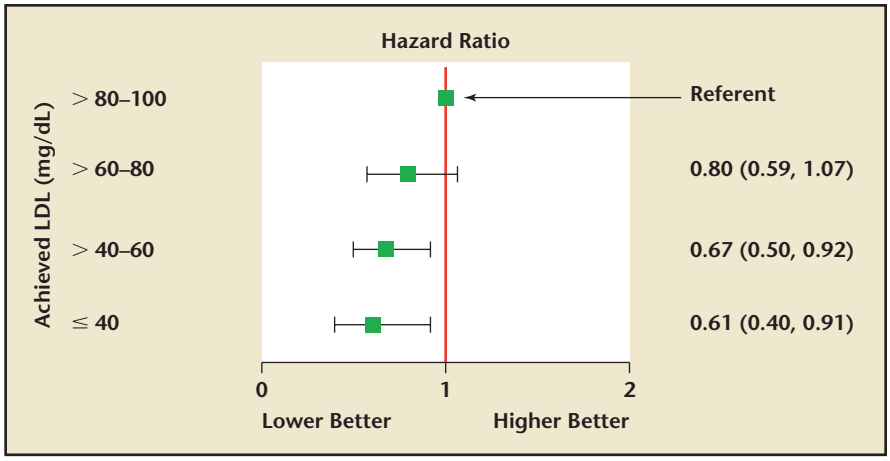

Figure 2. Hazard ratio of atherosclerotic cardiovascular disease composite (primary endpoint) vs range of on-statin low-density lipoprotein (LDL) cholesterol level (adjusted for age, sex, baseline LDL cholesterol, diabetes mellitus, and prior myocardial infarction). Adapted with permission from Wiviott SD et al.[16]

prevention trials using statins[3,14] (Figure 1), and similar results have been seen with statins in primary prevention.[3]

Several imaging studies of coronary plaque by intravascular ultrasound (IVUS) have been conducted with statin monotherapy and have shown reduced progression and even regression of plaque size.[4,5] These plaque changes are strongly and linearly proportional to on-treatment LDL-C levels, consistent with prior studies suggesting that atherosclerosis does not develop with very low LDL-C levels.[3]

The relationship between on-treatment LDL-C and non-HDL cholesterol (HDL-C) and ASCVD has been further studied in a large recent meta-analysis of 38,153 subjects in the eight major statin RCTs with ASCVD endpoints in which LDL-C, non-HDL cholesterol, and Apo B were all measured at 1 year.[15] Non–HDL-C was a significantly stronger predictor of ASCVD than was LDL-C, and together they accounted for 64% of the variability in ASCVD risk.

In addition, in analyses of on-treatment LDL-C versus ASCVD events from one large statin study showed progressively lower risk with lower on-treatment LDL-C levels (Figure 2). This relationship was stepwise from 80 to 100 mg/dL (referent) down to 60 to 80 mg/dL, 40 to 60 mg/dL, and even < 40 mg/dL(39% decrease in event risk), and there was no increase in adverse events.[16] Thus, lower LDL-C appears unequivocally to be better, without any apparent lower threshold for either increased risk or loss of benefit. With the potential future availability of a new class of LDL-C–lowering agents with lipid efficacy as great, or greater, than that of the statins, this lack of evident attenuation of favorable risk-to-benefit ratio at very low LDL-C levels may be of clinical importance in treating very high-risk patients.

These data all strongly support the concept that lower LDL-C is better, which is the major foundation for the use of LDL-C and non–HDL-C goals to guide clinical practice in lipid management for ASCVD prevention.

The largest meta-analysis of patient-level data (of nearly 170,000 individuals) from numerous statin ASCVD endpoint trials has assessed this relationship in a slightly different way, by looking at the change in LDL-C versus the change in ASCVD risk.[14] Per each 38.6 mg/dL (1 mmol) reduction in LDL-C, the weighted average reduction of ASCVD event risk was 28%,[14] and this relationship was independent of baseline LDL-C levels, even below 77 mg/dL.[14]

Lipid Goals and the 2013 American College of Cardiology/American Heart Association Cholesterol Guidelines

In November 2013, the American College of Cardiology (ACC) and the American Heart Association

(AHA) released guidelines on cholesterol treatment for ASCVD prevention,[17] resulting from a process originally sponsored by the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health. It is important to realize that the 2013 ACC/AHA cholesterol guidelines contrast significantly from the three prior NHLBI-sponsored guidelines from the National Cholesterol Education Program Adult Treatment Panel (NCEP-ATP I through NCEP-ATP III). First, the continuous involvement of a broad coalition of expert organizations with NCEP-ATP I through III was absent in their development. Second, the types of evidence considered were sharply limited compared with all other lipid guidelines written before and since. That is, instead of reviewing the full range of available scientific information—from multiple high-quality RCTs through single high-quality RCTs, lower-quality RCTs, observational data (prospective cholesterol cohort, case cholesterol control, and cross-sectional studies) mechanistic data in human, animal, and cell-culture studies, and expert opinion—evidence for the 2013 ACC/AHA cholesterol guidelines was limited just to multiple RCTs and meta-analyses of such trials. Third, their provenance was somewhat unusual. At the very end of the writing process of their new guidelines, the NHLBI announced that it would no longer sponsor clinical guidelines and therefore planned to publish the product of its multi-year effort simply as an evidence review[18]; 4 months later, the print version of this statement appeared with a second article in which the NHLBI further announced that the ACC and AHA were going to collaborate with other professional organizations to transform their evidence review into lipid guidelines.[19] Surprisingly, less than 2 months later, in November 2013, the document was published jointly by the ACC and AHA as a completed guideline. This major change in the sponsorship and intent of the document appears to have been made with only a cursory review by a few individuals in each of the two organizations, and with minimal revision of the text.[17] Since the 2013 ACC/AHA cholesterol guidelines clearly originated from a very different process than that of NCEP-ATP III (and its predecessors), the authors question whether they should be considered either as a direct successor to or update of NCEP-ATP III, or as the sole official US lipid guidelines.

Of particular importance to the clinician, the deletion of lipid goals (whether LDL-C or non-HDL-C) in the 2013 ACC/AHA cholesterol guidelines was not driven by new data showing such goals to be useless or harmful. Rather, it was because none of the few studies considered by the writing panel had overtly tested the use of lipid goals (vs a goal-free approach), nor had they directly tested one lipid goal versus another. Instead of relying on less-direct evidence (as outlined in detail above) or on expert opinion that on-treatment lipid levels are causal of ASCVD and should be a major clinical focus, the writing panel failed to endorse such goals and placed little or no emphasis on on-treatment lipid levels. After 25 years of NCEP-ATP guidelines, the primary focus of which was treatment to lipid goals, this change was considered radical by many lipidologists and has caused considerable uncertainty among clinicians and patients.

On the much less controversial side, the 2013 ACC/AHA cholesterol guidelines identify four groups of patients for whom statin benefits clearly outweigh risks, namely, those with (1) a prior clinical ASCVD event, (2) baseline (untreated) LDL-C $>$ 190 mg/dL, (3) type 1 or 2 diabetes with LDL-C $\geq$ 70 to 189 mg/dL (and aged 40-75 years), and (4) a 10-year ASCVD risk, as calculated by the new ACC/AHA risk calculator, of $\geq$ 7.5% (and with an LDL-C 70-189 mg/dL).[17] The guidelines also identify groups in whom statin benefit is said not to be supported by RCT data (but might be considered according to clinical judgment), including patients aged $<$ 40 or $>$ 75 years, receiving hemodialysis, or with congestive heart failure.[17]

LDL-C and Non–HDL-C Goals in Other Lipid Guidelines

In their rejection of LDL-C and non-HDL-C goals, the 2013 ACC/AHA cholesterol guidelines are not only at odds with NCEP-ATP I to III, but also with current guidelines in other developed countries. For example, the latest Canadian[20] and European lipid guidelines[21,22] have been centered on treating LDL-C (and non-HDL-C) to goal. Commentary on the 2013 ACC/AHA guidelines by both these panels gave several compelling reasons for maintaining the use of lipid treatment goals going forward.[22,23] Further, the most recent lipid guidelines, written by the International Atherosclerosis Society and published in 2014,[24] also have the same focus on lipid goals. Thus, the deletion of lipid goals is unique to the 2013 ACC/AHA guidelines, logically most clearly because of the fact that all other guidelines, before or since, have used the full range of scientific information available, whereas the 2013 ACC/AHA guidelines did not.

Residual ASCVD Risk and Combination Lipid Therapy

Although ASCVD risk is clearly reduced by statin monotherapy,[14] the risk reduction is approximately between 25% and 50%, meaning that the majority of ASCVD events are not prevented. Importantly, this residual risk is proportional to on-treatment LDL-C levels, strongly suggesting that further LDL-C lowering would further lower ASCVD.[3] Trials achieving lower LDL-C levels by using more intensive statin therapy have consistently shown further reduction in events both in individual trials[25,26] and in meta-analyses of trials,[1] and the same is true with differences among individuals in their LDL-C responses to a given statin regimen.[16] These findings have given rise to the concept that residual dyslipidemia is related to residual ASCVD risk and that this risk might be addressed with non-statins as statin adjuncts or replacements. Unfortunately, the word *residual* does not appear in the 2013 ACC/AHA cholesterol guidelines and non-statin treatment is strikingly downplayed.

Despite statin monotherapy, a significant number of patients still have elevated LDL-C and/or non-HDL-C levels and that insufficiency of LDL and non-HDL-C control may be exacerbated by the presence of diabetes, metabolic syndrome, or by other factors elevating ASCVD risk and/or elevating non-HDL cholesterol out of proportion to LDL-C.[27,28] In addition, adverse side effects from statins are relatively common,[29] limiting or preventing statin use in many patients.

For these reasons, there is increasing interest in non-statin therapies to lower residual elevations in LDL-C levels and, it is hoped, manage residual ASCVD risk. Most currently available lipid medications are compatible with statins and may reduce ASCVD as statin adjuncts, but compelling evidence for such additive effects is lacking. In fact, due to the exclusion of most levels of scientific information, the 2013 ACC/AHA cholesterol guidelines saw no evidence for such benefits, and stated that no statin adjuncts had a favorable risk-to-benefit ratio. For example, clear evidence for the ASCVD effects of ezetimibe, the most commonly used statin adjunct, are yet to be reported,[30] although added benefit has been suggested in one trial of ezetimibe plus a statin.[31] Further, fenofibrate[32] and niacin[33] have recently failed to establish ASCVD benefit additive to a statin, although such benefit has been suggested in subanalyses in patients with high TG and low baseline HDL-C levels.[32,34] One statin adjunct study, using a relatively high dose of an omega-3 agent (pure eicosapentaenoic acid), did show reduced ASCVD,[35] and that reduction was increased in patients with high TG and low HDL-C.[36] Granted, the background statin doses were low and the study was open label, but these results provide further data supporting ASCVD benefits from statin adjuncts.

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PCSK9 Biology and Its Emerging Role in LDL Metabolism

Plasma LDL-C level is generally determined more by the catabolic rate of LDL than by its production rate. LDL catabolism is regulated by several factors, the most important of which is the number of LDL-R on the hepatocyte surface. LDL-R is a transmembrane molecule that aggregates (via action of the LDL-R-adaptor protein on the LDL-R intracellular domain) in clathrin cholesterol-coated pits that are then internalized. Inside the resulting vesicles, LDL particles are dissociated from the LDL-R and the former are degraded by proteolysis, releasing their lipid content. In contrast to LDL itself, the LDL-R can meet either one of two fates: (1) it can be recycled back to the cell surface to bind another LDL particle and promote its catabolism, or (2) it can be diverted to an endosome where it is degraded and prevented from recycling. These two fates have divergent effects on LDL metabolism and LDL-C levels, and a recently discovered human protein, PCSK9, plays a surprising role in determining which of these two divergent pathways is taken by the LDL-R.

The key aspects of PCSK9 metabolism and action are becoming clear (Figure 3).[37] PCSK9 is synthesized as an inactive precursor 73-kDa zymogen with 692 amino acids. It consists of a signal peptide, a prodomain, a catalytic domain, and a large C-terminal domain.[38] Immediately after its synthesis, this PCSK9 precursor protein cleaves

In the extracellular space, PCSK9 binds to the epidermal growth factor-like repeat A domain of the LDL-R. When this complex is internalized in clathrin-coated endosomes, LDL-R bound to PCSK9 undergoes lysosomal degradation. The resulting reduction in LDL-R number decreases the catabolism of LDL, tending to raise plasma LDL-C levels.

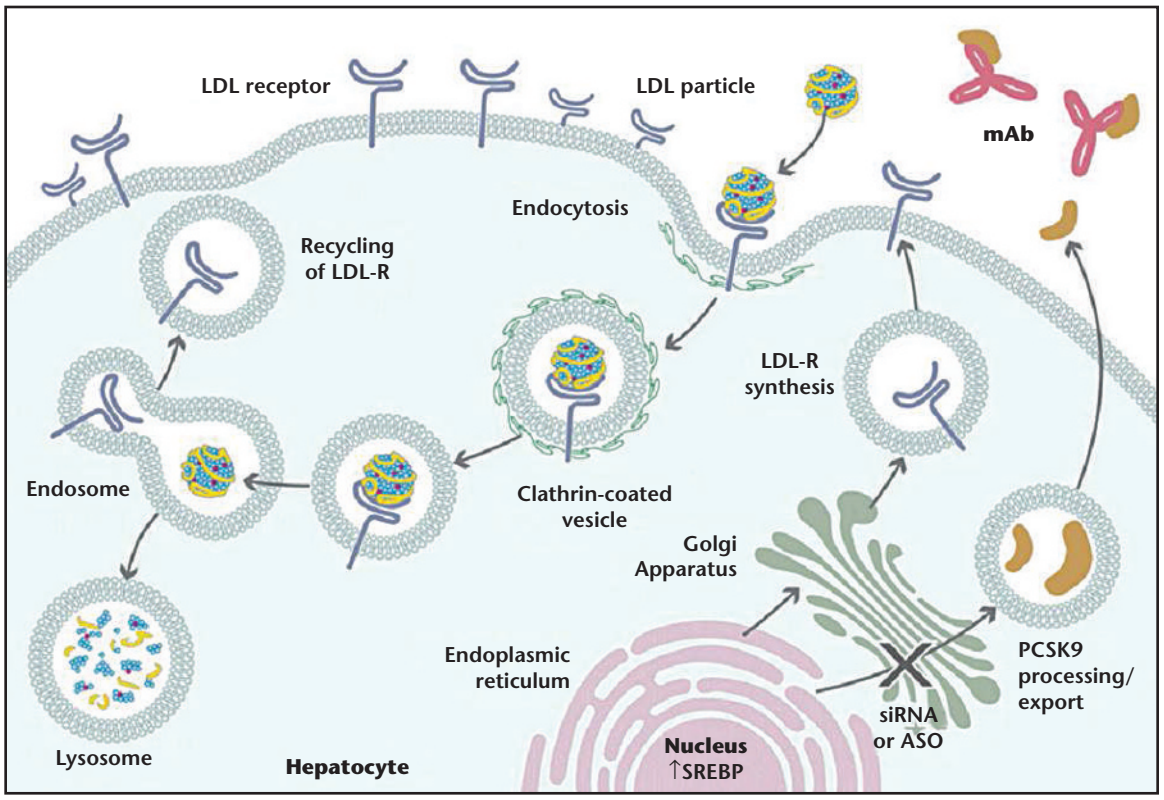

Figure 3. Schematic of LDL-R and PCSK9 metabolism in the hepatocyte. At the bottom of the figure, increased SREBP activity (in response to low intrahepatic cholesterol) is shown to stimulate production of LDL-R and of PCSK9 in the endoplasmic reticulum and Golgi. Also, inhibition of PCSK9 synthesis with siRNA or ASO inhibition is shown. In the absence of PCSK9 inhibition, the LDL-R would be degraded (*not shown*) along with LDL in the endosome (*left side*). In contrast, in the presence of mAb to PCSK9 (*upper right*), its binding to the LDL-R is inhibited and the LDL-R separates from the LDL particle in the endosome, allowing LDL-R recycling back to the cell surface. ASO, antisense oligonucleotide; LDL-R, low-density lipoprotein receptor; mAb, monoclonal antibodies; siRNA, small interfering RNA; SREBP, sterol regulatory element-binding protein. Reprinted with permission from Lambert G et al.[37]

off a portion of itself, a 14-kDa prodomain from the mature 63-kDa PCSK9.[39] Interestingly, the cleaved prodomain attaches to the substrate-binding site of the mature PCSK9, blocking its ability to bind to the LDL-R.[40] Also, this cleavage is required for subsequent secretion of PCSK9.[41] In the extracellular space, PCSK9 binds to the epidermal growth factor-like repeat A (EGF-A) domain of the LDL-R.[41,42] When this complex is internalized in clathrin-coated endosomes, LDL-R bound to PCSK9 undergoes lysosomal degradation.[43] The resulting reduction in LDL-R number decreases the catabolism of LDL, tending to raise plasma LDL-C levels. Alternatively, when PCSK9 is not bound to the LDL-R, the latter is free to recycle to the cell surface where it can bind and facilitate the degradation of another LDL particle, which, under physiologic conditions, may happen roughly. In the absence of PCSK9 an individual LDL-R can be recycled up to 150 times.[44,45] Thus, PCSK9 serves to downregulate LDL-R–mediated LDL uptake (primarily by the liver), diverting cholesterol delivery to the periphery. Further, the availability of PCSK9 to bind to the LDL-R plays a key role in regulation of plasma LDL levels and in resulting delivery of cholesterol and intrahepatic cholesterol homeostasis. Although it appears possible for PCSK9 to bind to the LDL-R inside the hepatocyte,[43] this pathway seems to be of lesser importance based on three lines of evidence: (1) small interfering RNA (siRNA) inhibiting PCSK9 synthesis reduces LDL-C levels by only 40% despite reducing PCSK9 synthesis by over 70%,[46] (2) monoclonal antibodies (mAbs) to PCSK9 reduce LDL-C levels by as much as 60% or more despite binding the LDL-R only in the plasma,[47,48] and (3) the degree of increase of plasma levels of PCSK9 with statin therapy strongly and inversely predicts the degree of LDL-C lowering.[49]

Endogenous regulation of PCSK9 production appears in large part related to sterol regulatory element-binding protein-2 (SREBP-2) (Figure 3).[50] SREBP-2 is upregulated in response to low levels of cholesterol in the key intrahepatic regulatory pools,[51] which can result from treatment with statins and other lipid-lowering therapies such as cholesterol absorption inhibitors and bile acid sequestrants. SREBP-2

in turn induces increased expression of both LDL-R and PCSK9, and because these two have opposite effects, the balance between these factors in the degree of their upregulation should have profound effects on LDL catabolism, intrahepatic cholesterol levels, and plasma LDL-C levels.

Interestingly, among human mutations in the *PCSK9* gene, the first to be discovered were two uncommon gain-of-function mutations (ser127-to-arg and F216L). These were found in a pedigree with an unusual pattern of autosomal dominant hypercholesterolemia, related to a mutation at chromosome 1p32.3[52] and later identified as the gene coding for *PCSK9*.[52-54]

Loss-of-function mutations in *PCSK9* were discovered soon thereafter.[7] The reduced LDL-R activity resulted in only a relatively modest 15% to 28% decrease in plasma LDL-C but a striking 47% to 88% reduction in cardiovascular disease events, the surprisingly greater event reduction perhaps due to lifetime exposure to lower LDL-C.[55] The clinical benefits and lack of evident adverse consequences seen in patients with these loss-of-function mutations suggest that inhibition of PCSK9 activity is a good target for lipid drug development.

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PCSK9 Inhibition by Human mAbs

Of all possible pharmacologic means to interfere with PCSK9 activity, antibody-mediated inhibition has been the primary focus in clinical development (Figure 3).[38] Methods for development of fully human mAbs in mice now allow agents with minimal risk of provoking autoantibody production by the recipient.[56] The many mAbs being developed include alirocumab (REGN727; sanofi-aventis [Bridgewater, NJ] and Regeneron [Tarrytown, NY])[57]; evolocumab (AMG 145; Amgen, Thousand Oaks, CA)[58]; RN316 (Pfizer; New York, NY)[59]; RG7652 (Roche [Basel, Switzerland] and Genentech [San Francisco, CA])[60]; LGT209 (Novartis, East Hanover, NJ)[61]; 1D05-IgG2 and 1B20 (Merck, Whitehouse Station, NJ); and J10, J16, and J17 (Pfizer). Of these, the first two are the farthest along in development and their phase II and III trial results are detailed next.

Evolocumab (AMG 145)

Several phase I, II, and III trials in patients with hypercholesterolemia have been conducted (Table 1) and showed roughly similar results with additive or nearly fully additive effects of evolocumab when given with statins and ezetimibe. In the very earliest studies, subcutaneous administration was found to have similar results to those with intravenous dosing, and so the former is now used exclusively.

Evolocumab therapy has shown excellent dose- and frequency-dependent LDL-C reduction, comparable with that with alirocumab (Table 1). Biweekly dosing from 70 to 140 mg and monthly dosing from 280 to 420 mg (three- to fourfold the biweekly dosing) resulted in mean LDL-C reductions of 39% to 75%.[47,48,58,62-68] The various evolocumab studies have reported similar rates of treatment emergent side effects for both evolocumab and control groups. The most frequently reported adverse events were nasopharyngitis, upper respiratory tract infection, influenza, nausea, and back pain. Rates of injection site reactions were similar for evolocumab and placebo. The incidence of myalgias and myositis was generally not reported, but in the two trials enrolling statin-intolerant patients,[63,66] they were no higher with evolocumab. Study drug discontinuations were similar between evolocumab and placebo in all studies. Serious adverse events reported included coronary artery disease, acute pancreatitis, appendicitis, atrial fibrillation, hip fracture, humerus fracture, and syncope, although the relationship to evolocumab was unclear.

Antibodies to evolocumab have been found in a very small number of patients in several trials. In two separate trials (LDL-C Assessment With PCSK9 Monoclonal Antibody Inhibition Combined With Statin Therapy [LAPLACE]-2[48] and Durable Effect of PCSK9 Antibody Compared With Placebo Study [DESCARTES][68]), one and two patients, respectively, appeared to have cross-reacting antibodies (ie, they were present at baseline and study end). In another trial (Monoclonal Antibody Against PCSK9 to Reduce Elevated LDL-C in Subjects Currently Not Receiving Drug Therapy for Easing Lipid Levels [MENDEL]),[64] two patients developed anti-evolocumab antibodies but both were seen only transiently, and one of the two patients was in the placebo arm. None of these were reported as neutralizing antibodies. Antibodies were reported to be absent in the other evolocumab trials.[47,62,63,65-67]

TABLE 1

Summary of Design and Results of Completed and Ongoing Clinical Trials With Evolocumab and Alirocumab

Study/Description	Subjects	N	Intervention	Duration	LDL-C Decrease[b] (%)	Background Therapy
Evolocumab[a]						
Dias CS et al[58]; safety & feasibility	Healthy volunteers	56	Single dose: SQ 7-420 mg, IV 21-420 mg	12-16 wk	Up to 64	None
Dias CS et al[58]; safety & feasibility	Elevated LDL-C on statins (incl. HeFH)	57	Dose-escalation: Q2wk or Q4wk 14-420 mg	12-14 wk	Up to 81	Statins
Raal F et al[62]; RUTHERFORD	HeFH with LDL-C ≥ 100 mg/dL	168	Q4wk 350 vs 420 mg	12 wk	43-55	Statins ± ezetimibe
Stein EA et al[69]; effect on HoFH	HoFH	8	Q4wk 420 mg then Q2wk 420 mg	24 wk	14 (range +40 to −43)	OMT
Giugliano RP et al[47]; LAPLACE-TIMI	LDL-C ≥ 85 mg/dL	631	Q2wk 70, 105, or 140 mg vs Q4wk 280, 350, or 420 mg	12 wk	42-66	Statins ± ezetimibe
Sullivan D et al[63]; GAUSS	Statin-intolerant patients	160	Q4wk 280, 350, or 420 mg	12 wk	41-63	None
Koren MJ et al[64]; MENDEL	LDL-C 100 to 189 mg/dL, TG < 398 mg/dL & FRS ≤ 10%	411	Q2wk 70, 105, or 140 mg vs Q4wk 280, 350, or 420 mg	12 wk	39-51	None
Koren MJ et al[65]; MENDEL-2	LDL-C 100-190 mg/dL & FRS ≤ 10%/10 y	614	Q2wk 140 mg vs Q4wk 420 mg		55-57	None
Robinson JG et al[48]; LAPLACE-2	LDL-C ≥ 150 (no statin), ≥ 100 (low statin) or ≥ 80 (high statin)	1896	Q2wk 140 mg vs Q4wk 420 mg	12 wk	63-75	Statins
Stroes E et al[66]; GAUSS-2	Statin-intolerant patients	307	Q2wk 140 mg vs Q4wk 420 mg	12 wk	53-56	None
Raal F et al[67]; RUTHERFORD-2	HeFH with LDL-C > 100 mg/dL	331	Q2wk 140 mg vs Q4wk 420 mg	12 wk	56-61	Statins ± ezet
Blom DJ et al[68]; DESCARTES	LDL-C > ATP III goal	901	Q4wk 420 mg wk	52 wk	57	Atorvastatin ± ezetimibe
GLAGOV[70]; ongoing	CAD & LDL-C ≥ 60-80 mg/dL (per risk)	~950	Q4wk dose NA	78 wk	NA (1° endpoint: IVUS)	Statins
FOURIER[71]; ongoing	Prior CHD event & LDL-C ≥ 70 mg/dL (on "effective statin" = atorvastatin ≥ 20 mg/d)	~23,000	Q2wk or Q4wk dose NA	~5 y	NA (1° endpoint: CHD death, NFMI, stroke, cor revasc, USA hosp)	Statins

Alirocumab[a]						
Stein EA et al[57]; safety	Healthy volunteers	40	Sequential dosing at 0.3, 1, 3, 6, and 12 mg/kg IV	15 wk	28-65	None
Stein EA et al[57]; safety	Healthy volunteers	32	Sequential dosing 50, 100, 150, & 250 mg	15 wk	33-46	None
Stein EA et al[57]; safety	HeFH/non-FH with LDL-C $\geq$ 100 on atorvastatin or non-FH w/ LDL-C $\geq$ 130 mg/dL on diet	61	On day 1, 29, 43 given 50, 100, or 150 mg	8 wk	38-65	Atorvastatin
Roth EM et al[72]; combination therapy	LDL-C $\geq$ 100 mg/dL on atorvastatin, 10 mg	92	Q2wk 150 mg	8 wk	66-73	Atorvastatin, 10 or 80 mg
Stein EA et al[73]; combination therapy	HeFH, on-treatment LDL-C $\geq$ 100	77	Q2wk 150 mg vs Q4wk 150, 200, or 300 mg	12 wk	29-68	Statins $\pm$ ezetimibe
McKenney JM et al[74]; efficacy, combination therapy	On-treatment LDL-C $\geq$ 100 mg/dL	183	Q2wk 50, 100, or 150 mg vs Q4wk 200 or 300 mg	12 wk	40-72	Atorvastatin 10, 20, 40 mg
Roth EM et al[75]; ODYSSEY MONO	LDL-C 100-190 mg/dL & 10-y fatal CV risk 1%-5% (SCORE)	101	Q2wk 75 mg	24 wk	47	None
ODYSSEY Outcomes[76]; ongoing	ACS in past 1-12 mo & LDL-C $>$ 70 mg/dL on OMT	$\sim$18,000	Dose and frequency NA	$\sim$5 y	NA (1° endpoint: CHD death, NFMI, stroke, USA hosp)	OMT

[a]All evolocumab and alirocumab was given subcutaneously except where noted as IV.

[b]Mean LDL-C decrease with mAb corrected for response in placebo arm. *P* value is vs control arms and all were $<$ .01 to $<$ .0001, except where noted. Data comparing mAb with statins or ezetimibe (as active comparators) are not shown.

ACS, acute coronary syndrome; ATP III, Adult Treatment Panel III; CAD, coronary artery disease; CHD, coronary heart disease; cor revasc, coronary revascularization; CV, cardiovascular; DESCARTES, Durable Effect of PCSK9 Antibody Compared With Placebo Study; FH, familial hypercholesterolemia; FOURIER, Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk; FRS, Framingham risk score; GAUSS, Goal Achievement After Utilizing an Anti-PCSK9 Antibody in Statin Intolerant Subjects; GLAGOV, Global Assessment of Plaque Regression With a PCSK9 Antibody as Measured by Intravascular Ultrasound; HeFH, heterozygous familial hypercholesterolemia; HoFH, homozygous familial hypercholesterolemia; IV, intravenous; IVUS, intravascular (intracoronary) ultrasound; LAPLACE-TIMI, LDL-C Assessment With PCSK9 Monodonal Antibody Inhibition Combined With Statin Therapy-Thrombolysis In Myocardial Infarction; LDL-C, low-density lipoprotein cholesterol; mAB, monoclonal antibody; MENDEL, Monoclonal Antibody Against PCSK9 to Reduce Elevated LDL-C in Subjects Currently Not Receiving Drug Therapy for Easing Lipid Levels; NFMI, nonfatal myocardial infarction; ODYSSEY Mono, Efficacy and Safety of Alirocumab SAR236553 (REGN727) Versus Ezetimibe in Patients With Hypercholesterolemia; ODYSSEY Outcomes, Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab SAR236553 (REGN727); OMT, optimal medical therapy; Q2wk, every 2 weeks; Q4wk, monthly; RUTHERFORD, Reduction of LDL-C with PCSK9 Inhibition in Heterozygous Familial Hypercholesterolemia Disorder; SQ, subcutaneous; TG, triglycerides; USA hosp, hospitalization for unstable angina.

Evolocumab was tested in an uncontrolled study of eight patients with homozygous familial hypercholesterolemia.[69] At the end of the trial, on biweekly evolocumab, 420 mg for 12 weeks, the mean LDL-C change from baseline was a 13.9% decrease, but there was considerable heterogeneity in the response. Two of the subjects were LDL-R negative (null) whereas the other six were LDL-R defective. As expected, the two LDL-R negative patients had no LDL-C response to evolocumab (with a 40% increase and a 10% decrease from baseline at the end of the study). Among the six LDL-R defective patients, however, the LDL-C response varied widely. Three had little or no response, ranging from a 2% increase to a 17% decrease in LDL-C. The remaining three had substantial decreases in LDL-C, ranging from −36% to −43%.[69]

Two larger and longer RCTs with evolocumab have recently begun. One is the Global Assessment of Plaque Regression With a PCSK9 Antibody as Measured by Intravascular Ultrasound trial (GLAGOV)[70] (Table 1), in which monthly administration of an as-yet undisclosed dose is being tested versus placebo against background statin use in approximately 950 patients with established coronary artery disease and an LDL-C of either ≥ 60 or ≥ 80 mg/dL (depending on the degree of background ASCVD risk). Patients will be followed for 78 weeks with IVUS at beginning and end of the trial. The primary endpoint will be nominal change in percent atheroma volume by IVUS at week 78. The other large evolocumab trial is Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk (FOURIER)[71] (Table 1), in which biweekly or monthly administration of as-yet undisclosed doses will be tested versus placebo against background statin use in approximately 22,500 patients with history of a prior coronary heart disease (CHD) event and with an LDL-C ≥ 70 mg/dL. Patients will be followed for approximately 5 years with the primary endpoint being a composite of CHD death, nonfatal myocardial infarction, stroke, coronary revascularization, or unstable angina requiring hospitalization.

Alirocumab (REGN727)

Several phase I, II, and III trials in patients with hypercholesterolemia have been conducted (Table 1) and showed roughly similar results with additive or nearly fully additive effects of alirocumab when given with statins and ezetimibe. In the very earliest studies, subcutaneous administration was found to have similar results to those with intravenous dosing, and so the former is now used exclusively.

Alirocumab therapy has shown excellent dose- and frequency-dependent LDL-C reduction. Biweekly dosing from 50 to 150 mg and monthly dosing from 150 to 300 mg resulted in mean LDL-C reductions of 28.9% to 73.2%, comparable with that with evolocumab (Table 1).[57,72-75] The various alirocumab studies have reported similar rates of treatment-emergent side effects for both alirocumab and control groups. The most frequently reported adverse events included mild injection site reactions, noted more commonly with alirocumab. In early trials of intravenous administration, one patient had elevated bilirubin and one had an elevated creatine kinase level. Serious adverse events reported included small bowel obstruction on day 75 after a single dose; and dehydration, neutropenia, chest pain, chronic obstructive pulmonary disease requiring hospitalization, and leukocytoclastic vasculitis with low detectable anti-drug antibody titers at 20 weeks (same patient also later required surgery for a humerus fracture). The relationship of these serious adverse events to alirocumab is unclear. Antibodies against alirocumab were not reported in most alirocumab trials, but in addition to the aforementioned case, low titers were seen in 12% of patients (7 of 56) in one study at week 8.[72]

The one large clinical endpoint trial is ODYSSEY Outcomes[76] (Table 1), in which alirocumab, at as-yet undisclosed doses and dose frequency, will be tested versus placebo against optimal medical lipid treatment in approximately 18,000 patients with history of an acute coronary syndrome episode in the prior 1 to 12 months before presentation and with an LDL-C ≥ 70 mg/dL on optimal medical treatment. The primary endpoint is a composite of CHD death, nonfatal myocardial infarction, fatal and nonfatal ischemic stroke, and unstable angina requiring hospitalization, and follow-up is planned for slightly more than 5 years.

Nonantibody PCSK9 Inhibition

Synthetic peptides mimetic for the C-terminal domain of PCSK9 have been created in an attempt to block its binding to the EGF-A binding domain of LDL-R, but they have not yet been tested in humans. Adnectins are a new family of therapeutic proteins that bind to targets with very high affinity and specificity, similar to antibodies, but are easier to genetically manipulate.[77] An anti-PCSK9 adnectin, BMS-962476, is currently in phase I human trials.[78]

Although small molecules might be developed to directly inhibit PCSK9 binding to the LDL-R, agents capable of blocking the large

domains involved have not been reported and indeed may not be feasible.

Antisense oligonucleotides (siRNA) to inhibit *PCSK9* gene expression and synthesis have been developed and studied in humans; however, the development of one such inhibitor, SPC5001, was prematurely terminated recently in phase I trial for unclear reasons. A second siRNA, in a phase I trial, showed a 70% reduction in circulating PCSK9 levels but only a 40% reduction from baseline in LDL-C ($P < .0001$ vs placebo).[46]

Conclusions

LDL is the major atherogenic particle in most patients at high risk for ASCVD events and non-HDL incorporates all atherogenic lipoproteins. Statin monotherapy reduces ASCVD in proportion to on-treatment LDL-C and non-HDL-C, but residual elevations predict residual ASCVD risk. In 2013, a new set of US-based guidelines encouraged moderate- to high-intensity statin monotherapy but sharply downplayed the potential value of non-statin treatments and the use of goals or targets for on-treatment LDL-C or non-HDL-C levels. Nevertheless, treating to achieve low LDL-C and non-HDL-C levels remains a top priority for high-risk patients. Statin-based LDL-C lowering is the mainstay of ASCVD prevention, but many patients tolerate statins poorly or do not achieve adequate LDL-C control with maximal available treatment, including non-statins. PCSK9 recently has been discovered as a powerful endogenous factor for down-regulating LDL-R number (and hence activity) and increasing LDL-C levels. Among several classes of PCSK9-inhibitor agents under clinical testing, mAbs to PCSK9 are the farthest developed. They appear to be as or more effective than statins for LDL-C lowering, and are well tolerated and appear safe in clinical trials to date. Ongoing cardiovascular disease endpoint trials with PCSK9 mAbs will determine if they have adequate safety and efficacy in ASCVD prevention to warrant their approval for clinical use. ■

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MAIN POINTS

- Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of death and disability in the United States and other developed nations, and is rising rapidly in other parts of the world. Low-density lipoprotein (LDL) is the major atherogenic particle in most patients at high risk for ASCVD events.
- The 2013 ACC/AHA cholesterol guidelines encouraged moderate- to high-intensity statin monotherapy but sharply downplayed the potential value of nonstatin treatments and the use of goals for on-treatment LDL cholesterol (LDL-C) or non–high-density lipoprotein cholesterol levels. This surprising and controversial departure from usual guideline content was explained as resulting from a lack of randomized clinical trial data directly supporting these traditional lipid guideline elements.
- PCSK9 binds to the epidermal growth factor-like repeat A (EGF-A) domain of the LDL receptor (LDL-R), stimulating LDL-R degradation. This increased loss of LDL-R decreases the catabolism of LDL, thus raising plasma LDL-C levels.
- Of all possible pharmacologic means to interfere with PCSK9 activity, antibody-mediated inhibition has emerged as the primary pathway of clinical pharmaceutical development. Monoclonal antibodies to PCSK9 appear to be as or more effective than statins for LDL-C lowering, are well tolerated, and appear safe in clinical trials to date.

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Activity Evaluation Form and Application for Continuing Medical Education Credit
Management of Hypercholesterolemia for Prevention of Atherosclerotic Cardiovascular Disease: Focus on the Potential Role of Recombinant Anti-PCSK9 Monoclonal Antibodies

Instructions to Receive Credit
In order to receive credit for this activity, the participant must complete the post-test available online at www.mrcme-online.com.
I am a: ☐ MD ☐ DO ☐ PharmD ☐ RN ☐ NP ☐ PA ☐ Other _____

Upon completion of this activity, participants will be able to:	**Strongly disagree**	**Disagree**	**Agree**	**Strongly agree**
• Explain the relationship between LDL-C levels and cardiovascular risk, emphasizing the need to achieve at least current NCEP treatment guidelines	**1**	**2**	**3**	**4**
• Identify CHD and CHD-equivalent patients requiring treatment to achieve secondary modification goals	**1**	**2**	**3**	**4**
• Identify areas of resistance in achieving and exceeding NCEP treatment goals	**1**	**2**	**3**	**4**
• Review the role of PCSK9 inhibition as solo and combination therapy in clinical trials relative to LDL-C levels, safety, and efficacy	**1**	**2**	**3**	**4**
Please indicate the extent of your agreement with the following statements:	**Strongly disagree**	**Disagree**	**Agree**	**Strongly agree**
• This activity was effective	**1**	**2**	**3**	**4**

- Overall, was this activity free from bias?
  Yes
  No
- Of the patients you will see in the next week, about how many will benefit from the information you learned today?
  More than 50
  26 to 50
  11 to 25
  1 to 10
  Not applicable
- Based on what I learned in this activity, I will improve my practice by incorporating the following (check all that apply):
  Improved diagnosis/patient assessment
  Useful therapies and appropriate uses
  Cutting-edge science in this therapeutic area
  Best practices of my colleagues and leaders
  I do not plan to make any changes to my practice at this time
  Other (explain) _____
- Which ONE delivery method do you find the most effective for CME/CE learning?
  Live symposia at national/regional conferences
  Live local meetings
  Live grand rounds
  Internet webcasts
  Internet/print monographs
  Other (explain) _____
- Please rate the professional practice value of each of the following in terms of improving your practice:

	Least Valuable	**Somewhat Valuable**	**Valuable**	**Most Valuable**
This CME activity	1	2	3	4
Direct to consumer advertising	1	2	3	4
Sales representative visits	1	2	3	4
Promotional/other noncertified education	1	2	3	4

- Based on your experience, which of the following are the primary barriers to implementing changes in practice (check all that apply):
  Lack of knowledge regarding evidence-based strategies
  Lack of convincing evidence to warrant change
  Lack of time/resources to consider change
  Insurance, reimbursement, or legal issues
  Other (explain)
- What motivated you to participate in this activity?
  CME credits
  Faculty
  Topic or therapeutic area
  Format type

SELF-ASSESSMENT POST-TEST

Management of Hypercholesterolemia for Prevention of Atherosclerotic Cardiovascular Disease: Focus on the Potential Role of Recombinant Anti-PCSK9 Monoclonal Antibodies

1. The use of statin monotherapy generally reduces atherosclerotic cardiovascular disease (ASCVD) risk by 40% to 60%.
   A. True
   B. False

2. According to the 2013 American College of Cardiology/American Heart Association (ACC/AHA) cholesterol guidelines, patients for whom statin benefits outweigh risks are
   A. Those with a 10-year ASCVD risk as calculated by the new ACC/AHA risk calculator of ≥ 7.5% (and low-density lipoprotein [LDL-C] ≥ 70-189 mg/dL)
   B. Those with type 2 diabetes, but not type 1 diabetes
   C. Those with a prior ASCVD event
   D. Both A and C

3. A surprising and controversial change from prior lipid guidelines to the 2013 ACC/AHA cholesterol guidelines was the lack of endorsement of LDL-C and non-HDL-C goals. This change was driven by
   A. A lack of evidence between randomized statin trials that lower on-treatment LDL-C predicts lower ASCVD risk
   B. A lack of evidence within any given randomized statin trials lower on-treatment LDL-C predicts lower ASCVD risk
   C. New randomized statin trial evidence showing that use of lipid goals distracts providers and patients from needed focus on statin compliance
   D. None of the above

4. Loss-of-function mutations in PCSK9 result in modest (15%-28%) reductions in plasma LDL-C but significant (47%-88%) reductions in ASCVD, and no apparent adverse effects. This suggests that PCSK9 inhibition is a good target for lipid drug development.
   A. True
   B. False

5. LDL uptake by the liver is reduced when
   A. PCSK9 is reduced (genetically or otherwise) in its binding to the LDL receptor, causing a decrease in the binding affinity of LDL to its receptor
   B. PCSK9 binds excessively to the LDL receptor, increasing LDL receptor recycling
   C. PCSK9 synthesis is decreased in response to increased intrahepatic cholesterol levels
   D. PCSK9 activity is increased, reducing the normal rate of return of the LDL-receptor to the hepatocyte surface
   E. PCSK9 activity is increased, directly blocking internalization of the LDL-receptor complex (receptor bound to LDL)

6. Monoclonal antibodies to PCSK9 are at least as effective, if not more so, than statin drugs for LDL-C lowering.
   A. True
   B. False

7. A 66-year-old Hispanic woman presents with a history of an MI 5 years ago and a subsequent history of severe muscle pain and cramping when treated with simvastatin, atorvastatin, rosuvastatin and pravastatin. Her current fasting lipid panel shows:
   Total Chol, 208 mg/dL
   Triglycerides, 126 mg/dL
   HDL-C, 52 mg/dL
   LDL-C, 131 mg/dL
   Non-HDL-C, 161 mg/dL

   Which one of the following is the most correct about her best clinical management at this point?
   A. She should receive no lipid treatment because she doesn't tolerate statins and they are the only evidence-based lipid treatment for prevention of ASCVD
   B. She should receive no lipid treatment because she doesn't tolerate statins and non-statins have an unfavorable risk-benefit ratio
   C. She should be tried again on a statin along with nonsteroidal anti-inflammatory agents to manage her muscle symptoms
   D. She should receive non-statin lipid treatment because her ASCVD risk is high due to her likely having heterozygous familial hypercholesterolemia, and non-statins are allowed in such cases
   E. She should receive non-statin lipid treatment because she has had a prior ASCVD event, and randomized trials have shown secondary prevention of ASCVD with non-statin monotherapy