Hypercholesterolemia is a major risk factor for cardiovascular diseases, increasing the incidence of myocardial infarction and death. Statin-induced lowering of low-density lipoprotein cholesterol (LDL-C) reduces cardiovascular morbidity and mortality. However, many individuals treated with statins do not achieve their target levels of LDL-C, and thus, LDL-associated residual risk remains. Gain-of-function mutations of the proprotein convertase subtilisin/kexin type 9 (PCSK9) are associated with hypercholesterolemia and increased risk of cardiovascular events. Conversely, loss-of-function mutations are linked to low plasma LDL-C levels and a reduction of cardiovascular risk without known unwanted effects on individual health. Experimental studies have revealed that PCSK9 reduces the hepatic uptake of LDL-C by increasing the endosomal and lysosomal degradation of LDL receptors (LDLR). Low intracellular cholesterol levels in response to statin treatment activate the sterol regulatory element-binding protein-2 (SREBP-2), resulting in coexpression of LDLR and PCSK9. Although this self-regulatory mechanism contributes to maintain cholesterol homeostasis preventing excessive cholesterol uptake, it may limit the therapeutic effect of statins. A number of clinical studies have demonstrated that inhibition of PCSK9 alone and in addition to statins potently reduces serum LDL-C concentrations. Moreover, experimental studies indicate that PCSK9 might accelerate atherosclerosis by promoting inflammation, endothelial dysfunction, and hypertension by mechanisms independent of the LDLR. Further research is needed to characterize the potential therapeutic and to rule out unwanted off-target effects of PCSK9 inhibition. In this review we elucidate the role of PCSK9 in lipid homeostasis, highlight the impact of PCSK9 on atherosclerosis, and summarize current therapeutic strategies targeting PCSK9. (J Am Coll Cardiol 2013;62:1401–8) © 2013 by the American College of Cardiology Foundation
Molecular Basis of PCSK9 Function

PCSK9 is the latest member of the proprotein convertase family, which currently consists of 9 members. The first 8 of these family members (proprotein convertase-1 [PC1], PC2, furin, PC4, PC5, paired basic amino acid cleaving enzyme-4 [PACE4], PC7, and subtilisin kexin isozyme-1) cleave protein precursors of growth factors, hormones, receptors, and transmembrane transcription factors passing through the secretory pathway (11). In contrast, PCSK9 enhances the endosomal and lysosomal degradation of cell surface receptors that regulate lipid metabolism in a nonenzymatic fashion (12).

PCSK9 is synthesized as a 73-kDa zymogen of 692 amino acids and contains a signal peptide, a prodomain (residues 31 to 152) and a catalytic domain (residues 153 to 451) followed by a C-terminal domain (residues 452 to 692) (13). PCSK9 undergoes intramolecular autocatalytic processing at the FAQ152 SIP site in the endoplasmic reticulum (ER) to form a 14-kDa prodomain and a 63-kDa mature PCSK9 (14). After cleavage, the prodomain remains closely attached to the catalytic domain of PCSK9 blocking the substrate-binding site (1,15–17). Autocatalytic cleavage is required for trafficking PCSK9 from the ER to the secretory pathway (Fig. 1A) (18,19). In the extracellular pathway, PCSK9 is secreted from the trans-Golgi network and internalized together with the LDLR in clathrin-coated endosomes, promoting degradation of LDLR (18). This step requires binding of the cytosolic adaptor protein autosomal recessive hypercholesterolemia (ARH) protein (20). In the intracellular pathway, PCSK9 is directly sorted to lysosomes together with LDLR, leading to its degradation (5,12). The catalytic subunit of PCSK9 binds to the epidermal growth factor-like repeat homology domain (EGF-A) in human LDLR (17,21,22). Secretion of the prodomain together with a catalytically inactive PCSK9 was shown to promote regular degradation of LDLR, suggesting that secreted PCSK9 acts as a chaperone rather than as a catalytic enzyme (21,23).

Role of PCSK9 in Lipid Homeostasis

Hepatic cholesterol metabolism. The major part of circulating LDL-C is removed from the plasma by hepatic uptake. This process is mediated via transmembrane LDLR that internalizes bound LDL particles by endocytosis (Fig. 1A) (24). After intracellular dissociation, the LDLR recycles to the cell surface for reuse. Each LDLR is recycled up to 150 times, indicating that slight changes in LDLR availability by PCSK9-induced degradation might lead to considerable changes in LDL-C (25).
cholesterol levels activate the sterol regulatory element-binding protein-2 (SREBP-2), leading to increased LDLR gene expression, which enhances LDL-C clearance from the circulation (3,26). Of note, SREBP-2 also induces expression of PCSK9, leading to LDLR degradation, thus limiting hepatic cholesterol uptake and increasing circulating LDL-C (Fig. 2) (3,26). This highly coordinated expression pattern contributes to a self-regulatory system preventing excessive cholesterol uptake in order to preserve cholesterol homeostasis.

**Intestinal lipid metabolism.** PCSK9 is also expressed in the small intestine of mice and in human intestinal cells, which play a central role in the regulation of lipid absorption (27). In vitro, treatment of human intestinal epithelial cells with recombinant PCSK9 enhanced cholesterol uptake, reduced HMG-CoA reductase activity and thus cholesterol synthesis, and increased protein expression of the cholesterol transporters NPC1L1 and CD36 (28). In mice, gene inactivation of PCSK9 significantly reduced postprandial triglyceridemia and enhanced clearance of chylomicrons (27). In clinical studies, reduction of circulating PCSK9 by treatment with a monoclonal antibody (mAb) was associated with a reduction in serum triglyceride levels (29). The clinical effects of intestinal PCSK9 modulation deserve further investigation.

**Impact of PCSK9 on Atherosclerosis**

Hypercholesterolemia is a major cardiovascular risk factor that accelerates the process of atherosclerotic plaque formation, thus increasing the incidence of stroke and myocardial infarction. In mice fed a high-fat high-cholesterol diet, gene inactivation of PCSK9 significantly reduced aortic cholesteryl esters, which were markedly increased by overexpression of PCSK9, resulting in accelerated development of atherosclerotic plaque (30). Comparable effects were observed in apolipoprotein E (ApoE)-deficient mice expressing null, normal, or high levels of PCSK9 (30). Interestingly, circulating LDL-C levels differed only slightly among these animals, and it is unclear whether the slightly higher LDL-C level found in transgenic mice is the only cause of the marked increase in plaque burden observed in these animals (30). In LDLR-deficient mice expressing null, normal, or high levels of PCSK9, the circulating cholesterol levels and aortic accumulation of cholesteryl esters were similar to those of wild-type mice, indicating that the harmful effect of PCSK9 on atherogenesis is mediated mainly by degradation of LDLR (30). Transgenic mice expressing high levels of PCSK9 and low levels of LDLR in the liver were less prone to atherosclerosis than LDLR-deficient mice, pointing to a key role of a LDLR fraction that is resistant to PCSK9. This fraction might be located intracellularly, as PCSK9 acts primarily on the LDLR in the post-Golgi compartment and on the cell surface. In addition, extrahepatic LDLR, which might be less sensitive to circulating PCSK9, could contribute to LDL-C uptake in transgenic mice (30).

Recently, it has been shown that PCSK9 is also expressed in human atherosclerotic plaques (31). In vitro, PCSK9 secreted by vascular smooth muscle cells reduced LDLR expression and LDL-C uptake of human and murine macrophages, which might result in vascular lipid accumulation and oxidation (31). Interestingly, a number of experimental studies have identified additional mechanisms by which PCSK9 might affect vascular biology (Table 1).

**Inflammation.** It is well established that atherosclerosis is a chronic inflammatory disease (32). Systemic inflammation is closely related to alterations in lipid metabolism. Although interaction between metabolic and inflammatory pathways is required for homeostasis, impaired crosstalk between these pathways may also lead to metabolic dysregulation. In mice, systemic inflammation induced by administration of lipopolysaccharide led to increased expression of PCSK9 and decreased hepatic levels of LDLR, which was associated with a significant increase in circulating LDL-C (33). Furthermore, small interfering RNA (siRNA)-mediated knockdown of PCSK9 in human macrophages attenuated inhibitor of nuclear factor kappa B alpha (IκB-α) degradation and nuclear factor kappa beta (NF-κB) nuclear translocation, thereby increasing expression of proinflammatory genes (34). Another proinflammatory mechanism might be PCSK9-induced degradation of ApoE-receptor 2 (35), which maintains an anti-inflammatory phenotype in macrophages (36) and mediates antiapoptotic signaling (37). In contrast, in HepG2 cells expressing the naturally occurring gain-of-function mutation D374Y, microarray analysis revealed that this mutation reduces expression of stress-response genes and specific inflammatory pathways (38).
Taken together, the effects of PCSK9 on inflammatory pathways are of interest with regard to vascular biology and their clinical consequences remain to be established. **Apoptotic cell death.** Endothelial apoptosis and subsequent endothelial dysfunction plays a central role in the pathogenesis of atherosclerosis. In human endothelial cells, oxidized LDL (ox-LDL)-induced apoptosis was associated with increased expression of PCSK9. Knockdown of PCSK9 expression by siRNA significantly reduced ox-LDL-induced apoptosis by altering the Bcl-2/Bax ratio and by inhibiting the activation of both caspase-9 and -3 (39). Gene silencing of PCSK9 also decreased apoptotic cell death in cerebellar granule neurons (37). Reduced expression of PCSK9 was associated with increased levels of the ApoE-receptor 2. Knockdown of the ApoE-receptor 2 reversed the protective effect of PCSK9 RNA interference, indicating that pro-apoptotic effects of PCSK9 might be due to altered ApoE-receptor 2 function (37). In mice, ischemic stroke led to apoptotic effects of PCSK9 might be due to altered ApoE-receptor 2 function (37). In mice, gene inactivation of PCSK9 reduces insulin levels, resulting in glucose intolerance, which is associated with malformation, apoptosis, and inflammation of pancreatic islets. Transfection of epithelial cells with PCSK9 reduces expression of cell surface ENaC. In mice, gene inactivation of PCSK9 reduces insulin levels, resulting in glucose intolerance, which is associated with malformation, apoptosis, and inflammation of pancreatic islets.

**Blood pressure.** Hypertension enhances the progression of atherosclerosis (42). It is noteworthy that in pancreatic tissue of PCSK9(−/−) mice, expression of LDLR is increased while insulin levels are reduced, resulting in hyperglycemia and glucose intolerance (43). Glucose intolerance was associated with malformation, apoptosis, and inflammation of pancreatic islets, pointing to a potential regulatory role of PCSK9 in normal pancreatic function. However, in clinical studies inhibition of PCSK9 by mAb did not significantly alter glucose metabolism.

**Adipose tissue metabolism.** Obesity is related to increased prevalence of atherosclerotic risk factors (44). Interestingly, PCSK9(−/−) mice fed a normal chow diet for 6 months accumulated approximately 80% more visceral adipose tissue than wild-type mice (45). PCSK9 knockout was associated with adipocyte hypertrophy, enhanced in vivo fatty acid uptake, and ex vivo triglyceride synthesis. These effects were also observed in PCSK9(−/−)/LDLR(−/−) mice, indicating that degradation of the LDLR might not be involved. In addition to the LDLR, PCSK9 interacts with the very low density lipoprotein receptor (VLDLR), which is also expressing the EGF-A domain (35). In fact, PCSK9(−/−) mice showed significantly higher cell surface expression of VLDLR in perigonadal depots than wild-type mice. Hepatic expression of PCSK9 in PCSK9(−/−) female mice normalized both circulating PCSK9 levels and VLDLR levels. In contrast, inactivation of hepatic PCSK9 in wild-type females significantly increased perigonadal VLDLR expression, suggesting that PCSK9 may limit visceral adipogenesis via regulation of adipose VLDLR levels (45). However, PCSK9(−/−) mice do not develop liver steatosis and are not prone to obesity, suggesting that pharmacological inhibition of PCSK9 will probably not adversely affect central obesity. Ongoing clinical studies will address this point.

### Table 1: LDL-Independent Effects of PCSK9

<table>
<thead>
<tr>
<th>LDL-Independent Effect</th>
<th>Molecular Mechanism</th>
<th>Ref. #</th>
</tr>
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<tbody>
<tr>
<td>Inflammation</td>
<td>In mice, lipopolysaccharide-induced inflammation is associated with enhanced expression of PCSK9</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td>siRNA-mediated knockdown of PCSK9 in human macrophages attenuates oxLDL-induced IκB-α degradation and NF-κB nuclear translocation.</td>
<td>34</td>
</tr>
<tr>
<td></td>
<td>PCSK9 gain-of-function mutation D374Y reduces expression of stress response genes and specific inflammatory pathways in HepG2 cells.</td>
<td>38</td>
</tr>
<tr>
<td>Endothelial apoptosis</td>
<td>Knockdown of PCSK9 by siRNA reduces oxLDL-induced endothelial apoptosis by altering the Bcl-2/Bax ratio and by inhibiting the activation of both caspase-9 and -3.</td>
<td>39</td>
</tr>
<tr>
<td>Blood pressure regulation</td>
<td>Transfection of epithelial cells with PCSK9 reduces expression of cell surface ENaC.</td>
<td>41</td>
</tr>
<tr>
<td>Glucose metabolism</td>
<td>In mice, gene inactivation of PCSK9 reduces insulin levels, resulting in glucose intolerance, which is associated with malformation, apoptosis, and inflammation of pancreatic islets.</td>
<td>43</td>
</tr>
<tr>
<td>Adipogenesis</td>
<td>PCSK9 limits murine adipogenesis via regulation of adipose VLDLR levels.</td>
<td>45</td>
</tr>
</tbody>
</table>

**Bax** = Bcl-2-associated X protein; **Bcl-2** = B-cell lymphoma 2; **ENaC** = Epithelial (Na⁺) channel; **IκB-α** = inhibitor of nuclear factor kappaB alpha; **LDLR** = low-density lipoprotein receptor; **NF-κB** = nuclear factor kappaB; **oxLDL** = oxidized LDL; **PCSK9** = proprotein convertase subtilisin/kexin type 9; **siRNA** = small interfering RNA; **VLDLR** = very low-density lipoprotein receptor.

**Glucose tolerance.** Diabetes is associated with accelerated atherosclerosis (42). It is noteworthy that in pancreatic tissue of PCSK9(−/−) mice, expression of LDLR is increased while insulin levels are reduced, resulting in hyperglycemia and glucose intolerance (43). Glucose intolerance was associated with malformation, apoptosis, and inflammation of pancreatic islets, pointing to a potential regulatory role of PCSK9 in normal pancreatic function. However, in clinical studies inhibition of PCSK9 by mAb did not significantly alter glucose metabolism.

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Therapeutic Implications

Dyslipidemia is a major cardiovascular risk factor accountable for 54% of population-attributable risk for myocardial infarction (46). Statin-induced reduction in LDL-C by 1 mmol/l in 5 years is associated with a 12% decrease in all-cause mortality and a 19% decrease in cardiovascular mortality (47). However, a significant number of individuals with hypercholesterolemia do not achieve optimal levels of LDL-C using currently available therapies (48,49). In Europe and Canada, nearly 50% of hypercholesterolemic subjects are not at their individual LDL-C target despite treatment with statins (50). This fact might be explained by an inadequate statin dosing, adverse effects under required dose, statin-resistance, or insufficient adherence. Therefore, additional pharmacologic strategies to lower cholesterol are of significant interest (51).

In addition, statin treatment increases the expression of PCSK9 in both normolipidemic and dyslipidemic subjects (52,53). In the JUPITER (Justification for the Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) study, a randomized double-blind placebo-controlled trial, treatment with 20 mg of rosuvastatin resulted in a 28% increase in PCSK9 in men and 35% in women, respectively (54). This phenomenon might be explained by the fact that low intracellular cholesterol levels control gene expression of both LDLR and PCSK9 via nuclear translocation of SREBP-2 (55). Accordingly, missense mutations and loss-of function mutations in the PCSK9 gene are associated with increased statin response and hypocholesterolemia, pointing to the potential benefit of PCSK9 inhibition alone and its potentially additive effect in combination with statins (56,57). Table 2 summarizes the pharmacologic approaches targeting PCSK9 synthesis or function that are currently under development.

### Table 2 Therapeutic Approaches Targeting PCSK9

<table>
<thead>
<tr>
<th>Mechanism of Action</th>
<th>Agent</th>
<th>Company/Sponsor</th>
<th>Phase</th>
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<tbody>
<tr>
<td>Monoclonal antibodies</td>
<td>SAR236553/REGN727</td>
<td>Sanofi/Regeneron</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>AMG 145</td>
<td>Amgen</td>
<td>3</td>
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<tr>
<td></td>
<td>RN316</td>
<td>Pfizer</td>
<td>2</td>
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<tr>
<td></td>
<td>RG7652</td>
<td>Roche/Genentech</td>
<td>2</td>
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<tr>
<td></td>
<td>LGT-209</td>
<td>Novartis</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>1D05-lg02</td>
<td>Merck</td>
<td>Pre-clinical</td>
</tr>
<tr>
<td></td>
<td>1B20</td>
<td>Merck</td>
<td>Pre-clinical</td>
</tr>
<tr>
<td></td>
<td>1J10, 1J6</td>
<td>Pfizer</td>
<td>Pre-clinical</td>
</tr>
<tr>
<td></td>
<td>1J17</td>
<td>Pfizer</td>
<td>Pre-clinical</td>
</tr>
<tr>
<td>Adnectins</td>
<td>BMS-962476</td>
<td>Bristol-Myers Squibb/Adnexus</td>
<td>1</td>
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<tr>
<td>Mimetic peptides</td>
<td>EGF-AB peptide fragment</td>
<td>Schering-Plough</td>
<td>Pre-clinical</td>
</tr>
<tr>
<td></td>
<td>LDLR (H306Y) subfragment</td>
<td>U.S. National Institutes of Health</td>
<td>Pre-clinical</td>
</tr>
<tr>
<td></td>
<td>LDLR DNA construct</td>
<td>U.S. National Institutes of Health</td>
<td>Pre-clinical</td>
</tr>
<tr>
<td>Small-molecule inhibitors</td>
<td>SX-PCK9</td>
<td>Serometrix</td>
<td>Pre-clinical</td>
</tr>
<tr>
<td></td>
<td>TBD</td>
<td>Shifa Biomedical</td>
<td>Pre-clinical</td>
</tr>
<tr>
<td>Antisense oligonucleotides</td>
<td>ISIS 394814</td>
<td>Isis</td>
<td>Pre-clinical</td>
</tr>
<tr>
<td></td>
<td>SPC4061</td>
<td>Santaris-Pharma</td>
<td>Pre-clinical</td>
</tr>
<tr>
<td></td>
<td>SPCS011</td>
<td>Santaris-Pharma</td>
<td>1 (terminated)</td>
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<tr>
<td>RNA interference</td>
<td>ALN-PCS02</td>
<td>Alnylam</td>
<td>1</td>
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</table>

**Mimetic peptides and adnectins.** Mimetic peptides are designed as competitive inhibitors that mimic the EGF-A binding domain of the LDLR, which interacts with PCSK9 (Fig. 1B). In HepG2 cells, a synthetic EGF-A peptide that binds the LDLR, dose-dependently inhibits PCSK9-mediated degradation of LDLR (58). The isolated C-terminal domain of PCSK9 reduces PCSK9-mediated degradation of LDLR in vitro and in mice (59). Therefore, the use of short PCSK9 fragments that competitively bind to the LDLR without causing its degradation represents an alternative approach.

Adnectins are genetically engineered target-binding proteins comprising a scaffold of the human fibronectin. Adnectins have similarities with mAb but are smaller in size, as they are single domain structures without disulfide bonds (60). The adnectin BMS–962476 is currently tested in a phase I trial (see Table 2).

**Small-molecule inhibitors.** A promising strategy could be the development of small molecules, which can be administered orally. A pre-clinical trial of a small-molecule agent has been announced; however, the approach seems challenging. First, the stability and potency of small molecules in plasma is poor (12). Second, it is difficult to develop a molecule that targets the flat and large binding interface of LDLR and PCSK9 (61). Third, small molecules might arbitrarily affect PCSK9 function at different levels including intracellular processing, secretion, and interaction with LDLR (62).

**Gene Silencing.** Alternative techniques to inhibit PCSK9 function relate to the use of either antisense oligonucleotides or siRNAs targeting PCSK9 gene expression (Fig. 1B). In mice fed a high-fat diet, intraperitoneal administration of PCSK9-antisense oligonucleotides increased hepatic LDLR
expression by two-fold and reduced circulating LDL-C by 38% (63). Correspondingly, locked nucleic acid-antisense oligonucleotides such as SPC5001 significantly reduced PCSK9 levels and increased hepatic LDLR expression, resulting in lower circulating LDL-C levels in mice and nonhuman primates (64,65). However, a dose-escalating double-blind phase I trial with SPC5001 in healthy individuals and individuals with familial hypercholesterolemia was prematurely terminated in 2011 for unknown reasons.

In addition to antisense oligonucleotides, intravenously administered siRNAs targeting PCSK9 mRNA were shown to effectively reduce circulating LDL-C levels by 50% to 70% in mice and rats and by 50% in nonhuman primates (66). The injection of a PCSK9 siRNA (ALN-PCS) resulted in a dose-dependent and durable reduction of LDL-C by up to 50% relative to baseline and placebo and a mean reduction of 41% (p < 0.01) in 32 healthy individuals with elevated baseline LDL-C (>116 mg/dl). Further development and testing of the second-generation ALN-PCS02, and of the subcutaneously administered ALN-PCSc were announced (67).

Monoclonal antibodies. The most promising strategy to inhibit PCSK9–mediated degradation of LDLR seems to be the use of mAb (Fig. 1B). In 2009, the first mAb was intravenously administered to cynomolgus monkeys and resulted in an 80% reduction of LDL-C (68). In the following years, a number of other mAb, such as 1D05-IgG2 (Merck), 1B20 (Merck); and J10, J16, and J17 (Pfizer) were developed and successfully tested in mice and nonhuman primates (Table 2). Several human mAb have entered clinical phase 2 trials, including RN316 (Pfizer), LGT209 (Novartis), and AMG145 (Amgen) and SAR236553/REGN727 (Sano/Regeneron) are currently being evaluated in phase 3 trials.

In a phase 1 ascending single-dose study, AMG145 injected intravenously or subcutaneously reduced LDL-C by up to 64% versus placebo in healthy individuals (p < 0.0001) (69). In patients receiving a stable statin dose, AMG145 reduced circulating LDL-C by 75%, without report of serious adverse effects. In the following 4 phase 2 trials, the effect of AMG145 was investigated in patients with statin-intolerance (70), in patients with heterozygous familial hypercholesterolemia (71), or those with non-familial hypercholesterolemia with (72) or without lipid-lowering therapy (73). These trials examined the effect of different doses of AMG145 (70 to 420 mg) injected every 2 weeks or every 4 weeks on circulating LDL-C levels. In summary, subcutaneous administration of AMG145 every 2 weeks led to significant and sustained reduction of LDL-C, ranging from 41% to 66%. No treatment-related serious adverse events were reported (74). The effects of AMG145 on clinical outcomes are characterized in the large phase 3 PROFICIO study program. The most important trial is the FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects With Elevated Risk) study testing the effects of AMG145 on cardiovascular events in >20,000 patients with prior myocardial infarction or stroke, with at least 1 major or 2 minor coronary risk factors, and fasting LDL-C level >70 mg/dl or non-high-density lipoprotein cholesterol level of ≥100 mg/dl taking stable maximal tolerated doses of atorvastatin with or without ezetimibe (75).

The mAb SAR236553/REGN727 was compared to placebo in several clinical studies in healthy volunteers with LDL-C concentration >100 mg/dl, in patients with heterozygous familial hypercholesterolemia or nonfamilial hypercholesterolemia receiving stable doses of atorvastatin, and in patients with nonfamilial hypercholesterolemia (76). These studies were followed by multicenter, double-blinded, phase 2 trials including patients with hypercholesterolemia (LDL-C >100 mg/dl) despite treatment with stable doses of atorvastatin (29), patients with heterozygous familial hypercholesterolemia receiving stable doses of statins with or without ezetimibe (77), and patients with hypercholesterolemia (LDL-C >100 mg/dl) despite treatment with atorvastatin (78). Consistently, SAR236553/REGN727 therapy resulted in reductions of LDL-C levels of 50% to 70%. The effects of SAR236553/REGN727 on clinical events are further assessed in the large phase 3 ODYSSEY study program including the ODYSSEY OUTCOME trial in 18,000 patients who recently suffered an acute coronary syndrome (74).

Conclusions and Future Perspectives

PCSK9 plays a central role in the regulation of cholesterol homeostasis by increasing the degradation of hepatic LDLR, resulting in hypercholesterolemia, a major cardiovascular risk factor for atherosclerosis. In clinical studies, inhibition of PCSK9 in addition to statin treatment potently reduced serum LDL-C. Ongoing studies will evaluate the impact of inhibiting PCSK9 on the incidence of cardiovascular events. Experimental studies report that PCSK9 might accelerate atherosclerosis by mechanisms beyond degradation of hepatic LDLR. These pre-clinical experimental data suggest that further research is needed to understand the potential beneficial therapeutic effects and to rule out unwanted off-target effects of PCSK9 inhibition. Specifically, it is of interest to systematically investigate the role of PCSK9 for the pathogenesis of diabetes, obesity, hypertension, inflammation, and endothelial dysfunction. These studies will help to further characterize and understand the function of PCSK9 in human health and disease.

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Key Words: atherosclerosis • LDL cholesterol • LDL receptor • PCSK9 • proprotein convertase subtilisin/kexin type 9.