Lipid Lowering Therapy and Circulating PCSK9 Concentration

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Hypercholesterolemia, particularly an increase in low-density lipoprotein cholesterol (LDL-C) levels, contributes substantially to the development of coronary artery disease and the risk for cardiovascular events. As the first-line pharmacotherapy, statins have been shown to reduce both LDL-C levels and cardiovascular events. However, despite intensive statin therapy, a sizable proportion of statin-treated patients are unable to achieve the recommended target LDL-C levels, and not all patients can avoid future cardiovascular events. Proprotein convertase subtilisin/kexin type 9 (PCSK9) plays a key role in cholesterol homeostasis by enhancing the degradation of hepatic low-density lipoprotein receptor (LDLR). Owing to its importance in lipid metabolism, PCSK9 has emerged as a novel pharmacological target for lowering LDL-C levels. In this review, the potential role of circulating PCSK9 as a new biomarker of lipid metabolism is described. Next, previous studies evaluating the effects of lipid-modifying pharmacological agents, particularly statins, on circulating PCSK9 concentrations are summarized. Statins decrease hepatic intracellular cholesterol, resulting in increased LDLRs as well as increased PCSK9 protein. There is a clear dose-response effect of statin treatment on PCSK9 level, as increasing doses of statins also increase the level of circulating PCSK9. Finally, the available therapeutic strategies to inhibit PCSK9 are present. Monoclonal antibodies against PCSK9, in combination with statins, are one of the most promising and novel approaches to achieve further reduction of LDL-C levels and reduce the risk of cardiovascular events.

Key words: Familial hypercholesterolemia (FH), Low-density lipoprotein cholesterol (LDL-C), Low-density lipoprotein receptor (LDLR), Proprotein convertase subtilisin/kexin type 9 (PCSK9), Statin

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The serum PCSK9 level does not reflect total hepatic PCSK9 secretion, as the high levels of PCSK9 are cleared from circulation by binding to hepatic LDLRs. However, the mechanism by which PCSK9 is cleared from the circulation is not fully understood, as Cameron et al. have reported that plasma PCSK9 is cleared by an LDLR-independent mechanism. Circulating PCSK9 is present not only in its free form, but is also as a complex with apoB-containing lipoproteins. Furthermore, PCSK9 directly increases hepatic production of apoB-containing lipoproteins. Among several ELISAs that have been developed to measure PCSK9 concentrations, it remains unclear which form of PCSK9 is detected by each assay, except for two reports of the detection of both mature and furin-cleaved PCSK9. Moreover, PCSK9 concentrations varied widely between different assays (80–4000 ng/mL). Finally, PCSK9 concentrations are reduced with fasting (up to 58% lower following 36 h of fasting). Despite wide fluctuations in plasma PCSK9 concentrations over the course of a day, however, little diurnal variation in plasma LDL-C levels has been reported. Thus, additional factors may contribute to the relationship between circulating PCSK9 and LDL-C levels.

**Lipid-Modifying Pharmacological Agents and PCSK9 Concentrations**

Statins

Statins, HMG-CoA reductase inhibitors, are the...
The effect of statin therapy on circulating PCSK9 concentration is summarized in Table 1. Mayne et al. reported that 6 weeks of treatment with 10 mg of atorvastatin significantly increased plasma PCSK9 by 7.4% \(^{37}\). Costet et al. also reported that 10 mg of atorvastatin treatment increased PCSK9 by 14% at 6 weeks \(^{38}\). Guo et al. reported that atorvastatin 10 mg slightly increased serum PCSK9 by 5–7%, although the effect was not significant, while atorvastatin 20 mg significantly increased serum PCSK9 by 35% at 8 weeks \(^{39}\). Careskey et al. reported that 16 weeks of treatment with 40 mg of atorvastatin reduced LDL-C levels by 42%, with a significant 34% increase in serum PCSK9 levels \(^{15}\). Welder et al. reported that 80 mg of atorvastatin increased PCSK9 levels by 47% and decreased LDL-C levels by 55% \(^{33}\). Finally, Khera et al. reported that 16 weeks of treatment with 10 mg and 80 mg atorvastatin increased circulating PCSK9 levels by 19% and 27%, respectively \(^{40}\). These results suggest a clear dose-response effect of atorvastatin on PCSK9 levels, with higher doses of atorvastatin causing a greater increase in circulating PCSK9 concentrations. However, the effects of other types of statins on
an increase in plasma PCSK9 concentration, although the extent of the increase in circulating PCSK9 may be dependent on the dose and the lipophilic or hydrophilic natures of the statin.

It is important to understand the rapidity with which statins increase PCSK9 levels, or whether this effect is sustained over time. Welder et al. reported that serum PCSK9 levels increased by 47% after 4 weeks of 80 mg atorvastatin, and this increase was sustained at 8, 12, and 16 weeks. They concluded that high-dose atorvastatin caused a rapid, sustained increase in serum PCSK9.

Guo et al. also reported that atorvastatin 10 mg showed a tendency to increase PCSK9 levels but this effect was not statistically significant, although atorvastatin 20 mg significantly increased serum PCSK9 by 30% at 4 weeks and by 35% at 8 weeks. They further investigated the rapidity of atorvastatin treatment on PCSK9 level, and found that serum PCSK9 rapidly increased by 13% following 24 h treatment with atorvastatin 10 mg and by 27% with atorvastatin 80 mg. Thus, they concluded that the short-term impact of low-dose atorvastatin on PCSK9 level was time and dose dependent, with a

- **Table 1. Effect of statins on circulating PCSK9 levels**

<table>
<thead>
<tr>
<th>Types of statin</th>
<th>Dose (mg/day)</th>
<th>Duration of treatment</th>
<th>% change in PCSK9</th>
<th>Author (reference)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>10</td>
<td>1 day</td>
<td>13%</td>
<td>Guo (39)</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>1 day</td>
<td>24%</td>
<td>Costet (38)</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>4 weeks</td>
<td>5.7%</td>
<td>Guo (39)</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>6 weeks</td>
<td>7.4%</td>
<td>Mayne (37)</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>6 weeks</td>
<td>14%</td>
<td>Costet (38)</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>8 weeks</td>
<td>7.2%</td>
<td>Guo (39)</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>16 weeks</td>
<td>19%</td>
<td>Khera (40)</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>4 weeks</td>
<td>30%</td>
<td>Guo (39)</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>8 weeks</td>
<td>35%</td>
<td>Guo (39)</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>8 weeks</td>
<td>39%</td>
<td>Guo (98)</td>
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<td></td>
<td>40</td>
<td>12 weeks</td>
<td>38%</td>
<td>Tremblay (99)</td>
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<td></td>
<td>40</td>
<td>16 weeks</td>
<td>34%</td>
<td>Careskey (15)</td>
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<tr>
<td></td>
<td>80</td>
<td>1 day</td>
<td>27%</td>
<td>Guo (39)</td>
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<tr>
<td></td>
<td>80</td>
<td>4 weeks</td>
<td>37%</td>
<td>Raal (42)</td>
</tr>
<tr>
<td></td>
<td>80</td>
<td>16 weeks</td>
<td>27%</td>
<td>Khera (40)</td>
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<tr>
<td></td>
<td>80</td>
<td>16 weeks</td>
<td>47%</td>
<td>Welder (33)</td>
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<tr>
<td>Simvastatin</td>
<td>10</td>
<td>6 weeks</td>
<td>no change</td>
<td>Lakoski (21)</td>
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<td></td>
<td>20</td>
<td>16 weeks</td>
<td>13%</td>
<td>Khera (40)</td>
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<td></td>
<td>40</td>
<td>14 days</td>
<td>68%</td>
<td>Berthold (41)</td>
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<tr>
<td></td>
<td>80</td>
<td>16 weeks</td>
<td>41%</td>
<td>Khera (40)</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>20</td>
<td>1 year</td>
<td>28-35%</td>
<td>Awan (22)</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td>4 weeks</td>
<td>37%</td>
<td>Raal (42)</td>
</tr>
<tr>
<td>Pitavastatin</td>
<td>4</td>
<td>8 months</td>
<td>31%</td>
<td>Nozue (43)</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>20</td>
<td>8 months</td>
<td>34%</td>
<td>Nozue (43)</td>
</tr>
</tbody>
</table>

PCSK9; proprotein convertase subtilisin/kexin type 9.
rapid increase in PCSK9 level observed within 24 h. This indicates that, although atorvastatin may up-regulate both the LDLR and PCSK9 genes by activating SREBP-2, the PCSK9 gene response to atorvastatin might be faster or more sensitive – or more dose-dependent – than the LDLR gene. By comparison, Okada et al. reported that plasma PCSK9 levels were significantly increased at 12 weeks of statin therapy, although this increase was not sustained and was lower at 52 weeks. Therefore, increases in serum PCSK9 levels caused by statin therapy appear to differ over short-, middle-, and long-term periods. Statins likely increase the expression and secretion of the PCSK9 protein to such an extent that circulating PCSK9 levels exceed LDLR binding capacity, resulting in increased PCSK9 protein being detected in the serum at an early stage of treatment. However, the increased PCSK9 protein subsequently binds to LDLR and this complex is cleared from the circulation. Thus, circulating PCSK9 may reach a plateau concentration in the long term.

More importantly, statin treatment completely abolishes the correlation between PCSK9 and plasma LDL-C level, restricting its putative usefulness as a biomarker of lipid metabolism in routine clinical practice. It is therefore relevant to consider whether baseline circulating PCSK9 levels can predict the efficacy of statins on LDL-C reduction. At least three studies have addressed this question, leading to discrepant results. First, Dubuc et al. observed a significant positive correlation between baseline plasma PCSK9 level and the percentage reduction in LDL-C after statin therapy. Welder et al. reported a modest relationship between baseline PCSK9 level and change in LDL-C, with a relatively higher baseline PCSK9 level tending to be associated with a numerically greater decrease in LDL-C; however, this correlation did not achieve statistical significance. Finally, another study failed to show a significant relationship between baseline PCSK9 level and response to LDL-lowering therapy. Additional randomized studies with higher doses and other types of statins are therefore needed to explicitly address this question.

Another question is whether the statin-induced increase in PCSK9 correlates with the magnitude of statin-induced reduction in LDL-C level. Awan et al. observed a significant relationship between LDL-C reduction and increased PCSK9 concentration in response to statin therapy. Berthold et al. also reported that increased PCSK9 was inversely correlated with the percentage change in LDL-C concentration. Welder et al. showed a trend toward an inverse correlation between percentage change in PCSK9 level and in LDL-C level, although this trend did not achieve statistical significance. However, Careskey et al. observed no significant relationship between increased PCSK9 level and reduced LDL-C after 4 months of treatment with 40 mg atorvastatin. Lakoski et al. also reported that changes in plasma PCSK9 level did not correlate with the magnitude of the LDL-C lowering response achieved with 10 mg of simvastatin. Consistent with these reports, we previously showed that the percentage change in PCSK9 level did not correlate with the LDL-C reduction observed after statins therapy. Furthermore, although the reduction in LDL-C was greater with pitavastatin than with pravastatin, the level of increase in PCSK9 did not differ between these statins. Therefore, it should be noted that the serum PCSK9 level might not reflect the full extent of the modulation of hepatic synthesis and secretion of the PCSK9 protein by statins.

Ezetimibe

Another commonly prescribed LDL-C-lowering drug is ezetimibe, a cholesterol absorption inhibitor that potently inhibits the absorption of biliary and dietary cholesterol by binding the cholesterol transport protein Niemann-Pick C1-Like 1. Ezetimibe lowers hepatic cholesterol levels by decreasing the amount of cholesterol supplied to the liver through intestinal uptake, leading to increased hepatic LDLR expression, which results in increased LDL uptake from the plasma and thus decreased circulating LDL-C levels. LDL-C reductions of approximately 21% and 23% were achieved by ezetimibe monotherapy and combination therapy with statins, respectively. Compared with statins, fewer studies have been reported on the effect of ezetimibe (alone or combined with statins) on PCSK9 levels. In a pre-clinical study, ezetimibe therapy alone for 7 months significantly increased plasma PCSK9 levels by 37% in dyslipidemic monkeys. Davignon et al. showed that ezetimibe added to statin therapy further increased PCSK9 levels beyond the increases observed with a statin alone. Dubuc et al. also reported that treatment with ezetimibe in combination with statins was associated with a significant increase in plasma PCSK9 levels compared with statin therapy alone. Berthold et al. investigated the effect of ezetimibe and simvastatin, alone and in combination, on circulating PCSK9 concentrations in healthy men. They found that ezetimibe treatment alone for 2 weeks increased plasma PCSK9 con-
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concentrations by 10%, although this increase was not significant. Furthermore, when ezetimibe was added to 40 mg of simvastatin, an incremental increase in PCSK9 concentration was not observed. Lakoski et al. reported 6 weeks of ezetimibe monotherapy had no significant effect on PCSK9 concentration, although LDL-C levels were lowered by 20%. Miyoshi et al. also reported that PCS99 concentrations were unchanged following ezetimibe monotherapy or in combination with strong statins for 24 weeks. Thus, although there are some discrepancies regarding the effect of ezetimibe on circulating PCSK9 levels, a recent meta-analysis reported that there was no significant elevation in plasma PCSK9 levels with statin/ezetimibe combination therapy compared with statin monotherapy. There are a number of potential explanations for these discrepancies. First, these differences may be related to the study period, as increases in serum PCSK9 levels caused by statin therapy differ according to treatment duration. Indeed, Okada et al. reported that ezetimibe as add-on to statin therapy had no effect on plasma PCSK9 levels at 12 weeks, but that PCSK9 was significantly increased at 52 weeks. Second, statin treatment maximally increases circulating PCSK9 to a plateau concentration, after which no further increase is possible by further lowering of LDL-C using ezetimibe. Third, statins upregulate peroxisome proliferator-activated receptor (PPAR)-α, β, γ, and δ, which are involved in the regulation of PCSK9 expression in the liver. Finally, ezetimibe might be unable to increase PCSK9 concentrations because of its weak LDL-C-lowering effect.

Fibrates

Activators of PPAR-α, fibrates are the next most commonly prescribed class of lipid-lowering drugs. Following its activation by fibrates, PPAR-α alters the transcription of multiple target genes that play a key role in lipid metabolism. Fibrates thus reduce plasma levels of triglycerides by approximately 30–50% and increase high-density lipoprotein cholesterol levels by 5–15%. Unlike statin treatment, the effect of fibrate treatment on LDL-C and PCSK9 is less clear. Kourimat et al. demonstrated that fibrate treatment reduced PCSK9 mRNA levels and PCSK9 protein expression in hepatocytes. Post-hoc analysis of a subgroup of the FIELD (Fenofibrate Intervention and Event Lowering in Diabetes) study indicated that 6-week treatment with 200 mg of fenofibrate moderately decreased plasma PCSK9 concentrations by 8.5% in patients with type 2 diabetes. Chan et al. also reported that 12-week treatment with fenofibrate 145 mg decreased serum PCSK9 concentrations by 13% in patients with type 2 diabetes who were treated with statins. However, in contrast to these results, Mayne et al. reported that 24-week treatment with fibrates increased serum PCSK9 levels by 17%, while Cost et al. reported that 6-week treatment with fenofibrate 160 mg increased PCSK9 by 26%. Truett et al. reported that fenofibrate (200 mg for 12 weeks) significantly increased circulating PCSK9 levels by 25%. The precise reasons for these discrepancies in the effect of fibrate on circulating PCSK9 concentrations and the mechanisms of fibrate-induced changes in PCSK9 remain unclear. Noguchi et al. compared the effects of bezafibrate (400 mg), a pan-agonist for PPAR-α, β, and δ with fenofibrate (200 mg), a more selective ligand for PPAR-α, on plasma PCSK9 concentrations. They reported that plasma PCSK9 concentrations at 8 weeks were significantly increased by 39.7% for bezafibrate and 66.8% for fenofibrate. Thus, the effect of fibrate on circulating PCSK9 may differ according to type of fibrate. Additional studies are therefore required to better understand the mechanism by which fibrate induces changes in PCSK9 concentrations.

Nicotinic Acid (Niacin)

Nicotinic acid (niacin) has been used clinically as an LDL-C lowering drug for more than 50 years, although the mechanism behind its LDL-C lowering effect remains unclear. Khera et al. reported that one year of treatment with a combination of simvastatin 20 mg and niacin decreased PCSK9 levels by 13%, suggesting that niacin offsets the statin-mediated increase in PCSK9. Furthermore, niacin decreased PCSK9 levels by 17% in patients treated with both atorvastatin and fenofibrate. This reduction was significantly positively correlated with LDL-C reduction (r = 0.62, p = 0.006). Thus, the LDL-C reduction observed with niacin therapy may be due in part to a reduction in PCSK9.

Inhibitors of PCSK9

Several therapeutic approaches to inhibit PCSK9 are summarized in Table 2. These approaches include blocking the binding of PCSK9 to LDLR using antibodies, adnectins, or mimetic peptides; inhibiting PCSK9 expression with CRISPR/Cas9 genome-editing technology, antisense oligonucleotides (ASOs), or small interfering RNA (siRNA); and interfering with PCSK9 secretion from the endoplasmic reticulum.

Monoclonal Antibodies

Monoclonal antibodies to PCSK9 are the most common method of PCSK9 inhibition since this approach was first described in 2009. These antibodies bind to a specific region of PCSK9 to inhibit the
interaction between PCSK9 and LDLR. The first neutralizing anti-PCSK9 antibody was shown to increase LDLR expression in hepatocytes and reduce LDL-C concentrations by 30%61). Several other monoclonal antibodies have since been described, with dose-dependent reductions of 20–50% in LDL-C levels62-63). Many clinical trials of monoclonal antibodies against PCSK9, including evolocumab and alirocumab, have been reported64-75). In phase II studies lasting 8–12 weeks, alirocumab lowered LDL-C levels by 40–70% when added to statin therapy64-66). Evolocumab has been shown to reduce LDL-C levels by approximately 60% in phase III trials67-73). Thus, significant reductions in LDL-C levels have been reported for each PCSK9 antibody. Furthermore, the effects of PCSK9 antibodies on LDL-C levels are not affected by age, gender, body mass index, LDL-C concentration, background statin intensity, or dose of statins64-73). Thus, PCSK9 antibody therapy represents one of the most promising and novel approaches to reducing LDL-C levels. However, unlike evolocumab and alirocumab, which are fully humanized monoclonal antibodies, bococizumab is a humanized monoclonal antibody with 3% murine sequence remaining in the antigen-binding complementarity-determining regions74). Bococizumab lowered LDL-C by 54.2% at 12 weeks, but this reduction was attenuated to 40.4% at 52 weeks. After 1 year of bococizumab treatment, 48% of patients had detectable antidrug antibodies, and a titer-dependent attenuation in LDL-C reduction was noted. Thus, the development of bococizumab was discontinued in November 2016.

It remains questionable whether the reduction of LDL-C using PCSK9 antibodies might reduce the risk of cardiovascular events. Sabatine et al. reported that evolocumab reduced LDL-C levels by 61%, and the rate of cardiovascular events following 1 year of treatment was reduced to 0.95% from 2.18% in the control group (hazard ratio, 0.47; p = 0.003)75). In a post-hoc analysis of the ODYSSEY LONG TERM (Long-term Safety and Tolerability of Alirocumab in High Cardiovascular Risk Patients with Hypercholesterolemia Not Adequately Controlled with Their Lipid Modifying Therapy) trial, the rate of major adverse cardiovascular events (death from coronary heart disease, nonfatal myocardial infarction, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization) was lower with alirocumab than with placebo (hazard ratio, 0.52; p = 0.02)76). A systematic review and meta-analysis of 24 randomized control trials showed that use of PCSK9 antibodies was associated with a lower rate of all-cause mortality (odds ratio, 0.45; 95% confidence interval [CI], 0.23–0.86; p = 0.015) and myocardial infarction (odds ratio, 0.49; 95% CI, 0.26–0.93; p = 0.03) and no statistically significant reduction in cardiovascular mortality (odds ratio, 0.50; 95% CI, 0.23–1.10; p = 0.084) compared with no anti-PCSK9 treatment77). Furthermore, the more recent randomized, double-blind, placebo-controlled FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk) trial demonstrated that evolocumab as add-on to statin therapy decreased LDL-C levels from 92 mg/dL to 30 mg/dL (−69%). Relative to placebo, evolocumab treatment significantly reduced the risk of the primary composite endpoint such as cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization (hazard ratio, 0.85; 95% CI, 0.79–0.92; p < 0.001)78). However, this reduction in events was less than would be expected for such a significant reduction in LDL-C, and the reasons for this disconnect between LDL-C lowering effect and cardiovascular events remain unclear.

The next question is whether elevated circulating PCSK9 and inhibition of PCSK9 affect the progres-

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**Table 2. A new approach to PCSK9-targeting drugs**

<table>
<thead>
<tr>
<th>Mechanisms</th>
<th>Representative agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blocking the combination of PCSK9 and LDLR</td>
<td>Mimetic peptides, Adnectins, Monoclonal antibodies (alirocumab, evolocumab, bococizumab)</td>
</tr>
<tr>
<td>Inhibiting PCSK9 expression</td>
<td>CRISPR/Cas9 technology, Small molecule (berberine, oleanoic acid), Antisense oligonucleotides, Small interfering RNA</td>
</tr>
<tr>
<td>Interfering with PCSK9 secretion</td>
<td>Sortilin, Sec24a</td>
</tr>
</tbody>
</table>

PCSK9: proprotein convertase subtilisin/kexin type 9, LDLR: low-density lipoprotein receptor.
PCSK9 inhibitors can stabilize coronary artery plaques, a role in Lp(a) catabolism. However, statins, whose main action of atherosclerosis using intravascular ultrasound85). Thus, the PCSK9 protein appears to be a key modulating factor in atherosclerosis86,87. However, Zhu et al. reported that there was no significant relationship between PCSK9 concentration and cardiovascular events. They concluded that although PCSK9 is an important therapeutic target for reducing LDL-C, it is unlikely to present a biomarker of atherosclerotic risk88. A recent meta-analysis also reported that circulating PCSK9 concentration was not significantly associated with the risk of cardiovascular events89. To date, no trial has evaluated whether LDL-C lowering with a PCSK9 antibody has favorable effects on coronary atherosclerosis, and no data have assessed whether the very low LDL-C levels achieved with a PCSK9 antibody lead to an incremental benefit in reducing disease progression compared with statins alone. The GLAGOV (Global Assessment of Plaque Regression with a PCSK9 Antibody as Measured by Intravascular Ultrasound) trial was designed to evaluate the effects of evolocumab on the progression of atherosclerosis using intravascular ultrasound85. This trial demonstrated that 420 mg of evolocumab in addition to statins for 76 weeks reduced LDL-C levels from 92.6 mg/dL to 36.6 mg/dL (~56.3%), and significantly decreased the percent atheroma volume by ~0.95% compared with placebo90. Thus, a PCSK9 antibody in combination with statin therapy had a favorable effect on progression of coronary artery plaques. However, no trial to date has examined whether PCSK9 inhibitors can stabilize coronary artery plaques, as reported with statins.

It has been reported that PCSK9 antibodies reduce lipoprotein (Lp)(a) levels65,66,77,87. However, the mechanisms of this effect are poorly understood. Serum Lp(a) levels in FH with LDLR mutations have been shown to be elevated, suggesting that Lp(a) is catabolized via the LDLR pathway85. In addition, serum Lp(a) was elevated in patients with FH as a result of PCSK9 gain-of-function mutations to the same extent as that caused by LDLR mutations in FH90. This suggests that LDLR plays an important role in Lp(a) catabolism. However, statins, whose main mechanism of action involves the up-regulation of LDLR, are incapable of reducing Lp(a) levels90. Furthermore, apoB in Lp(a) does not interact with LDLR, suggesting that LDLR does not play a role in Lp(a) kinetics91. Recently, we have reported that serum PCSK9 levels were positively correlated with serum levels of Lp(a), small, dense LDL, and oxidized LDL in patients with CAD48. Thus, the interaction between serum PCSK9 and apoB-containing lipoproteins plays a role in atherosclerosis92. Although there are no reports about the effects of PCSK9 antibodies on small, dense LDL or oxidized LDL, our findings suggest that PCSK9 antibodies might reduce Lp(a) to the same extent that they reduce small, dense LDL and oxidized LDL levels. Indeed, only one study to date has reported that PCSK9 antibodies reduced LDL-C levels and particle numbers92. These effects of PCSK9 antibodies on apoB-containing atherogenic lipoproteins might be responsible for the associated reduction in risk for cardiovascular events.

Antisense Oligonucleotides (ASO) and Small Interfering RNA (siRNA)

ASO and siRNA induce PCSK9 mRNA degradation. Thus, both strategies ultimately result in the silencing of the gene. Graham et al. demonstrated that an ASO for PCSK9 reduced total cholesterol by 53% in mice fed a high-fat diet, while also causing a two-fold increase in hepatic LDLR protein levels92. Similarly, Gupta et al. reported that an ASO lowered PCSK9 mRNA expression by 60% in mice and increased hepatic LDLR protein expression almost threefold93. Furthermore, Yamamoto et al. reported that the strong inhibition of PCSK9 by twice weekly ASO administration for 6 weeks reduced LDL-C levels by 43% in atherogenic diet-fed mice94. Administration of siRNA against PCSK9 mRNA in rats reduced LDL-C concentrations by 30%, while in monkeys, LDL-C was reduced by 56–70% and the effects lasted for a week95. Fitzgerald et al. reported the results of a phase I trial which investigated the safety and efficacy of an administration of siRNA in healthy volunteers. siRNA produced a 70% reduction in circulating PCSK9 protein levels and a 40% reduction in LDL-C from baseline96. This study was the first to demonstrate the use of an siRNA therapy to modulate a clinically validated endpoint in humans. These results support the further assessment of siRNA therapy in patients with hypercholesterolemia, including those treated with statins. However, relative to antibody-based therapies, siRNA represents a novel treatment strategy and their long-term safety remains unknown. Therefore, further trials are necessary to evaluate the efficacy and safety of siRNA for reducing LDL-C levels and risk of cardiovascular events.
Conclusions

PCSK9 has been identified as a key regulator of serum cholesterol levels and represent a novel pharmacological target for hypercholesterolemia. The major classes of commonly prescribed lipid-lowering agents, particularly statins, clearly increase circulating PCSK9 levels and which likely diminishes the effect of these drugs on the reduction of LDL-C concentrations. Thus, PCSK9 inhibitors, particularly monoclonal antibodies against PCSK9, in combination with statins, are one of the most promising and effective approaches to achieving very low LDL-C levels and reducing the risk of cardiovascular events.

Disclosure

None.

Conflict of Interest

None.

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