The discovery in 2003 that variants in the PCSK9 (proprotein convertase subtilisin/kexin type 9) gene cause autosomal dominant hypercholesterolemia revealed a new aspect of LDL cholesterol (LDL-C) metabolism (1). PCSK9, a protein of 692 amino acid residues produced at high concentrations in the liver, kidney, and intestine, has profound effects on LDL-C concentrations (2). Both gain-of-function and loss-of-function PCSK9 variants that cause higher and lower LDL-C concentrations, respectively, have been described, and variants in PCSK9 contribute to population variation in LDL-C values (3). The mechanism by which PCSK9 affects LDL-C concentrations involves direct binding of the protein to epidermal growth factor–like repeat A in the extracellular domain of the LDL receptor (LDLR), thereby accelerating degradation of the receptor (4).

PCSK9 is a secreted protein that circulates in the blood. Several ELISA assays have been developed to measure PCSK9 concentrations (5, 6) and relate them to various biological correlates and differences in response to therapy, which may have implications for the therapeutic targeting of this protein. The interactions of statins with PCSK9 are of great interest, not only because statins are the predominant therapeutic agents used to decrease LDL-C but also because both the LDLR and PCSK9 share a common transcriptional regulator, sterol regulator element–binding protein 2 (SREBP-2) (7). Statin exposure produces an increase in the concentrations of both LDLR and PCSK9 mRNAs. The upregulation of PCSK9, which promotes the degradation of the LDLR, serves as a counterregulatory molecular brake on LDL-C lowering. The study described by Awan et al. (8) in this issue of Clinical Chemistry examines the relationship between plasma PCSK9 and LDL-C lowering in patients treated with statins in the JUPITER (Justification for Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) trial. This clinical trial included apparently healthy participants with concentrations of LDL-C <130 mg/dL (<3.4 mmol/L) and high-sensitivity C-reactive protein >2.0 mg/L randomized to either 20 mg rosuvastatin or placebo. A random sample of 500 men and 500 women allocated equally to each treatment group were selected for measurement of LDL-C and PCSK9 concentrations. A modest correlation was found between baseline PCSK9 and LDL-C concentrations ($r = 0.15$; $P < 0.0001$). No association between these markers was found after statin treatment. Finally, a modest inverse correlation was apparent between the percentage change in PCSK9 concentrations and the change in LDL-C values ($r = -0.15$; $P < 0.0005$) for those on rosuvastatin treatment.

Several other groups have found a modest correlation between untreated PCSK9 and LDL-C concentrations (5, 6, 9, 10) that likely reflects coordinated upregulation of the LDLR and PCSK9 by SREBP-2 in response to higher cholesterol concentrations. The magnitude of the correlation between PCSK9 values and plasma LDL-C concentrations has been less than expected. Several factors may contribute to the low level of correlation between these 2 variables. First, the ELISA assays used to measure PCSK9 were able to capture only a subset of the circulating protein. Second, PCSK9 may bind to proteins and lipoproteins that affect its clearance. Currently, it is not known how PCSK9 is cleared from the circulation in humans. Third, there are significant diurnal changes in PCSK9, and PCSK9 concentrations are reduced with fasting (up to 58% lower after 36 h of fasting) (11, 12). Despite wide fluctuations in plasma PCSK9 concentrations over the course of a day, there is little diurnal variation in plasma LDL-C. Thus, additional factors must contribute to the relationship between plasma PCSK9 and LDL-C concentrations.

These same variability issues may also contribute to the very modest inverse correlation found in the JUPITER study ($r = -0.15$) between the on-treatment change in LDL-C and the change in PCSK9. Others have reported this correlation to be either negligible ($r = 0.05$) (10) or of a magnitude similar to that reported in this study (9). Importantly, in the setting of statin treatment, statin dosing and concentrations may be more important determinants of PCSK9 than LDL-C concentrations, especially given the potent effects of sta-
tins on SREBP-2. In companion studies, administration of 40 mg and 80 mg atorvastatin in 2 cohorts produced increases in plasma PCSK9 concentrations of 34% and 47%, respectively (9, 13). In another observational study, PCSK9 values showed a graded relationship across rosuvastatin dosing: 45% higher in participants receiving 40-mg doses than in those receiving 5 mg (5). This same dosing increment would be anticipated to lead to only an 18% further lowering of LDL-C. Indeed, statin-induced increases in PCSK9 have been postulated to blunt the LDL-C-lowering effects of escalating the statin dosage and to lead to the well-known “rule of 6’s,” in which each doubling of the dosage after initial statin dosing further lowers the LDL-C concentration by only 6% (9). Similarly in the JUPITER study, PCSK9 concentrations increased significantly in the statin-treated arm.

What are the implications of these findings, and what is the relevance for use of statins and PCSK9 inhibitors in development? First of all, baseline PCSK9 concentrations are likely not predictors of the response to statin therapy. In the study by Awan et al. (8), genotyping of a small number of individuals for PCSK9 variants revealed that the response to statin therapy was proportionally similar in those with loss-of-function PCSK9 mutations and lower baseline PCSK9 and LDL-C concentrations compared with those without such mutations. Baseline PCSK9 concentrations have also correlated poorly with statin response in some studies (10), but not others (5). Given the excellent safety profile and low cost of generic statins, however, a strategy of empirical statin treatment to gauge the clinical LDL-C-lowering response seems to be a more cost-effective and viable strategy than the conditional use of statins based on other testing, including measuring PCSK9 concentrations.

A second possible conclusion of the study by Awan et al. is that individuals with the most robust LDL-C response to statins may also have the greatest response to adjunctive PCSK9 inhibition, given the modest inverse correlation between change in LDL-C and PCSK9. A recent study of a mouse model of human-like lipid patterns demonstrated marked further reductions in LDL subfractions, non-HDL-C, and apolipoprotein B when PCSK9 inhibition was added to rosuvastatin or to the combination of rosuvastatin and ezetimibe (14). The additive effects of PCSK9 inhibition according to PCSK9 values were not assessed, however, and whether the response to such inhibitors is dependent on an increment in these concentrations is unknown.

PCSK9 inhibition as a therapeutic option for LDL-C lowering shows great promise, and there are currently active clinical trials including agents that degrade PCSK9 mRNA and antibodies to PCSK9 that prevent binding with the LDLR. Human studies have come to fruition after favorable results in mice and nonhuman primates (15), with numerous agents currently being tested. Statins remain the first-line cholesterol-lowering drugs for most people, and a better understanding of the complex relationships between statins, LDL-C, and PCSK9 can help determine how to apply PCSK9 inhibitors most effectively in clinical practice.

Author Contributions: All authors have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.

Acknowledgments: I thank Helen Hobbs for her thoughtful review of this manuscript.

References