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Objectives: Reduction of low-density lipoprotein cholesterol (LDL-C) has been shown to lower morbidity and mortality from cardiovascular disease (CVD) when patients are treated with statins or ezetimibe plus statins. PCSK9 inhibitors, such as alirocumab, significantly reduce LDL-C and can enable patients not controlled on statins to reach LDL-C goals. Their impact on cardiovascular outcomes is under clinical investigation. Here, we describe the development of a PhysioPD platform to investigate mechanisms underlying LDL-C changes with therapy and their potential impact on atherosclerotic plaque dynamics.

Methods: The PhysioPD platform is a quantitative systems pharmacology model that incorporates cholesterol metabolism and transport including LDL receptor (LDLR) trafficking, reverse cholesterol transport (RCT), and SREBP regulation of cholesterol synthesis, LDLR expression, and PCSK9 expression. In the platform, mechanistic hypotheses linking plasma LDL-C to atherosclerotic lipid core deposition, fibrosis, and inflammation in a representative coronary plaque lesion are included. Simulated treatments include PCSK9 antibodies, statins, fibrates, and ezetimibe. The platform was developed and calibrated with published data in accordance with Rosa’s Model Qualification Method.

Results: Simulated changes in lipid profiles following therapy were consistent with published clinical data, including the influence of concomitant therapies on LDL-C reduction by alirocumab. Platform research highlighted the impact of patient-specific factors, such as LDLR expression and RCT, on the dynamics of circulating LDL-C levels and potential changes in plaque size, composition, and stability.

Conclusions: A PhysioPD platform was developed to investigate the mechanisms through which cholesterol-lowering therapies affect lipid profiles and plaque characteristics. This platform, upon further development and qualification, may support dose optimization and clinical trial design for PCSK9 inhibitors and other lipid-modulating drugs and, in the future, help inform therapeutic management of patients with CVD.
Figure 1. PhysioPD platform overview and simulation examples. Top: Graphical overview of the PhysioPD platform. Bottom: PhysioPD simulations (right) with a representative Virtual Patient (VP) of multiple-dose alirocumab therapy (days 1, 29, 43) with or without atorvastatin compared to clinical data (left) published by Stein et al. NEJM. 2012; 366(12): 1108-1118.