Differentiation of anti-PCSK9 antibodies and synthesis inhibitors using Drug-Disease modeling of lipoprotein metabolism

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Objectives: Proprotein convertase subtilisin/kexin type 9 (PCSK9) has become a commonly targeted protein in anti-hypercholesterolemia therapies. In this work, we evaluated differences in lipid-lowering properties between two major classes of anti-PCSK9 therapies, represented by monoclonal antibodies (mAb; evolocumab, alirocumab, RG-7652, LY3015014) and synthesis inhibitors (inclisiran, ALN-PCS).

Methods: A systems physiology & pharmacology model of lipoprotein metabolism was expanded from previous work \([1,2]\) using differential equations that describe time profiles of LDLc, VLDLc, HDLc, PCSK9, apolipoprotein B (ApoB), total cholesterol (TC), lipoprotein A (Lp(a)) and triacylglycerides (TAG) (Fig.1). Open-source data from all phases of clinical trials that included healthy subjects and patients with hypercholesterolemia on statin treatment were used to build the model. The model was developed using the IQM toolbox for MATLAB 2013b \([2]\).

Results: Evolocumab and alirocumab with background statin treatment resulted in a further 10% decrease in LDLc vs. populations without statin administration. Treatment-induced plasma PCSK9 decreases were proportional to LDLc decreases in the same manner, for both classes of therapies: overlapping 95% CI; and evolocumab (a mAb) exhibiting only 2-3% further LDLc reduction vs. inclisiran (a synthesis inhibitor). No differential effects on Lp(a), TAG or ApoB were found, suggesting that intracellular disruption of PCSK9 synthesis has no additional effects on lipoproteins in hypercholesterolemic patient populations on top of statin treatment. In addition, 35 published studies were compiled to next perform a model-based meta-analysis that allows for prediction of major adverse cardiac events (MACE) risk, based on predicted plasma lipoprotein profiles using a systems physiology model.

Conclusions: Under background statin treatment, anti-PCSK9 therapies further decrease LDLc. At equal levels of plasma PCSK9 lowering, levels of LDLc reductions were comparable across drug modalities, and no quantitative differences were observed between LDLc and other lipid biomarkers.


Figure 1: Model scheme