Design of a knowledge-based mechanistic model of atherosclerotic cardiovascular disease for in silico trials


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A mechanistic computational model of ASCVD (including 72 biological entities, 750 parameters) was built from knowledge and calibrated. The next step is validation before using the model to run in silico clinical trials. In silico clinical trials provide an attractive option to complement randomized clinical trials by adding comparative effectiveness data and facilitating demonstration of drug benefit.

Abbreviations - anti-PCSK9 mAb: anti-PCSK9 monoclonal antibody, ASCVD: atherosclerotic cardiovascular disease, CV: cardiovascular, eGFR: estimated glomerular filtration rate, LDL: low density lipoprotein, LDLR: LDL receptor, Lp(a): lipoprotein(a), LLT: lipid-lowering therapies, PAD: peripheral arterial disease, Ray et al. (2020) - Ray et al. (2020) - Percentage of LDL-C change - % change in LDL-C - EVOLVE-2 PAD 5995 5000 4000 3000 2000 1000 0 % LDL-C LDL-C (mg/dl)

RESULTS – An ASCVD model predicting lipoprotein levels and CV events to support the development of new LLT

The model is calibrated to reproduce inclisiran effect on LDL-C levels

The model can also predict resulting efficacy on CV outcomes

A Virtual Population is a collection of virtual patients. Each virtual patient is generated by drawing randomly a value for each parameter of the model (e.g. age, sex, reaction rate constants) from the parameter distributions derived from available data sets and literature, or determined during calibration.

CONCLUSIONS

A mechanistic computational model of ASCVD (including 72 biological entities, 750 parameters) was built from knowledge and calibrated. The next step is validation before using the model to run in silico clinical trials.