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


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In silico trials applying a computational model (CM) of atherosclerotic cardiovascular disease (ASCVD) to virtual patients receiving alternative treatments provide an attractive option to complement randomised clinical trials (RCTs) by adding comparative effectiveness data and facilitating the demonstration of drug benefit. In silico modelling allows comparison between treatments with each virtual patient being his own control, and is not limited by the number of patients, comparative arms or trial duration.

This study aims at building a knowledge-based mechanistic model of ASCVD. Once validated, the model will be used to run in silico clinical trials to compare the benefit of inclisiran, an siRNA targeting PCSK9 mRNA, vs other lipid-lowering therapies (LLT) on cardiovascular (CV) events in patients with ASCVD.

An extensive literature review was performed to identify pathophysiological mechanisms involved in ASCVD and therapeutic mechanisms of action (MOAs). Every piece of knowledge extracted from the literature is awarded a strength of evidence grading to allow tracking of uncertainty in the model. A panel of multidisciplinary experts reviewed knowledge models and subsequent modelling hypotheses to validate their relevance. Knowledge was translated into mathematical equations. Each functional relationship between entities is represented by a biochemical/biophysical reaction with its reaction rate. A system of ordinary differential equations provides dynamics of modelled biological entities. A strategy of model calibration/validation was defined with the expert panel, by selecting relevant RCT and registry data, that the model should be able to reproduce. A virtual population was generated to account for inter-patient variability.

A mechanistic CM of ASCVD (including 72 biological entities, 750 parameters) was built from knowledge, describing lipoproteins metabolism and cholesterol homeostasis, dynamics of atherosclerotic plaque growth with lipoproteins infiltration in the intima and evolution of lipidic, necrotic and fibrotic tissues as well as plaque rupture leading to myocardial infarction, ischemic stroke, lower extremity arterial disease or CV death. It also includes the impact of several risk factors (age, sex medical history, diabetes, hypertension, smoking, systemic inflammation, chronic kidney disease) and available LLT (atorvastatin, rosuvastatin, ezetimibe, evolocumab and inclisiran). After calibration, the model and virtual population reproduce pharmacokinetics of LLT, lipoproteins decrease under combinations of LLT and associated reduction in clinical events.

ASCVD is ideally suited for in silico modelling: extensive literature is available regarding the pathophysiology, therapeutic MOAs are known and easily integrated in the model, clinically relevant outcomes are adequate model outputs, RCT and registry data exist to calibrate/validate the model. The next step is validation of the model before using it to run in silico trials.
Multi-scale in silico model