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

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PURPOSE

This study aims at building a **knowledge-based mechanistic model of atherosclerotic cardiovascular disease** (**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.

METHODS

- ➔ **ASCVD pathophysiological mechanisms** and **therapeutic mechanisms of action** were described into a knowledge model following an extensive literature review.
- ➔ Every piece of knowledge extracted from the literature was awarded a **strength of evidence** grading to allow **tracking of uncertainty** in the model.
- ➔ A panel of **multidisciplinary clinical experts** reviewed knowledge models and subsequent modelling hypotheses to **validate their relevance**.
- ➔ Knowledge was translated into **mathematical equations**. Each functional relationship between entities was represented by a biochemical/biophysical reaction with its reaction rate. A system of ordinary differential equations provided dynamics of modelled biological entities over time.
- ➔ **A calibration and validation strategy** was defined with the panel of experts by selecting relevant randomized clinical trials and registry data, that the model should be able to reproduce.
- ➔ **Inter-patient variability** was accounted for by virtual populations* by making a set of model parameters vary.

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.

In silico clinical trials provide an attractive option to complement randomized clinical trials by **adding comparative effectiveness data** and **facilitating demonstration of drug benefit**.

** 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 (eg age, sex, reaction rate constants) from the parameter distributions derived from available data sets and literature, or determined during calibration.*

Abbreviations - *anti-PCSK9 mAb: anti-PCSK9 monoclonal antibody, ASCVD: atherosclerotic cardiovascular disease, CV: cardiovascular, eGFR: estimated glomerular filtration rate, HDL: High density lipoproteins, hsCRP: high sensitivity C-reactive protein, LDL: low density lipoprotein, LDLR: LDL receptor, Lp(a): lipoprotein(a), LLT: lipid-lowering therapies, PAD: peripheral arterial disease, PCSK9: proprotein convertase subtilisin/kexin type 9, NPC1L1: Niemann–Pick C1-like 1, 3P-MACE: 3 point major adverse cardiovascular events, MALE: Major adverse limb events, RCT: reverse cholesterol transport, VLDL: very low density lipoprotein, VSMC: vascular smooth muscle cells.*

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

An ASCVD knowledge model synthesizes pathophysiology

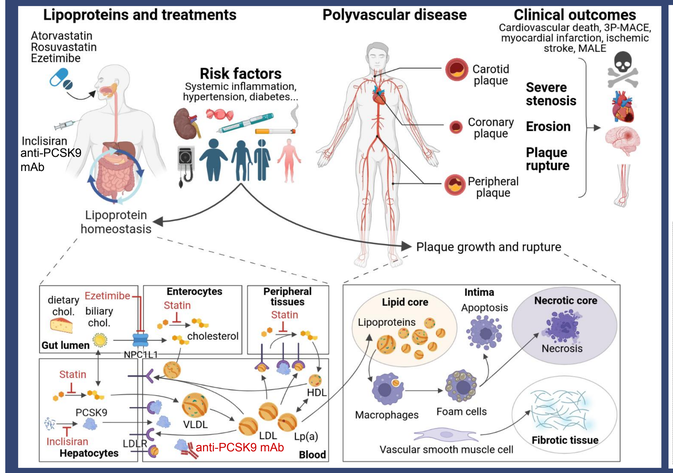


Figure 1: Multi-scale *in silico* model combining lipoprotein homeostasis, efficacy of lipid lowering treatments, atherosclerotic plaque growth and rupture leading to clinical outcomes and impact of risk factors (not exhaustively listed) on the pathophysiology.

Knowledge is translated into a mathematical model (eg. ASCVD plaque submodel)

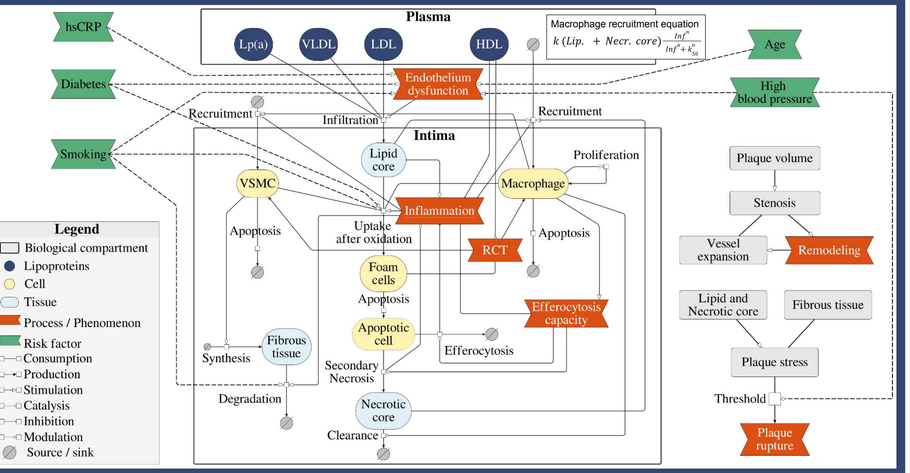


Figure 2: Graphical representation of the plaque growth and rupture submodel describing interactions between biological entities (eg. lipoproteins, macrophage, VSMC and foam cells) involved in atherosclerosis plaque evolution, atherosclerosis patho-physiological processes, and impact of risk factors (eg. diabetes, hypertension and smoking).

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

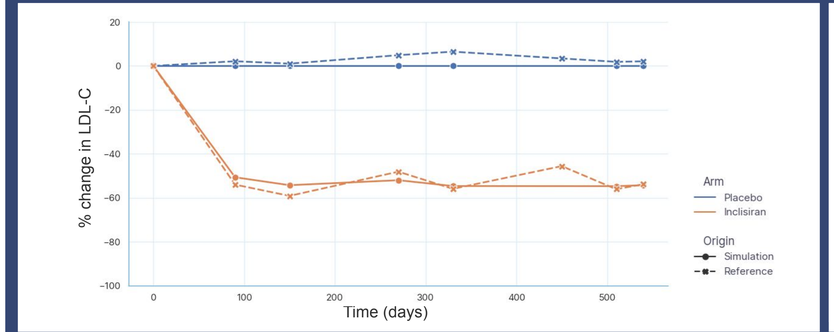
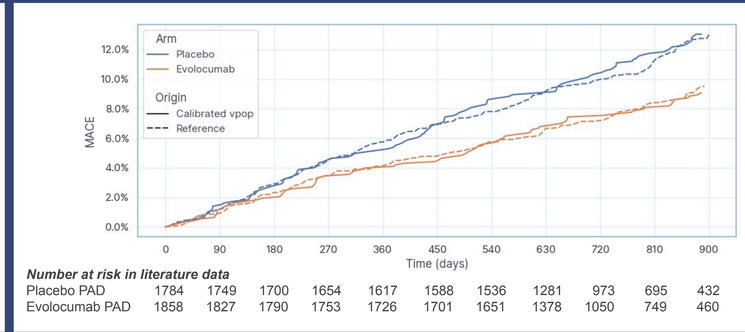


Figure 3: Comparison of population-mean percentage change in LDL-C levels following inclisiran (orange) or placebo (blue) administered as add-on to background LLT (statin with or without ezetimibe) as observed in ORION 10 trial (dotted lines; N=780 per arm) Ray et al. (2020) vs simulated by the model with a calibrated virtual population (solid lines; N=780).

The model can also predict resulting efficacy on CV outcomes



Number at risk in literature data

Placebo PAD	1784	1749	1700	1654	1617	1588	1536	1281	973	695	432
Evolocumab PAD	1858	1827	1790	1753	1726	1701	1651	1378	1050	749	460

Figure 4: MACE (first occurrence of CV death, MI or stroke) by treatment (evolocumab in orange, placebo in blue) in patients with symptomatic PAD as observed in FOURIER (dashed lines) Bonaca et al. (2018) and simulated in a virtual population (solid lines, N=929). *Note that all strokes are modeled as a consequence of a plaque rupture.*