A multiscale **model of atherosclerotic cardiovascular disease** to predict **lipid lowering therapies** effect on **clinical events**

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OBJECTIVES

In atherosclerotic cardiovascular disease (ASCVD), while direct effects of lipid-lowering therapies (LLT) reducing plasma cholesterol, can be quickly evaluated, assessing the long-term clinical benefit on clinical outcomes including myocardial infarction (MI), ischemic stroke (IS), major adverse limb event (MALE) and cardiovascular (CV) death requires several years of follow-up.

Here, we present **calibration results** of a **multi-scale model of ASCVD** and associated **Virtual Population** (Vpop) reproducing LLT effect on major CV events (MACE) and how they were used to **explore the link between LDL-C decrease and reduction in MACE**.

METHODS

- A **knowledge-based mechanistic** model of ASCVD was built (Fig 1 & 2). A system of ordinary differential equations provided modeled biological entities' dynamics over time.
- A secondary prevention ASCVD Vpop (N=29,446) was generated to account for inter-patient variability and calibrated at the population and subgroup levels to reproduce ORION-10 [1] (N=1,561) and FOURIER [2] trials (N=27,564).

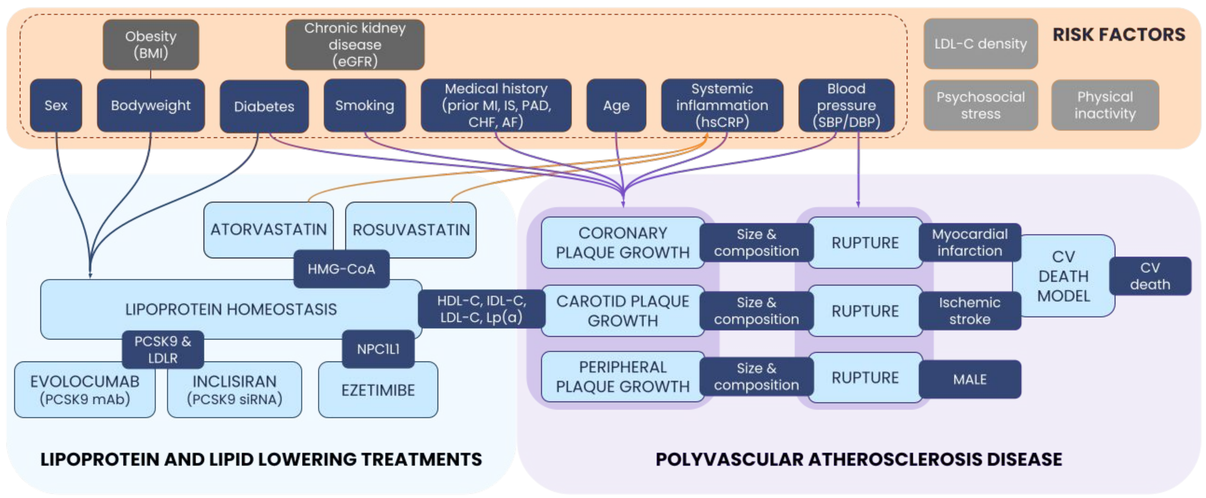

Figure 1: ASCVD model architecture. The model describes lipoproteins homeostasis, effects of LLT, growth and rupture of atherosclerotic plaques in coronary, carotid and/or peripheral vascular beds *(at most one per bed)* leading to CV clinical outcomes, respectively MI, IS and MALE and impact of risk factors. CV deaths are added in post-process, drawn from an exponential law depending of CV risk factors (RF) (*links not shown*). *Among RF, those included in dark blue boxes mechanistically impact the pathophysiology, those in dark gray boxes have indirect impacts via their links with other RF and those in light gray boxes have indirect impacts via the variability of unknown patient-dependent model parameters.*

Acronyms: **chol** cholesterol, **HDLc** high density lipoprotein cholesterol, **LDLc** low density lipoprotein cholesterol, **LDLR** low density lipoprotein receptor, **Lp(a)** lipoprotein A, **NPC1L1** Niemann–Pick C1-like 1, **PCSK9** Proprotein convertase subtilisin/kexin type 9, **VLDLc**: very low density lipoprotein cholesterol

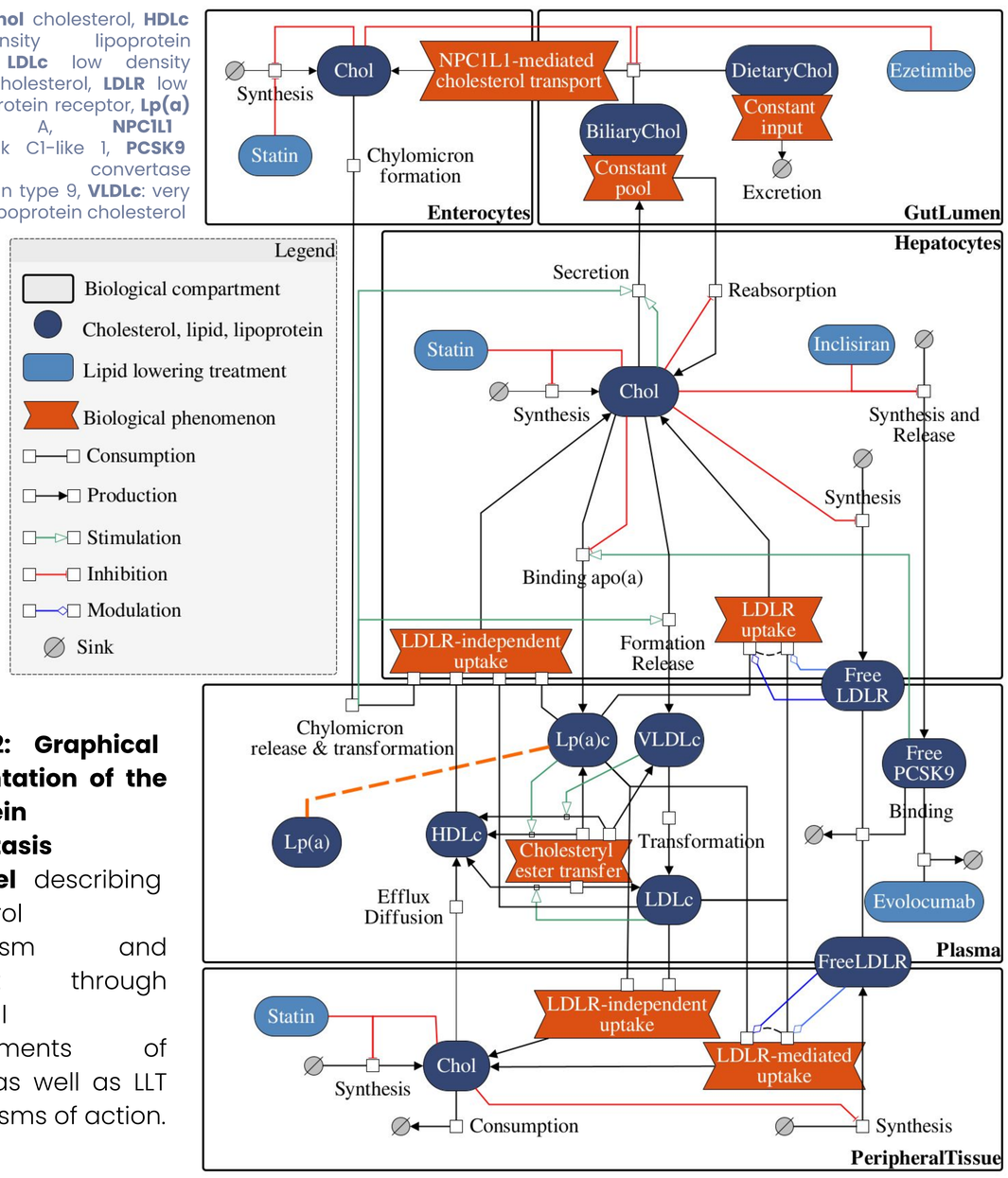

Figure 2: Graphical representation of the lipoprotein homeostasis submodel describing cholesterol metabolism and transport through biological compartments of interest as well as LLT mechanisms of action.

RESULTS

The calibrated model and Vpop reproduce evolocumab effect on LDL-C levels

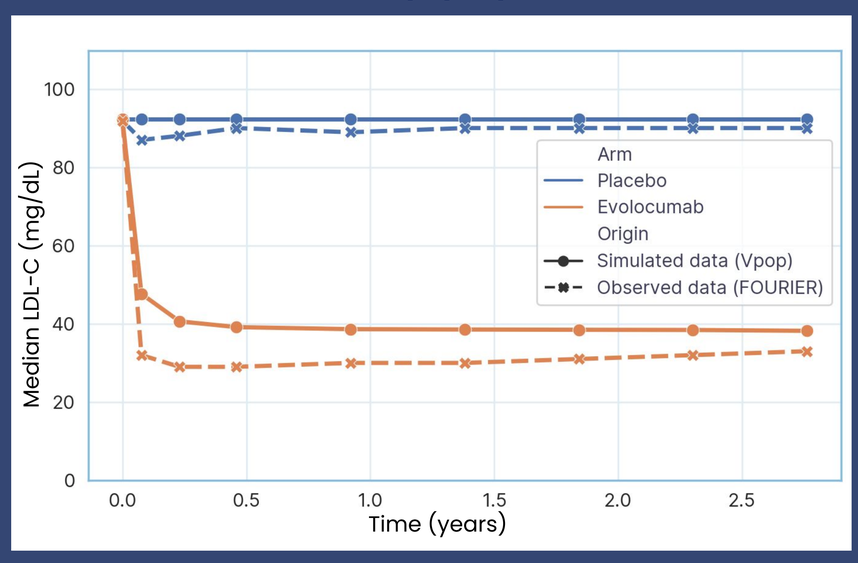

Figure 3 - Simulated lipoprotein baseline levels under statins & ezetimibe and decrease under evolocumab obtained with the Vpop match FOURIER observed data.

The calibrated model and Vpop reproduce evolocumab effect on MACE

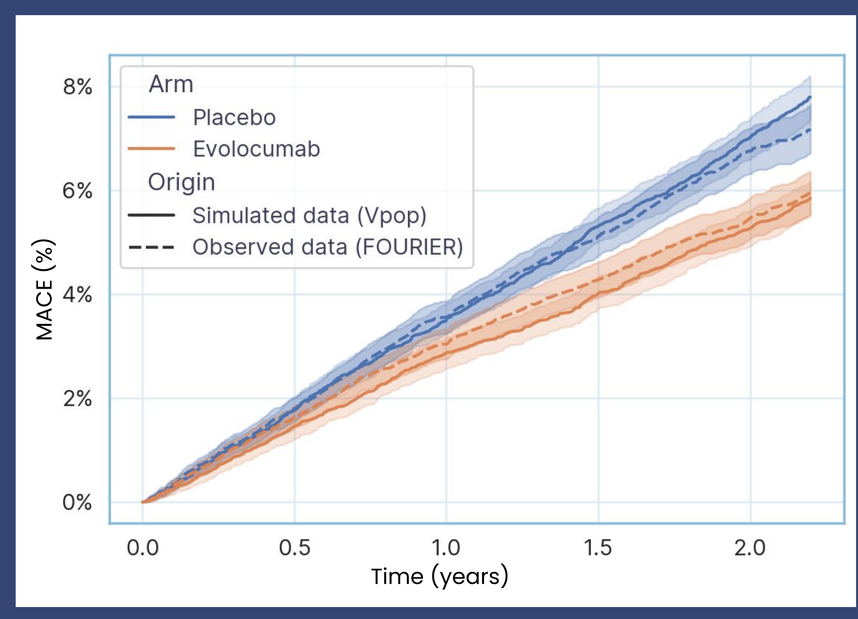

Figure 4 - Incidence of MACE (first occurrence of CV death, nonfatal MI or nonfatal IS) observed in FOURIER during a median follow up of 2.2 yrs is correctly simulated with the Vpop.

The calibrated Vpop shows a strong association between LDL-C levels and MACE incidence

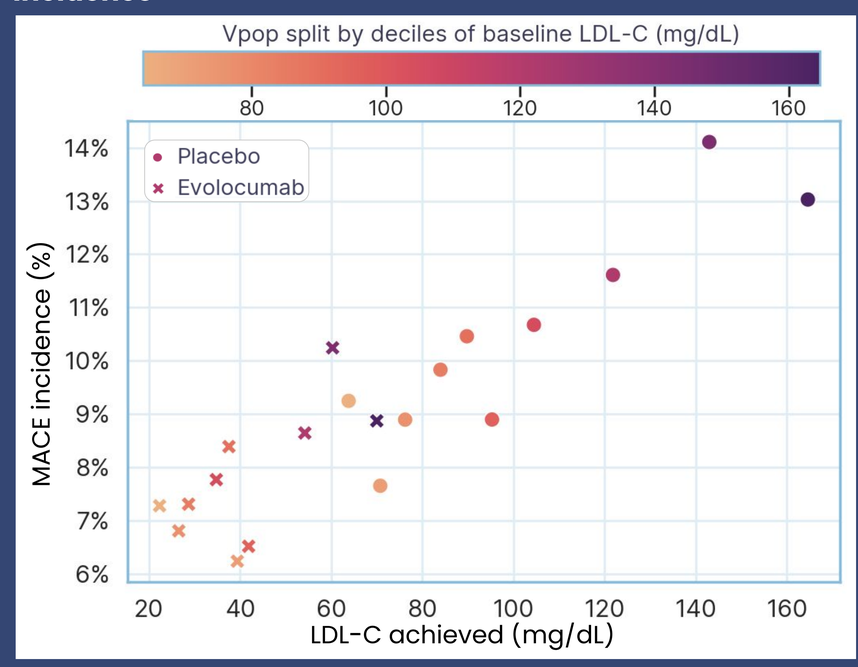

Figure 5 - Link between LDL-C achieved at 3 yrs and MACE (first occurrence of CV death, nonfatal MI or nonfatal IS) incidence during a follow-up of 3 yrs simulated within the calibrated Vpop stratified into baseline LDL-C deciles.

CONCLUSION

- An ASCVD model and secondary prevention Vpop was built and **calibrated** to reproduce **observed trial data** including FOURIER and ORION-10 results.
- Exploration of the calibrated model and Vpop showed a **strong association between the decrease in LDL-C** levels achieved at 3 years under background lipid lowering therapy with or without add-on evolocumab treatment **and the decrease of MACE incidence**.
- Next steps are to (1) **demonstrate the credibility** of the ASCVD model and Vpop with additional independent clinical data to validate its use to accurately predict the effect of lipid lowering therapies on CV outcomes and (2) use the model to perform the ***in silico* SIRIUS trial** (study NCT05974345) evaluating the effect of inclisiran compared to the current recommended therapeutic strategy on CV events in an ASCVD secondary prevention Vpop.

REFERENCES [1] Ray et al. 2020 (PMID: 32187462), [2] Sabatine et al. 2017 (PMID: 28304224)