In Silico Clinical Trials Using Mechanistic Knowledge-Based Model, an Innovative Approach to Accelerate Data Generation and Support Health Technology Assessment

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OBJECTIVES

Demonstrating cardiovascular (CV) benefits with lipid-lowering therapy (LLT) requires long-term randomized clinical trials (RCT) with thousands of patients. Innovative approaches such as **in silico trials** applying a disease computational model to virtual patients receiving multiple treatment combinations provide a valuable option to **complement RCTs** by **rapidly generating supplementary comparative effectiveness data** and reinforce data package for drug value demonstration to health technology assessment (HTA) bodies.

Here, we present **calibration results** of a **computational model of atherosclerotic cardiovascular disease (ASCVD)** built with the aim to predict the benefit of inclisiran, an siRNA targeting PCSK9 mRNA, vs other LLT on CV events.

METHODS

- A **knowledge-based mechanistic** model of ASCVD was built (Fig 1). 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 6 **multidisciplinary clinical experts** reviewed knowledge models and subsequent modelling hypotheses to validate their relevance. They also contributed in defining the calibration and validation strategy by selecting relevant RCTs and registry data, that the model should be able to reproduce and assessed the model credibility by analyzing simulation results.
- A secondary prevention ASCVD **Virtual Population*** (Vpop) was generated (N=29,446) to account for inter-patient variability and calibrated at the population and subgroup levels to reproduce ORION-10 [1] and FOURIER [2] RCTs data.

  ** 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.*

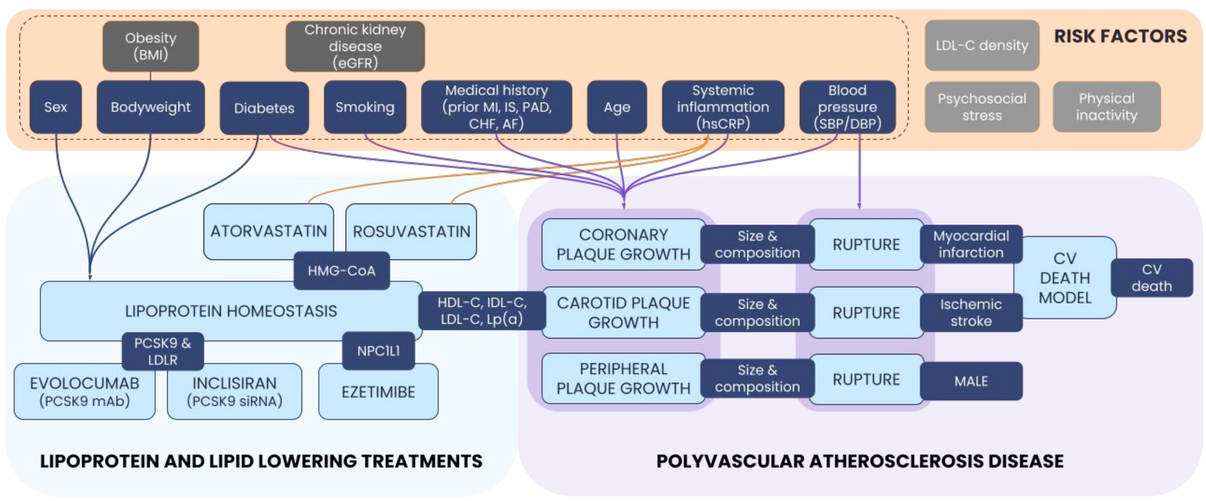


Figure 1: ASCVD model architecture. The model describes lipoprotein homeostasis, effects of LLT, growth and rupture of atherosclerotic plaques in coronary, carotid and/or peripheral vascular beds *(at most one per bed)* leading to CV clinical outcomes, respectively myocardial infarction (MI), ischemic stroke (IS) and major acute limb event (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.*

CONCLUSION

- An ASCVD model and secondary prevention Vpop were built and **successfully calibrated** to reproduce **observed trial data** including FOURIER and ORION-10 results at the level of both the whole population and subgroups.
- Next steps are:
  - **Credibility assessment** of the ASCVD model to demonstrate its ability to predict data that were not used for its conception nor calibration.
  - Use the model to predict **inclisiran** effect compared to the current recommended therapeutic strategy on CV events in an ASCVD secondary prevention population in the upcoming **SIRIUS** in silico trial (NCT05974345).
- **The acceptance of in silico approaches by the HTA bodies could accelerate patient access to this innovative drug.**

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

RESULTS

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

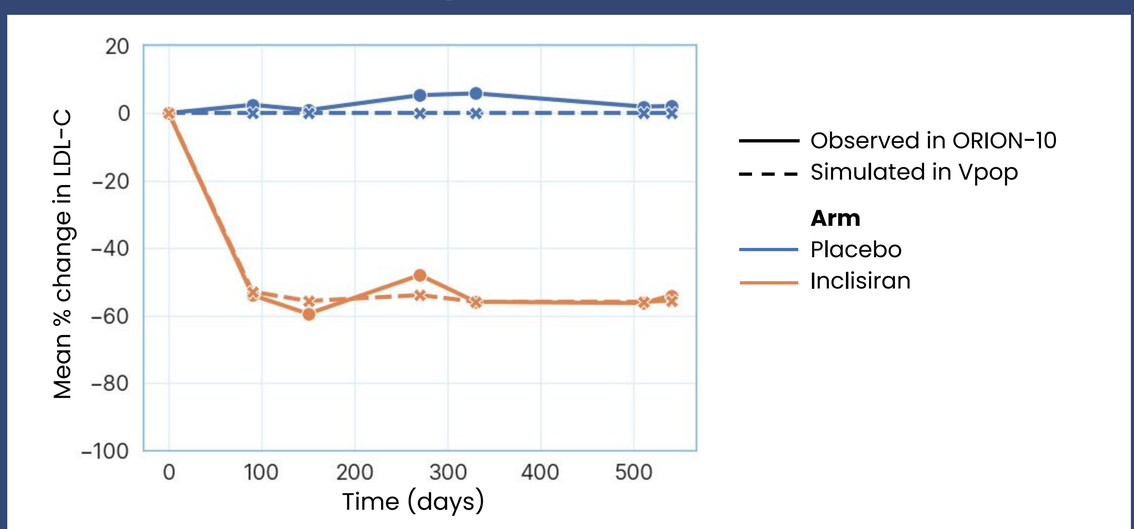


Figure 2 - Comparison of population-mean percentage change in LDL-C levels following inclisiran (orange) or placebo (blue) administered as add-on to background LLT (statin with or without ezetimibe) as observed in ORION-10 [1] (solid lines; N=780 per arm) vs simulated by the model (dotted lines; N=780).

The calibrated model and Vpop reproduce evolocumab effect on CV outcomes at the population-level

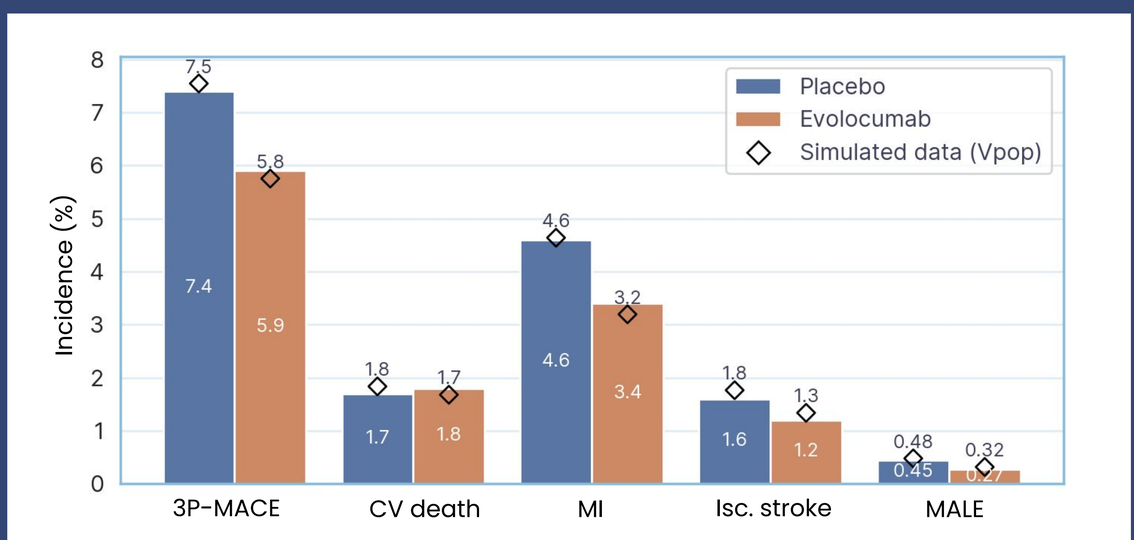
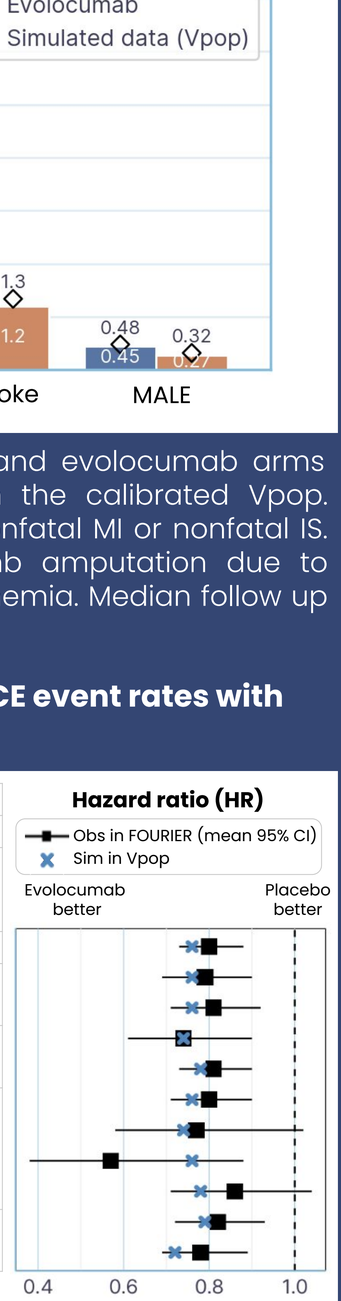


Figure 3 - CV outcomes incidence in both placebo and evolocumab arms reported in FOURIER trial [2] are well reproduced in the calibrated Vpop. 3P-MACE is defined as first occurrence of CV death, nonfatal MI or nonfatal IS. MALE includes acute lower limb ischemia, lower limb amputation due to ischemia, or urgent lower limb revascularization for ischemia. Median follow up duration is 2.5 yrs for MALE and 2.2 yrs for other events.

The calibrated model and Vpop reproduce 3P-MACE event rates with evolocumab and placebo at the subgroup-level

(A)

Subgroups		Patients in FOURIER	3P-MACE event rate (%) Evolocumab Obs in FOURIER	Evolocumab Sim in Vpop	Placebo Obs in FOURIER	Placebo Sim in Vpop
Overall		27564	5.9	5.8	7.4	7.6
Age	<65	15310	5.5	5.1	6.9	6.8
	>=65	12254	6.4	6.9	7.9	8.9
Sex	Female	6769	5.1	5.6	6.7	7.2
	Male	20795	6.2	5.9	7.5	7.7
Type of disease	MI alone	19113	5.2	5.1	6.4	6.9
	Stroke alone	3366	5.0	5.3	6.5	6.8
	PAD alone	1505	4.5	7.3	7.8	9.3
	Polyvascular	3563	11.1	9.1	12.9	11.3
Diabetes	Yes	11031	10.2	10.5	12.2	13.3
	No	16533	6.4	6.3	8.4	8.8



(B)

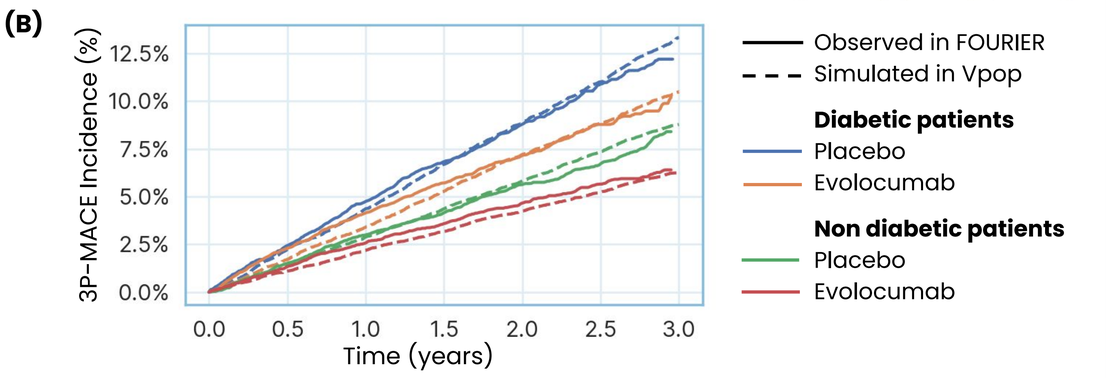


Figure 4 - (A) 3P-MACE and CV death rates observed in FOURIER [2] with evolocumab or placebo in key subgroups vs simulated results in the calibrated Vpop. Median follow up duration is 2.2 yrs, except for diabetes 3 yrs. Numbers of patients in each subgroup in the Vpop are similar to the ones in FOURIER. (B) 3P-MACE incidence in diabetics vs non diabetics.