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Predicting the efficacy of inclisiran on cardiovascular outcomes in patients with established atherosclerotic cardiovascular disease: primary results of the *in silico* SIRIUS trial

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BACKGROUND & OBJECTIVES

Inclisiran, an siRNA targeting PCSK9 mRNA, administered twice-yearly after initial and 3-month doses, substantially and sustainably reduced LDL-C in patients with atherosclerotic cardiovascular disease (ASCVD) as demonstrated in ORION-10 and ORION-11 trials [1].

Whether lowering LDL-C with inclisiran translates into a reduced risk of major adverse cardiovascular events (MACE) is not yet established.

In silico trials applying a disease computational model to virtual patients receiving new treatments allow to simulate large scale trials.

SIRIUS *in silico* study aimed to predict the effect of inclisiran on major CV events in virtual patients with established ASCVD.

Virtual population (VPOP)

- **Inclusion Criteria:**
  1. Patients with ASCVD, defined as any of the following: previous MI and/or previous IS and/or previous symptomatic peripheral arterial disease as evidenced by either intermittent claudication with ABI <0.85, prior peripheral arterial revascularization procedure, or amputation due to atherosclerotic disease.
  2. Fasting LDL-C ≥ 70 mg/dL.
  3. Under stable (≥ 4 weeks) well-tolerated high-intensity (HI) statin +/- ezetimibe.
- **Exclusion Criteria:** Patients with acute coronary syndrome, IS, peripheral arterial revascularization procedure or amputation due to atherosclerotic disease < 4 weeks prior to the defined trial start day.

The VPOP is computer-generated, according to predefined rules, as to present baseline characteristics representative of a contemporary ASCVD population (mainly inspired by the FOURIER study [2], a recent randomized controlled trial). In addition, to reflect current trends in the use of lipid-lowering drugs, the % of virtual patients receiving atorvastatin versus rosuvastatin or ezetimibe was based on several recent observational studies [5].

METHODS

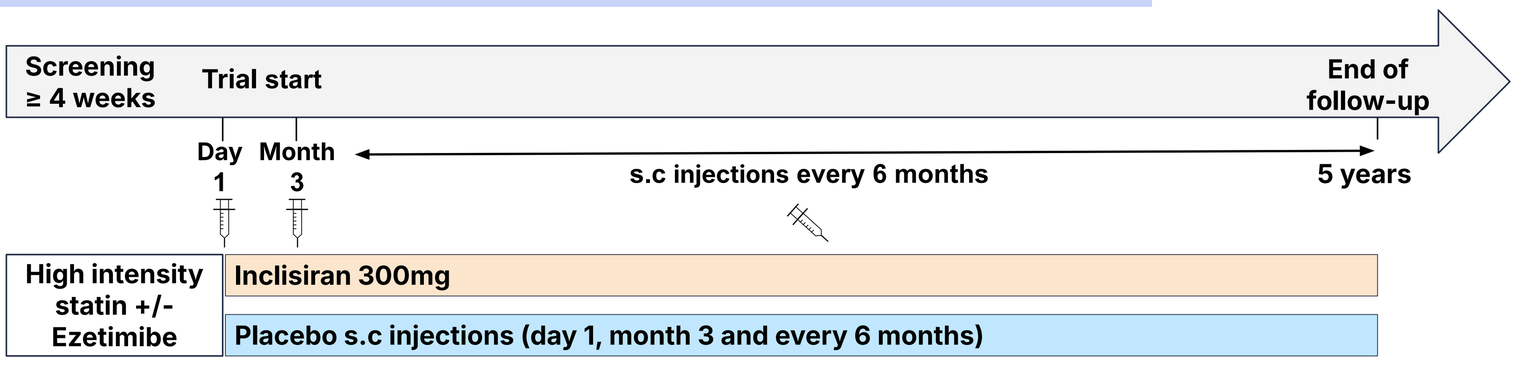
A mechanistic computational model of ASCVD was built from knowledge to describe lipoprotein homeostasis, effects of lipid lowering therapies (LLT), growth and rupture of atherosclerotic plaques in coronary, carotid and/or peripheral vascular beds leading to CV clinical outcomes, respectively myocardial 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 connected to CV risk factors.

The model was calibrated at the population and subgroup levels to reproduce among other data from ORION-10 [1] and FOURIER [2] and validated using data from ORION-11 [1], FOURIER-OLE [3] and ODYSSEY OUTCOMES [4].

The SIRIUS *in silico* trial (NCT05974345), was conducted by applying this ASCVD model to a virtual population (VPOP) with established ASCVD and LDL-C ≥ 70 mg/dL.

***In silico* paradigm specificities**

- *In silico* trials do not use sampling theory and thus do not require the usual statistical tests.
- *In silico* trials assess the treatment net efficacy which is
  - Not biased by interpatient variability as each patient is his own control;
  - Free from sampling fluctuation, since it is determined on a large virtual population whose number of virtual patients is not limited and will be extended until predictions converge.
- Uncertainty of the predictions is reported through the 95% predicted percentile intervals (PPI) calculated using a bootstrap approach. By construct, it includes both modeling errors and inter-patient variability as reflected in the virtual population. Uncertainty is qualified as low, medium or high for a width of the 95% PPI of < 0.2, 0.2-0.5 and > 0.5 respectively.



Co-primary endpoints

- Time to the first occurrence of 3P-MACE (composite of CV death, nonfatal MI or nonfatal IS)
- Time to CV death

Secondary endpoints

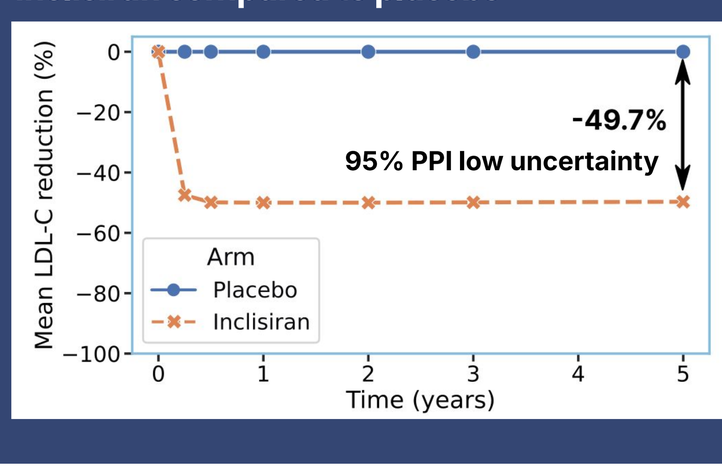
- Time to the first occurrence of nonfatal or fatal MI
- Time to the first occurrence of nonfatal or fatal IS
- Change in LDL-C from baseline to specified time points

RESULTS

Baseline characteristics of the SIRIUS VPOP (N=204,691)

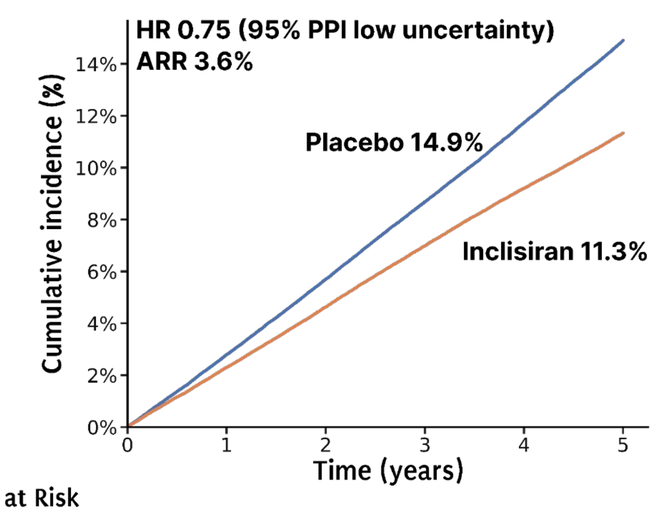
Patients characteristics and CV risk factors	
Age (yr) - mean (SD)	62.5 (8.7)
Male sex (%)	75.0
BMI (kg/m2) - median (IQR)	29 (26-33)
Mean sitting SBP (mmHg) - median (IQR)	129 (115-143)
Mean sitting DBP (mmHg) - median (IQR)	80 (73-87)
Current smoker (%)	28.8
Diabetes (%)	36.8
eGFR (mL/min/1.73 m2) - median (IQR)	76 (62-89)
Qualifying ASCVD events (%)	
MI	82.4
IS	19.2
Symptomatic PAD	13.7
Treatments (%)	
Rosuvastatin (20-40 mg QD)	19.7
Atorvastatin (40-80 mg QD)	80.3
Ezetimibe combination	20.6
LDL-C baseline levels - median (IQR)	
LDL-C (mg/dL)	91 (79-116)

Mean percentage reduction in LDL-C with inclisiran compared to placebo



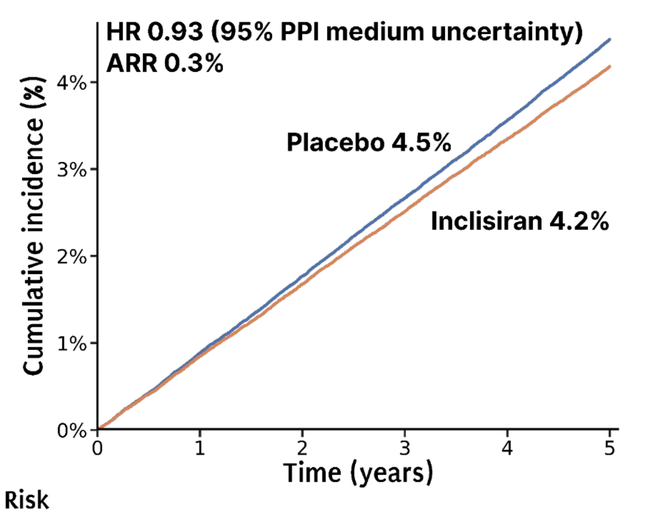
Cumulative incidence of cardiovascular events under inclisiran versus placebo after 5 years of follow-up

A. 3P-MACE



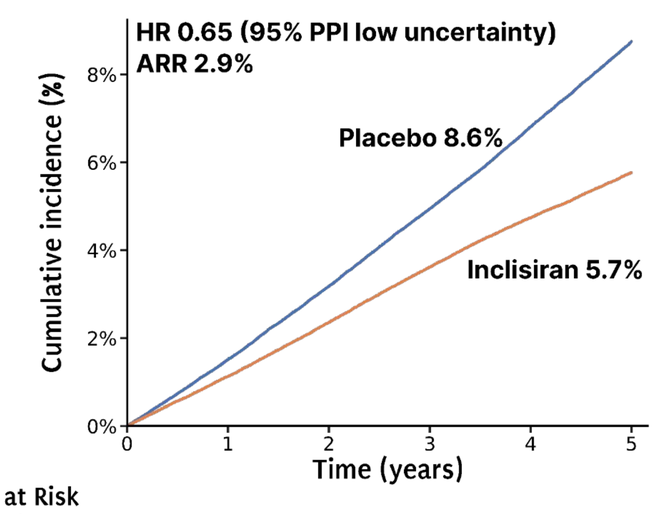
No. at Risk						
Placebo	204691	198979	193031	186925	180679	174173
Inclisiran	204691	199986	195215	190392	185854	181491

B. Cardiovascular death



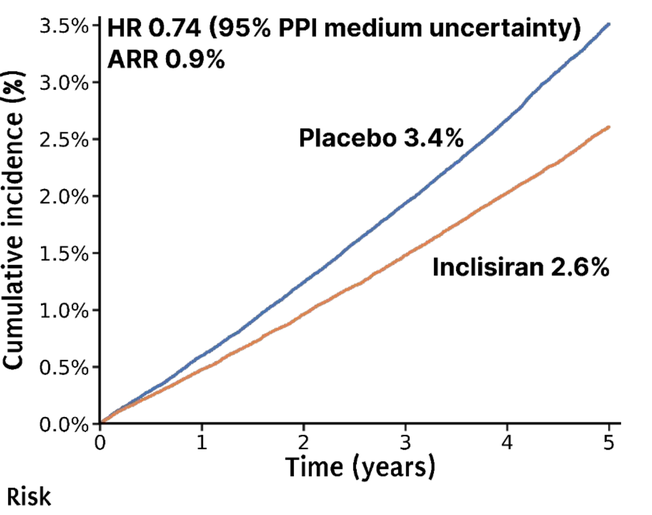
No. at Risk						
Placebo	204691	202882	201074	199238	197406	195498
Inclisiran	204691	202958	201262	199551	197848	196135

C. Fatal or nonfatal MI



No. at Risk						
Placebo	204691	199972	195058	189997	184777	179428
Inclisiran	204691	200795	196801	192780	189062	185549

D. Fatal or nonfatal IS



No. at Risk						
Placebo	204691	201852	198953	195951	192915	189653
Inclisiran	204691	202128	199611	197033	194429	191766

DISCUSSION

In the *in silico* SIRIUS study, inclisiran as compared with placebo was predicted to be associated with a lower risk of 3P-MACE, fatal and nonfatal MI, fatal and nonfatal IS at 5 years.

Regarding **cardiovascular death**, the SIRIUS study predicted a low CV death reduction (relative risk reduction (RRR) 7%) at 5 years in virtual ASCVD patients receiving inclisiran on top of background LDL-C lowering therapies compared to placebo treatment. Among CV death causes, inclisiran was associated with a RRR of 34% for fatal MI and 28% for fatal IS compared to placebo, while no impact on other CV death causes was predicted.

These predictions need to be considered in light of modeling hypotheses structuring the ASCVD model. In particular, no mechanistic hypothesis has been implemented in the model regarding potential effect of LLTs on other causes of CV death than fatal MI and fatal IS. By preventing the risk of recurrent cardiovascular events such as myocardial infarction, LLTs, including inclisiran, could also indirectly help to reduce these other CV death causes. Our ASCVD model does not simulate recurrent events in a given vascular bed and consequently does not capture this potential beneficial effect.

***References**: [1] Ray et al. 2020 (PMID 32187462), [2] Sabatine et al. 2017 (PMID 28304224), [3] O'Donoghue et al. 2022 (PMID 36031810), [4] Schwartz et al. 2018 (PMID 30403574), [5] Ray et al. 2023 (PMID 37090089), [6] NCT03705234, [7] NCT05030428.*

CONCLUSION

In silico trials applying a disease computational model to virtual patients receiving multiple treatment combinations is an innovative approach. It provides a valuable option to complement randomized clinical trials by rapidly generating supplementary comparative effectiveness data.

This *in silico* trial provides early insights into the potential effect of inclisiran on CV events suggesting a substantial 3P-MACE reduction, several years before the results of ongoing phase III trials (ORION-4 [6], VICTORION-2-Prevent [7]).

***Abbreviations**: ARR, absolute risk reduction; ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; HR, hazard ratio; IS, ischemic stroke; LDL-C, low-density lipoprotein cholesterol; LLT, lipid lowering therapy; MACE, major adverse cardiovascular event; MALE, major adverse limb event; MI, myocardial infarction; PCSK9, proprotein convertase subtilisin/kexin type 9; PPI, prediction percentile interval; RRR, relative risk reduction; VPOP, Virtual Population.*