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Estimating potential cardiovascular health benefits of improved population level control of LDL cholesterol through a twice-yearly siRNA-based approach: A simulation study of a health-system level intervention

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ABSTRACT

Background and aims: Inclisiran, an siRNA therapy, consistently reduces low-density lipoprotein cholesterol (LDL-C) with twice-yearly dosing. Potential cardiovascular benefits of implementing inclisiran at a population level, added to statins, were evaluated through simulation.

Methods: For each participant in the ORION-10 and ORION-11 trials comparing inclisiran with placebo, baseline 10-year cardiovascular risk was estimated using the SMART equation. The time-adjusted LDL-C difference from baseline observed 90–540 days after baseline was assumed to persist and used to estimate potential reduction in 10-year cardiovascular risk. Impact on 500,000 ORION-like individuals was simulated with Monte-Carlo.

Results: Mean baseline LDL-C and predicted 10-year major vascular risk among patients randomized to inclisiran (n = 1288) *versus* placebo (n = 1264) were 2.66 mmol/L *versus* 2.60 mmol/L and 24.9% *versus* 24.6%, respectively. Placebo-corrected time-adjusted absolute reduction in LDL-C with inclisiran was −1.32 mmol/L (95% CI −1.37 to −1.26; $p < 0.001$), which predicted a 10-year cardiovascular risk of 18.1% with inclisiran *versus* 24.7% with placebo (absolute difference [95% CI], −6.99% [−7.33 to −6.66]; $p < 0.001$) NNT 15. Extrapolating to 500,000 inclisiran-treated individuals, the model predicted large population shifts towards lower quintiles of risk with fewer remaining in high-risk categories; 3350 to 471 (≥80% risk), 11,793 to 3332 (60–<80% risk), 52,142 to 22,665 (40–<60% risk), 197,752 to 141,014 (20–<40% risk), and more moving into the lowest risk category (<20%) from 234,963 to 332,518.

Conclusions: Meaningful gains in population health might be achieved over 10 years by implementing at-scale approaches capable of providing substantial and sustained reductions in LDL-C beyond those achievable with statins.

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1. Introduction

Atherosclerosis results from the accumulation of cholesterol contained within apolipoprotein B (apoB)- lipoproteins in the walls of blood vessels throughout the life course, resulting in a spectrum of atherosclerotic cardiovascular diseases (ASCVD) [1–3]. As the majority of apoB in the circulation consists of low-density lipoproteins, it can be inferred that most of the cholesterol in the vessel wall is derived from low-density lipoprotein cholesterol (LDL-C). Today, ASCVD accounts for the majority of the 18 million deaths per year from cardiovascular disease, worldwide [4]. To tackle this, the recent update of the World Heart Federation (WHF) Cholesterol Roadmap set out public health and implementation strategies for health systems to reduce lifelong LDL-C exposure, with approaches tailored towards achieving lifetime benefits [1]. Recommendations include routine use of combination lipid-lowering treatments (LLTs) for those with ASCVD, reflecting the advanced nature of the underlying pathology and those at highest risk requiring early treatment intensification [5,6], as well as advocating the development of streamlined care pathways that can bring together the three major components for the management of any non-communicable disease, namely the healthcare system, the healthcare professional, and the patient.

However, if combination therapies are needed then an additional medication burden is placed on patients. Furthermore, when LDL-C reductions are reliant on therapies requiring frequent dosing, poor adherence over the long-term impacts average LDL-C levels achieved, potentially attenuating therapeutic benefits. The emergence of small interfering RNA (siRNA)-based therapies such as inclisiran, with two annual doses (after the initial and 3-month dose), provides the opportunity to achieve consistent reductions in LDL-C at the population level [7,8]. Administration by a healthcare professional is a system-level paradigm change, potentially reducing the reliance on patient adherence to add-on therapy [9,10].

To provide estimates of the potential health benefits of this novel approach, as an adjunct to statins, we used the ORION-10 and ORION-11 randomised trial data to calculate the 10-year risk for cardiovascular events in individuals with ASCVD and elevated LDL-C on maximally tolerated statins over the next decade and compared this with the estimated 10-year risk predicted from further lowering LDL-C that could be achieved with inclisiran. We then analyzed the potential impact of these changes on a simulated population of approximately half-a-million individuals who were identical to the placebo or inclisiran groups to estimate the impact on health outcomes if this approach were implemented at scale.

2. Patients and methods

2.1. Study population

ORION-10 and ORION-11 were phase 3, placebo-controlled, randomised trials that included patients with ASCVD (ORION-10) and ASCVD plus high-risk primary prevention patients (ORION-11) with elevated LDL-C despite receiving maximum tolerated dose of statin therapy and compared LDL-C reductions with inclisiran versus placebo over 18 months [11]. Patients enrolled in ORION-10 or ORION-11 with ASCVD and familial hypercholesterolaemia (FH), or without ASCVD, were excluded from the present analysis as they are not included in the Second Manifestations of ARTerial disease (SMART) equation. This present analysis therefore included adult patients aged ≤80 years with ASCVD and LDL-C >1.80 mmol/L (>70 mg/dL) and was restricted to those without FH or high-sensitivity C-reactive protein (hs-CRP) levels ≤15 mg/L to allow ten-year risk estimation for cardiovascular events using the SMART equation.

2.2. Interventions and visits

Patients were randomised 1:1 at baseline to receive a 1.5 mL subcutaneous (SC) injection of either inclisiran 284 mg (equivalent to 300 mg inclisiran sodium) or a matching placebo, administered first on Day 1 and subsequently administered on Day 90 and every 6 months thereafter for up to 540 days. Laboratory assessments were performed on injection visits (days 1, 90, 270, and 450) and follow-up visits (Days 150, 330, 510, and 540).

2.3. Endpoints

The co-primary endpoints were (i) the 10-year risk of cardiovascular events projected from the mean time-adjusted absolute change in LDL-C

Table 1
Baseline demographic and clinical characteristics by treatment in patients with ASCVD in the ORION-10 and ORION-11 trials (aged ≤80 years and hs-CRP levels ≤15 mg/L).

Characteristics	Inclisiran (n = 1288)	Placebo (n = 1264)
Age, years, mean (SD)	65.2 (7.7)	65.0 (8.2)
Male, n (%)	936 (72.7)	940 (74.4)
Cerebrovascular disease, n (%)	229 (17.8)	199 (15.7)
Coronary heart disease, n (%)	1129 (87.7)	1139 (90.1)
Peripheral artery disease, n (%)	157 (12.2)	148 (11.7)
Abdominal aortic aneurysm, n (%)	30 (2.3)	40 (3.2)
Current smoker, n (%)	241 (18.7)	196 (15.5)
Diabetes mellitus, n (%)[a]	516 (40.1)	454 (35.9)
Statin use, n (%)	1083 (84.1)	1060 (83.9)
High-intensity statin use, n (%)	970 (75.3)	956 (75.6)
Ezetimibe use, n (%)	107 (8.3)	108 (8.5)
Systolic blood pressure, mmHg, mean (SD)	133 (15.1)	133 (16.1)
Total cholesterol, mmol/L, mean (SD)	4.66 (1.1)	4.60 (1.0)
HDL-C, mmol/L, mean (SD)	1.23 (0.4)	1.23 (0.4)
hs-CRP, mg/L, median (IQR [q25, q75])	1.60 (0.8, 3.8)	1.70 (0.8, 3.9)
Estimated glomerular filtration rate, (mL/min/1.73 m^2), mean (SD)	78.4 (20.8)	77.5 (20.1)
Time since first diagnosis of cardiovascular events, years, mean (SD)[b]	8.61 (1.68)	8.59 (1.70)
LDL-C, mmol/L, mean (SD)	2.66 (0.9)	2.60 (0.9)
Baseline SMART score, (10-year risk of cardiovascular events), %, mean (SD)	24.9 (14.2)	24.6 (14.5)

Values were provided during VISIT 1 = baseline.
CV, cardiovascular; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; n, number of patients; SD, standard deviation; SMART, Second Manifestations of ARTerial disease; q25, 25th percentile; q75, 75th percentile.
[a] The preferred term diabetes mellitus was used in the calculation of SMART score instead of diabetic status.
[b] Imputed variable.

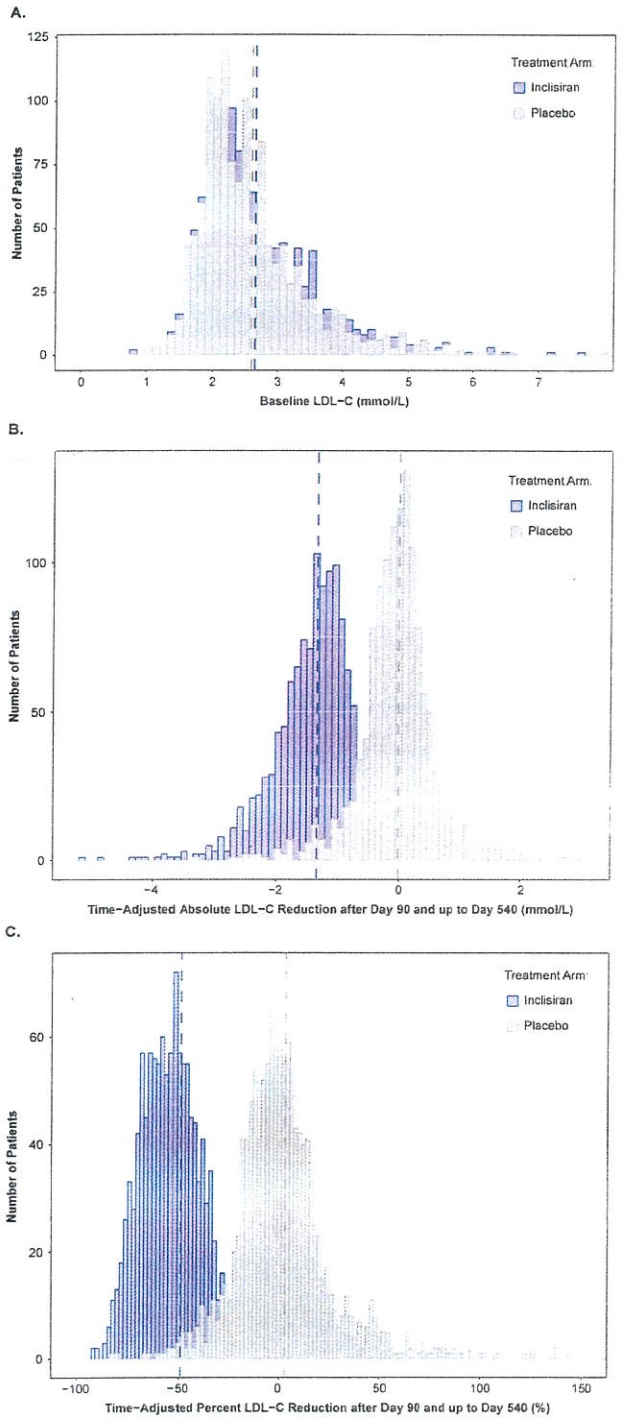

Fig. 1. (A) Baseline LDL-C levels; (B) time-adjusted absolute LDL-C levels after Day 90 and up to Day 540; (C) time-adjusted percentage change in LDL-C from baseline after Day 90 and up to Day 540 by treatment in patients with ASCVD in the ORION-10 and ORION-11 trials (aged ≤80 years and hs-CRP levels ≤15 mg/L).
The between-group difference average time-adjusted absolute and percentage changes in LDL-C after Day 90 and up to Day 540 were −1.32 mmol/L (−50.9 mg/dL; 95% CI, −1.37 to −1.26; $p < 0.001$) and −52.2% (95% CI, −54.1 to −50.4; $p < 0.001$), respectively. ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol.

after Day 90 and up to Day 540 in the ORION-10 and ORION-11 trials, assuming that these levels were maintained over 10 years in each treatment group, (ii) the relative and absolute 10-year estimated cardiovascular risk in each treatment group projected from the assumed LDL-C trajectories, and the intergroup difference in 10-year risk.

2.4. Estimation of 10-year risk and change in 10-year risk with inclisiran treatment

The individual 10-year risk of a composite endpoint of cardiovascular death, myocardial infarction, and stroke for each eligible patient was estimated using the SMART equation at baseline (supplementary material appendix 1) [6]. The SMART variable – time since first diagnosis of cardiovascular disease – was not collected in either trial and was therefore imputed (details of data imputation are provided in supplementary material appendix 1). Each individual 10-year risk was then used to estimate the mean and distribution of 10-year risk of the ORION-10 and ORION-11 populations.

For each trial participant included in the analysis population, the time-adjusted change in LDL-C from baseline after Day 90 and up to Day 540 in mmol/L was calculated using a control-based pattern mixture model (CB-PMM) to impute missing LDL-C values. The time-adjusted percentage LDL-C change from baseline was calculated similarly to the time-adjusted within trial absolute LDL-C change. Using the Cholesterol Treatment Trialists (CTT) risk ratio (95% confidence interval [CI]) (0.78 [0.76 to 0.80] per 1 mmol/L (38.67 mg/dL) reduction of LDL-C) [12,13], the 10-year cardiovascular relative risk reduction was calculated for each individual based on the within trial absolute LDL-C risk reduction, and the predicted relative benefits thereof under inclisiran treatment (supplementary material appendix 1), assuming that the observed LDL-C changes from baseline overserved in each treatment group between Days 90–540 were maintained over 10 years. The projected relative risk reduction for each trial participant was then applied to the baseline 10-year risk to estimate absolute cardiovascular risk reduction.

Statistical differences of 10-year estimated cardiovascular risk between treatment groups were assessed using an analysis of variance (ANOVA) model. Geometric least square means (standard error [SE]) were derived based on the estimate of SE from the ANOVA. A corresponding p-value of an ANOVA test lower than 10^{-3} was reported as $p < 0.001$.

The formula to estimate the number needed to treat (NNT) to prevent one cardiovascular event over a 10-year time period can be found in the supplementary material (supplementary material appendix 1).

2.5. Estimating population effects

2.5.1. Population kinetic-pharmacodynamic model

During the clinical development of inclisiran, a population kinetic-pharmacodynamic (K-PD) model was established based on the mechanism of action of inclisiran to describe levels of LDL-C during inclisiran treatment [14]. The K-PD model was used to simulate the population-level variability of LDL-C resulting from inclisiran treatment by taking into account associated factors from simple re-sampling of the ORION population. The factors considered in the K-PD model included covariates such as age, bilirubin, baseline LDL-C, proprotein convertase subtilisin/kexin type 9 (PCSK9), triglycerides, body weight, sex, and statin use [14]. The basic goodness-of-fit plots, including visual predictive checks plots, indicated the robustness of the estimates of LDL-C in patients with ASCVD (Supplementary Fig. S1), and thus the K-PD model was considered qualified to predict the effect of inclisiran on LDL-C levels in the subset of patients with ASCVD included in the analysis population to be used in a Monte Carlo simulation [14,15].

2.5.2. Monte Carlo simulations

Estimates and corresponding variability of pharmacodynamic (PD)

Table 2
Change in 10-year cardiovascular risk[a] by treatment.

	Inclisiran (n = 1288)	Placebo (n = 1264)
10-year risk of cardiovascular events at baseline, %, mean (SD)	24.9 (14.2)	24.6 (14.5)
Time-adjusted absolute change in LDL-C, mmol/L, mean (SD)	−1.32 (0.7)	−0.0042 (0.6)
Predicted Relative Risk Reduction		
Relative change in 10-year risk		
10-year difference in relative risk, %, (95% CI)[b]	−27.5 (−28.3, −26.6) ($p<0.001$)	
Absolute Risk		
10-year risk of cardiovascular events if LDL-C changes are maintained, %, mean (SD)	18.1 (10.8)	24.7 (15.1)
Absolute change in predicted 10-year risk, %, LS mean (SE)[c]	−6.99 (0.21)	0.15 (0.15)
Between-group difference in the change in 10-year risk, %, LS mean (95% CI)	−6.99 (−7.33, −6.66) ($p < 0.001$)	

ANOVA, analysis of variance; CI, confidence interval; CV, cardiovascular; LDL-C, low-density lipoprotein cholesterol; LS, least square; N, number of patients; SE, standard error; SMART, Second Manifestations of ARTerial disease; SD, standard deviation.

[a] The model predicts the 10-year risk of cardiovascular events which includes cardiovascular death, myocardial infarction, and ischemic stroke.

[b] The 95% CI was derived based on bootstrap approach.

[c] Values were measured using ANOVA with the change from baseline as the dependent variable, and treatment as a covariate

parameters along with residual random error were used to simulate absolute change from baseline LDL-C at visits after Day 90 and up to Day 540 in mmol/L during recommended inclisiran treatment in a total of 500,000 simulated patients with ASCVD per treatment arm. The patient characteristics at baseline included in the population K-PD model were selected based on a re-sampling approach.

All patients were simulated to have received four SC injections of 284 mg inclisiran at Days 1, 90, 270, and 450. The population K-PD model with estimates and corresponding variability presented in Supplementary Table 1 was used to simulate LDL-C at baseline and at days 150, 270, 330, 450, 510, and 540.

The time-adjusted absolute change in LDL-C levels (mmol/L) after Day 90 and up to Day 540 were simulated with the population K-PD model, and the predicted 10-year estimated cardiovascular risk reduction was derived based on the CTT risk ratio using predicted relative risk reduction from absolute LDL-C change (supplementary material appendix 2).

The proportion of simulated patients within different cardiovascular risk categories showing a reduction or increase in risk were computed based on distributions at baseline, and with inclisiran or placebo treatment. The predicted 10-year cardiovascular risk at baseline and with inclisiran treatment, along with the absolute change in 10-year cardiovascular risk with inclisiran treatment within each category, were derived.

The distribution of the baseline LDL-C (mmol/L) and the predicted 10-year cardiovascular risk reduction, as well as the time-adjusted LDL-C after Day 90 and up to Day 540 (mmol/L), and predicted 10-year cardiovascular risk reduction in the simulated population, are illustrated with log-scale histograms and heatmap plots. Only 95% prediction intervals of simulated data were retained as part of the figures. Changes in risk category for placebo- or inclisiran-treated patients are shown as shift tables.

Dataset exploration was performed, and figures were developed using R® (Version 4.0.1). ANOVA on the predicted 10-year cardiovascular risk reduction between placebo and inclisiran in ORION-10 and ORION-11 was performed in Phoenix (Version 8.3). Monte Carlo simulations were performed in NONMEM (Version 7.3).

3. Results

Of 3178 patients from the ORION-10 and ORION-11 trials, 2552 patients aged ≤80 years with clinical ASCVD and without diagnosed FH, and hs-CRP levels ≤15 mg/L, were considered eligible for this analysis; 1288 were randomised to inclisiran and 1264 to placebo (Table 1). At baseline, the mean LDL-C level and the predicted 10-year cardiovascular risk were similar across inclisiran and placebo groups (2.66 mmol/L [103.0 mg/dL] *vs* 2.60 mmol/L [101.0 mg/dL]; Table 1 and Fig. 1A, and 24.9% versus 24.6% [Table 1], respectively).

3.1. Low-density lipoprotein cholesterol

The average time-adjusted absolute changes in LDL-C after Day 90 and up to Day 540 were −1.32 mmol/L (−51.0 mg/dL) with inclisiran and −0.0042 mmol/L (−0.163 mg/dL) with placebo, resulting in a between-group treatment difference of −1.32 mmol/L (−50.9 mg/dL; 95% CI, −1.37 to −1.26; $p < 0.001$) favouring inclisiran (Fig. 1B). These absolute changes corresponded to average time-adjusted percentage changes in LDL-C after Day 90 and up to Day 540 of −49.3% with inclisiran and +2.87% with placebo, resulting in a between-group treatment difference of −52.2% (95% CI, −54.1% to −50.4%; $p < 0.001$; Fig. 1C).

3.2. 10-Year cardiovascular risk in the ORION trial

The predicted relative reduction in risk of cardiovascular events estimated from LDL-C reductions with inclisiran was 27.5% (Table 2). Over a decade, the projected 10-year absolute risk of cardiovascular events with inclisiran was 18.1% but was mostly unchanged with placebo (24.7%), reflecting a predicted mean (95% CI) between-group absolute difference of −6.99% (−7.33% to −6.66%; $p < 0.001$) NNT 15.

3.3. Population health simulation to an ORION-like population

The simulation analysis comprised 500,000 hypothetical patients per treatment arm who were identical in characteristics to the cohort of ORION trial patients. The population distributions of risk at baseline were similar between treatment groups (right-skewed). Over 10 years in the placebo group overall there was little change in the distribution of risk (based on changes in LDL-C between Day 90–540) (Fig. 2A). However, in the inclisiran group with the change of LDL-C the distribution of risk shifted to the left with the change in risk (left-skewed as compared to baseline), with a greater proportion of individuals moving into lower risk categories versus few changing into higher risk categories, estimated from the LDL-C changes (Fig. 2B, 2C, 2D, and Fig. 3). Although the overall distribution of risk based on post-baseline LDL-C changes in the placebo group suggested that overall risk in the cohort was unchanged, among individuals, risk could increase or decrease markedly (Fig. 2C). Whereas, among the inclisiran simulated cohort, very few would be predicted to have an increase in risk (Fig. 2D).

To assess the potential impact of changes in LDL-C on outcomes at a population level, the simulation cohort was divided into quintiles of predicted 10-year risk. The shift table shows the absolute number of individuals predicted to change cardiovascular risk categories from baseline with placebo or inclisiran (Table 3). For placebo, the simulation

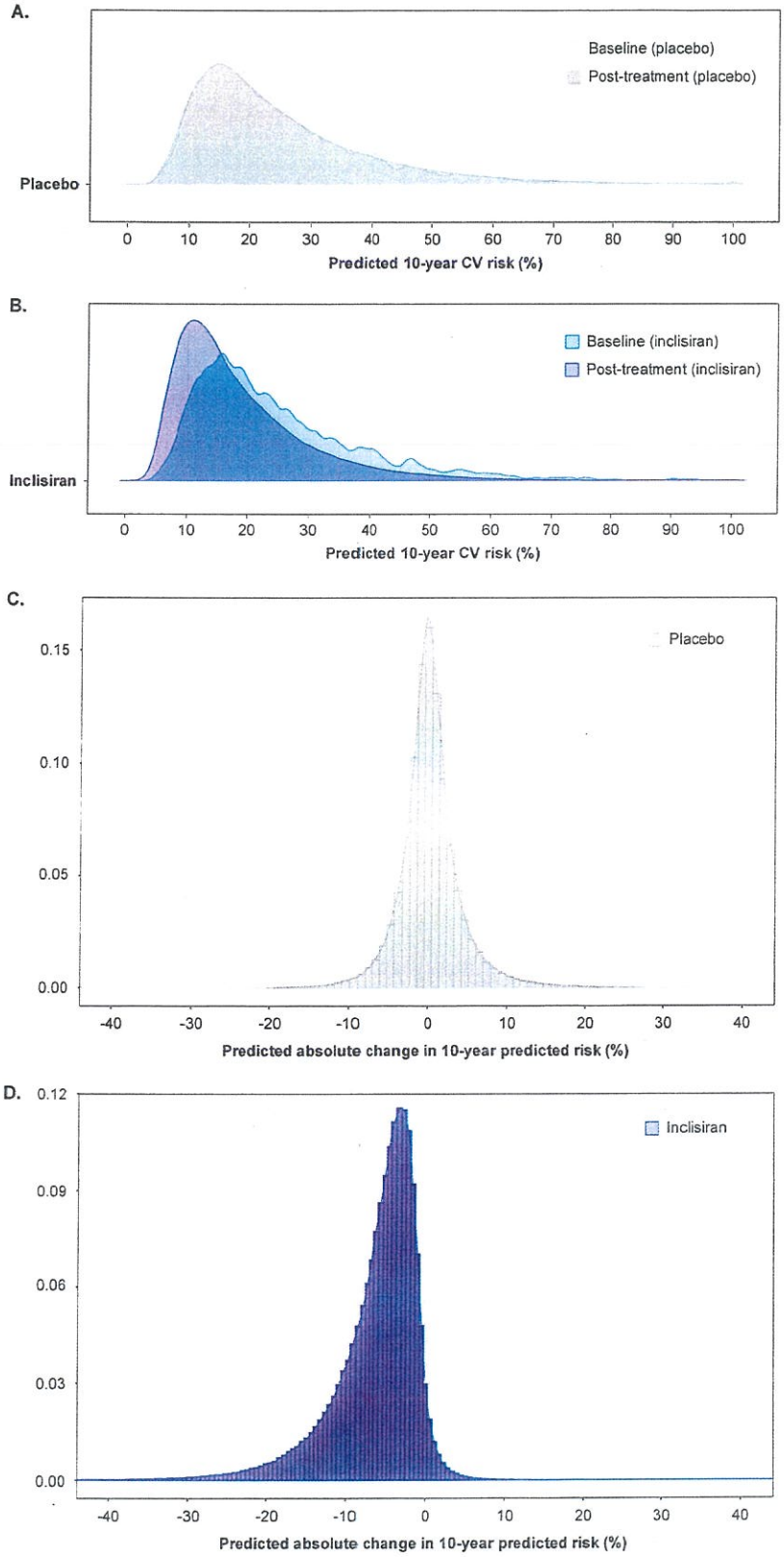

Fig. 2. Distributions of simulated patients within predicted 10-year cardiovascular risk categories at baseline and after treatment with inclisiran in 500,000 or placebo in 500,000 hypothetical patients with ASCVD. (A) Placebo (B) inclisiran and distribution of (C) predicted absolute change in 10-year predicted risk with placebo, (D) predicted absolute change in 10-year predicted risk with inclisiran.
ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular.

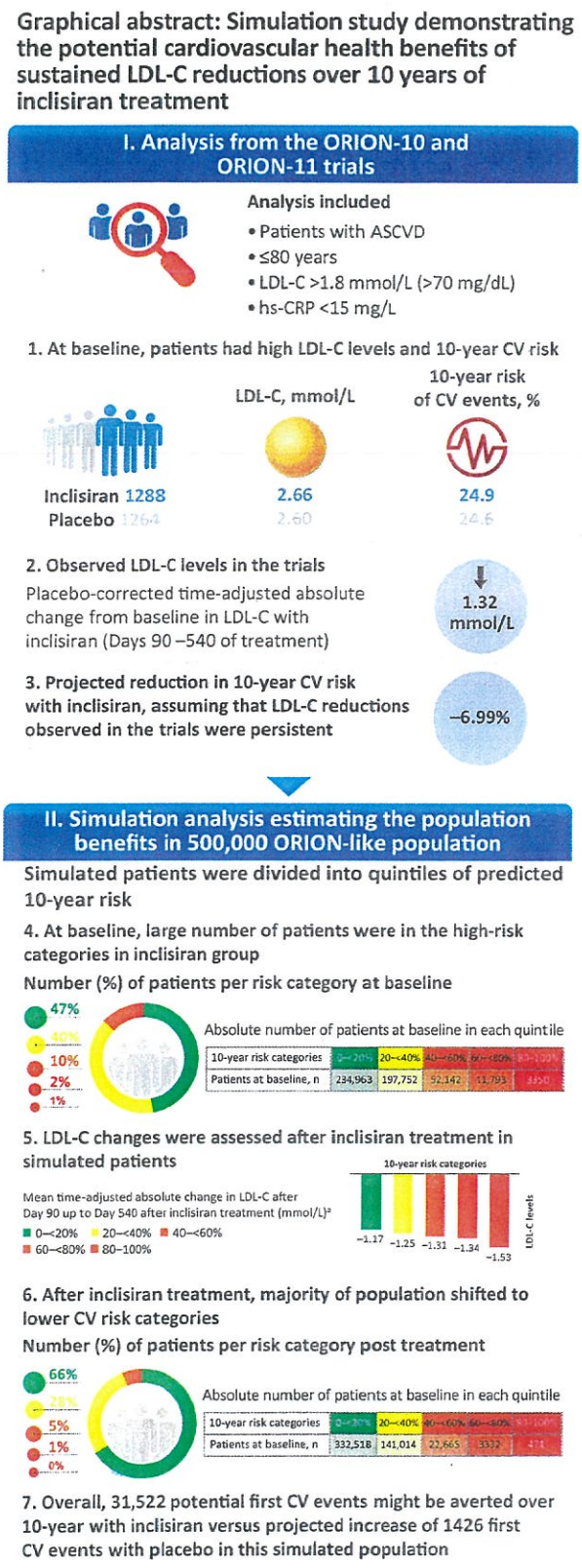

Fig. 3. Graphical abstract.
Simulation study demonstrating the potential cardiovascular health benefits of sustained LDL-C reductions over 10 years of inclisiran treatment. [a]After the initial and 3-month dosing. ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; LDL-C, low-density lipoprotein cholesterol.

suggests there were 234,963 patients in the <20% category, and of these, 215,175 would be expected to remain in that risk category, but 19,781 would move up to the next highest category of 20–<40% risk if averaged LDL-C increases between Day 90 and Day 540 were maintained. Similarly, of the 197,752 placebo individuals in the 20–<40% risk, 165,933 would be expected to remain in this category, but 19,095 would move down into the <20% category, whereas 12,626 would move up the higher 40–<60% category. Although at an individual level some patients will move up risk categories and others move down, the overall proportion of individuals in each risk category would be largely unchanged between baseline and post-treatment; 47.0% *versus* 46.9% (<20% risk), 39.6% *versus* 39.1% (20–<40% risk), 10.4% *versus* 10.5% (40–<60 risk), 2.4% *versus* 2.7% (60–<80% risk) and 0.7% *versus* 0.9% (≥80% risk).

For inclisiran, the simulation suggests that although a small number may move up in risk category, the vast majority of those shifting groups move down by one or more categories to lower risk groups (Table 3). For instance, with inclisiran, of the original 3350 patients in the ≥80% risk category, only 408 would be predicted to remain in the same risk category, with 1381 moving into the 60–<80% risk category, 1353 moving to the 40–60% category, and 208 moving to even lower categories. Similarly, only 1704 patients would be expected to remain in the 60–<80% category, with 7985 moving to the 40–<60% category and 2027 moving to the 20–<40% category. Only 12,822 would be expected to remain in the 40–<60% risk category, with 99,975 predicted to remain in the 20–<40% category. These large shifts in absolute numbers to lower risk categories predict that only a small proportion of higher-risk individuals are likely to remain in their original risk category between baseline and post-treatment; 0.1 versus 0.7% (≥80% risk), 0.7% versus 2.4% (60–<80% risk), 4.5% versus 10.4% (40–<60% risk), 28.2% versus 39.6% (20–<40% risk), with an increase in those in the lowest risk category (<20%) rising from 234,963 to 332,518 (predicted increase from 47.0% to 66.5% of the population).

In this simulated cohort, the overall 10-year cardiovascular risk would be predicted to fall by 6.3% (24.8–18.5%) if the time-adjusted reductions of 1.32 mmol/L (51.0 mg/dL) in LDL-C were maintained over 10 years with inclisiran. A further estimate would suggest that potentially 31,522 first cardiovascular events might be averted over 10 years with inclisiran, while there would be a projected increase of 1426 first cardiovascular events with placebo in the simulated cohort. However, this approach does not consider the population distribution across each quintile of absolute risk. Furthermore, although the difference in the reduction in LDL-C with inclisiran versus placebo between the lowest and highest quintiles of risk ranged from 1.17 mmol/L (45.4 mg/dL) to 1.53 mmol/L (60.1 mg/dL), respectively, the absolute predicted reductions in risk were larger (3.4%, 7.1%, 12.5%, 18.1%, and 26.0%) with increasing quintile of risk (Supplementary Fig. S2). Implementing this approach for a population of half-a-million would redistribute risk through consistent LDL-C lowering (Supplementary Fig. S3), potentially reducing as many as 31,522 first cardiovascular events per 500,000 population at risk (Supplementary Fig. S2).

4. Discussion

Currently, there are an estimated 272.1 million individuals living with ASCVD globally [4]. These individuals are at the highest risk of further atherothrombotic events throughout their lifetime [5]. These largely preventable events exert a heavy price on those affected in terms of quality of life years lost and the fiscal burden placed on health systems providing care for these individuals. Recognising this, guidelines recommend a multi-factorial approach, targeting all modifiable risk factors, such as LDL-C, more intensively [5,6]. However, at a population level, statin-based monotherapy rarely achieves the recent lower goals recommended in guidelines, with only one-fifth of patients achieving a level <1.40 mmol/L (<55 mg/dL) through monotherapy [16], which means that similar to management of blood pressure greater use of

Table 3
Proportion and number of simulated patients within predicted 10-year cardiovascular risk categories at baseline and with inclisiran or placebo treatment (500,000 hypothetical patients with ASCVD per treatment arm).

	Inclisiran, n					Total post-treatment n (%)	Placebo, n					Total post-treatment n (%)
Risk category baseline	<20%	20–<40%	40–<60%	60–<80%	80–100%		<20%	20–<40%	40–<60%	60–<80%	80–100%	
Post-treatment <20%	233,840	97,450	1209	17	2	332,518 (66.5)	215,175	19,095	7	0	0	234,277 (46.9)
Post-treatment 20–<40%	1123	99,795	37,863	2027	206	141,014 (28.2)	19,781	165,933	9547	37	1	195,299 (39.1)
Post-treatment 40–<60%	0	505	12,822	7985	1353	22,665 (4.5)	7	12,626	37,044	2764	60	52,501 (10.5)
Post-treatment 60–<80%	0	2	245	1704	1381	3332 (0.7)	0	93	5326	7209	846	13,474 (2.7)
Post-treatment 80–100%	0	0	3	60	408	471 (0.1)	0	5	218	1783	2443	4449 (0.9)
Total baseline, n (%)	234,963 (47.0)	197,752 (39.6)	52,142 (10.4)	11,793 (2.4)	3350 (0.7)		234,963 (47.0)	197,752 (39.6)	52,142 (10.4)	11,793 (2.4)	3350 (0.7)	

In the table, green cells indicate the number of patients changing into a lower risk category; yellow cells, the number changing into a higher risk category; and white cells represents number of patients with no change in risk category.
ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; n, number of patients.

combination LLTs will be required for the majority of patients [17].

Through simulation studies, we quantified the limitations of current approaches to LDL-C management, which rely on patient adherence to small molecules requiring daily dosing, and the potential population health benefits of implementing siRNA-based therapies for further LDL-C lowering at scale. In the ORION trial population of patients with ASCVD, at baseline, the mean residual 10-year risk of cardiovascular events ranged between 24.6% and 24.9%, with mean LDL-C levels of 2.60–2.66 mmol/L (101–103 mg/dL), despite the use of maximally tolerated statins. The addition of twice-yearly inclisiran to maximally tolerated statins resulted in a reduction in the time-averaged LDL-C of 1.32 mmol/L (51 mg/dL) over 15 months, which takes into account LDL-C variability, known to be associated with cardiovascular events [18]. If this LDL-C reduction were unchanged in the inclisiran group maintained over 10 years, the absolute risk of further events would be expected to fall by 6.99% in the inclisiran treated group placebo, but in placebo risk would be predicted to remain unchanged from estimates at baseline. Extrapolating these data to a population of half-a-million individuals with identical characteristics to the ORION trial population could result in the prevention of up to 31,522 first events over 10 years (Graphical abstract). The findings from this analysis are consistent with the initial prespecified exploratory pooled safety analysis of the ORION Phase 3 program which demonstrated that treatment with inclisiran was associated with a 25% lower risk of MACE ascertained through safety reporting [19]. Confirmation of these findings await the results of ongoing larger and longer duration cardiovascular outcomes trials.

We have previously shown in placebo-controlled trials of inclisiran that in patients on stable prescribed doses of statins and assigned to placebo, LDL-C levels may go up or down by as much as 50% when measured at two time points 180 days apart, even though the average LDL-C appears unchanged for the overall placebo cohort [20,21]. These fluctuations probably result from differences in adherence to statins between the two measurements. In the present study, we were able to provide estimates of the potential impact of observed variations of LDL-C on cardiovascular risk. At an individual level, a 50% increase or decrease in time-adjusted LDL-C levels mean that individual risk could go up or down by as much as 20%, despite being on stable doses of statins. When the denominator of the at-risk population is 500,000, several thousands of patients move to higher or lower risk categories based on differences in time-adjusted LDL-C. By contrast, the additional effects of inclisiran, administered by a healthcare professional in the trial, were more predictable. Not only would the overall distribution of risk be shifted to a lower average level of risk, but at an individual level, very few patients administered inclisiran by a healthcare professional appeared to show an increase in risk, thus potentially offsetting the limitations of add-on LLTs that require self-administration and near-perfect adherence due to their shorter duration of action.

Within the simulation cohort of half-a-million, 47% of patients (234,963) with an estimated risk of <20% would be expected to see a fall in absolute risk of 3.4% with inclisiran (Fig. 3). Of the remaining 53% (265,037) with a predicted risk of ≥20% before inclisiran, the additional reduction in LDL-C derived would be expected to move 98,678 individuals into the lowest category of risk of <20% (Table 3). Although, this means 166,359 patients would remain at ≥20% risk, a larger number would have moved to a lower quintile of risk, by one to two categories. Therefore, over 10 years, in the 265,037 individuals at ≥20% risk for cardiovascular events, as many as 23,552 first cardiovascular events might be averted with inclisiran vs projected increase of 1426 first cardiovascular events in the group receiving placebo. Both treatments were administered on top of the maximum tolerated dose of statin +/- other LLTs.

Recognition of the burden cardiovascular disease places on public health globally has led to healthcare systems improving the earlier diagnosis of those with ASCVD and initiating preventive therapies. Furthermore, the implementation of changes at the level of the health system, such as the large-scale delivery of better acute care for life-threatening presentations of ASCVD, means that today many individuals will survive beyond their first acute presentation. Multiple registries and real-world data suggest a considerable gap between guideline recommendations and the implementation of evidence-based treatments contributing to the burden of cardiovascular disease globally. The WHF Cholesterol Roadmap highlighted the limitations of current approaches and potential roadblocks across global health systems to achieving better population-level cholesterol control to reduce

ASCVD events [1]. Implementing an intervention directed against the underlying disease (atherosclerosis), deliverable at the level of the population, could help alleviate much of the future burden which will be placed on patients and health systems.

The present study provides information for healthcare practitioners, public health, and policy makers about the importance of how even small changes in cardiovascular risk factors if sustained over time in many individuals potentially impacts cardiovascular outcomes at a population level. Furthermore due consideration about how health systems, physician behaviours, and patient perspectives might need to change if governments wish to achieve the commitment to reduce the number of premature deaths related to non-communicable diseases by 25% by the year 2025 as part of the World Health Organization global action plan 2013–2020 [22]. This will require the creation and implementation of strategies which are easily scalable and which in a relatively short timescale could result in a reduction in risk at the level of the population (improve population health).

4.1. Limitations

The present study is based upon simulation, using the risk calculator recommended by the European Society of Cardiology Prevention guidelines [23] for estimating individual 10-year cardiovascular risk, rather than observed events. Potential benefits from further LDL-C lowering were estimated from the CTT meta-regression equation rather than observed data. While both LDL-C change and CTT risk ratio were used to calculate the 10-year CV risk reduction from baseline SMART score for each patient with ASCVD included in the ORION-10 and ORION-11 trials, the Monte Carlo simulation method, built on a population K-PD model, was used to estimate the potential impact of inclisiran on LDL-C levels and 10-year CV risk in the simulated 500,000 ORION-like patients. This variation in statistical methods resulted in a minor difference in the 10-year CV risk reduction projected in the clinical study (−6.99%) and the simulation (−6.4%) analysis. Whilst this simulation study provides estimates of efficacy based on LDL-C changes in clinical trials with duration <10 years and an empiric relation of LDL-C changes to clinical benefit, the long-term efficacy of inclisiran may vary in non-trial settings [24,25]. Accordingly, the current analysis may reflect a 'best case scenario'. Notwithstanding this limitation, there was evidence of clinical benefit with inclisiran based on non-adjudicated safety reporting, [19] analogous to the observations with anti-PCSK9 monoclonal antibodies prior to the definitive CV outcome trials that comprised a modest number of CV events and had wide confidence intervals [26,27]. Thus, the present simulation should be taken in the context of the fact that cardiovascular outcome data with inclisiran from randomized, double-blind, placebo-controlled trials are still awaited, but are available for four other LDL-C–lowering therapies [13,28–31]. In addition, although pooled safety [10] and open-label extension studies [32] do not show any off-target effects of inclisiran, these will also be evaluated in ongoing large trials.

We assumed that changes in LDL-C using the Day 90 to Day 540 window were maintained for 10 years in both placebo and inclisiran simulated patients, whereas the longest observed period of efficacy with inclisiran is 4 years in an open-label extension study [32], where general safety and efficacy were similar to observations in placebo-controlled trials over 18 months [10]. Moreover, real-world adherence to inclisiran treatment may differ from clinical trial settings. The model ignores potential changes in background LLT over 10 years among placebo-assigned patients while guidelines continue to evolve [5,6] and the likelihood of treatment intensification over a 10-year period. This would diminish the potential for further LDL-C lowering and event reduction with inclisiran. Inclisiran administered by a health-system does not overcome the adherence issues associated with the first dose, however, by being administered through a health care professional, overcomes the adherence issue with the second dose. In the future, the injection visits could be used as a reminder to patients to adhere to their background statin therapy, as most patients with ASCVD require combination therapies rather than monotherapy to reach treatment goals. Finally, the number of events averted through additional LDL-C lowering depends upon the residual risk of cardiovascular events and the LDL-C levels in the population, hence the present simulation refers to an ORION like population. That said, the LDL-C at baseline and predicted risk are not too dissimilar, from recent data derived through health records in routine clinical practice, which provide estimates of residual risk and current levels of cholesterol control in real world settings [33]. In that study of a cohort of 244,578 individuals with ASCVD, the median age was 67.3 years, 62.1% were male and non-HDL-C despite lipid lowering therapy was approximately 3.4 mmol/L (which roughly approximates to an LDL-C of 2.6 mmol/L). The observed 10-year risk of cardiovascular events was 29.1% in men and 26.6% in women, with a total of 45,327 cardiovascular events observed. The 10-year risk predicted in that real world cohort using the SMART equation, closely approximated to the observed, providing a reasonable basis for the estimated risks using the SMART equation in the present study.

In conclusion, the present simulation study, using established mathematical models and observed trial data, provides insights into the advantages for population health which might be achieved through implementing novel approaches at a scale capable of providing consistent LDL-C lowering through convenient dosing (Fig. 3) [34].

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Ethical approval

Regarding the clinical trials ORION-10 and ORION-11 included in this simulation analysis, the trial protocols were approved by the relevant Institutional Review Board (IRB) or Independent Ethics Committee (IEC) and were conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki and in compliance with Good Clinical Practice. All patients provided written informed consent.

Pre-registered clinical trial number

The pre-registered clinical trial number for ORION-10 is NCT03399370 and ORION-11 is NCT03400800.

CRediT authorship contribution statement

Kausik K. Ray: Conceptualization, Formal analysis, Investigation, Methodology, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Laura H. Gunn:** Conceptualization, Formal analysis, Investigation, Methodology, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Lorena Garcia Conde:** Conceptualization, Investigation, Methodology, Supervision, Validation, Writing – original draft, Writing – review & editing. **Frederick J. Raal:** Conceptualization, Investigation, Methodology, Validation, Writing – original draft, Writing – review & editing. **R. Scott Wright:** Conceptualization, Investigation, Methodology, Validation, Writing – original draft, Writing – review & editing. **Nathalie H. Gosselin:** Conceptualization, Formal analysis, Investigation, Methodology, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Lawrence A. Leiter:** Conceptualization, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing. **Wolfgang Koenig:** Conceptualization, Investigation, Methodology, Validation, Writing – original draft, Writing – review & editing. **Gregory G. Schwartz:** Conceptualization, Formal analysis, Investigation, Methodology, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Ulf Landmesser:** Conceptualization, Formal analysis,

Investigation, Methodology, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2024.117472.

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