Received: 31 January 2024 | Revised: 26 April 2024 | Accepted: 26 April 2024

DOI: 10.1111/dom.15650

ORIGINAL ARTICLE

WILEY

Inclisiran in individuals with diabetes or obesity: Post hoc pooled analyses of the ORION-9, ORION-10 and ORION-11 Phase 3 randomized trials

Lawrence A. Leiter MD[1] | Frederick J. Raal PhD[2] | Gregory G. Schwartz MD[3] | Wolfgang Koenig MD[4,5,6] | Kausik K. Ray FMedSci[7] | Ulf Landmesser MD[8] | Jackie Han MS[9] | Lorena Garcia Conde MD[10] | R. Scott Wright MD[11]

[1]Li Ka Shing Knowledge Institute, St. Michael's Hospital, University of Toronto, Toronto, Canada

[2]Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

[3]Division of Cardiology, University of Colorado School of Medicine, Aurora, Colorado, USA

[4]Deutsches Herzzentrum München, Technische Universität München, Munich, Germany

[5]DZHK (German Centre for Cardiovascular Research), Partner Site Munich Heart Alliance, Munich, Germany

[6]Institute of Epidemiology and Medical Biometry, University of Ulm, Ulm, Germany

[7]Imperial Centre for Cardiovascular Disease Prevention, Department of Primary Care and Public Health, Imperial College, London, UK

[8]Department of Cardiology, Angiology and Intensive Care Medicine, Deutsches Herzzentrum der Charité, Charité University Medicine Berlin, Friede Springer Cardiovascular Prevention Center od Charité, Berlin Institute of Health, DZHK, Partner Site Berlin, Berlin, Germany

[9]Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, USA

[10]Novartis Pharma AG, Basel, Switzerland

[11]Division of Preventive Cardiology and Department of Cardiology, Mayo Clinic, Rochester, Minnesota, USA

Correspondence
Lawrence A. Leiter, Li Ka Shing Knowledge Institute, St. Michael's Hospital, University of Toronto, Toronto, M5T 2S8, Canada.
Email: lawrence.leiter@unityhealth.to

Funding information
Novartis Pharma AG, Basel, Switzerland

Abstract

Aims: To conduct a pooled analysis of Phase 3 trials investigating the efficacy and safety of inclisiran across glycaemic and body mass index (BMI) strata.

Materials and Methods: Participants were randomized 1:1 to receive 300 mg inclisiran sodium or placebo twice yearly, after initial and 3-month doses up to 18 months, with background oral lipid-lowering therapy. Analyses were stratified by glycaemic status (normoglycaemia, prediabetes, and diabetes) or BMI (<25, ≥25 to <30, ≥30 to <35, and ≥35 kg/m^2). Co-primary endpoints were percentage and time-adjusted percentage change in low-density lipoprotein (LDL) cholesterol from baseline. Safety was also assessed.

Results: Baseline characteristics were balanced between treatment arms and across strata. Percent LDL cholesterol change (placebo-corrected) with inclisiran from baseline to Day 510 ranged from −47.6% to −51.9% and from −48.8% to −54.4% across glycaemic/BMI strata, respectively. Similarly, time-adjusted percentage changes after Day 90 and up to Day 540 ranged from −46.8% to −52.0% and from −48.6% to

Clinical Trial Information: ORION-9 (NCT03397121), ORION-10 (NCT03399370), and ORION-11 (NCT03400800).

−53.3% across glycaemic/BMI strata, respectively. Inclisiran led to significant reductions in proprotein convertase subtilisin/kexin type 9 and other atherogenic lipids and lipoproteins versus placebo across the glycaemic/BMI strata. The proportions of individuals achieving LDL cholesterol thresholds of <1.8 mmol/L and <1.4 mmol/L with inclisiran increased with increasing glycaemic and BMI strata. Across the glycaemic/BMI strata, a higher proportion of individuals had mild/moderate treatment-emergent adverse events (TEAEs) at the injection site with inclisiran (2.8%–7.7%) versus placebo (0.2%–2.1%).

Conclusion: Inclisiran provided substantial and sustained LDL cholesterol lowering across glycaemic/BMI strata, with a modest excess of transient mild-to-moderate TEAEs at the injection site.

KEYWORDS

clinical trial, dyslipidaemia, glycaemic control, lipid-lowering therapy, randomized trial, type 2 diabetes

1 | INTRODUCTION

Individuals with diabetes mellitus (DM) or dyslipidaemia often have atherosclerotic cardiovascular disease (ASCVD).[1–4] Indeed, the global burden of cardiovascular (CV) diseases attributable to metabolic risk factors is rising and predicted to keep increasing over the next decade.[5]

In individuals with DM or prediabetes (pre-DM) ASCVD is the leading cause of death and disability, adding to increased risks of stroke, coronary heart disease and myocardial infarction versus those with normoglycaemia.[2–6]

Obesity is also frequently associated with the development of ASCVD, partly because it contributes to other CV risk factors, including type 2 DM and atherogenic dyslipidaemia (elevated triglyceride-rich lipoproteins and low high-density lipoprotein [HDL] cholesterol).[7–8]

Cumulative exposure to elevated levels of low-density lipoprotein (LDL) cholesterol contributes to the pathogenesis, progression and clinical risk of ASCVD. Conversely, continuous and consistent LDL cholesterol lowering leads to a reduction in lifetime ASCVD risk.[9] Clinical practice guidelines recommend high-intensity or maximally tolerated statin therapy, sometimes in conjunction with a non-statin lipid-lowering therapy (LLT), to achieve LDL cholesterol treatment goals in very-high-risk populations, including those with DM.[3–10] However, a substantial proportion of individuals with ASCVD and metabolic abnormalities have inadequately controlled LDL cholesterol levels and thus do not achieve recommended LDL cholesterol goals, highlighting the need for more aggressive lipid management with newer LDL cholesterol-lowering therapies, including those that target the proprotein convertase subtilisin/kexin type 9 (PCSK9) pathway.[11–13] Inclisiran is a small interfering RNA targeting the PCSK9 mRNA. Inclisiran binds to the RNA-induced silencing complex, directing it to degrade the PCSK9 mRNA, thereby inhibiting its translation into the PCSK9 protein.[14] Inclisiran is well tolerated in patients with ASCVD, ASCVD risk equivalent, and heterozygous familial hypercholesterolemia (HeFH) and provides effective and consistent LDL cholesterol lowering over the long term, with an infrequent, healthcare professional-administered dosing schedule (twice-yearly dosing after the initial and 3-month doses).[15,16] To date, the effect of inclisiran in individuals with metabolic abnormalities such as DM and obesity has not been fully characterized. This post hoc analysis examined the efficacy and safety of inclisiran across different baseline glycaemic and body mass index (BMI) strata.

2 | MATERIALS AND METHODS

2.1 | Population

Participants from the ORION-9, ORION-10 and ORION-11 trials with HeFH, ASCVD and ASCVD or ASCVD risk equivalent, respectively, were included. These individuals had elevated LDL cholesterol levels despite receiving maximally tolerated statins (defined in Appendix S1), with or without additional oral LLTs. In all three trials, participants were required to be receiving stable LLT ≥30 days prior to screening. Individuals treated with anti-PCSK9 monoclonal antibodies (mAbs) within 90 days before screening were excluded.

In this post hoc pooled analysis, the population was stratified by baseline glycaemic status: normoglycaemia (individuals with glycated haemoglobin [HbA1c] levels <5.7% [<39 mmol/mol] and fasting glucose <100 mg/dL [<5.6 mmol/L] at baseline, no medical history of DM, and no antihyperglycaemic medication use at baseline), pre-DM (individuals with HbA1c ≥5.7% [≥39 mmol/mol] or fasting glucose ≥100 mg/dL [≥5.6 mmol/L] at baseline, and either HbA1c <6.5% [<48 mmol/mol] or fasting glucose <126 mg/dL [<7.0 mmol/L] at baseline, no medical history of DM, and no use of antihyperglycaemic agents at baseline), and DM (individuals with a medical history of DM, or HbA1c ≥6.5% [≥48 mmol/mol] and fasting glucose ≥126 mg/dL

[≥7.0 mmol/L] at baseline, or use of antihyperglycaemic agents at baseline for treatment of DM). The population was also stratified according to baseline BMI into subgroups based on the National Institutes of Health categorization: <25 kg/m^2 (normal), ≥25 to <30 kg/m^2 (overweight), ≥30 to <35 kg/m^2 (obesity Class I) and ≥35 kg/m^2 (obesity Class II/III).[17,18]

The study was conducted in accordance with the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use E6 guideline for Good Clinical Practice, which originates from the Declaration of Helsinki. The study protocol and all amendments were approved by the independent ethics committee or institutional review board of all participating centres. All individuals provided written informed consent.

2.2 | Study design

Trial protocols and details pertaining to trial oversight have been published.[19,20] Briefly, ORION-9, ORION-10 and ORION-11 were double-blind, placebo-controlled, parallel-group, Phase 3 trials. Individuals were randomized 1:1 to receive either 300 mg inclisiran sodium (equivalent to 284 mg inclisiran) or placebo on Days 1, 90, 270 and 450, along with background oral LLT. Individuals had visits on Days 30, 150, 330 and 510 for biochemical measurements and safety assessments. The final visit was on Day 540. Randomization was stratified according to background use of statins in all trials and according to country in the ORION-9 and ORION-11 trials.

The study protocols of the ORION-9 (NCT03397121), ORION-10 (NCT03399370) and ORION-11 (NCT03400800) trials were approved by the institutional review board or independent ethics committee of each participating institution. Informed consent was obtained from all individual participants included in the trials.

2.3 | Endpoints

The prespecified co-primary endpoints for each trial were percentage change in LDL cholesterol from baseline to Day 510 and time-adjusted percentage change in LDL cholesterol from baseline after Day 90 and up to Day 540, the latter assessing the average percentage reduction of LDL cholesterol from baseline across visits from the second dose until the end of the study. Key secondary endpoints were absolute change in LDL cholesterol from baseline to Day 510, time-adjusted absolute change in LDL cholesterol from baseline after Day 90 and up to Day 540, and percentage changes from baseline to Day 510 in PCSK9, total cholesterol, non-HDL cholesterol and apolipoprotein B (ApoB) levels. Other secondary endpoints included the percentage change from baseline in triglycerides and lipoprotein(a) [Lp(a)] levels from baseline to Days 510 and 540, respectively.

The percentage change in remnant cholesterol from baseline to Day 510 and the proportions of individuals achieving prespecified LDL cholesterol (<2.6, <1.8 and <1.4 mmol/L), ApoB (<1818.2 nmol/L [<100 mg/dL], <1454.5 nmol/L [<80 mg/dL] and <1181.8 nmol/L [<65 mg/dL]), and non-HDL cholesterol (<3.4, <2.6 and <2.2 mmol/L) thresholds from baseline to Day 510 were also analysed. Safety analyses included the incidence of treatment-emergent adverse events (TEAEs), treatment-emergent serious adverse events (TESAEs), TEAEs leading to study discontinuation, clinically relevant TEAEs at the injection site, and clinically relevant laboratory measurements. The incidence of postbaseline new-onset diabetes (NOD) was also analysed. NOD was defined by the earliest date after the first study drug administration when any of the following occurred: identification of DM-related TEAE terms, initiation of antidiabetic medication, and meeting laboratory criteria (HbA1c ≥6.5% [≥48 mmol/mol] or fasting glucose ≥126 mg/dL [≥7.0 mmol/L] on two occasions or both on the same occasion, HbA1c ≥6.5% [≥48 mmol/mol] on one occasion and fasting glucose ≥126 mg/dL [≥7.0 mmol/L] on the succeeding occasion, or fasting glucose ≥126 mg/dL [≥7.0 mmol/L] on one occasion and HbA1c ≥6.5% [≥48 mmol/mol] on the succeeding occasion) as detailed in Appendix S2.

2.4 | Analysis set

Baseline characteristics and efficacy were analysed in the intention-to-treat population comprising all randomized individuals. Safety was evaluated in the safety population comprising all individuals who received ≥1 dose of the study drug.

2.5 | Statistical methods

The percentage and absolute changes in LDL cholesterol from baseline to Day 510 were analysed using an analysis of covariance model with multiple imputation for missing data. The time-adjusted percentage change in LDL cholesterol from baseline after Day 90 and up to Day 540 was analysed using a mixed-effects model for repeated measures (MMRM) with a control-based pattern mixture model for missing data imputation. The time-adjusted absolute change in LDL cholesterol from baseline after Day 90 and up to Day 540 and the percentage change in PCSK9, total cholesterol, non-HDL cholesterol, ApoB, remnant cholesterol and triglyceride levels from baseline to Day 510 were analysed using an MMRM model without imputation for missing data (Appendix S3). The percentage change in Lp(a) from baseline to Day 540 was analysed using a quantile regression model without imputation. Tests for the interaction of treatment with glycaemic or BMI subgroups as well as the interaction of treatment with continuous baseline HbA1c or BMI were conducted for the efficacy endpoints. Analyses by BMI and DM were not prespecified and therefore not adjusted for multiplicity. Nominal p values and 95% confidence intervals (CIs) are considered descriptive measures for the strength of the association between treatment arms and endpoints and not formal criteria to claim statistical significance. The Medical Dictionary for Regulatory Activities version v20.1 was used in the ORION-9, ORION-10 and ORION-11 Phase 3 studies for safety analyses.

2.6 | Data and resource availability

Qualified researchers can request access to patient-level data and related study documents after publication, including the statistical analysis plan and dataset specifications. Patient-level data will be anonymized and study documents will be redacted to protect the privacy of the trial participants.

3 | RESULTS

3.1 | Study population

This pooled analysis comprised 3658 individuals stratified by glycaemic status and 3658 stratified by baseline BMI. Of all individuals stratified by glycaemic status, 784 (21.4%) had normoglycaemia, 1503 (41.1%) had pre-DM and 1371 (37.5%) had DM (of whom 32 [2.3%] had type 1 DM [16 individuals in each treatment arm]). In the BMI subgroups, 507 individuals (13.9%) had a BMI <25 kg/m^2, 1398 (38.2%) had a BMI ≥25 to <30 kg/m^2, 1091 (29.8%) had a BMI ≥30 to <35 kg/m^2 and 662 (18.1%) had a BMI ≥35 kg/m^2. Baseline demographic and clinical characteristics were generally balanced between treatment arms across strata, irrespective of baseline glycaemic or BMI status (Table 1).

Baseline characteristics were generally balanced between the inclisiran and placebo groups, except that in individuals with pre-DM, baseline levels of LDL cholesterol, total cholesterol, non-HDL cholesterol and ApoB were statistically higher in the inclisiran versus the placebo arm. However, the differences in mean levels were small and clinically insignificant (Table 1). Baseline LDL cholesterol, non-HDL cholesterol, ApoB, and proportion of individuals with familial hypercholesterolaemia were higher in the normoglycaemia subgroup than in the DM and pre-DM subgroups. Accordingly, the number of individuals using ezetimibe at baseline was higher in the normoglycaemia subgroup. Conversely, baseline triglyceride levels were progressively higher in the normoglycaemia, pre-DM and DM subgroups. As expected, individuals with normoglycaemia had lower BMI than those with pre-DM or DM, and individuals with BMI <25 kg/m^2 had numerically higher levels of baseline LDL cholesterol and total cholesterol, lower levels of triglycerides, and a higher frequency of ezetimibe use than those in higher BMI categories. Moreover, across the BMI strata, differences in waist circumference were observed with increasing BMI. The proportions of individuals with ASCVD increased with worsening glycaemic status, and the presence of ASCVD risk equivalent was associated with a more normal glycaemic status. Levels of HbA1c and fasting serum glucose were also higher with worsening glycaemic status and increased BMI.

3.2 | Efficacy

3.2.1 | Co-primary endpoints

The mean (95% CI) placebo-corrected percentage change in LDL cholesterol from baseline to Day 510 with inclisiran was −47.6% (- 51.9 to −43.3) in individuals with normoglycaemia, −51.6% (−55.0 to −48.3) in those with pre-DM, and −51.9% (−55.7 to −48.1) in those with DM (each $p < 0.001$; treatment by glycaemic category interaction effect $p = 0.29$ [Figure 1A]). The corresponding mean (95% CI) placebo-corrected time-adjusted percentage changes in LDL cholesterol from baseline after Day 90 and up to Day 540 were −46.8% (−50.2 to −43.5), −51.4% (−53.8 to −48.9) and −52.0% (−54.6 to −49.4; each $p < 0.001$, treatment by glycaemic category interaction $p = 0.03$ [Figure 1A]). Thus, with worsening glycaemic status, a larger time-adjusted percentage reduction in LDL cholesterol was observed with inclisiran. Similarly, considering HbA1c as a continuous variable, higher baseline HbA1c was associated with a larger time-dependent reduction of LDL cholesterol ($p = 0.01$ [Table S1]).

The mean (95% CI) placebo-corrected percentage changes in LDL cholesterol from baseline to Day 510 with inclisiran were −48.8% (−54.7 to −42.9), −49.0% (−52.3 to −45.8), −54.4% (−58.5 to −50.2), and −50.5% (−56.0 to −45.0) in individuals with BMI <25, ≥25–30, ≥30–<35, and ≥35 kg/m^2, respectively (each $p < 0.001$). The corresponding mean (95% CI) placebo-corrected time-adjusted percentage changes in LDL cholesterol from baseline after Day 90 and up to Day 540 were −48.6% (−53.0 to −44.2), −48.8% (−51.2 to −46.4), −53.3% (−56.2 to −50.3) and −51.8% (−55.8 to −47.8; each $p < 0.001$ [Figure 1B]). The time-adjusted percentage reduction in LDL cholesterol with inclisiran was greater with increasing BMI category (interaction $p = 0.05$) and with increasing BMI as a continuous variable (interaction $p = 0.003$ [Table S2]).

3.2.2 | Key secondary endpoints

The mean (95% CI) placebo-corrected absolute change in LDL cholesterol from baseline to Day 510 with inclisiran was −1.4 mmol/L (−1.5 to −1.3) in individuals with normoglycaemia, pre-DM, and DM ($p < 0.001$ for all). The corresponding mean (95% CI) placebo-corrected time-adjusted absolute change in LDL cholesterol from baseline after Day 90 and up to Day 540 was −1.4 mmol/L (−1.5 to −1.3; each $p < 0.001$ [Table S3]).

The mean (95% CI) placebo-corrected absolute changes in LDL cholesterol from baseline to Day 510 with inclisiran were −1.4 mmol/L (−1.5 to −1.2), −1.4 mmol/L (−1.5 to −1.3), −1.4 mmol/L (−1.5 to −1.3), and −1.3 mmol/L (−1.5 to −1.2) in individuals with BMI <25, ≥25 to <30, ≥30 to <35, and ≥ 35 kg/m^2, respectively (each $p < 0.001$ [Table S3]). The corresponding mean (95% CI) placebo-corrected time-adjusted absolute changes in LDL cholesterol from baseline after Day 90 and up to Day 540 were −1.4 mmol/L (−1.5 to −1.3), −1.4 mmol/L (−1.5 to −1.3), −1.4 mmol/L (−1.5 to −1.4), and −1.4 mmol/L (−1.5 to −1.3) (each $p < 0.001$ [Table S3]).

Treatment with inclisiran resulted in a greater percent lowering of LDL cholesterol in individuals with both DM (or pre-DM) and obesity. A greater percent and time-adjusted percent reduction of LDL cholesterol was observed in individuals with DM/pre-DM and obesity compared with those with normoglycaemia and BMI <25 kg/m^2

TABLE 1 Baseline demographic and clinical characteristics.

	Normoglycaemia		Prediabetes		Diabetes		BMI < 25 kg/m^2		BMI ≥ 25 to <30 kg/m^2		BMI ≥ 30 to <35 kg/m^2		BMI ≥ 35 kg/m^2	
	Inclisiran	Placebo	Inclisiran	Placebo	Inclisiran	Placebo	Inclisiran	Placebo	Inclisiran	Placebo	Inclisiran	Placebo	Inclisiran	Placebo
Characteristic	(*n* = 388)	(*n* = 396)	(*n* = 733)	(*n* = 770)	(*n* = 711)	(*n* = 660)	(*n* = 269)	(*n* = 238)	(*n* = 706)	(*n* = 692)	(*n* = 536)	(*n* = 555)	(*n* = 322)	(*n* = 340)
Male, *n* (%)	246 (63.4)	249 (62.9)	507 (69.2)	558 (72.5)	473 (66.5)	437 (66.2)	156 (58.0)	129 (54.2)	503 (71.2)	487 (70.4)	379 (70.7)	401 (72.3)	188 (58.4)*	226 (66.5)*
Age, years	60.1 ± 13.0	61.2 ± 12.0	64.6 ± 9.0	64.5 ± 9.7	65.7 ± 8.4*	64.8 ± 8.3*	64.0 ± 11.1	63.1 ± 11.3	64.4 ± 10.5	64.9 ± 10.1	64.1 ± 9.1	63.9 ± 9.5	63.5 ± 9.2	62.4 ± 8.8
White, n (%)	364 (93.8)	377 (95.2)	695 (94.8)	732 (95.1)	610 (85.8)*	598 (90.6)*	251 (93.3)	228 (95.8)	646 (91.5)*	659 (95.2)*	485 (90.5)	513 (92.4)	288 (89.4)	306 (90.0)
BMI, kg/m^2	28.3 ± 4.9	28.4 ± 4.8	30.2 ± 5.4	30.0 ± 5.2	*n* = 711 31.8 ± 5.9*	*n* = 658 32.9 ± 6.3*	23.1 ± 1.6	22.9 ± 1.9	27.7 ± 1.4	27.7 ± 1.4	32.2 ± 1.4	32.2 ± 1.4	39.5 ± 4.9	39.9 ± 4.9
Medical history and comorbidities														
ASCVD, *n* (%)	294 (75.8)	288 (72.7)	624 (85.1)*	691 (89.7)*	633 (89.0)	576 (87.3)	209 (77.7)	184 (77.3)	595 (84.3)	588 (85.0)	474 (88.4)	486 (87.6)	274 (85.1)	295 (86.8)
ASCVD risk equivalent, n (%)	94 (24.2)	108 (27.3)	109 (14.9)	79 (10.3)	78 (11.0)	84 (12.7)	60 (22.3)	54 (22.7)	111 (15.7)	104 (15.0)	62 (11.6)	69 (12.4)	48 (14.9)	45 (13.2)
FH, *n* (%)	139 (35.8)	138 (34.8)	144 (19.6)	140 (18.2)	57 (8.0)	73 (11.1)	79 (29.4)	66 (27.7)	124 (17.6)	144 (20.8)	81 (15.1)	84 (15.1)	56 (17.4)	58 (17.1)
Concomitant medications														
Statin, *n* (%)	351 (90.5)	362 (91.4)	672 (91.7)	709 (92.1)	663 (93.2)	603 (91.4)	246 (91.4)	226 (95.0)	652 (92.4)	618 (89.3)	493 (92.0)	517 (93.2)	295 (91.6)	312 (91.8)
High-intensity statin, *n* (%)	273 (70.4)	263 (66.4)	556 (75.9)	599 (77.8)	527 (74.1)	483 (73.2)	195 (72.5)	178 (74.8)	520 (73.7)	487 (70.4)	399 (74.4)	419 (75.5)	242 (75.2)	259 (76.2)
Ezetimibe, *n* (%)	76 (19.6)	89 (22.5)	124 (16.9)	115 (14.9)	51 (7.2)	65 (9.8)	54 (20.1)	54 (22.7)	93 (13.2)	104 (15.0)	73 (13.6)	74 (13.3)	31 (9.6)	38 (11.2)
Laboratory measurements														
LDL cholesterol, mmol/L	3.2 ± 1.4	3.1 ± 1.3	2.9 ± 1.2*	2.8 ± 1.1*	2.7 ± 0.9	2.8 ± 1.0	3.1 ± 1.5	3.0 ± 1.2	2.9 ± 1.1	2.9 ± 1.1	2.8 ± 1.1	2.8 ± 1.1	2.8 ± 1.0	2.8 ± 1.2
Total cholesterol, mmol/L	*n* = 388 5.2 ± 1.6	*n* = 395 5.2 ± 1.6	*n* = 732 5.0 ± 1.3*	*n* = 769 4.8 ± 1.3*	*n* = 708 4.7 ± 1.1*	*n* = 658 4.8 ± 1.1*	*n* = 269 5.2 ± 1.6	*n* = 237 5.1 ± 1.3	*n* = 702 4.9 ± 1.3	*n* = 689 4.9 ± 1.3	4.8 ± 1.3	4.8 ± 1.2	4.8 ± 1.1	4.8 ± 1.3
Non-HDL cholesterol, mmol/L	*n* = 388 3.8 ± 1.5	*n* = 395 3.8 ± 1.4	*n* = 732 3.7 ± 1.3*	*n* = 769 3.5 ± 1.2*	*n* = 708 3.5 ± 1.1*	*n* = 658 3.7 ± 1.1*	*n* = 269 3.7 ± 1.6	*n* = 237 3.6 ± 1.2	*n* = 702 3.7 ± 1.3	*n* = 692 3.6 ± 1.2	3.7 ± 1.2	3.7 ± 1.2	3.6 ± 1.1	3.6 ± 1.3
Remnant cholesterol, mmol/L	*n* = 388 0.7 ± 0.3	*n* = 395 0.7 ± 0.3	*n* = 732 0.8 ± 0.4	*n* = 769 0.7 ± 0.4	*n* = 708 0.8 ± 0.4	*n* = 658 0.9 ± 0.5	*n* = 269 0.6 ± 0.4	*n* = 237 0.6 ± 0.3	*n* = 702 0.7 ± 0.4	*n* = 689 0.7 ± 0.3	0.8 ± 0.4	0.8 ± 0.4	0.8 ± 0.4	0.8 ± 0.4
ApoB, nmol/L	*n* = 387 1864.4 ± 630.23	*n* = 396 1854.6 ± 584.3	1815.9 ± 535.7*	1749.4 ± 517.8*	*n* = 708 1764.1 ± 468.0	*n* = 658 1813.0 ± 465.8	*n* = 268 1826.9 ± 639.8	*n* = 238 1776.9 ± 515.0	*n* = 705 1810.6 ± 521.0	*n* = 691 1791.7 ± 514.0	*n* = 535 1809.9 ± 519.1	*n* = 555 1809.1 ± 509.6	*n* = 320 1772.6 ± 488.3	*n* = 339 1793.8 ± 537.1
Triglyceride, mmol/L	1.4 ± 0.7	1.4 ± 0.7	1.6 ± 0.8	1.6 ± 0.8	1.8 ± 1.0	1.9 ± 1.1	1.4 ± 0.8	1.3 ± 0.7	1.6 ± 0.9	1.6 ± 0.8	1.8 ± 0.9	1.8 ± 1.0	1.8 ± 0.9	1.9 ± 1.0
Lp(a), nmol/L, median (Q1, Q3)	*n* = 387 48.0 (18.0, 186.0)	*n* = 396 50.0 (20.0, 191.5)	*n* = 733 58.0 (19.0, 197.0)	*n* = 769 44.0 (20.0, 192.0)	*n* = 708 41.5 (17.0, 170.0)	*n* = 658 48.0 (18.0, 166.0)	*n* = 268 62.5 (19.0, 198.0)	*n* = 238 54.5 (21.0, 195.0)	*n* = 705 53 (19.0, 190.0)	*n* = 691 45 (19.0, 181.0)	*n* = 535 48 (17.0, 185.0)	*n* = 555 47 (18.0, 185.0)	*n* = 320 42 (18.0, 161.0)	*n* = 338 42 (19.0, 175.0)

(Continues)

TABLE 1 (Continued)

Characteristic	Normoglycaemia		Prediabetes		Diabetes		BMI < 25 kg/m^2		BMI ≥ 25 to <30 kg/m^2		BMI ≥ 30 to <35 kg/m^2		BMI ≥ 35 kg/m^2	
	Inclisiran	Placebo	Inclisiran	Placebo	Inclisiran	Placebo	Inclisiran	Placebo	Inclisiran	Placebo	Inclisiran	Placebo	Inclisiran	Placebo
	(*n* = 388)	(*n* = 396)	(*n* = 733)	(*n* = 770)	(*n* = 711)	(*n* = 660)	(*n* = 269)	(*n* = 238)	(*n* = 706)	(*n* = 692)	(*n* = 536)	(*n* = 555)	(*n* = 322)	(*n* = 340)
PCSK9, ng/mL	*n* = 386	*n* = 395	*n* = 733	*n* = 768	*n* = 707	*n* = 658	*n* = 267	*n* = 238	*n* = 704	*n* = 690	*n* = 535	*n* = 553	*n* = 320	*n* = 339
	381.3 ± 110.7	379.3 ± 114.0	407.0 ± 173.5*	390.6 ± 132.9*	393.6 ± 130.5	393.4 ± 133.1	398.8 ± 131.2	386.3 ± 118.6	390.7 ± 135.7	391.4 ± 130.3	402.6 ± 182.9	384.9 ± 137.1	396.2 ± 105.1	394.1 ± 121.3
HbA1c, %	5.4 ± 0.2	5.4 ± 0.2	*n* = 731	*n* = 768	*n* = 708	*n* = 656	*n* = 269	*n* = 237	*n* = 705	*n* = 691	*n* = 533	*n* = 555	*n* = 320	*n* = 335
			5.9 ± 0.3	5.8 ± 0.3	7.3 ± 1.5	7.4 ± 1.6	6.0 ± 1.1	5.9 ± 1.1	6.2 ± 1.2	6.1 ± 1.1	6.4 ± 1.3	6.4 ± 1.4	6.7 ± 1.5	6.8 ± 1.5
Fasting glucose, mg/dL	89.6 ± 6.4	89.3 ± 6.7	102.3 ± 11.6	102.8 ± 12.2	148.4 ± 62.5	150.9 ± 64.9	108.3 ± 47.9	104.1 ± 37	112.3 ± 39.3	111.6 ± 41.5	122.7 ± 50.2	120.8 ± 49.1	127.9 ± 52.7	132.0 ± 57.6

Note: Baseline characteristics were analysed in the intention-to-treat population comprising all randomized individuals. Data shown are mean ± SD unless otherwise indicated. Continuous outcomes were compared using two-sample *t* tests and categorical outcomes were compared using Fisher's exact tests.

Abbreviations: ApoB, apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease. FH, familial hypercholesterolaemia; HbA1c, glycated haemoglobin, LDL, low-density lipoprotein; Lp(a), lipoprotein(a); HDL, high-density lipoprotein.

*Indicates $p < 0.05$.

(Table S4). Similar observations were noted for reductions in non-HDL cholesterol and remnant cholesterol levels (Table S4). Treatment-by-DM status and BMI subgroup interaction effects are presented in Table S5.

Percentage changes in PCSK9, total cholesterol, non-HDL cholesterol, ApoB, triglycerides, Lp(a), and remnant cholesterol from baseline to Day 510 [Day 540 for Lp(a)] were all significantly greater with inclisiran than with placebo across all glycaemic and BMI strata (Figure 2).

Similar interaction effects between treatment arm and glycaemic or BMI strata were observed for absolute reductions for PCSK9 and other atherogenic lipids, except triglycerides. The interaction test results between treatment arm and glycaemic strata or HbA1c as a continuous variable are shown in Table S1 and between treatment arm and BMI strata or BMI as a continuous variable in Table S2.

Substantial and sustained lowering of LDL cholesterol from baseline to Day 510 was observed with inclisiran versus placebo across glycaemic and BMI strata, regardless of baseline age, background LLT, antihyperglycaemic agents, triglyceride levels, BMI, and waist circumference (Figure 3A,B).

The proportions of individuals achieving prespecified lipid and lipoprotein thresholds at Day 510 and from Day 90 and up to Day 540 are summarized in Table S6. A significantly larger proportion of individuals treated with inclisiran achieved prespecified LDL cholesterol thresholds of <2.6, <1.8, and <1.4 mmol/L at Day 510 as compared with placebo. This was observed across all glycaemic and BMI categories with $p < 0.001$ for all comparisons of inclisiran versus placebo. These goals were achieved least often among those with normoglycaemia or BMI < 25 kg/m^2 and most often among those with DM or BMI ≥35 kg/m^2. The percentages of individuals achieving a ≥ 50% reduction in LDL cholesterol from baseline at Day 510 were also significantly higher with inclisiran than with placebo in the subgroups for normoglycaemia, pre-DM, and DM (inclisiran: 50.6%, 61.3%, and 68.1%, respectively; placebo: 0.8%, 1.7%, and 3.7%, respectively) and with BMI <25, ≥25 to <30, ≥30 to <35, and ≥35 kg/m^2 (inclisiran: 48.3%, 59.5%, 67.1% and 67.7%, respectively; placebo: 1.4%, 1.7%, 3.4%, and 1.8%, respectively; $p < 0.001$ for all comparisons). A higher percentage of individuals treated with inclisiran also reached prespecified ApoB levels of <1818.2 nmol/L (<100 mg/dL), <1454.5 nmol/L (<80 mg/dL), and <1181.8 nmol/L (<65 mg/dL) across the glycaemic and BMI strata versus placebo ($p < 0.001$ for all comparisons; Table S6). Similarly, across the glycaemic and BMI strata, a larger proportion of individuals treated with inclisiran achieved prespecified non-HDL cholesterol thresholds of <3.4, <2.6, and <2.2 mmol/L (Table S6) versus placebo ($p < 0.001$ for all comparisons).

3.3 | Safety

The safety population comprised 3654 individuals stratified by glycaemic status and 3653 by BMI. Key safety findings are summarized in Table S7. Across glycaemic and BMI strata, the incidence of TEAEs was broadly similar between treatment arms; a higher incidence of clinically relevant TEAEs at the injection site was observed with

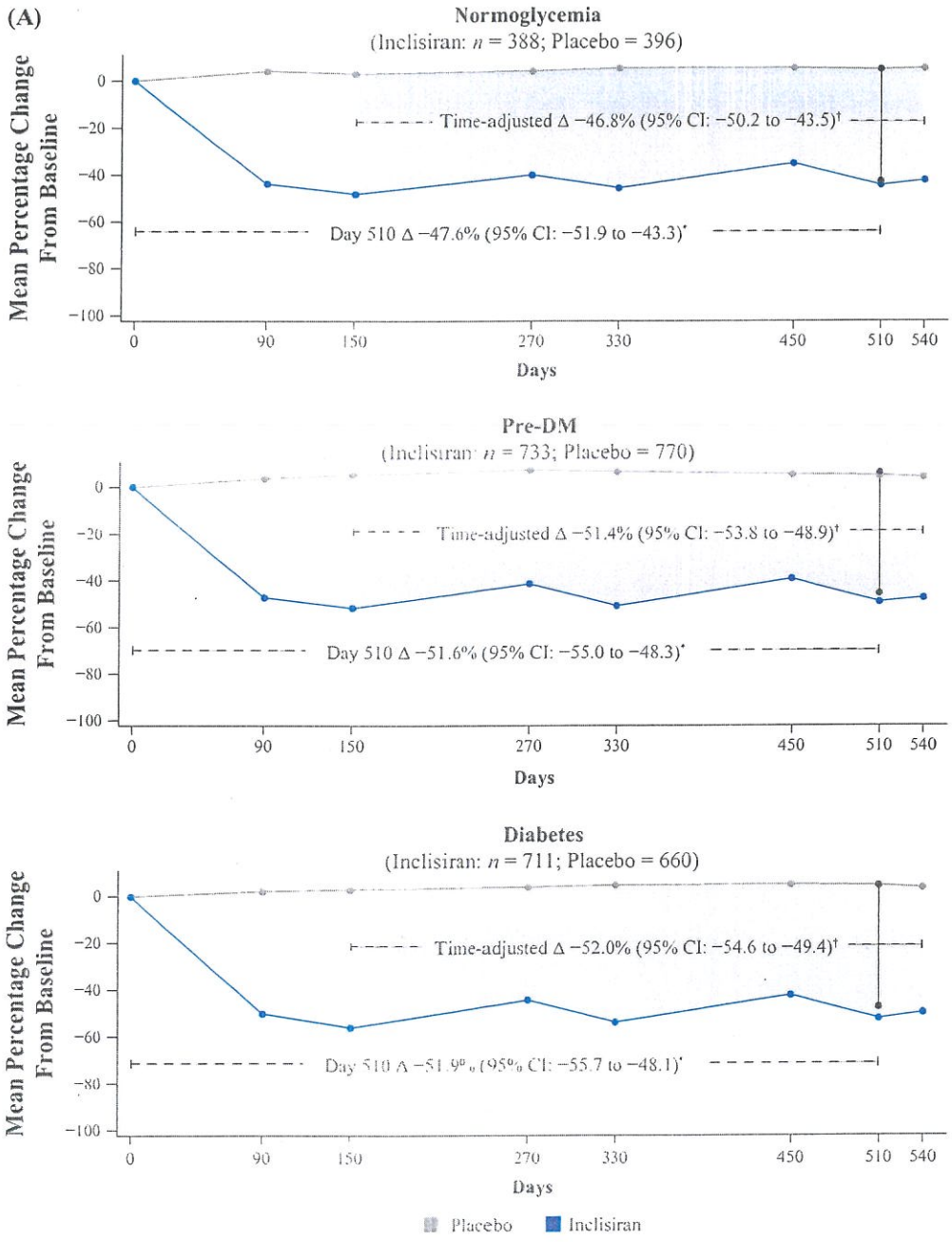

FIGURE 1 Percent and time-adjusted change in low-density lipoprotein (LDL) cholesterol over time across glycaemic and body mass index (BMI) strata. Mean percentage change in LDL cholesterol over time for the population across (A) glycaemic strata and (B) BMI strata. Data are presented as least squares (LS) mean change in LDL cholesterol at each postbaseline visit, analysed by a mixed-effects model for repeated measures (MMRM) without imputation assuming missing data are missing at random unless otherwise indicated. The black vertical line and data points represent the first co-primary endpoint, LS mean (95% confidence interval [CI]) percentage change from baseline to Day 510, assessed by analysis of covariance with a multiple imputation washout model. The second co-primary endpoint, time-adjusted LS mean (95% CI) percentage change from baseline after Day 90 and up to Day 540, analysed by an MMRM with a control-based pattern mixture model for data imputation, is stated and indicated in shaded blue. $p < 0.001$ for inclisiran versus placebo for all comparisons; *$p = 0.29$ (treatment-by-diabetes subgroup interaction effect); $p = 0.40$ (treatment-by-glycated haemoglobin [HbA1c] interaction effect); †$p = 0.03$ (treatment-by-diabetes subgroup interaction effect); $p = 0.01$ (treatment-by-continuous HbA1c interaction effect); ‡$p = 0.22$ (treatment-by-BMI subgroup interaction effect); $p = 0.15$ (treatment-by-BMI interaction effect); §$p < 0.05$ (treatment-by-BMI subgroup interaction effect); $p = 0.003$ (treatment-by-continuous BMI interaction effect). Pre-DM, prediabetes.

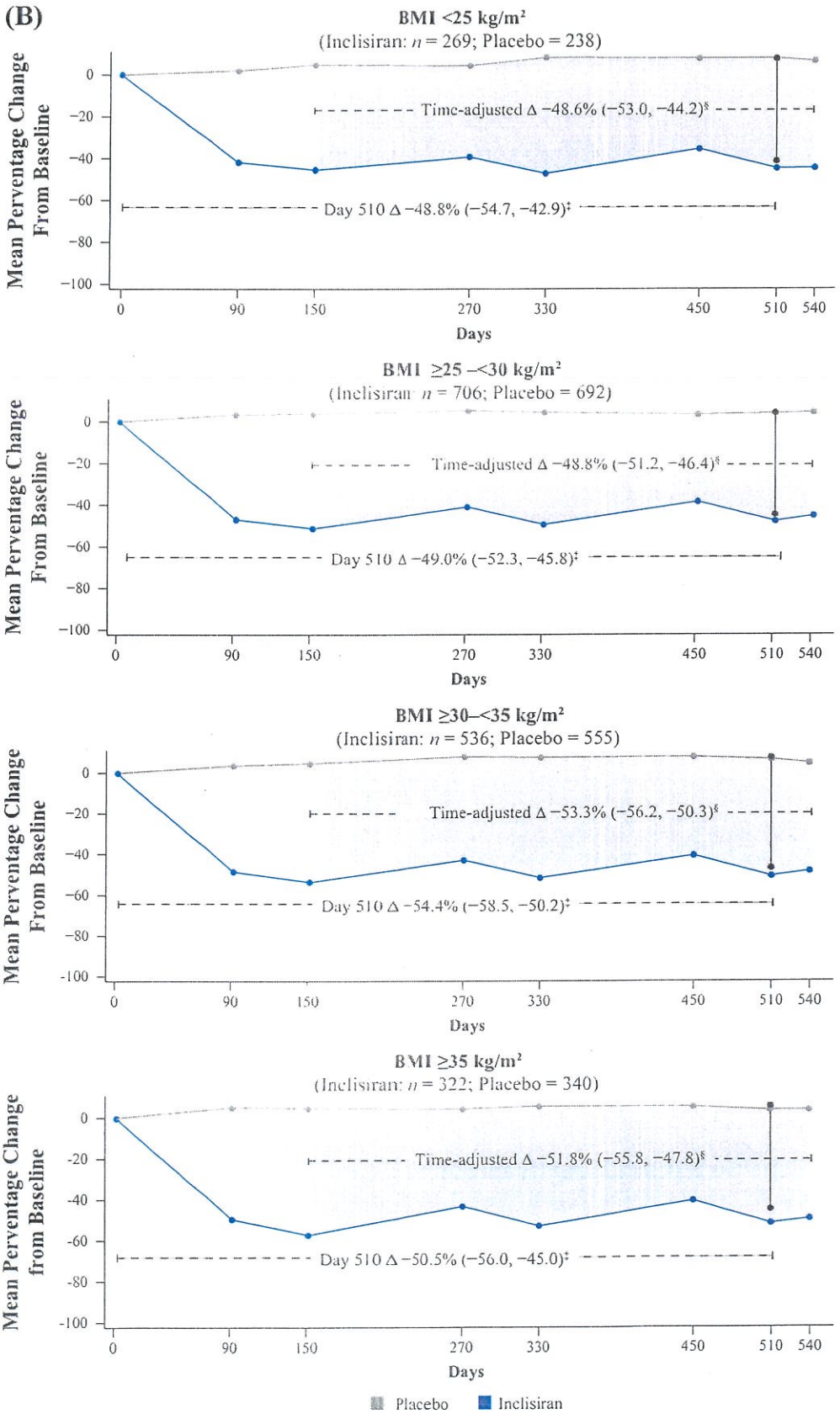

FIGURE 1 (Continued)

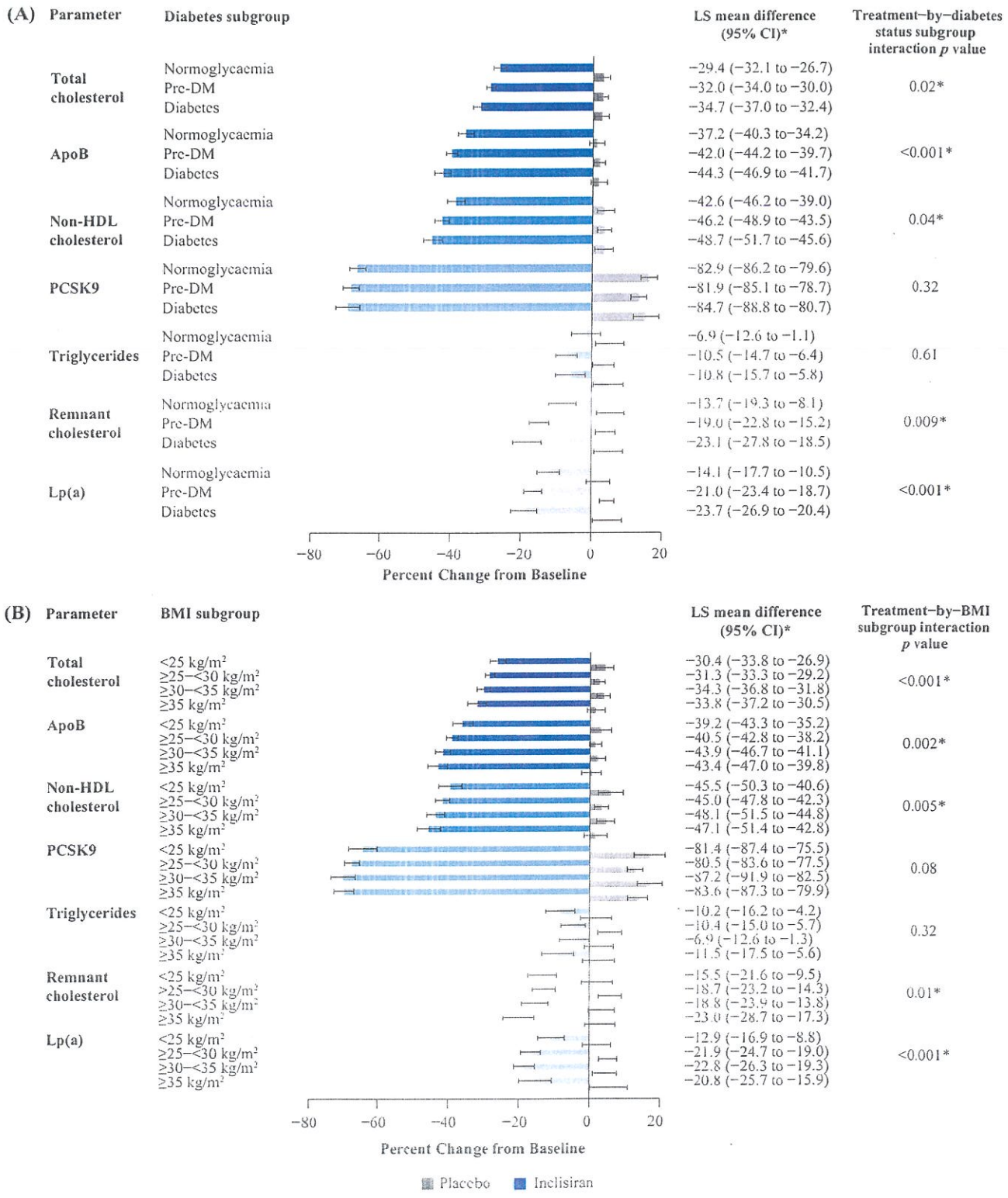

FIGURE 2 Percentage change in proprotein convertase subtilisin/kexin type 9 (PCSK9) and other atherogenic lipids and lipoproteins from baseline to Day 510. The values presented are least squares (LS) mean (95% confidence interval [CI]) at Day 510 (A) *$p < 0.001$ (inclisiran vs. placebo for all comparisons) except for triglycerides for normoglycaemia, where $p = 0.02$) (B) *$p < 0.001$ (inclisiran vs. placebo for all comparisons) except for triglycerides for body mass index (BMI) <25 kg/m^2 ($p = 0.001$), BMI ≥ 30 to <35 kg/m^2 ($p = 0.02$), and BMI ≥35 kg/m^2 ($p < 0.01$). ApoB, apolipoprotein B; Lp(a), lipoprotein(a); HDL, high-density lipoprotein; pre-DM, prediabetes.

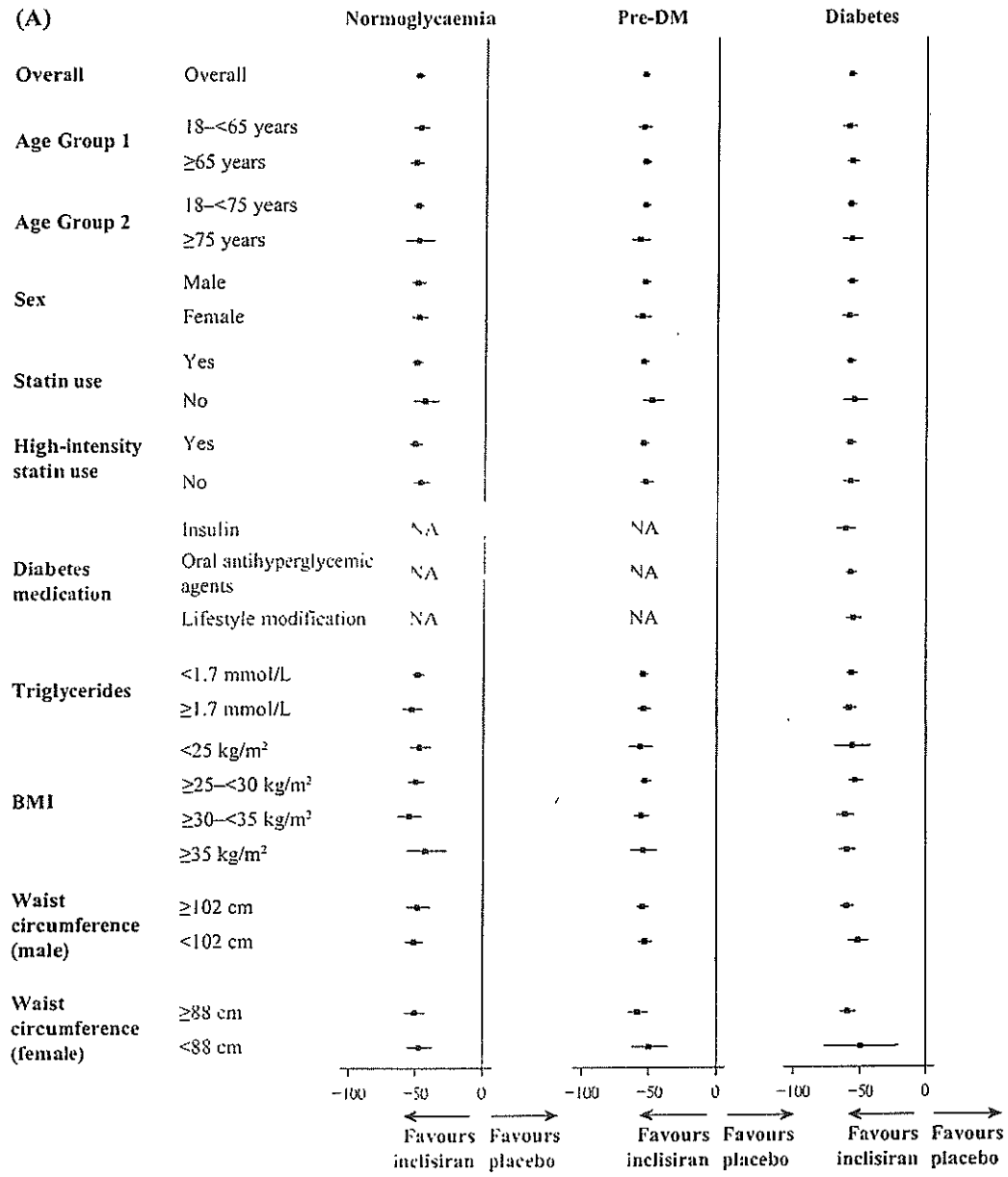

FIGURE 3 Percentage change in low-density lipoprotein (LDL) cholesterol from baseline to Day 510, stratified by important baseline characteristics. The values are presented as least squares mean placebo-corrected percentage changes in LDL cholesterol from baseline to Day 510 with inclisiran stratified by baseline demographic and clinical characteristics across glycaemic strata (A) and body mass index (BMI) strata (B). NA, not available; pre-DM, prediabetes.

inclisiran versus placebo (normoglycaemia: 7.7% vs. 0.8%: pre-DM: 5.6% vs. 0.3%; DM: 2.8% vs. 1.1%; BMI <25 kg/m^2: 5.9% vs. 0.4%; BMI ≥25 to <30 kg/m^2: 4.7% vs. 0.4%; BMI ≥30 to <35 kg/m^2: 4.3% vs. 0.2%; ≥35 kg/m^2: 5.9% vs. 2.1%). However, all events were mild to moderate and none was severe or persistent.

3.3.1 | New-onset diabetes

The incidence of postbaseline NOD was similar in both the inclisiran (8.8%; $n = 99$) and placebo (9.5%; $n = 110$) arms (Table S8). In the inclisiran arm, 0.5% ($n = 6$) individuals with normoglycaemia at baseline and 8.3% ($n = 93$) with pre-DM at baseline experienced postbaseline NOD, while in the placebo arm, the incidence rates were 0.6% ($n = 7$) and 8.9% ($n = 103$), respectively.

4 | DISCUSSION

Metabolic abnormalities such as DM and obesity are associated with an elevated risk of CV events, frequently warranting intensive LLT to reduce this risk.[7–21] In this analysis of the pooled population of

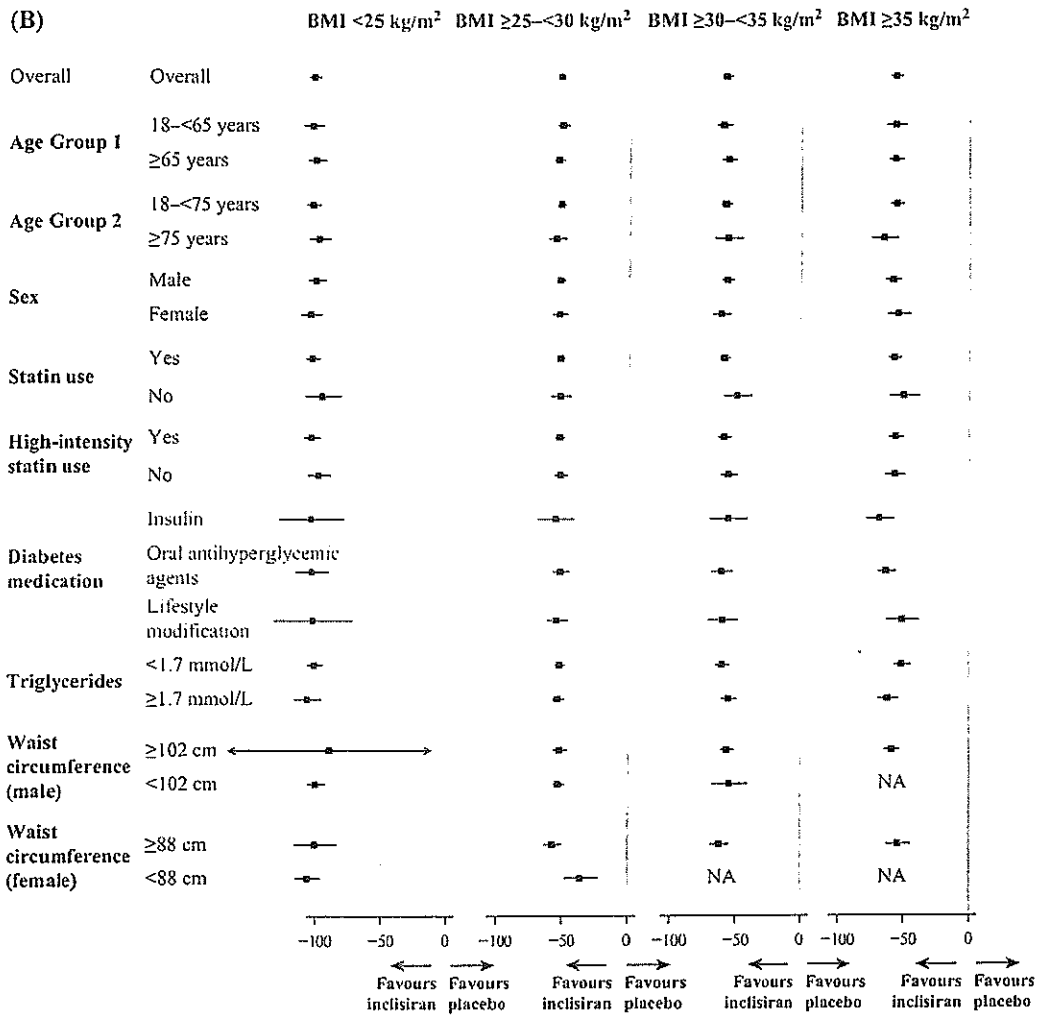

FIGURE 3 (Continued)

ORION-9, ORION-10 and ORION-11, twice-yearly inclisiran (after the initial and 3-month doses) for up to 18 months provided substantial and sustained LDL cholesterol reductions after the second dose until the end of the study (time-adjusted percentage change), ranging from −46.8% to −52.0% across glycaemic strata and −48.6% to −53.3% across BMI strata. The LDL cholesterol reductions in these population subgroups are consistent with those reported for the overall ORION-9, ORION-10 and ORION-11 pooled population, in which the time-adjusted percentage reduction in LDL cholesterol after Day 90 and up to Day 540 was 50.5% with inclisiran.[16] Baseline factors such as background LLT, DM medication, triglyceride levels, BMI, and waist circumference had no influence on the LDL cholesterol reduction with inclisiran. A higher use of ezetimibe at baseline in individuals with normoglycaemia can be attributed to a higher percentage of individuals with HeFH in this group (53% of the population with HeFH in ORION-9 were prescribed ezetimibe).

Significant reductions in PCSK9 levels (>80%), along with reductions in all other atherogenic lipids and lipoproteins tested, were also achieved with inclisiran across the glycaemic and BMI strata. Specifically, at Day 510, levels of non-HDL cholesterol, a unifying measure of total atherogenic cholesterol content, were reduced by >42% across the glycaemic and BMI strata with inclisiran, and levels of ApoB, reflecting the total number of atherogenic particles, were reduced by >37%, highlighting the robust lipid-lowering effects of inclisiran when added to other background LLTs. Interestingly, greater percentage reductions with inclisiran (at Day 510) in total cholesterol, non-HDL cholesterol, ApoB, remnant cholesterol, and Lp(a) (at Day 540) and in time-adjusted LDL cholesterol (between Day 90 and Day 540) were observed in individuals with DM versus those with normoglycaemia or pre-DM and in those with a higher versus lower BMI. As pre-DM and DM were associated with a progressively higher BMI, it was not possible to determine whether glycaemic and BMI categories were independently associated with the efficacy of inclisiran treatment.

Greater percentage reductions in LDL cholesterol with inclisiran among individuals with DM and pre-DM versus those without DM could be partially explained by the modulation of the asialoglycoprotein receptor (ASGPR) influenced by BMI. The uptake of inclisiran into

hepatocytes is dependent on ASGPR. In obese Zucker rats, the hepatic expression of ASGPR is greater than in lean Zucker rats.[22] In a study of 27 individuals who underwent bariatric surgery and whose BMI declined from a baseline mean of 43.3 kg/m^2 before surgery to 27.5 kg/m^2 1 year after surgery, the circulating concentration of extracellular vesicles expressing ASGPR declined significantly at 1 year.[23] Together, these studies suggest that the greater expression of ASGPR on hepatocytes in obesity (and by association in DM) might modulate the uptake of drugs such as inclisiran into the liver.[24,25] Although, in the present analysis, some interactions of treatment and glycaemic or BMI category were statistically significant, absolute differences in LDL cholesterol reduction by inclisiran across these categories were small. Large, ongoing placebo-controlled CV trials with inclisiran will provide more information about the potential interaction of treatment and glycaemic or BMI category with lipid-lowering and CV outcomes.[26–28] Notably, large placebo-controlled trials with the anti-PCSK9 mAbs, evolocumab and alirocumab, showed nearly uniform relative reductions in LDL cholesterol among individuals with normoglycaemia, pre-DM or DM.[29–31]

PCSK9 mAbs are not dependent on ASGPR for their mechanism of action; this may explain some of the differences observed in LDL cholesterol reductions with inclisiran versus PCSK9 mAbs.

Despite conclusive evidence for the causal role of LDL cholesterol in the progression of ASCVD, most individuals with or without cardiometabolic abnormalities do not receive optimal LDL cholesterol lowering to reduce CV risk.[14–32] The 2023 American Diabetes Association Standards of Care recommends LDL cholesterol targets of <70 mg/dL or ≤ 55 mg/dL, depending on the individual CV risk alongside an LDL cholesterol reduction of ≥50% from baseline in individuals with DM and ASCVD.[2] Current European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS) clinical practice guidelines recommend LDL cholesterol goals of <1.4 mmol/L (<55 mg/dL) or <1.8 mmol/L (<70 mg/dL), plus an LDL cholesterol reduction of ≥1.3 mmol/L (≥50 mg/dL) from baseline, in very-high-risk or high-risk populations with DM, respectively.[11] The 2022 American College of Cardiology Expert Consensus Decision Pathway provides practical guidance for the use of novel non-statin therapies for the lowering of LDL cholesterol in ASCVD risk management.[33] The 2023 American Heart Association advisory for management of CV-kidney-metabolic syndrome notes the potential of novel therapies (anti-PCSK9 mAbs and inclisiran) in reducing the risk of CVD through lipid lowering for at-risk populations.[34] Barriers to LDL cholesterol goal attainment include the underutilization of combination therapies and poor long-term adherence to LLTs.[35–39] Together, these factors can lead to prolonged, cumulative LDL cholesterol exposure, leaving individuals at risk of future CV events. As such, combination therapies that can provide consistent LDL cholesterol-lowering effects may be beneficial to ensure long-term treatment continuity and facilitate improved LDL cholesterol goal attainment.[36–40] The findings presented in this analysis demonstrate that infrequent dosing with inclisiran, in addition to maximally tolerated background oral LLTs, has the potential to facilitate the attainment of LDL cholesterol goals, with >61% and >48% of all individuals treated with inclisiran achieving LDL cholesterol levels of <1.8 mmol/L and <1.4 mmol/L, respectively, regardless of metabolic disorder. Moreover, a larger proportion of individuals treated with inclisiran also achieved ≥50% LDL cholesterol reduction from baseline across BMI and glycaemic strata. Inclisiran maintained its efficacy and safety without any dose adjustments, even in individuals who were severely obese.

Depending on the level of CV risk, ESC/EAS clinical practice guidelines also recommend ApoB goals of <1454.5 nmol/L (<80 mg/dL) or <1181.8 nmol/L (<65 mg/dL) and non-HDL cholesterol goals of <2.6 mmol/L or <2.2 mmol/L as secondary therapy objectives in individuals with type 2 DM or metabolic syndrome, respectively. In these populations, LDL cholesterol levels often remain in the normal range, making non-HDL cholesterol and ApoB measurements better surrogate markers for CV risk.[11] In the current analysis, >76% and > 60% of individuals achieved ApoB levels of <1454.5 nmol/L (<80 mg/dL) and <1181.8 nmol/L (<65 mg/dL), respectively, with inclisiran, and > 68% and > 57% achieved non-HDL cholesterol levels of <2.6 mmol/L and <2.2 mmol/L, respectively. In addition, the proportions of individuals achieving LDL cholesterol goals of <2.6 mmol/L, <1.8 mmol/L and <1.4 mmol/L generally increased with a continued increase in HbA1c levels and BMI, although these individuals had lower baseline LDL cholesterol levels. These findings establish inclisiran as an effective LLT option that may facilitate the attainment of LDL cholesterol, ApoB and non-HDL cholesterol goals in the high-risk cohort with metabolic disorders.

Lipoprotein(a) is a genetic, causal, and independent risk factor for CVD, and several guidelines recommend screening of Lp(a) levels; however, there are few current treatment options for the management of elevated Lp(a).[41] In this study, reductions in Lp(a) levels with inclisiran were affected by glycaemic and BMI status. In subgroups with pre-DM or DM, compared with normoglycaemia, and in individuals with greater BMI, larger percentage reductions in Lp(a) were observed. Observational cohort analyses have shown an association between low Lp(a) levels and risk of incident DM.[41–44] Genetic studies have suggested that loss of function variants in PCSK9 are associated with greater risk of incident DM.[9] Despite those observations, PCSK9 mAbs have had an overall neutral effect on the risk of incident type 2 DM in large placebo-controlled studies.[29,45] The current analysis was not powered to identify a possible relationship between Lp(a) lowering by inclisiran and changes in glycaemic status.

Inclisiran was generally well tolerated regardless of glycaemic or BMI category, with similar proportions of TEAEs and TESAEs observed between treatment arms and across strata. The incidence of postbaseline NOD was comparable between the inclisiran- and placebo-treated cohort. Clinically relevant TEAEs at the injection site were more common with inclisiran than with placebo across all strata, although all were mild to moderate, with none being severe or persistent. Data from a long-term study show that the efficacy of inclisiran is maintained over 4 years with no new safety signals.[15] In addition, the results of the open-label long-term extension study of these Phase 3 trials, ORION-8 (NCT03814187), will provide further safety data on the long-term use of inclisiran.

This analysis demonstrates the ability of inclisiran to effectively lower LDL cholesterol levels across strata of metabolic disorders, although its effect on CV outcomes remains unknown and is currently being investigated in the ongoing dedicated CV outcomes trials, ORION-4 (NCT03705234) and VICTORION-2 Prevent (NCT05030428).[26–28]

This analysis of three Phase 3 trials demonstrates that twice-yearly inclisiran (after the initial and 3-month doses) along with maximally tolerated statins with or without other oral LLTs provides substantial and sustained reductions in LDL cholesterol levels regardless of glycaemic and BMI status. The mean reductions in atherogenic lipoproteins were at least as high as or higher in individuals with DM versus those with pre-DM or normoglycaemia; the same was true in for those with obesity versus those who were overweight or who had a normal weight. Moreover, the findings confirm that inclisiran is well tolerated in each of these population subgroups without an increase in NOD, although a higher proportion of mild-to-moderate clinically relevant TEAEs at the injection site was consistently observed with inclisiran versus placebo. Inclisiran therefore provides a therapeutic option for substantial and sustained LDL cholesterol lowering in individuals across all categories of glycaemia and BMI who require additional lipid-lowering measures.

AUTHOR CONTRIBUTIONS

The lead author (Lawrence A. Leiter) directed the analysis and manuscript development and is the guarantor of this work. All authors contributed to its revision and concurred with the decision to submit the final manuscript for publication.

ACKNOWLEDGEMENTS

The authors thank all the investigators, trial site staff, and individual volunteers who participated in the trials. The authors thank Ritika Paul, MPhil (Novartis Healthcare Pvt. Ltd., Hyderabad, India) for providing medical writing support in accordance with the Good Publication Practice guidelines 2022, which was funded by Novartis Pharma AG, Basel, Switzerland, and Klaus Molle, PhD (Novartis Pharma AG) for critical review of the manuscript and editorial guidance. Kausik K. Ray acknowledges support from the National Institute for Health Research (NIHR) Imperial Biomedical Research Centre and his institution (Imperial College London) receives support from the NIHR Applied Research Collaboration Northwest London. This work was supported by Novartis Pharma AG, Basel, Switzerland.

CONFLICT OF INTEREST STATEMENT

Lawrence A. Leiter reports receiving grant support paid to his institution, advisory board fees, and fees for continuing medical education (CME) from Amgen and Novartis, fees for serving on a steering committee and advisory board fees from Esperion, grant support paid to his institution and fees for serving on a steering committee from Kowa, The Medicines Company and Novartis, and advisory board fees and fees for CME from Amarin, AstraZeneca, HLS, Merck, Pfizer and Sanofi. Frederick J. Raal reports receiving advisory board fees and lecture fees from Amgen, Sanofi-Aventis, Regeneron Pharmaceuticals, Novartis and LIB Therapeutics. Gregory G. Schwartz reports receiving research support paid to his institution from AstraZeneca, Sanofi, Silence Therapeutics and The Medicines Company. Wolfgang Koenig reports receiving consulting fees and lecture fees from AstraZeneca, Novartis and Amgen, consulting fees from Pfizer, The Medicines Company, DalCor Pharmaceuticals, Kowa, Corvidia Therapeutics, Esperion, Genentech, OMEICOS, Novo Nordisk, LIB Therapeutics, Daiichi Sankyo, New Amsterdam Pharma and TenSixteen Bio, lecture fees from Berlin-Chemie, Bristol-Myers Squibb and Sanofi, and grant support and provision of reagents from Singulex, Abbott, Roche Diagnostics and Dr Beckmann Pharma. Kausik K. Ray reports receiving grant support paid to his institution from Amgen, Regeneron Pharmaceuticals/Sanofi and Daiichi Sankyo, personal fees for serving on Steering Committee, Executive committee or advisory boards from Novartis, Esperion, Daiichi Sankyo, Abbott, Bayer, Eli Lilly, Silence Therapeutics, CSL Behring, New Amsterdam Pharma, Sanofi, Amgen, Novo Nordisk, BI, Scribe, Vaxxinity, CRISPR, AstraZeneca, Kowa and Cargene, and personal fees for CME and non-CME lectures from Novartis, Novo Nordisk, Boehringer Ingelheim, AstraZeneca, Viatris, Daiichi Sankyo, Amgen and Sanofi. Ulf Landmesser reports receiving lecture fees and advisory fees from AstraZeneca, Boehringer, Sanofi, Berlin-Chemie and Abbott, advisory fees from The Medicines Company, and grant support, lecture fees and advisory fees from Amgen, Bayer and Novartis. Jackie Han and Lorena Garcia Conde report being employed by Novartis at the time of publication. R. Scott Wright reports receiving advisory board fees from Boehringer Ingelheim and fees for consulting on lipid issues from Novartis and The Medicines Company.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.15650.

DATA AVAILABILITY STATEMENT

Qualified researchers can request access to patient-level data and related study documents after publication, including the statistical analysis plan and dataset specifications. Patient-level data will be anonymized and study documents will be redacted to protect the privacy of the trial participants.

ORCID

Lawrence A. Leiter https://orcid.org/0000-0002-1040-6229
Gregory G. Schwartz https://orcid.org/0000-0003-2954-0695
Kausik K. Ray https://orcid.org/0000-0003-0508-0954

REFERENCES

1. Cai X, Zhang Y, Li M, et al. Association between prediabetes and risk of all cause mortality and cardiovascular disease: updated meta-analysis. *BMJ*. 2020;370:m2297.
2. ElSayed NA, Aleppo G, Aroda VR, et al. 10. Cardiovascular disease and risk management: standards of Care in Diabetes-2023. *Diabetes Care*. 2023;46:S158-S190.
3. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/-ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/N-LA/PCNA guideline on the management of blood cholesterol: executive summary: a report of the American College of

Cardiology/American Heart Association task force on clinical practice guidelines. *J Am Coll Cardiol*. 2019;73:3168-3209.
4. Powell-Wiley TM, Poirier P, Burke LE, et al. Obesity and cardiovascular disease. A scientific statement from the American Heart Association. *Circulation*. 2021;143:e984-e1010.
5. Wang H, Liu J, Feng Y, Ma A, Wang T. The burden of cardiovascular diseases attributable to metabolic risk factors and its change from 1990 to 2019: a systematic analysis and prediction. *Front Epidemiol*. 2023;3:1.
6. The Emerging Risk Factors Collaboration, Sarwar N, Gao P, Seshasai SR, et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *Lancet*. 2010;375:2215-2222.
7. Afshin A, Forouzanfar MH, Reitsma MB, et al. Health effects of overweight and obesity in 195 countries over 25 years. *N Engl J Med*. 2017;377:13-27.
8. Neeland IJ, Ross R, Despres JP, et al. Visceral and ectopic fat, atherosclerosis, and cardiometabolic disease: a position statement. *Lancet Diabetes Endocrinol*. 2019;7:715-725.
9. Ference BA, Ginsberg HN, Graham I, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European atherosclerosis society consensus panel. *Eur Heart J*. 2017;38:2459-2472.
10. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, Chapman MJ, de Backer GG, Delgado V, Ference BA, Graham IM, Halliday A, Landmesser U, Mihaylova B, Pedersen TR, Riccardi G, Richter DJ, Sabatine MS, Taskinen MR, Tokgozoglu L, Wiklund O, Mueller C, Drexel H, Aboyans V, Corsini A; ESC Scientific Document Group. 2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J* 2020;41:111–188.
11. Fox KM, Tai MH, Kostev K, Hatz M, Qian Y, Laufs U. Treatment patterns and low-density lipoprotein cholesterol (LDL-C) goal attainment among patients receiving high- or moderate-intensity statins. *Clin Res Cardiol*. 2018;107:380-388.
12. Klimchak AC, Patel MY, Iorga SR, Kulkarni N, Wong ND. Lipid treatment and goal attainment characteristics among persons with atherosclerotic cardiovascular disease in the United States. *Am J Prev Cardiol*. 2020;1:100010.
13. Ray KK, Molemans B, Schoonen WM, et al. EU-wide cross-sectional observational study of lipid-modifying therapy use in secondary and primary care: the DA VINCI study. *Eur J Prev Cardiol*. 2021;28:1279-1289.
14. Kosmas CE, Munoz Estrella A, Sourlas A, et al. Inclisiran: a new promising agent in the management of hypercholesterolemia. *Diseases*. 2018;6:63.
15. Ray KK, Troquay RPT, Visseren FLJ, et al. Long-term efficacy and safety of inclisiran in patients with high cardiovascular risk and elevated LDL cholesterol (ORION-3): results from the 4-year open-label extension of the ORION-1 trial. *Lancet Diabetes Endocrinol*. 2023;11:109-119.
16. Wright RS, Ray KK, Raal FJ, et al. ORION phase III investigators. Pooled patient-level analysis of inclisiran trials in patients with familial hypercholesterolemia or atherosclerosis. *J Am Coll Cardiol*. 2021;77:1182-1193.
17. Cleveland Clinic. Class III Obesity (Formerly Known as Morbid Obesity). https://my.clevelandclinic.org/health/diseases/21989-class-iii-obesity-formerly-known-as-morbid-obesity. Accessed November 11 2023
18. Weir CB, Jan A. *BMI Classification Percentile and Cut off Points*. StatPearls; 2023.
19. Raal FJ, Kallend D, Ray KK, et al. ORION-9 investigators. Inclisiran for the treatment of heterozygous familial hypercholesterolemia. *N Engl J Med*. 2020;382:1520-1530.
20. Ray KK, Wright RS, Kallend D, et al. ORION-10 and ORION-11 investigators. Two phase 3 trials of inclisiran in patients with elevated LDL cholesterol. *N Engl J Med*. 2020;382:1507-1519.
21. Centers for Disease Control and Prevention. National diabetes statistics report: estimates of diabetes and its burden in the United States. 2022. National Diabetes Statistics Report | Diabetes | CDC. Accessed November 28 2023.
22. Mishra A, Castaneda TR, Bader E, et al. Triantennary GalNAc molecular imaging probes for monitoring hepatocyte function in a rat model of nonalcoholic steatohepatitis. *Adv Sci*. 2020;7:2002997.
23. Rega-Kaun G, Ritzel D, Kaun C, et al. Changes of circulating extracellular vesicles from the liver after roux-en-Y bariatric surgery. *Int J Mol Sci*. 2019;20:2153.
24. Willoughby JLS, Chan A, Sehgal A, et al. Evaluation of GalNAc-siRNA conjugate activity in pre-clinical animal models with reduced asialoglycoprotein receptor expression. *Mol Ther*. 2018;26:105-114.
25. Witzigmann D, Quagliata L, Schenk SH, Quintavalle C, Terracciano LM, Huwyler J. Variable asialoglycoprotein receptor 1 expression in liver disease: implications for therapeutic intervention. *Hepatol Res*. 2016;46:686-696.
26. National Institutes of Health. A randomized trial assessing the effects of inclisiran on clinical outcomes among people with cardiovascular disease (ORION-4). https://classic.clinicaltrials.gov/ct2/show/NCT03705234. Accessed November 11 2023.
27. National Institutes of Health. A study of inclisiran to prevent cardiovascular (CV) events in participants with established cardiovascular disease (VICTORION-2P). https://clinicaltrials.gov/study/NCT05030428. Accessed November 11 2023.
28. National Institutes of Health. A study of inclisiran to prevent cardiovascular events in high-risk primary prevention patients. https://clinicaltrials.gov/study/NCT05739383. Accessed November 11 2023.
29. Ray KK, Colhoun HM, Szarek M, et al. Effects of alirocumab on cardiovascular and metabolic outcomes after acute coronary syndrome in patients with or without diabetes: a prespecified analysis of the ODYSSEY OUTCOMES randomised controlled trial. *Lancet Diabetes Endocrinol*. 2019;7:618-628.
30. Robinson JG, Farnier M, Krempf M, et al. Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. *N Engl J Med*. 2015;372:1489-1499.
31. Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med*. 2017;376:1713-1722.
32. Catapano ALM, Manu MC, Burden A, Ray KK. LDL-C goal achievement and lipid-lowering therapy in patients by atherosclerotic cardiovascular disease subtype: the SANTORINI study. *Eur Heart J*. 2022;43:2373.
33. Lloyd-Jones DM, Morris PB, Ballantyne CM, et al. 2022 ACC expert consensus decision pathway on the role of nonstatin therapies for LDL-cholesterol lowering in the management of atherosclerotic cardiovascular disease risk: a report of the American College of Cardiology Solution set Oversight Committee. *J Am Coll Cardiol*. 2022;80:1366-1418.
34. Ndumele CE, Rangaswami J, Chow SL, et al. Cardiovascular-kidney-metabolic health: a presidential advisory from the American Heart Association. *Circulation*. 2023;148:1606-1635.
35. May HT, Knowlton KU, Anderson JL, Lappe DL, Bair TL, Muhlestein JB. High-statin adherence over 5 years of follow-up is associated with improved cardiovascular outcomes in patients with atherosclerotic cardiovascular disease: results from the IMPRES study. *Eur Heart J Qual Care Clin Outcomes*. 2022;8:352-360.
36. Ray KK, Ference BA, Severin T, et al. World heart federation cholesterol roadmap 2022. *Glob Heart*. 2022;17:75.
37. Rodriguez F, Maron DJ, Knowles JW, Virani SS, Lin S, Heidenreich PA. Association of statin adherence with mortality in patients with atherosclerotic cardiovascular disease. *JAMA Cardiol*. 2019;4:206-213.

38. Shau WY, Lai CL, Huang ST, et al. Statin adherence and persistence on secondary prevention of cardiovascular disease in Taiwan. *Heart Asia*. 2019;11:e011176.
39. Underberg J, Toth PP, Rodriguez F. LDL-C target attainment in secondary prevention of ASCVD in the United States: barriers, consequences of nonachievement, and strategies to reach goals. *Postgrad Med*. 2022;134:752-762.
40. Brandts J, Ray KK. Low density lipoprotein cholesterol-lowering strategies and population health: time to move to a cumulative exposure model. *Circulation*. 2020;141:873-876.
41. Saeedi R, Frohlich J. Lipoprotein (a), an independent cardiovascular risk marker. *Clin Diabetes Endocrinol*. 2016;2:1-6.
42. Mora S, Kamstrup PR, Rifai N, Nordestgaard BG, Buring JE, Ridker PM. Lipoprotein(a) and risk of type 2 diabetes. *Clin Chem*. 2010;56:1252-1260.
43. Paige E, Masconi KL, Tsimikas S, et al. Lipoprotein(a) and incident type-2 diabetes: results from the prospective Bruneck study and a meta-analysis of published literature. *Cardiovasc Diabetol*. 2017;16:38.
44. Gudbjartsson DF, Thorgeirsson G, Sulem P, et al. Lipoprotein (a) concentration and risks of cardiovascular disease and diabetes. *J Am Coll Cardiol*. 2019:74:2982-2994.
45. Sabatine MS, Leiter LA, Wiviott SD, et al. Cardiovascular safety and efficacy of the PCSK9 inhibitor evolocumab in patients with and without diabetes and the effect of evolocumab on glycaemia and risk of new-onset diabetes: a prespecified analysis of the FOURIER randomised controlled trial. *Lancet Diabetes Endocrinol*. 2017;5(12):941-950.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Leiter LA, Raal FJ, Schwartz GG, et al. Inclisiran in individuals with diabetes or obesity: Post hoc pooled analyses of the ORION-9, ORION-10 and ORION-11 Phase 3 randomized trials. *Diabetes Obes Metab*. 2024;26(8):3223-3237. doi:10.1111/dom.15650