RABIN MEDICAL CENTER
BEILINSON • HASHARON

ESC Summary Conference Scientific Update Meeting

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Cardiology Division

What we will discuss

- Dapagliflozin in Patients with Heart Failure and Deterioration in Estimated Glomerular Filtration Rate to <25ml/min/1.73m2
- ORION-8: Long-term efficacy and safety of twice-yearly inclisiran in high cardiovascular risk patients
- Small Interfering RNA to Reduce Lipoprotein(a) in Cardiovascular Disease

Dapagliflozin in Patients with Heart Failure and Deterioration in Estimated Glomerular Filtration Rate to <25ml/min/1.73m^2

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Introduction

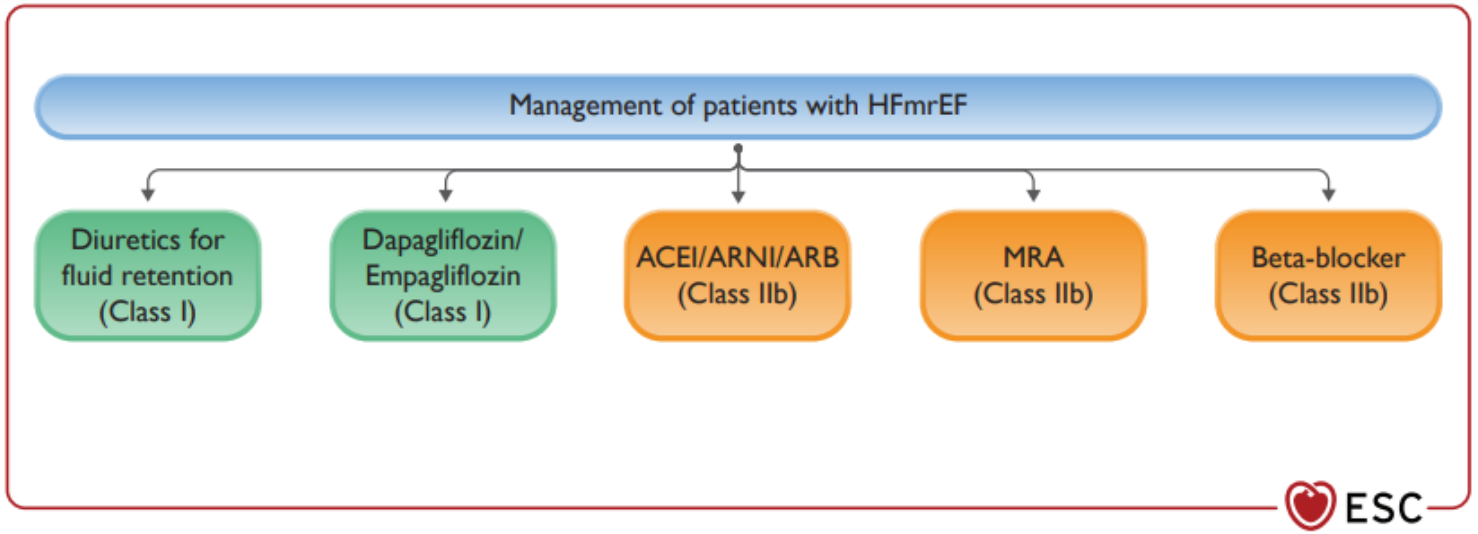


Figure 1 Management of patients with heart failure with mildly reduced ejection fraction. ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; HFmrEF, heart failure with mildly reduced ejection fraction; MRA, mineralocorticoid receptor antagonist.

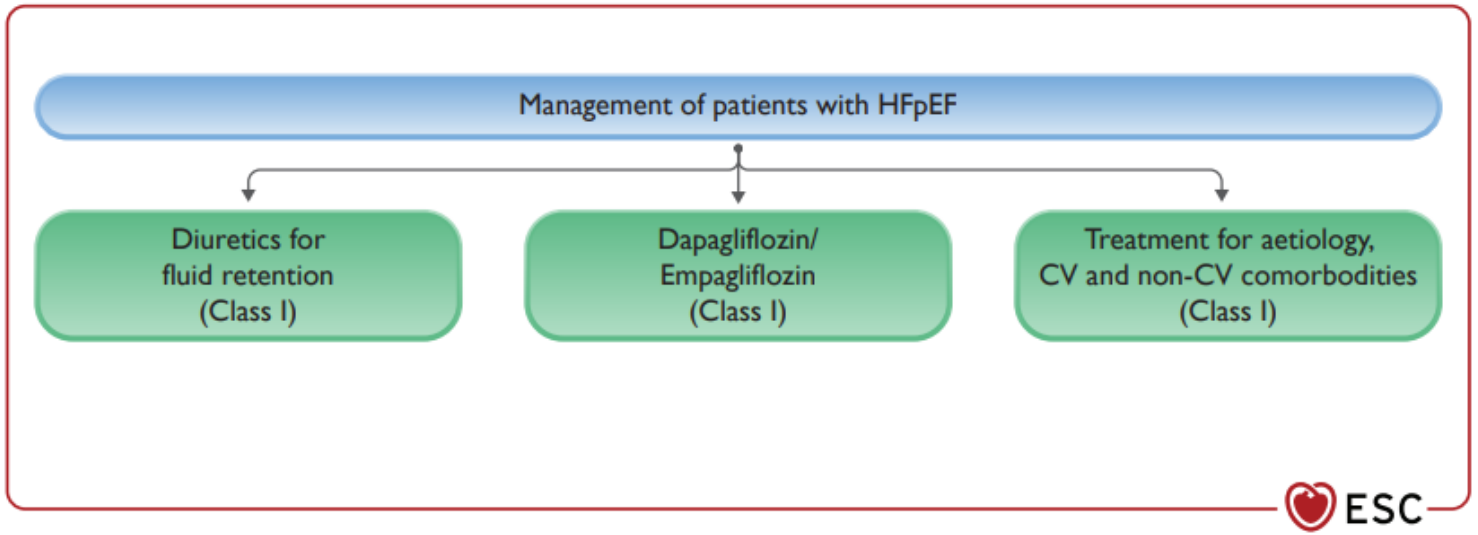


Figure 2 Management of patients with heart failure with preserved ejection fraction. CV, cardiovascular; HFpEF, heart failure with preserved ejection fraction.

Introduction

Recommendation Table 4 — Recommendations for the prevention of heart failure in patients with type 2 diabetes mellitus and chronic kidney disease

Recommendations	Class[a]	Level[b]
In patients with T2DM and CKD,[c] SGLT2 inhibitors (dapagliflozin or empagliflozin) are recommended to reduce the risk of HF hospitalization or CV death.[5,7,35]	I	A
In patients with T2DM and CKD,[c] finerenone is recommended to reduce the risk of HF hospitalization.[10,11,34,40]	I	A

CKD, chronic kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HF, heart failure; SGLT2, sodium–glucose co-transporter 2; T2DM, type 2 diabetes mellitus.

[a]Class of recommendation.

[b]Level of evidence.

[c]CKD was defined as follows: an eGFR 25–75 mL/min/1.73 m^2 and a urinary albumin-to-creatinine ratio ≥200–5000 mg/g in DAPA-CKD;[5] an eGFR 20–45 mL/min/1.73 m^2 or an eGFR 45–90 mL/min/1.73 m^2 with a urinary albumin-to-creatinine ratio ≥200 mg/g in EMPA-KIDNEY;[7] an eGFR 25–60 mL/min/1.73 m^2, a urinary albumin-to-creatinine ratio 30–300 mg/g, and diabetic retinopathy, or an eGFR 25–75 mL/min/1.73 m^2 and a urinary albumin-to-creatinine ratio 300–5000 mg/g, in FIDELIO-DKD;[10] and an eGFR 25–90 mL/min/1.73 m^2 and a urinary albumin-to-creatinine ratio 30 to <300 mg/g, or an eGFR >60 mL/min/1.73 m^2 and a urinary albumin-to-creatinine ratio 300–5000 mg/g, in FIGARO-DKD.[11]

Design

- This analysis was carried out using a participant-level, pooled dataset of the DAPA-HF and DELIVER
- The protocols of both trials did not mandate study drug discontinuation if the eGFR fell below the trial threshold for patient inclusion
- All patients who experienced a deterioration in eGFR to less than 25ml at least once in follow-up were identified.

Results

Table 1 Baseline Characteristics According Deterioration in eGFR,to Below 25ml/min/1.73m^2

	No Deterioration in eGFR<25 ml/min/1.73m^2 (n=10,660)	**Deterioration in eGFR<25 ml/min/1.73m^2 (n=347)**	**P-value**
Age, yrs	69 ± 11	73 ± 10	<0.001
Sex, n(%)	6978 (65.5%)	173 (49.9%)	<0.001
New York Heart Association Class			0.67
II	7675 (72.0%)	241 (69.5%)	
III	2926 (27.4%)	103 (29.7%)	
IV	58 (0.5 %)	3 (0.9 %)	
Baseline LVEF	44 ± 14	50 ± 13	<0.001
LVEF>40%	5991(56.2%)	269(77.5%)	<0.001
LVEF≤40%)	4669(43.8%)	78(22.5%)	<0.001

Results

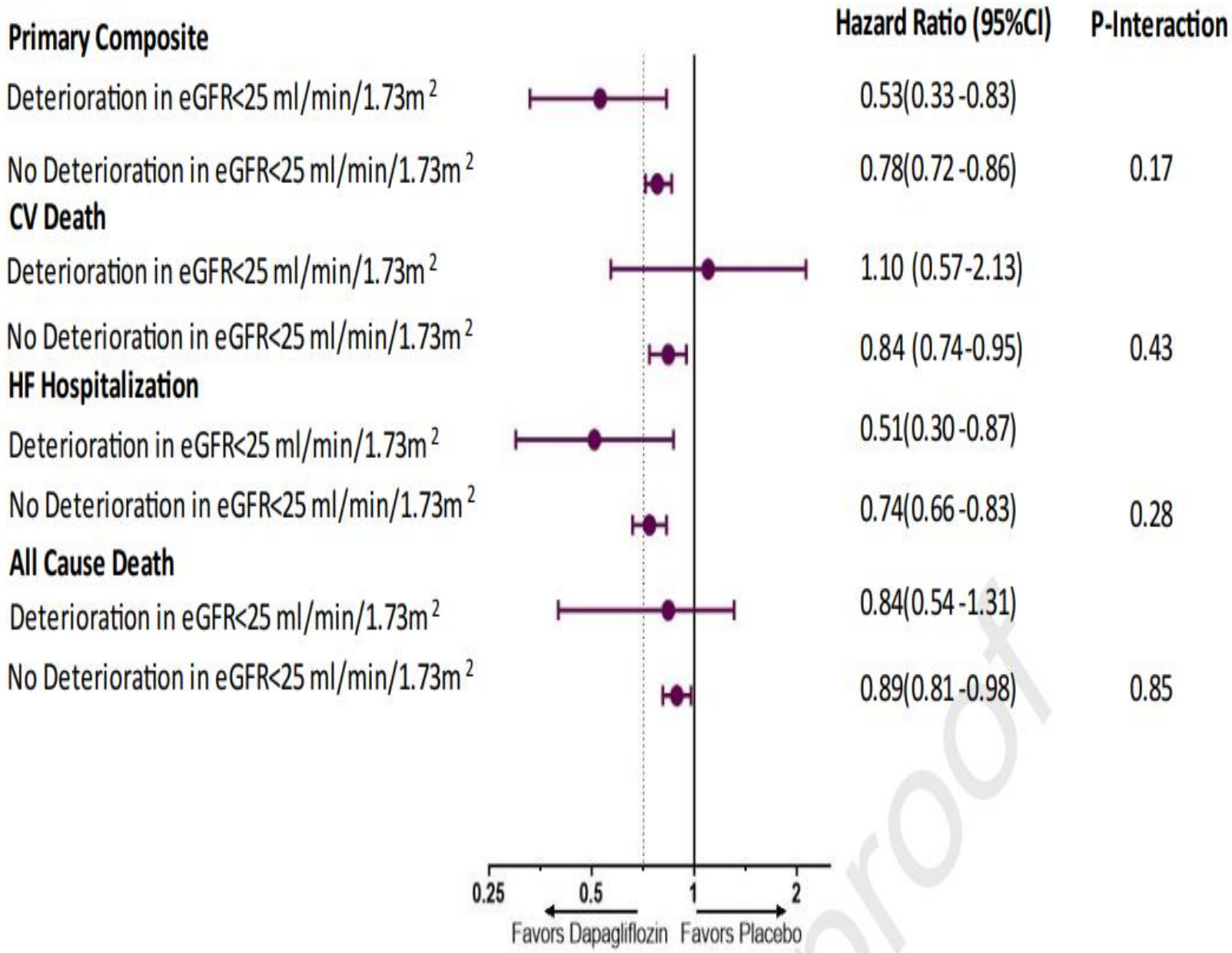
Table 2 Association Between Deterioration in eGFR to <25ml/min/1.73m^2 and Subsequent Outcomes

	No Deterioration in eGFR<25 ml/min/1.73m^2	Deterioration in eGFR<25 ml/min/1.73m^2	P-Value
Primary Composite			
No Events (n)	1934	76	
Event Rate(per 100 py)	10.2(9.7-10.6)	18.6(14.9-23.5)	
Hazard Ratio	1.87(1.48-2.35)		<0.001
CV Death			
No Events(n)	955	37	
Event Rate(per 100 py)	4.7(4.4-5.0)	7.3(5.3-10.4)	
Hazard Ratio	1.50(1.07-2.08)		0.02
Hospitalization for HF			
No Events(n)	1240	56	
Event Rate(per 100 py)	6.5(6.1-6.8)	13.5(10.4-17.7)	
Hazard Ratio	2.16(1.65-2.83)		<0.001
All Cause Death			
No Events (n)	1547	81	
Event Rate(per 100 py)	7.6(7.2-8.0)	16.0(12.9-20.1)	
Hazard Ratio	1.92(1.53-2.40)		<0.001

Time-to-first events analyses were performed using Cox proportional hazards models.

CV=Cardiovascular; PY=Person Years

Results


Primary Composite
Hazard Ratio (95%CI)
P-Interaction
Deterioration in eGFR<25 ml/min/1.73m 2
0.53(0.33 -0.83)
No Deterioration in eGFR<25 ml/min/1.73m 2
0.78(0.72 -0.86)
0.17
CV Death
Deterioration in eGFR<25 ml/min/1.73m 2
1.10 (0.57-2.13)
No Deterioration in eGFR<25 ml/min/1.73m 2
0.84 (0.74-0.95)
0.43
HF Hospitalization
Deterioration in eGFR<25 ml/min/1.73m 2
0.51(0.30 -0.87)
No Deterioration in eGFR<25 ml/min/1.73m 2
0.74(0.66 -0.83)
0.28
All Cause Death
Deterioration in eGFR<25 ml/min/1.73m 2
0.84(0.54 -1.31)
No Deterioration in eGFR<25 ml/min/1.73m 2
0.89(0.81 -0.98)
0.85
0.25
0.5
1
2
Favors Dapagliflozin
Favors Placebo

Conclusions

- Deterioration in kidney function to an eGFR threshold below that allowed for trial inclusion was infrequent but was associated with a heightened risk of developing subsequent CV outcomes.
- The beneficial effects of dapagliflozin relative to placebo on CV outcomes appeared to be preserved, irrespective of a decline in renal function
- Taken together, these data suggest that the benefit-to-risk ratio may favor continuation of dapagliflozin in patients with HF experiencing a deterioration in kidney function below eGFR and highlight the need for randomized evidence in advanced CKD.

ORION-8: Long-term efficacy and safety of twice-yearly* inclisiran in high cardiovascular risk patients

RS Wright, FJ Raal, W Koenig, U Landmesser, LA Leiter, GG Schwartz, A Lesogor, P Maheux, Z Talloczy, S Vikarunnessa, X Zang, KK Ray

Long-term efficacy and safety of inclisiran

Introduction

- PCSK9 is a protein that promotes degradation of low-density lipoprotein receptors (LDLRs). This results in fewer LDLRs on the liver cell surface, increasing plasma LDL-C levels
- Inclisiran is a siRNA therapeutic which targets hepatic PCSK9 synthesis and reduces LDL-C levels by approximately 52%
- The approval of inclisiran, as an effective LDL-C–lowering agent, was based on a large Phase 3 clinical development program (ORION-9, ORION-10 and ORION-11) which examined the efficacy and safety of inclisiran versus placebo in 3660 patients treated for up to 18 months

Introduction

ORION-8 was a long-term extension study - follow-up in patients (N=3274) who were involved in previous inclisiran trials

ORION-8 followed patients from four previous trials – ORION-3, ORION-9, ORION-10 and ORION-11 – for up to three additional years[1,12].

Previous trial	Study population
ORION-3[13] (Phase II)	patients with ASCVD or at increased risk of ASCVD†
ORION-9[14] (Phase III)	patients with clinical or genetic evidence of heterozygous familial hypercholesterolemia (FH)
ORION-10[15] (Phase III)	patients with ASCVD
ORION-11[16] (Phase III)	patients with ASCVD or at increased risk of ASCVD†

† corresponds to conditions that confer a similar risk of an ASCVD event (e.g., diabetes)[17]

Methods

Objective:

To assess the long-term efficacy, safety, and tolerability of inclisiran

Key End

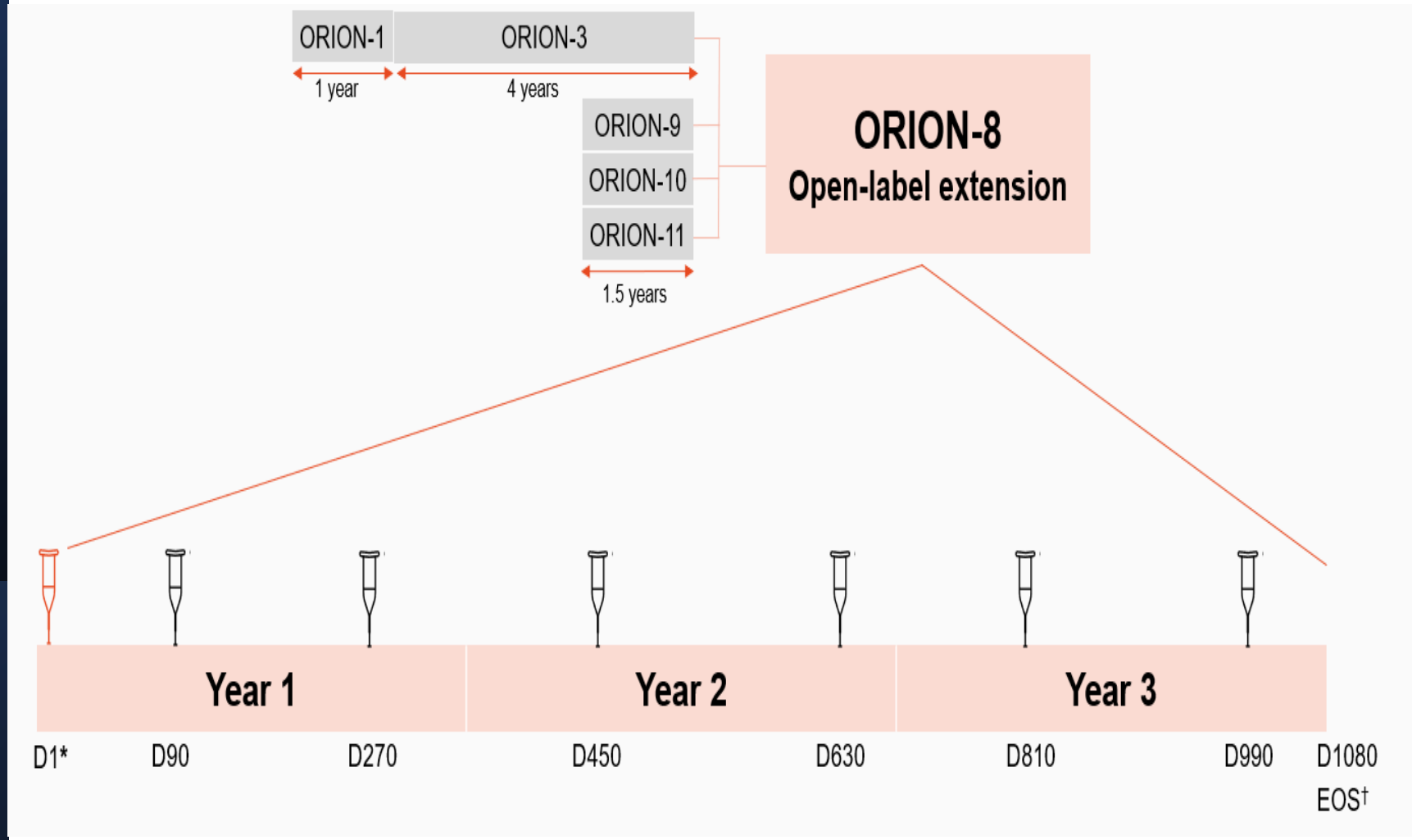
Primary endpoints:

- Proportion of patients achieving pre-specified LDL-C goals at EOS*
- Safety

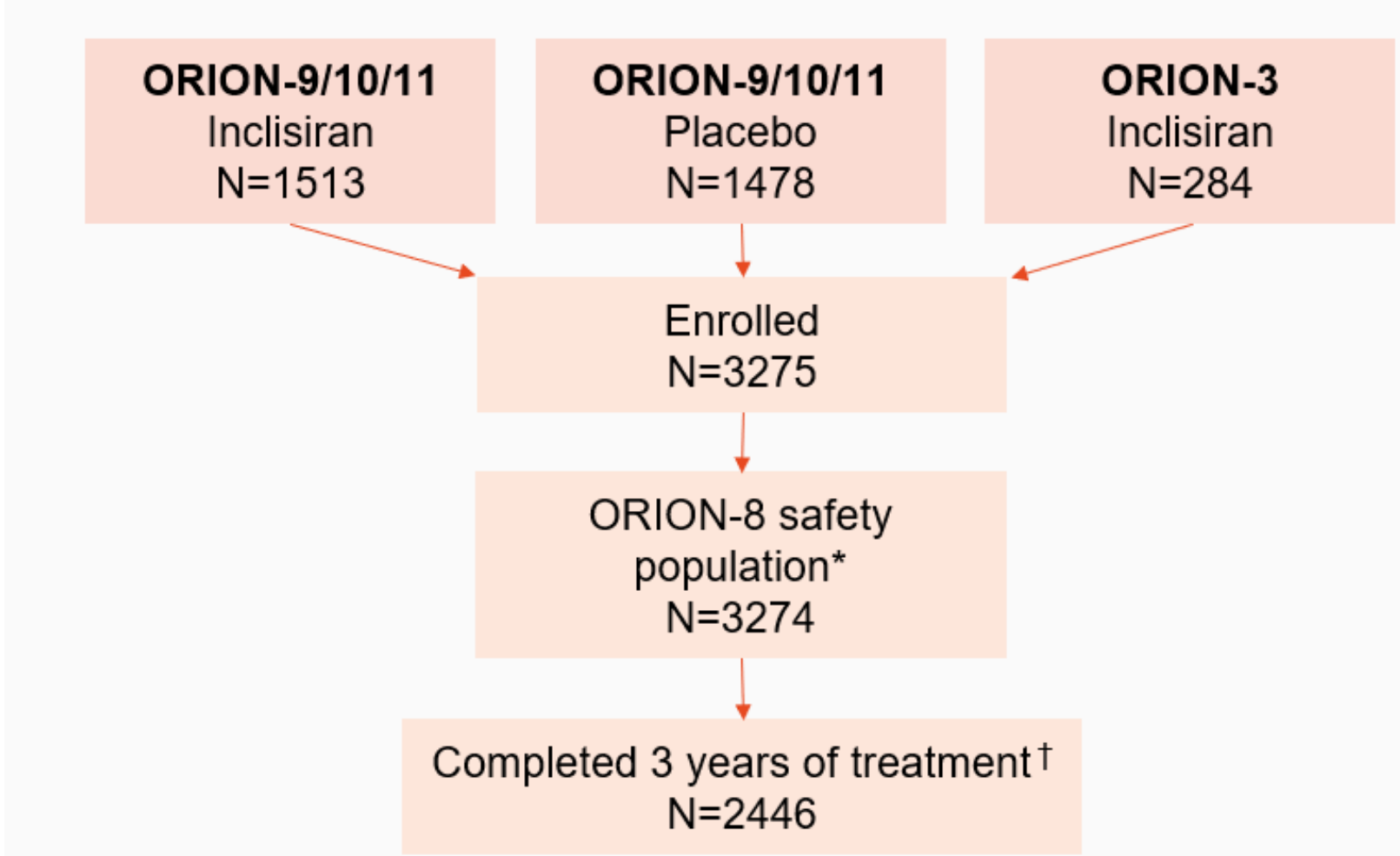
Secondary endpoint:

- Percent change in LDL-C from baseline to EOS

Methods


ORION-1
ORION-3
1 year
4 years
ORION-9
ORION-10
ORION-11
1.5 years
ORION-8
Open-label extension
Year 1
Year 2
Year 3
D1*
D90
D270
D450
D630
D810
D990
D1080
EOS†

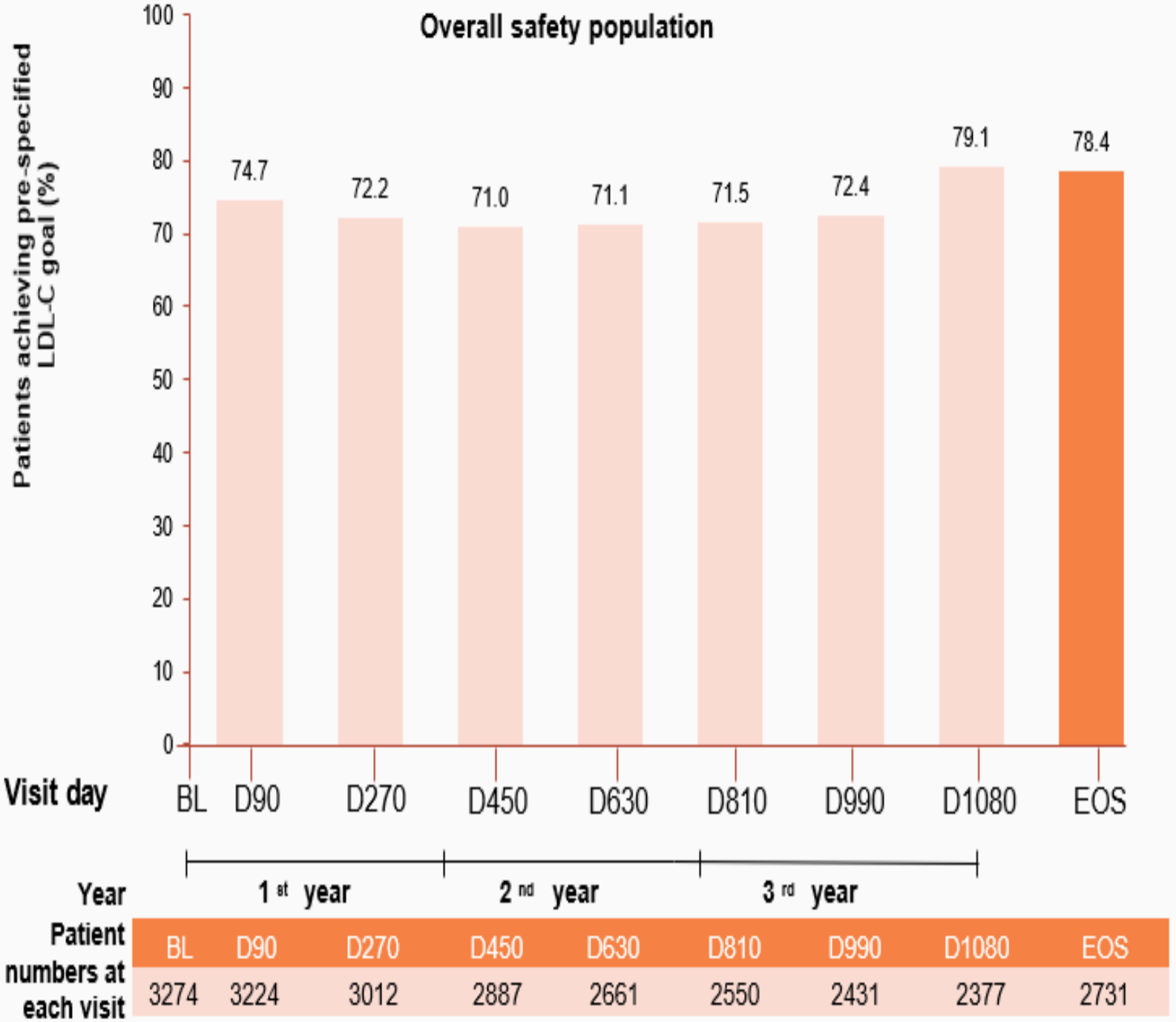
Methods


ORION-9/10/11
Inclisiran
N=1513
ORION-9/10/11
Placebo
N=1478
ORION-3
Inclisiran
N=284
Enrolled
N=3275
ORION-8 safety population*
N=3274
Completed 3 years of treatment†
N=2446

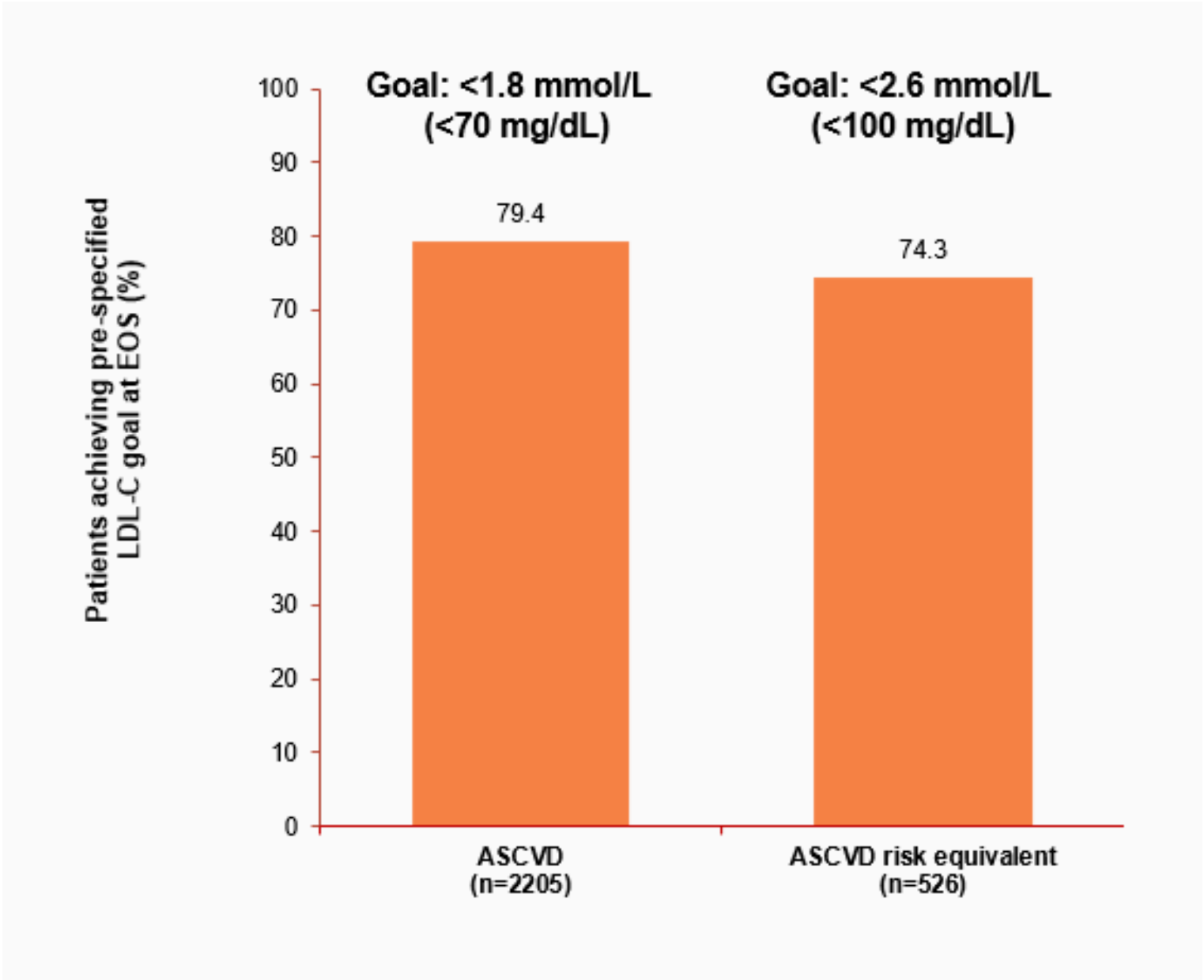
Results

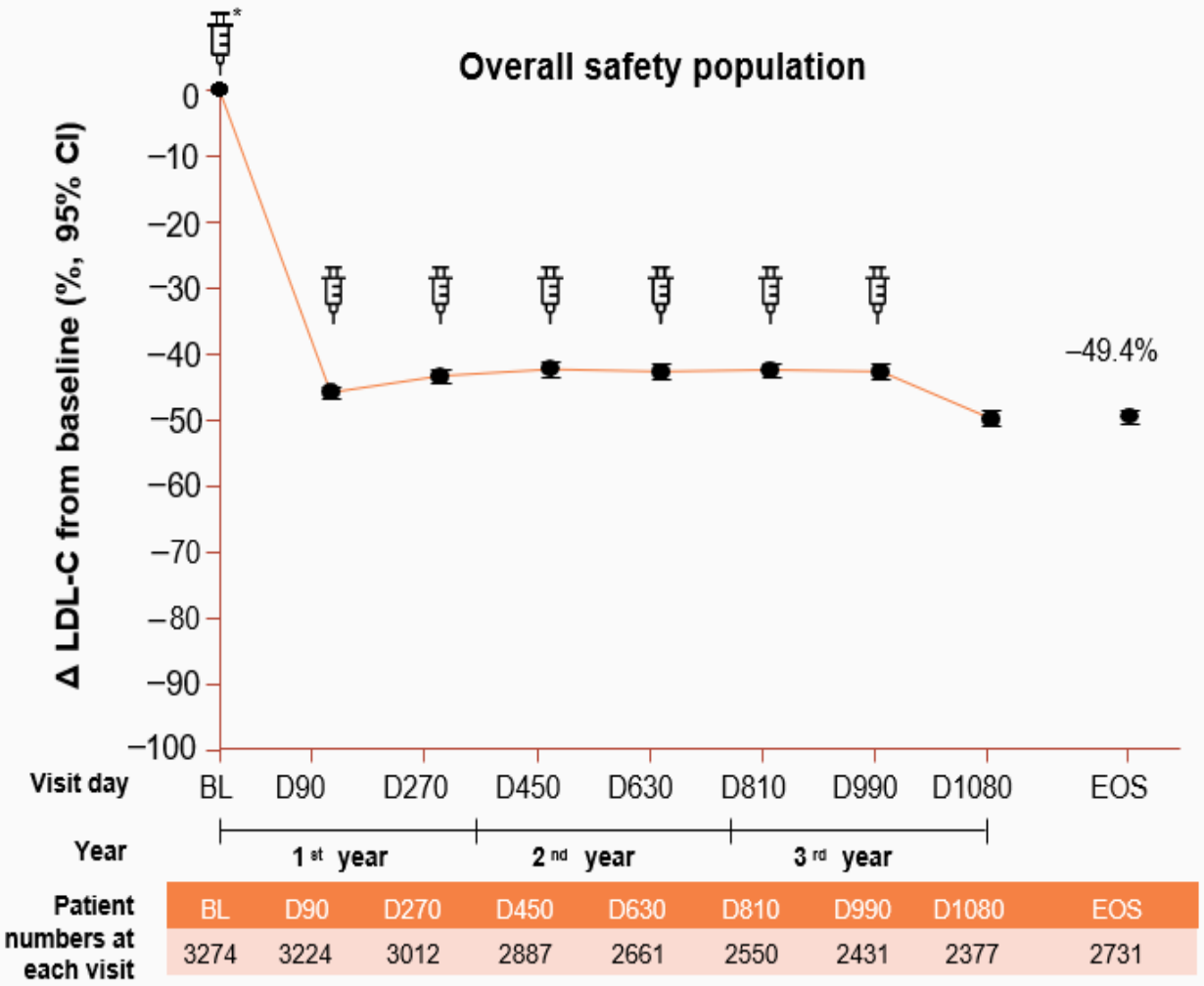
Parameter	ORION-8 safety population N=3274
Age (years), mean±SD	64.9±9.9
Age ≥65 years, n (%)	1849 (56.5)
Gender, male, n (%)	2216 (67.7)
Race, White, n (%)	3041 (92.9)
ASCVD status,* n (%)	
Established ASCVD – 'secondary prevention'	**2709 (82.7)**
ASCVD risk equivalent – 'high risk primary prevention'	**565 (17.3)**
Diabetes, n (%)*	1104 (33.7)
LDL-C (mmol/L), mean±SD*	**2.92±1.20**
At least one lipid-lowering therapy at baseline, n (%)	3052 (93.2)
Any statin, n (%)	2902 (88.6)
High-intensity statin, n (%)	2244 (68.5)
Ezetimibe, n (%)	544 (16.6)

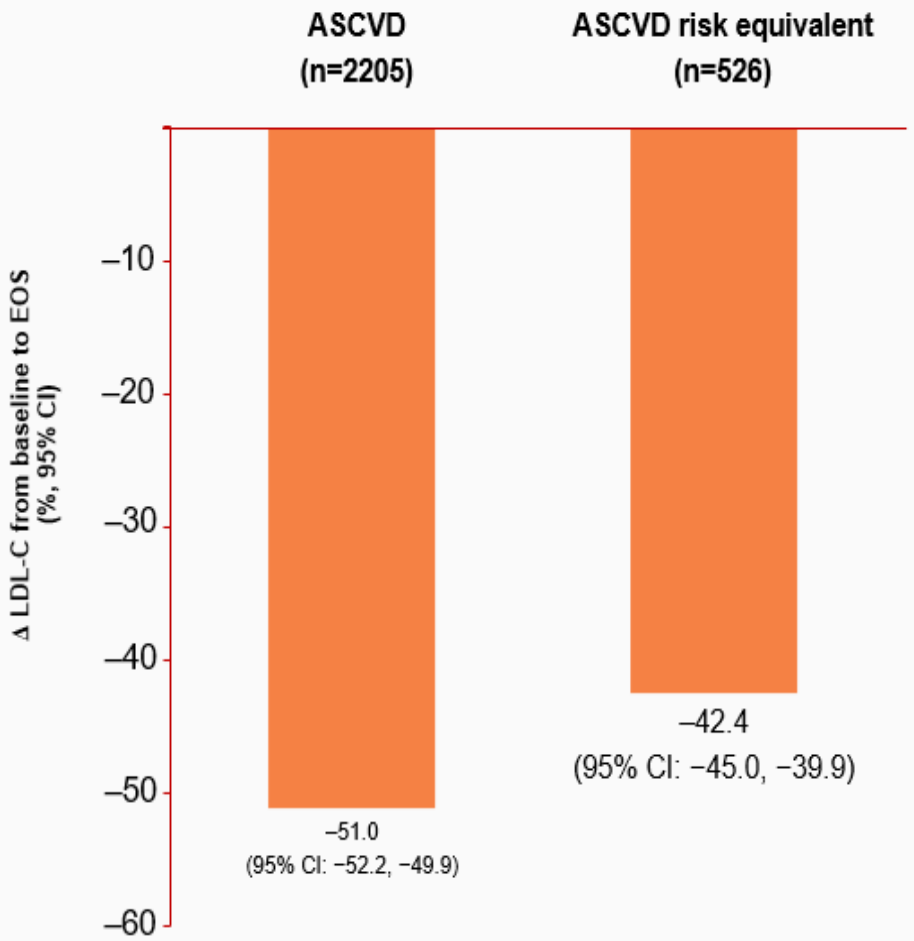
Results


Overall safety population
Patients achieving pre-specified LDL-C goal (%)
100
90
80
70
60
50
40
30
20
10
0
74.7
72.2
71.0
71.1
71.5
72.4
79.1
78.4
Visit day
BL
D90
D270
D450
D630
D810
D990
D1080
EOS
Year
1st year
2nd year
3rd year
Patient numbers at each visit
BL 3274
D90 3224
D270 3012
D450 2887
D630 2661
D810 2550
D990 2431
D1080 2377
EOS 2731

Results


Goal: <1.8 mmol/L
(<70 mg/dL)
Goal: <2.6 mmol/L
(<100 mg/dL)
Patients achieving pre-specified LDL-C goal at EOS (%)
100
90
80
70
60
50
40
30
20
10
0
79.4
74.3
ASCVD
(n=2205)
ASCVD risk equivalent
(n=526)


Overall safety population
Δ LDL-C from baseline (%, 95% CI)
0
−10
−20
−30
−40
−50
−60
−70
−80
−90
−100
−49.4%
Visit day
BL
D90
D270
D450
D630
D810
D990
D1080
EOS
Year
1st year
2nd year
3rd year
Patient numbers at each visit
BL 3274
D90 3224
D270 3012
D450 2887
D630 2661
D810 2550
D990 2431
D1080 2377
EOS 2731


ASCVD
(n=2205)
ASCVD risk equivalent
(n=526)
Δ LDL-C from baseline to EOS
(%, 95% CI)
−10
−20
−30
−40
−50
−60
−51.0
(95% CI: −52.2, −49.9)
−42.4
(95% CI: −45.0, −39.9)

Conclusions

A total of 3274 patients were evaluated in ORION-8, the largest trial with inclisiran to date

78.4% of patients achieved pre-specified lipid goals with an LDL-C reduction of 49.4% at end of study with inclisiran

The mean cumulative exposure to inclisiran in ORION-8 was 3.7 years with a maximum of 6.8 years providing a total of 12,109 PY of exposure

Conclusions

Inclisiran-associated ADAs were infrequent (5.1%), and did not impact efficacy and safety of inclisiran

The safety profile of inclisiran remained favorable and similar to previous reports with no new safety signals

ORION-8 provides additional evidence to support the long-term efficacy, safety and tolerability of inclisiran in patients with high cardiovascular risk and elevated LDL-C

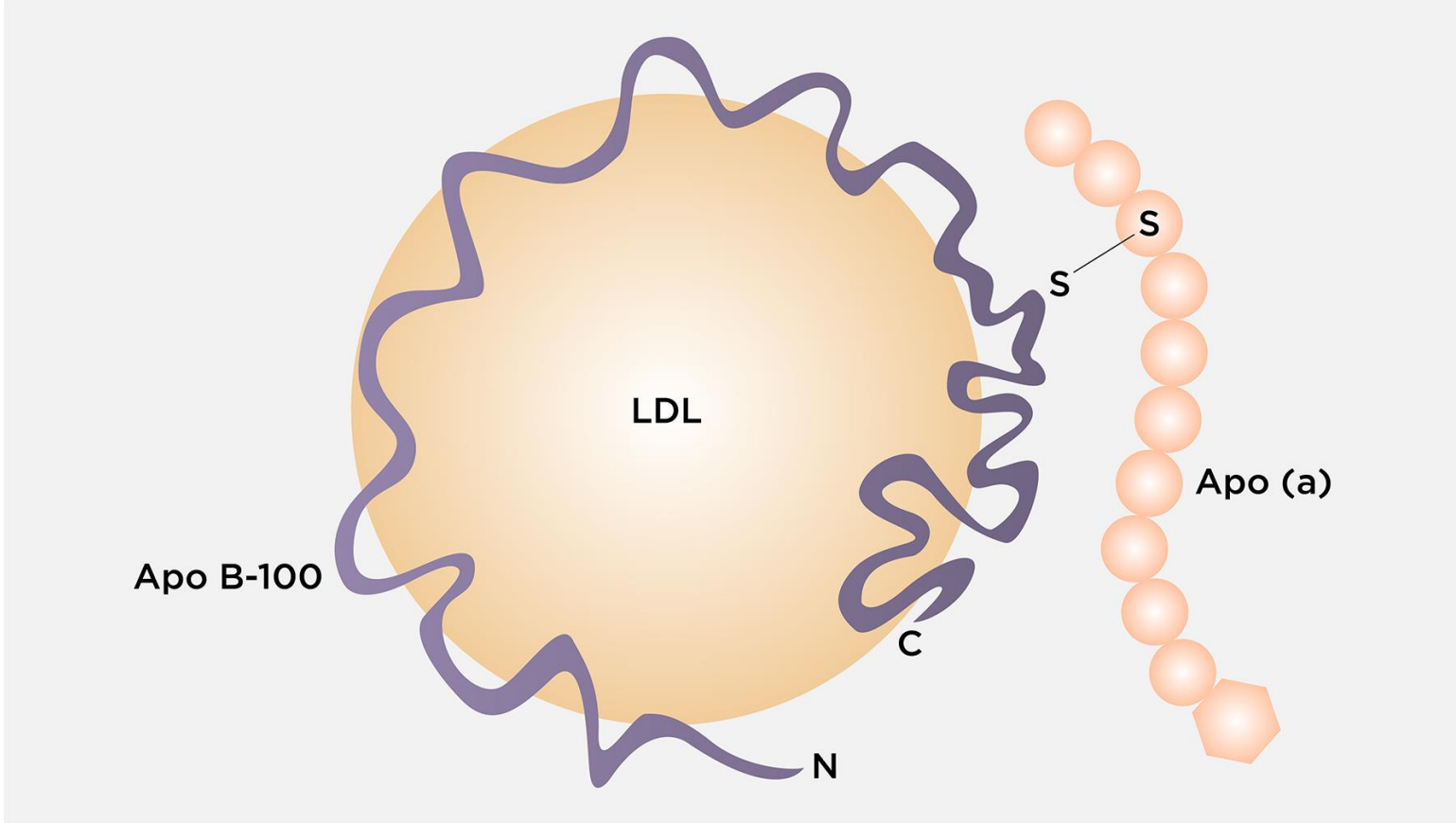
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

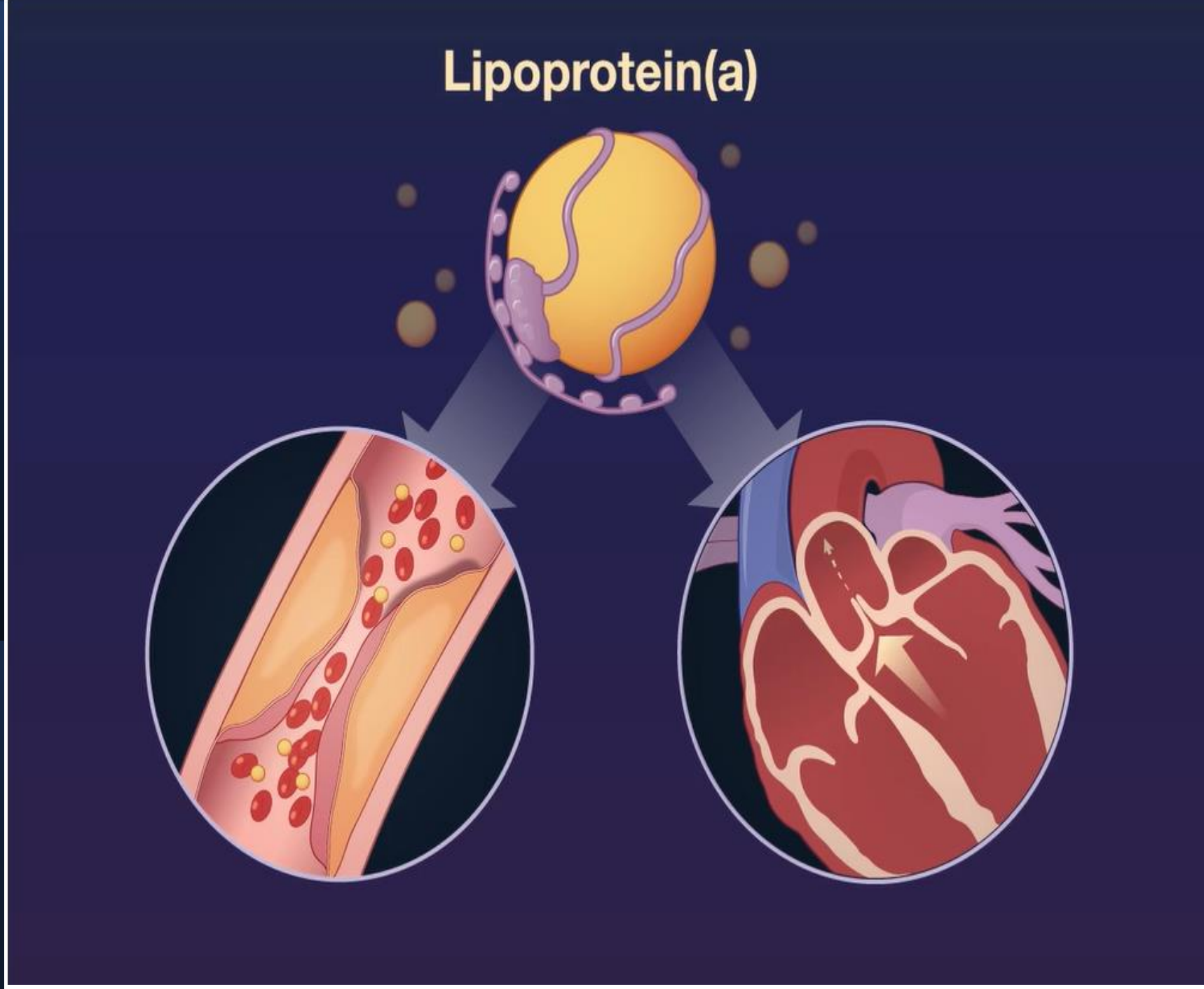
Small Interfering RNA to Reduce Lipoprotein(a) in Cardiovascular Disease

Michelle L. O'Donoghue, M.D., M.P.H., Robert S. Rosenson, M.D., Baris Gencer, M.D., M.P.H., J. Antonio G. López, M.D., Norman E. Lepor, M.D., Seth J. Baum, M.D., Elmer Stout, M.D., Daniel Gaudet, M.D., Ph.D., Beat Knusel, Ph.D., Julia F. Kuder, M.A., Xinhui Ran, M.S., Sabina A. Murphy, M.P.H., Huei Wang, Ph.D., You Wu, Ph.D., Helina Kassahun, M.D., and Marc S. Sabatine, M.D., M.P.H., for the OCEAN(a)-DOSE Trial Investigators*

Introduction



Introduction



Introduction

ESC European Society of Cardiology

European Heart Journal (2022) **43**, 3925–3946
https://doi.org/10.1093/eurheartj/ehac361

SPECIAL ARTICLE
Miscellaneous

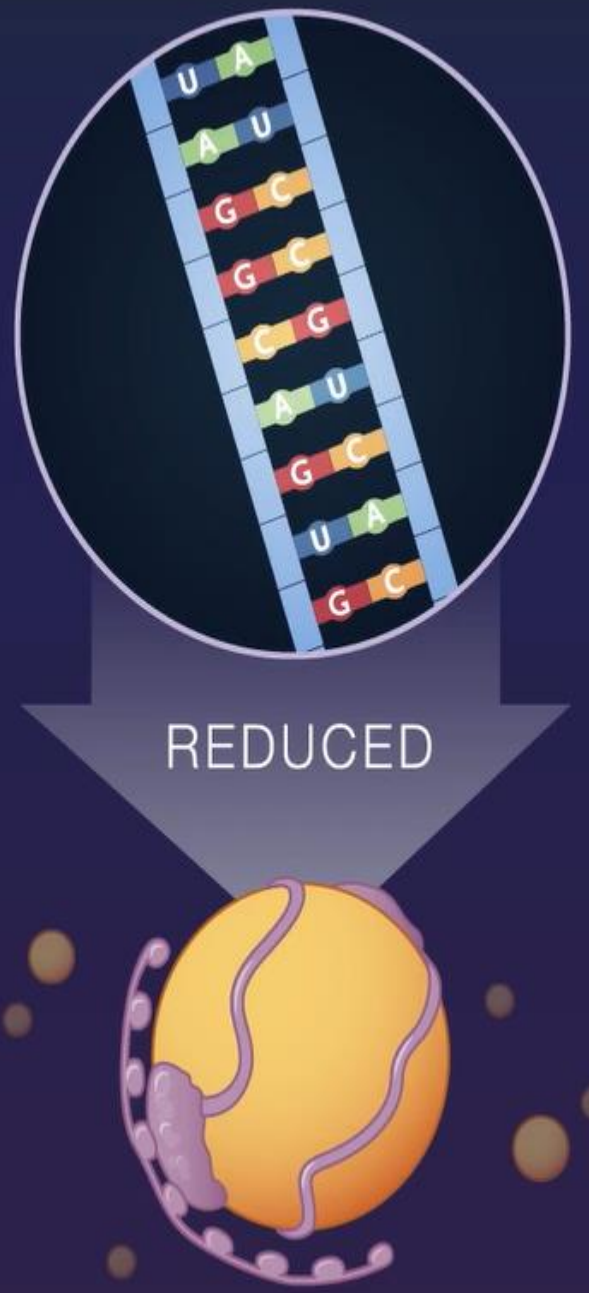
Lipoprotein(a) in atherosclerotic cardiovascular disease and aortic stenosis: a European Atherosclerosis Society consensus statement

Florian Kronenberg [1], Samia Mora [2], Erik S.G. Stroes [3], Brian A. Ference [4], Benoit J. Arsenault [5], Lars Berglund [6], Marc R. Dweck [7], Marlys Koschinsky [8], Gilles Lambert [9], François Mach [10], Catherine J. McNeal [11], Patrick M. Moriarty [12], Pradeep Natarajan [13], Børge G. Nordestgaard [14,15], Klaus G. Parhofer [16], Salim S. Virani [17], Arnold von Eckardstein [18], Gerald F. Watts [19], Jane K. Stock [20], Kausik K. Ray [21], Lale S. Tokgözoğlu [22], and Alberico L. Catapano [23,24]

Introduction

Olpasiran

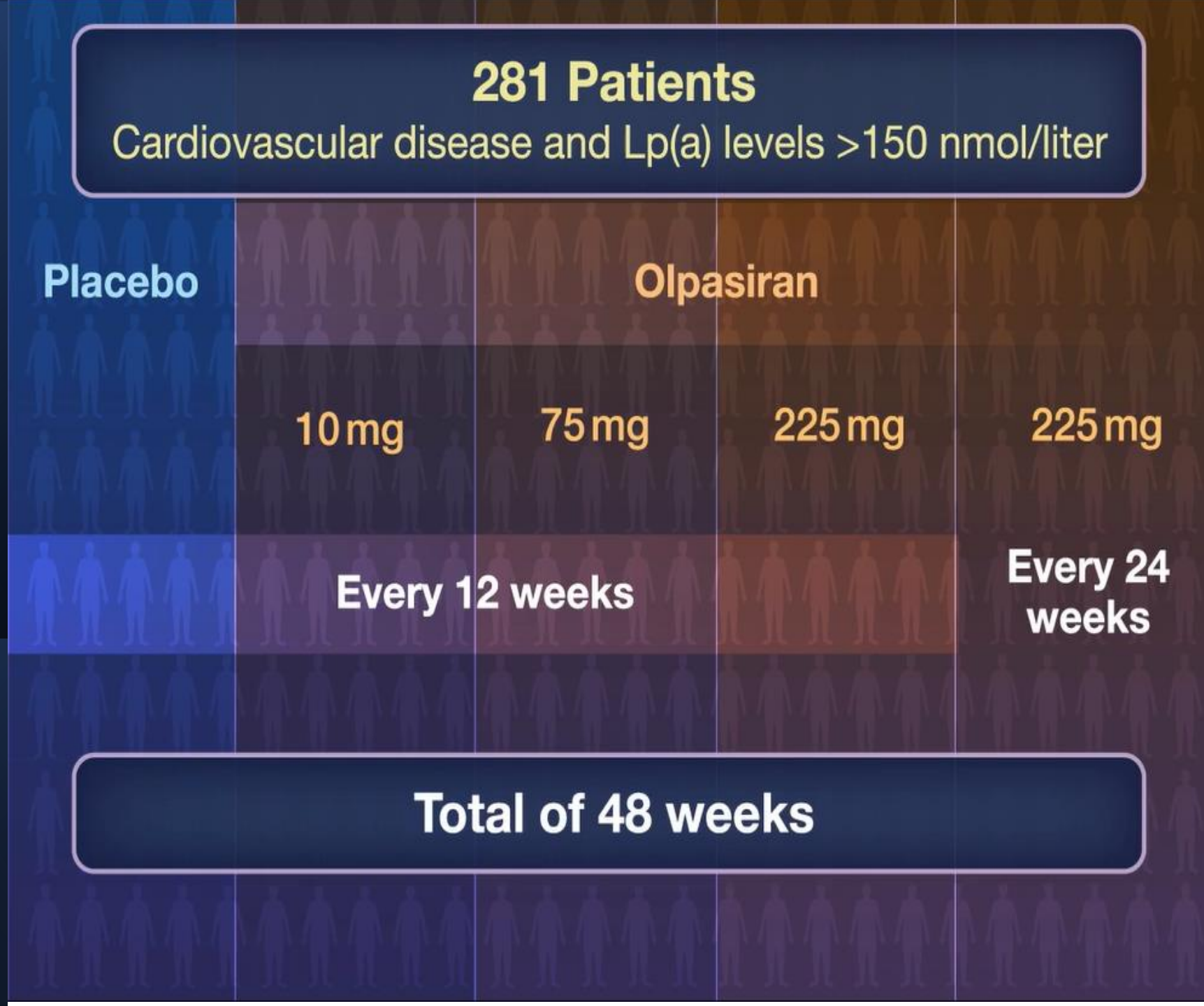
Small interfering RNA molecule



Lipoprotein(a)

in phase 1 testing

Methods


281 Patients
Cardiovascular disease and Lp(a) levels >150 nmol/liter
Placebo
Olpasiran
10 mg
75 mg
225 mg
225 mg
Every 12 weeks
Every 24 weeks
Total of 48 weeks

Results

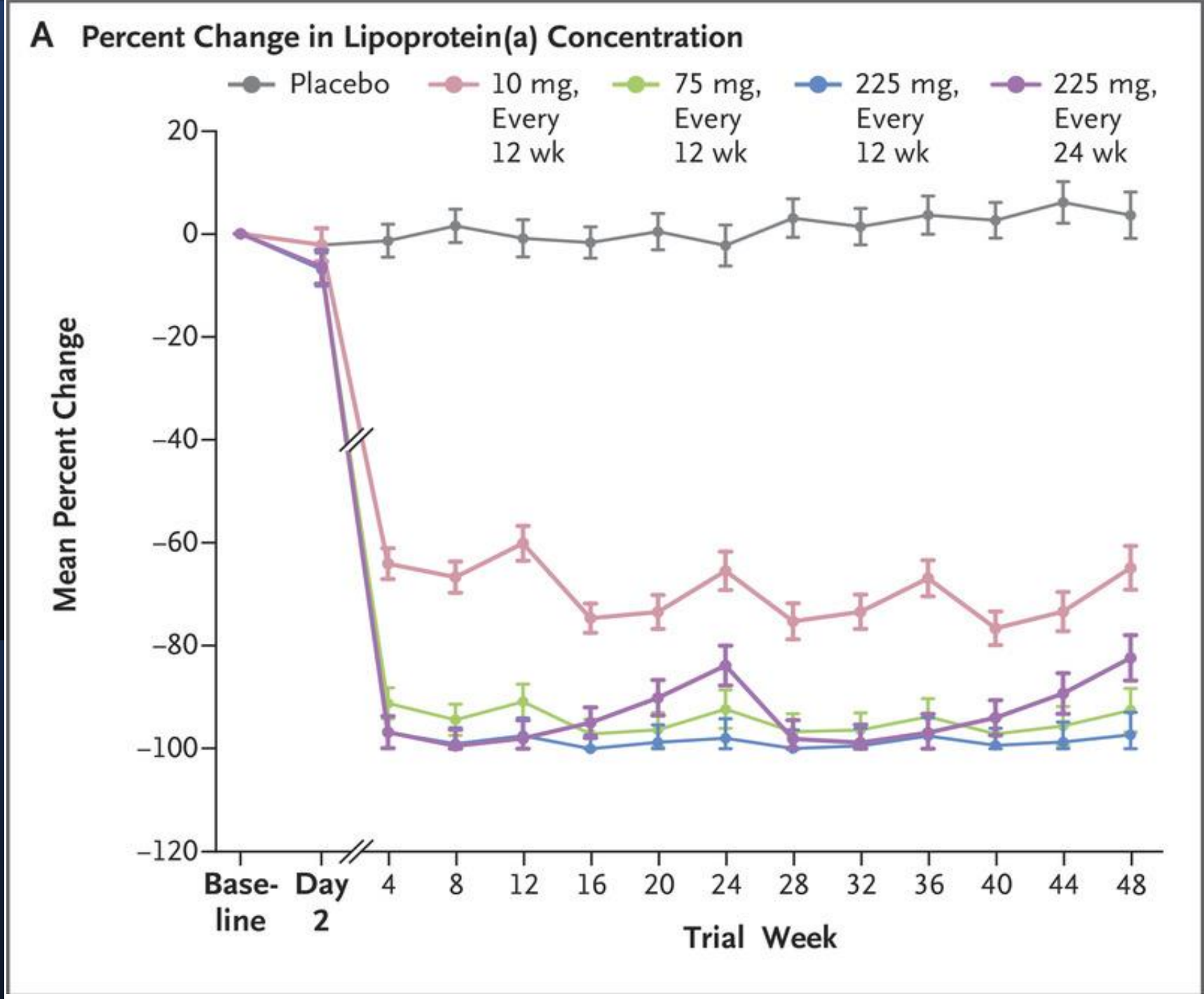
Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Placebo	Olpasiran			
	Every 12 Wk (N=54)	10 mg, Every 12 Wk (N=58)	75 mg, Every 12 Wk (N=58)	225 mg, Every 12 Wk (N=56)	225 mg, Every 24 Wk (N=55)
Age — yr	63.4±8.9	63.4±9.5	61.3±9.2	59.7±10.1	61.8±9.4
Male sex — no. (%)	36 (67)	46 (79)	35 (60)	41 (73)	33 (60)
Median laboratory values (IQR)					
Lipoprotein(a) — nmol/liter	246.1 (199.9–343.3)	304.0 (194.2–397.6)	227.5 (188.4–304.2)	265.4 (200.6–342.2)	283.4 (204.6–389.2)
LDL cholesterol — mg/dl	64.8 (47.5–81.0)	69.0 (52.0–83.5)	75.0 (53.5–90.0)	62.3 (48.5–80.5)	66.0 (50.5–79.5)
Apolipoprotein B — mg/dl	62.5 (48.5–76.0)	66.8 (51.5–81.5)	74.0 (59.5–85.0)	65.8 (49.5–80.8)	64.0 (56.5–79.0)

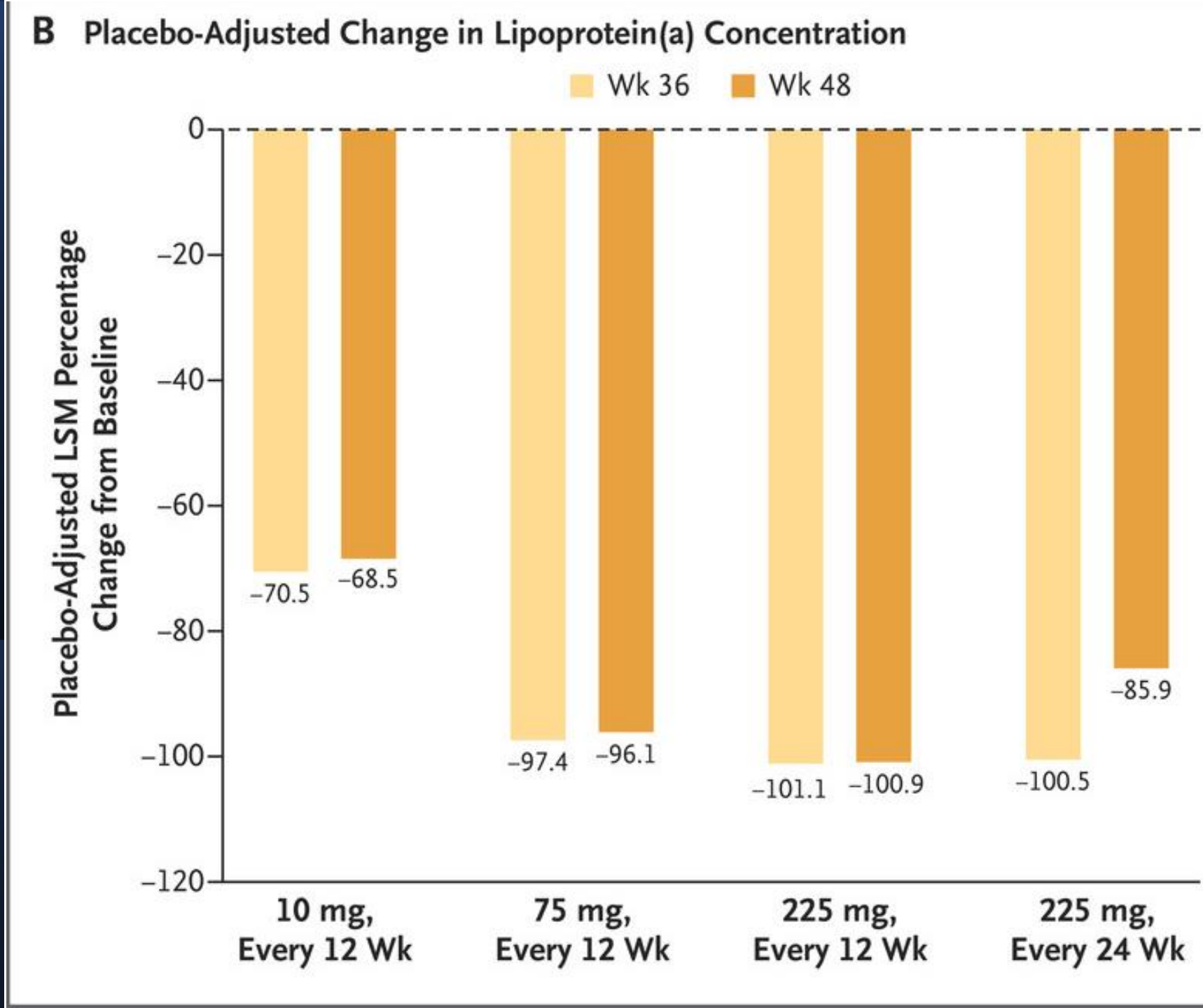
* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. IQR denotes interquartile range, LDL low-density lipoprotein, and PCSK9 proprotein convertase subtilisin–kexin type 9.

† Race and ethnic group were reported by the patient.

Results


A Percent Change in Lipoprotein(a) Concentration
Placebo
10 mg, Every 12 wk
75 mg, Every 12 wk
225 mg, Every 12 wk
225 mg, Every 24 wk
Mean Percent Change
20
0
−20
−40
−60
−80
−100
−120
Base-line
Day 2
4
8
12
16
20
24
28
32
36
40
44
48
Trial Week

Results


B Placebo-Adjusted Change in Lipoprotein(a) Concentration
Wk 36
Wk 48
Placebo-Adjusted LSM Percentage Change from Baseline
0
−20
−40
−60
−80
−100
−120
−70.5
−68.5
−97.4
−96.1
−101.1
−100.9
−100.5
−85.9
10 mg, Every 12 Wk
75 mg, Every 12 Wk
225 mg, Every 12 Wk
225 mg, Every 24 Wk

Results

Table 3. Adverse Events.

Event	Placebo	Olpasiran				
	Every 12 Wk (N=54)	10 mg, Every 12 Wk (N=58)	75 mg, Every 12 Wk (N=58)	225 mg, Every 12 Wk (N=56)	225 mg, Every 24 Wk (N=55)	Overall (N=227)
	number of patients (percent)					
Any adverse event during trial period	45 (83)	45 (78)	46 (79)	47 (84)	47 (85)	185 (81)
Serious adverse event	8 (15)	3 (5)	3 (5)	6 (11)	4 (7)	16 (7)
Adverse event reported as being related to placebo or olpasiran	11 (20)	7 (12)	13 (22)	16 (29)	14 (25)	50 (22)
Adverse event leading to discontinuation of placebo or olpasiran	1 (2)	1 (2)	1 (2)	1 (2)	1 (2)	4 (2)
Fatal adverse event	1 (2)	0	0	0	0	0
Myalgia	4 (7)	3 (5)	1 (2)	4 (7)	4 (7)	12 (5)
Peripheral neuropathy	0	1 (2)	2 (3)	0	1 (2)	4 (2)
Liver-related adverse event	2 (4)	1 (2)	2 (3)	1 (2)	1 (2)	5 (2)
Kidney-related adverse event	1 (2)	0	1 (2)	0	0	1 (<1)
Hyperglycemia or new-onset or worsening diabetes mellitus	3 (6)	5 (9)	3 (5)	5 (9)	3 (5)	16 (7)
Coagulopathy or bleeding diatheses, excluding thrombocytopenia	0	1 (2)	1 (2)	2 (4)	0	4 (2)
Thrombocytopenia	1 (2)	0	0	0	0	0
Injection-site reaction	6 (11)	3 (5)	11 (19)	12 (21)	13 (24)	39 (17)
Hypersensitivity reaction	1 (2)	1 (2)	4 (7)	3 (5)	5 (9)	13 (6)

Conclusions

- In this trial, the siRNA olpasiran led to a profound and sustained reduction in the lipoprotein(a) concentration when administered every 12 weeks.
- In the context of this short-term trial of moderate size, the drug appeared to be safe.
- These findings provide the foundation for a large-scale evaluation to confirm a causal role for lipoprotein(a) in atherosclerotic cardiovascular disease.

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Thank you for listening