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A phase III randomized trial evaluating alirocumab 300 mg every 4 weeks as monotherapy or add-on to statin: ODYSSEY CHOICE I

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ABSTRACT

Background and aims: In previous phase III studies, the PCSK9 monoclonal antibody alirocumab was administered at doses of 75 or 150 mg every 2 weeks (Q2W). CHOICE I (NCT01926782) evaluated 300 mg every 4 weeks (Q4W) in patients on either maximally tolerated statin or no statin, both ± other lipid-lowering therapies.

Methods: CHOICE I included patients with hypercholesterolemia at moderate-to-very-high cardiovascular risk. Patients were randomized to alirocumab 300 mg Q4W, 75 mg Q2W (calibrator arm), or placebo for 48 weeks, with dose adjustment for either alirocumab arm to 150 mg Q2W at Week (W) 12 if at W8 LDL-C levels were >70/100 mg/dL (1.8/2.6 mmol/L) depending on cardiovascular risk or LDL-C reduction was <30% from baseline. Co-primary endpoints were percent LDL-C change from baseline to W24, and to time-averaged LDL-C over W21–24.

Results: Approximately two-thirds of randomized patients were receiving statins. At W12, 14.7% (no statin) and 19.3% (statin) of patients receiving alirocumab 300 mg Q4W required dose adjustment. At W24, significant LDL-C reductions from baseline were observed with alirocumab 300 mg Q4W: mean differences were −52.7% (no statin; placebo: −0.3%) and −58.8% (statin; placebo: −0.1%). Average LDL-C reductions from baseline to W21–24 were also significantly greater with alirocumab 300 mg Q4W *vs.* placebo in patients not receiving (−56.9% *vs.* −1.6%) and receiving statin (−65.8% *vs.* −0.8%). Treatment-emergent adverse event rates ranged from 61.1 to 75.0% (placebo) and 71.5 to 78.1% (alirocumab 300 mg Q4W).

Conclusions: Alirocumab 300 mg Q4W is a viable additional treatment option in patients requiring LDL-C-lowering.

1. Introduction

Alirocumab is a fully human monoclonal antibody to proprotein convertase subtilisin/kexin type 9 (PCSK9), a key regulator of the low-density lipoprotein (LDL) receptor and ultimately LDL cholesterol (LDL-C) levels. In prior phase III studies, using a dosing regimen of 75 mg every 2 weeks (Q2W) (with possible dose adjustment to 150 mg Q2W) added to background statin with or without other lipid-lowering therapies (LLTs) or as monotherapy, alirocumab reduced LDL-C levels by 44–54% [1–3]. Alirocumab 150 mg Q2W reduced LDL-C levels by 61% on background statin ± other LLTs [4]. Beneficial effects were also seen on other atherogenic lipid parameters, including non-high-density

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lipoprotein cholesterol (non-HDL-C), apolipoprotein (Apo) B, and lipoprotein (a) [Lp(a)] [1–4]. For some patients a dosing regimen of alirocumab every 4 weeks (Q4W) might be a preferred option.

The magnitude and duration of LDL-C reductions with alirocumab are related to dose and its rate of elimination following administration [5–7]. Alirocumab elimination occurs through nonspecific mechanisms as well as specific mechanisms related to its binding to PCSK9 in a process known as target-mediated clearance [8]. Statins are known to increase PCSK9 levels [9,10] and, when co-administered with alirocumab, appear to reduce alirocumab's duration of effect via enhanced target-mediated clearance in the setting of Q4W dosing [8]. In contrast, fenofibrate and ezetimibe were associated with only limited impact on alirocumab duration of effect [11].

In a phase II study of patients with heterozygous familial hypercholesterolemia receiving stable statin, LDL-C reductions on alirocumab were not fully maintained over the dosing interval in all statin-treated patients. Although alirocumab 150 mg Q4W reduced LDL-C levels from baseline by 61% at Week 10 (2 weeks post-alirocumab dose), the mean reduction at Week 12 was 28.9% (4 weeks post-alirocumab dose) [5], suggesting that this dosing strategy may not be appropriate for those receiving concomitant statin. The effectiveness of this dose of alirocumab (150 mg Q4W) in patients with hypercholesterolemia who are not receiving statin therapy has been investigated further in the ODYSSEY CHOICE II study [12].

Using a higher dose of 300 mg Q4W (*vs.* 150 mg Q4W), a greater reduction of 42.5% was maintained at Week 12 in patients with heterozygous familial hypercholesterolemia receiving statin therapy, suggesting that this dose could be an option for some patients both with and without concomitant statin [5]. Furthermore, in a separate phase II study including patients with baseline LDL-C levels of ≥100 mg/dL (2.6 mmol/L) receiving stable atorvastatin 10–40 mg daily, LDL-C reductions of 43.2% with alirocumab 200 mg Q4W and 47.7% with alirocumab 300 mg Q4W were achieved [6].

The objective of the phase III ODYSSEY CHOICE I study (NCT01926782) was to determine the efficacy, long-term safety, and tolerability of a potential starting dose regimen of alirocumab 300 mg Q4W (with dose adjustment depending on individual patient response) either as add-on to maximally tolerated doses of statin (with or without other LLTs) or when used without statin. This study used alirocumab 75 mg Q2W as a calibrator arm.

2. Materials and methods

ODYSSEY CHOICE I was a randomized, double-blind, placebo-controlled, phase 3 multinational study which enrolled 803 patients from 105 study sites from the USA ($n = 63$), Canada ($n = 7$), Hungary ($n = 6$), the United Kingdom ($n = 10$), Bulgaria ($n = 5$), Israel ($n = 5$), Slovakia ($n = 6$), and Norway ($n = 3$). The study was initiated on October 24, 2013 (first patient screened), with the first patient randomized on November 4, 2013 and the last patient randomized on May 12, 2014. The study was conducted in accordance with the ethical principles in the Declaration of Helsinki and applicable amendments, and the International Conference on Harmonization for Good Clinical Practice guidelines. The protocol was approved by the relevant institutional review board or independent ethics committee, and all participating patients provided written informed consent.

2.1. Patients

The study included adult patients (aged >18 years) who did not have adequately controlled hypercholesterolemia, with (a) moderate-to-very-high cardiovascular disease (CVD) risk and receiving the maximally tolerated dose of statin, (b) moderate-to-very-high CVD risk and with statin-associated muscle symptoms (defined in protocol as muscle-related statin intolerance), or (c) moderate CVD risk and not receiving statin. Enrollment was stratified so that approximately two-thirds of the randomized patients were receiving concomitant statin therapy, with enrollment of patients receiving statins and with moderate CVD risk capped at 25% of the statin subgroup.

Patients receiving concomitant statin were to receive stable daily doses (for at least 4 weeks) of rosuvastatin 20–40 mg, atorvastatin 40–80 mg, or simvastatin 80 mg (which must have been at a stable dose for ≥1 year), or maximally tolerated dose of one of these three statins. Background treatment with LLTs other than statins was allowed for all patients, provided they had been on a stable dose for at least 4 weeks (6 weeks for fenofibrate) prior to study entry, excluding statins (other than atorvastatin, rosuvastatin, or simvastatin), fibrates other than fenofibrate, and red yeast rice products. A list of exclusion criteria is given in Supplementary Table 1. Patients were required to follow a stable diet equivalent to the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) Therapeutic Lifestyle Changes diet from screening to end of study [13].

Baseline LDL-C level was required to be ≥70 mg/dL (1.8 mmol/L) if the patient was considered at very high CVD risk or ≥100 mg/dL (2.6 mmol/L) if the patient was considered at high or moderate CVD risk, with these levels based on the NCEP ATP III guidelines available when the study was initiated [13]. In addition, the population of patients who were not on statin therapy was restricted to patients who were at moderate CVD risk with LDL-C ≥100 mg/dL (1.8 mmol/L) and <160 mg/dL (4.1 mmol/L) at screening. Patients considered statin intolerant were required to have LDL-C ≥70/100 mg/dL (1.8/2.6 mmol/L; depending on cardiovascular risk) and <160 mg/dL (4.1 mmol/L) if not on any non-statin LLT; however, there was no upper LDL-C limit for patients who were statin intolerant and receiving clinically appropriate LLT, as they were already on best standard of care.

Very-high, high, and moderate CVD risk were defined according to previously defined methods [14]. Very-high CVD risk was defined as documented coronary heart disease (CHD) or CHD risk equivalents (ischemic stroke, transient ischemic attack, carotid artery occlusion >50% without symptoms, carotid endarterectomy or carotid artery stent procedure, peripheral arterial disease, abdominal aortic aneurysm, renal artery stenosis, renal artery stent procedure, or type 1 or type 2 diabetes mellitus with target organ damage). High CVD risk was defined as no CHD/CVD but with a Systematic Coronary Risk Evaluation (SCORE) [15] 10-year fatal CVD risk ≥5%, moderate chronic kidney disease, type 1 or type 2 diabetes mellitus without target organ damage, or heterozygous familial hypercholesterolemia (by genetic or clinical criteria). Moderate CVD risk was defined as a SCORE of between ≥1 and <5%. Statin-associated muscle symptoms were defined as per a previous study in the protocol as statin intolerance, and included the inability to tolerate at least two statins: one statin at the lowest daily starting dose and another statin at any dose, due to skeletal muscle-related symptoms [14].

2.2. Study procedures

The study comprised a 3-week screening period, followed by 48 weeks of double-blind treatment and 8 weeks of follow-up (off-treatment). Patients were randomized using a permuted block design in a 4:2:1 ratio to receive alirocumab 300 mg Q4W, placebo, or alirocumab 75 mg Q2W (Fig. 1). Each treatment was administered subcutaneously as 2 × 1 mL injections (placebo or alirocumab) by pre-filled syringe. To maintain the blind, all patients

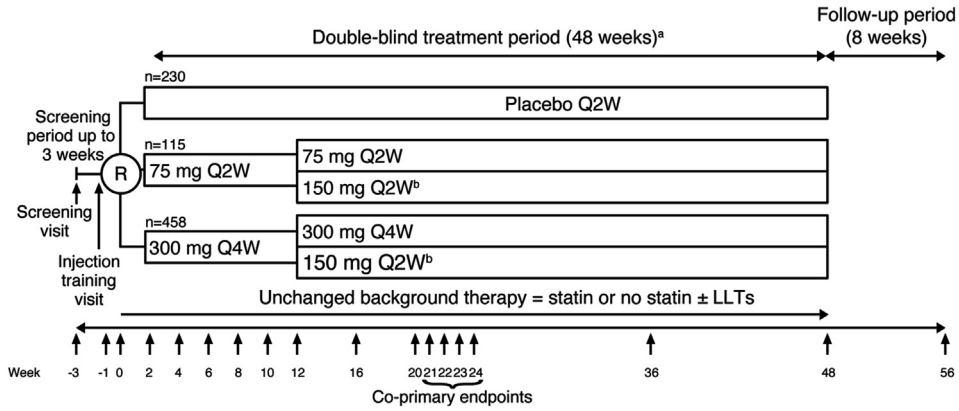

Fig. 1. CHOICE I study design. a. Dosing regimen changed in both alirocumab groups at Week 12 if LDL-C at Week 8 ≥70 mg/dL (1.8 mmol/L) or ≥100 mg/dL (2.6 mmol/L), depending on cardiovascular risk, or if LDL-C reduction was <30% from baseline at Week 8. b. The blind was maintained in all patients, including those receiving dose adjustment, by giving the study treatment as two 1 mL subcutaneous injections Q2W. Placebo group: 2 injections of placebo Q2W; alirocumab 75Q2W group: 1 injection of 75 mg alirocumab and 1 injection of placebo Q2W; alirocumab 300Q4W group: 2 injections Q2W, consisting of 2 injections of 150 mg alirocumab Q4W alternating with 2 injections of placebo Q4W. LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; R, randomization; Q2W, every 2 weeks; Q4W, every 4 weeks.

received 2 × 1 mL injections Q2W. The patient or designated person was trained to self-inject/inject using placebo. Randomization was stratified according to statin therapy *vs.* no statin therapy, and moderate *vs.* high and very-high CVD risk within the population receiving concomitant statin.

Alirocumab patients (in the alirocumab 300 mg Q4W and 75 mg Q2W treatment groups) not achieving target LDL-C levels of <70 mg/dL (1.8 mmol/L) or <100 mg/dL (2.6 mmol/L) (depending on CVD risk) at Week 8, or if their LDL-C level was reduced by ≤30% from baseline at Week 8, had their alirocumab dosing regimen changed to 150 mg Q2W at Week 12 in a blinded fashion.

On-site visits took place during the double-blind period at Weeks 0 (baseline, i.e., randomization visit), 2, 4, 6, 8, 10, 12, 16, 20, 21, 22, 23, 24, 36, and 48.

2.3. Endpoints

The co-primary endpoints were the percent change in calculated LDL-C from baseline to Week 24, and the percent change in calculated LDL-C from baseline to the average over Weeks 21–24 (alirocumab 300 mg Q4W *vs.* placebo, according to randomization) using all LDL-C values regardless of adherence to treatment (intent-to-treat [ITT] approach). This was analyzed separately for the study populations receiving concomitant statin and those not receiving statin. The weekly assessment between Weeks 21–24 evaluated the efficacy of alirocumab between the dosing intervals.

The percent change in calculated LDL-C from baseline to Week 24 was also assessed using all LDL-C values during the efficacy treatment period (on-treatment approach) (key secondary endpoint). Other key secondary endpoints included the percent change in calculated LDL-C from baseline to Week 12, the proportion of patients achieving LDL-C targets of <70 mg/dL (1.8 mmol/L; very high cardiovascular risk) or <100 mg/dL (2.6 mmol/L) at Week 24 (moderate or high cardiovascular risk), and the percent change in Apo B, non-HDL-C, total cholesterol, Lp(a), fasting triglycerides, HDL-C, and Apo A1 from baseline to Weeks 12 and 24. Other secondary endpoints included the percent change in calculated LDL-C from baseline to Week 48, and the proportion of patients achieving LDL-C targets at Weeks 12 and 48.

Safety was assessed primarily from the reporting of treatment-emergent adverse events (TEAEs), defined as those occurring between the date of first study drug injection to the date of the last study drug injection plus 70 days, and by laboratory parameters, vital signs, and electrocardiogram.

Safety events of interest, requiring completion of a special electronic case report form (e-CRF), included general allergic reactions, cardiovascular events, injection-site reactions, hemolytic anemia, neurologic events, ophthalmologic events, and increased alanine aminotransferase levels. Neurocognitive events, an additional safety event of interest, did not require completion of an e-CRF and were identified by custom Medical Dictionary of Regulatory Activities queries. For further details on safety events of interest and preferred terms for the adverse event categories, see the Supplementary material.

To assess development of anti-drug antibodies (ADAs) to alirocumab, blood samples were collected before study drug administration at baseline and scheduled clinic visit at Weeks 12, 24, 36, 48, and at the end of study visit. These were analyzed using a validated assay by Regeneron Pharmaceuticals, Inc. (Tarrytown, NY).

Free PCSK9 levels were determined using a specific validated enzyme-linked immunosorbent assay (Regeneron Pharmaceuticals Inc., Tarrytown, NY). The lower limits of detection were 31.2 ng/mL. Free PCSK9 levels were measured up to Week 24.

2.4. Statistical analysis

A total sample size of 39 patients receiving concomitant statin (26 patients on alirocumab 300 mg Q4W and 13 patients on placebo) or 30 patients not receiving statin (20 alirocumab and 10 placebo) was determined to have 95% power to detect a between treatment-group difference of 40% (no statin population) and 35% (statin population) in the primary endpoint using a two-sided significance level of 0.025 and assuming a common standard deviation of 25%. However, the total sample size was increased to 400 patients on alirocumab 300 mg Q4W and 200 patients on placebo to provide additional safety data for the 300 mg Q4W dose.

The primary efficacy analysis included all randomized patients with an LDL-C measurement available at baseline and at least one of the post-randomization time points between Weeks 4 and 24, regardless of treatment adherence (ITT population), and was analyzed using a mixed-effects model with repeated measures, with parameters to account for missing data as previously reported [14,16–18].

Key secondary lipid endpoints were analyzed in a predefined order using a hierarchical inferential approach to control type I

error. These endpoints were analyzed as for the primary endpoint, except Lp(a), which was analyzed using a multiple imputation approach then robust regression, and triglycerides and LDL-C goal achievement, which were analyzed using logistic regression.

The safety analysis included all randomized patients who received at least one dose or part of a dose of study drug. Safety data were analyzed by descriptive statistics.

3. Results

3.1. Patients

A total of 1491 patients were screened, of whom 803 were randomized according to their statin treatment status (Supplementary Fig. 1). For the no concomitant statin cohort, 146 patients were randomized to alirocumab 300 mg Q4W (with possible dose adjustment to 150 mg Q2W, to be further referred to as "300Q4W"), 73 to receive placebo, and 37 to alirocumab 75 mg Q2W (with possible dose adjustment to 150 mg Q2W, to be further referred to as "75Q2W"). For the concomitant statin cohort, 312 were randomized to alirocumab 300Q4W, 157 to receive placebo, and 78 to alirocumab 75Q2W. The ITT population included 792 patients overall, and the safety population included 802.

A total of 187 (73.0%) patients in the no statin population (alirocumab 300Q4W, 71.9%; placebo, 72.6%; alirocumab 75Q2W, 78.4%) and 466 (85.2%) patients in the concomitant statin population (alirocumab 300Q4W, 87.2%; placebo, 82.2%; alirocumab 75Q2W, 83.3%) completed the study treatment period. Reasons for study discontinuation are given in Supplementary Table 2. Over the 48-week treatment period, 8.2% and 6.2% of patients discontinued study treatment due to TEAEs in the no statin and the concomitant statin populations, respectively.

Baseline characteristics and lipid parameters were generally similar across the treatment arms of both the no statin and statin cohorts, with some discrepancies between groups not anticipated to have a clinically significant impact on the overall study results (Table 1). Statin-associated muscle symptoms were the reason that 42.2% (n = 108/256) of the patients were not receiving statin therapy. Other reasons are given in Supplementary Table 3. At randomization, 0.4% of patients in the no statin groups were receiving statin, due to randomization error, and 43.8% were on other LLT, whereas 99.8% of patients in the concomitant statin cohort were on statins and 36.4% of patients were on other LLT. In general, the percent of patients receiving background LLT (other than statin) was broadly comparable across patients (Table 1).

Comparing the study cohorts, patients not on statin had a higher mean baseline LDL-C level (142.1 mg/dL [3.7 mmol/L]) *vs.* those on concomitant statin (112.7 mg/dL [2.9 mmol/L]).

3.2. Efficacy endpoints

The least-squares mean (standard error) change from baseline to Week 24 in LDL-C level was −52.7% (1.9) with alirocumab 300Q4W (*vs.* −0.3% [2.7%] with placebo) in patients not receiving statin and −58.8% (1.6%) (*vs.* −0.1% [2.3%] with placebo) in patients receiving concomitant statin (both $p < 0.0001$, Supplementary Table 4). The average LDL-C reduction from baseline to averaged Weeks 21–24 was also significantly greater for alirocumab 300Q4W *vs.* placebo in both patient populations (−56.9% [1.8%] [alirocumab 300Q4W] and −1.6% [2.6%] [placebo] in patients not receiving statin; −65.8% [1.4%] [alirocumab 300Q4W] and −0.8% [2.0%] [placebo] in patients receiving concomitant statin; and both groups: $p < 0.0001$; Supplementary Table 5). Significant LDL-C reductions were maintained with alirocumab 300Q4W from baseline to Week 48 *vs.* placebo in patients not on statin (−45.7% [2.1%] *vs.* −1.0% [3.0%]) and those on statin (−51.9% [1.8%] *vs.* +6.2% [2.5%]; both: $p < 0.0001$) (Supplementary Table 5).

LDL-C reductions with alirocumab 300Q4W were observed from Week 4 and maintained through the treatment period. Overall, reductions in LDL-C in the alirocumab 300Q4W group were of a similar magnitude to those observed in the alirocumab 75Q2W group (Fig. 2 and Supplementary Table 5). With alirocumab 300Q4W, LDL-C reductions were more sustained between injections in the cohort not on statin *vs.* the cohort receiving concomitant statin (Fig. 2). Weekly analyses between Weeks 21 and 24 (i.e., after possible dosing regimen adjustment) found generally consistent alirocumab efficacy over this time, regardless of statin use (Fig. 2 and Supplementary Table 5).

Percent reductions in LDL-C at Week 12 (i.e., before dosing regimen adjustment) for all groups are shown in Supplementary Table 5. At Week 12, in the alirocumab 300Q4W group the dosing regimen was adjusted to alirocumab 150 mg Q2W in 14.7% and 19.3% of patients in the no statin and concomitant statin populations, respectively (Fig. 3). The adjusted dosing regimen was associated with reduced variability in LDL-C levels from week to week (as observed between Weeks 21 and 24), in particular for patients on concomitant statin (Figs. 2 and 3).

At Week 24, most patients receiving alirocumab 300Q4W (78.9% of patients not receiving statin; 85.2% of patients on concomitant statin) achieved LDL-C levels of <70 mg/dL (1.8 mmol/L) or <100 mg/dL (2.6 mmol/L), depending on their cardiovascular risk (both patient groups $p < 0.0001$ *vs.* placebo; Supplementary Table 5). At Week 48, 66.2% of patients not receiving statin and 78.2% of those on statin achieved their pre-defined goals in the alirocumab 300Q4W groups (Supplementary Table 5).

Alirocumab 300Q4W significantly improved all key secondary efficacy lipid parameters *vs.* placebo, regardless of statin use (all $p \leq 0.005$, with the exception of Apo A1 at Week 24 in patients on concomitant statin [$p = 0.0306$]; Supplementary Table 4), including Lp(a) (−21.3% [no statin group] and −19.3% [statin group]; $p < 0.0001$ *vs.* placebo). At Week 48, alirocumab resulted in generally consistent improvements of the secondary efficacy lipid parameters (Supplementary Table 6).

Across various subgroups defined by demographic and baseline characteristics, a consistent reduction in LDL-C was observed at Week 24 (Supplementary Fig. 2) and averaged Weeks 21–24 (Supplementary Fig. 3). Regardless of LDL-C baseline levels, patients randomized to the alirocumab 300Q4W group demonstrated reductions in LDL-C of 47.7–64.2% at Week 24 (Supplementary Fig. 2E and F) and 52.7–69.5% at averaged Weeks 21–24 (Supplementary Fig. 3E and F); however, patients on statin with baseline LDL-C of <100 mg/dL (2.6 mmol/L) tended to show a greater difference (Week 24: −60.4%; averaged Weeks 21–24: −69.5%) *vs.* placebo (+8.6% and +9.6%, respectively) than those with higher LDL-C levels (Supplementary Figs. 2F and 3F).

3.3. Free PCSK9

In general, predictable dynamics were apparent between PCSK9 and LDL-C levels, with reductions in free PCSK9 consistent with the observed reductions in LDL-C. Patients who were not on statin tended to have lower free PCSK9 levels at baseline and achieved extremely low free PCSK9 levels between Weeks 21–24 (5.0–24.8 ng/mL) (Fig. 2). In the statin group, free PCSK9 levels tended to be higher at baseline than in those not receiving statin and decreased to very low levels between Weeks 21–23 (10.6–26.3 ng/mL) before rising to 88.1 ng/mL towards the end of the dosing period at Week 24 (Fig. 2). Those patients who required dose adjustment at Week 12 tended to have higher LDL-C and higher free PCSK9 levels at both baseline and Week 12 (Fig. 3).

Table 1
Baseline characteristics (randomized population).

	Patients not receiving statin			Patients receiving statin		
	Alirocumab		Placebo ($n = 73$)	Alirocumab		Placebo ($n = 157$)
	75Q2W ($n = 37$)	300Q4W ($n = 146$)		75Q2W ($n = 78$)	300Q4W ($n = 312$)	
Baseline demographics						
Age, mean (SD)	59.3 (11.3)	59.2 (10.8)	59.4 (10.2)	60.7 (9.1)	61.6 (10.0)	61.6 (9.7)
Male, *n* (%)	14 (37.8)	66 (45.2)	40 (54.8)	51 (65.4)	190 (60.9)	101 (64.3)
Race, White, *n* (%)	32 (86.5)	123 (84.2)	62 (84.9)	68 (87.2)	279 (89.4)	137 (87.3)
Race, Black or African-American, *n* (%)	4 (10.8)	17 (11.6)	9 (12.3)	8 (10.3)	29 (9.3)	18 (11.5)
Ethnicity, Hispanic/Latino, *n* (%)	3 (8.1)	8 (5.5)	4 (5.5)	1 (1.3)	5 (1.6)	5 (3.2)
BMI, kg/m^2, mean (SD)	29.7 (5.0)	30.9 (5.7)	32.3 (6.7)	30.1 (4.9)	31.4 (6.2)	30.9 (6.2)
Diagnosis of HeFH, *n* (%)	0	2 (1.4)	1 (1.4)	6 (7.7)	26 (8.3)	12 (7.6)
By genotyping	0	0	0	2 (33.3)	13 (50.0)	2 (16.7)
By WHO/Simon Broome criteria	0	2 (100)	0	4 (66.7)	13 (50.0)	10 (83.3)
Diabetes mellitus (type 2), *n* (%)	4 (10.8)	28 (19.2)	17 (23.3)	22 (28.2)	96 (30.8)	50 (31.8)
Cardiovascular risk, *n* (%)						
Very high	7 (18.9)	33 (22.6)	20 (27.4)	55 (70.5)	204 (65.4)	102 (65.0)
High	8 (21.6)	22 (15.1)	15 (20.5)	12 (15.4)	66 (21.2)	31 (19.7)
Moderate	22 (59.5)	91 (62.3)	38 (52.1)	11 (14.1)	42 (13.5)	24 (15.3)
Lipid treatment						
Patients on atorvastatin, rosuvastatin, or simvastatin at randomization, *n* (%)	0	2 (1.4)[a]	0	78 (100)	310 (99.4)	157 (100)
Any LLT other than statins, n (%)[b]	12 (32.4)	67 (45.9)	33 (45.2)	21 (26.9)	125 (40.1)	53 (33.8)
Any LLT other than nutraceuticals, *n* (%)	5 (13.5)	41 (28.1)	20 (27.4)	16 (20.5)	86 (27.6)	38 (24.2)
Ezetimibe, *n* (%)	3 (8.1)	10 (6.8)	11 (15.1)	9 (11.5)	43 (13.8)	22 (14.0)
Nutraceuticals, *n* (%)	8 (21.6)	47 (32.2)	19 (26.0)	12 (15.4)	62 (19.9)	24 (15.3)
Baseline lipid parameters, mg/dL, *mmol/L or g/L*						
LDL-C (calculated), mean (SD)	148.4 (36.8)	146.1 (33.5)	131.0 (30.4)	114.9 (36.0)	112.4 (32.8)	112.1 (37.3)
	3.842 (0.953)	*3.785 (0.868)*	*3.392 (0.787)*	*2.977 (0.933)*	*2.912 (0.850)*	*2.903 (0.965)*
LDL-C (measured), mean (SD)	154.7 (39.2)	149.7 (34.1)	134.1 (28.9)	118.0 (35.1)	115.4 (30.6)	115.8 (37.2)
	4.006 (1.016)	*3.877 (0.884)*	*3.473 (0.749)*	*3.057 (0.910)*	*2.989 (0.793)*	*2.998 (0.962)*
Non-HDL-C, mean (SD)	175.7 (40.8)	176.5 (38.0)	162.8 (34.7)	146.4 (42.3)	141.3 (35.4)	140.0 (41.9)
	4.550 (1.056)	*4.572 (0.983)*	*4.218 (0.899)*	*3.791 (1.095)*	*3.658 (0.916)*	*3.626 (1.085)*
Total cholesterol, mean (SD)	233.9 (41.9)	228.9 (38.7)	212.6 (36.2)	195.3 (43.6)	191.4 (37.8)	190.5 (44.4)
	6.059 (1.085)	*5.930 (1.002)*	*5.507 (0.936)*	*5.058 (1.130)*	*4.956 (0.980)*	*4.935 (1.150)*
Apo B, mean (SD)	115.9 (24.7)	117.3 (22.7)	109.8 (21.6)	99.6 (25.0)	96.6 (21.3)	96.0 (24.3)
	1.159 (0.247)	*1.173 (0.227)*	*1.098 (0.216)*	*0.996 (0.250)*	*0.966 (0.213)*	*0.960 (0.243)*
Lp(a), median (Q1:Q3)	13.0 (6.0:45.0)	15.0 (7.0:42.0)	12.5 (6.0:39.0)	28.0 (9.5:58.0)	27.0 (7.0:65.0)	25.5 (7.0:73.0)
	0.130	*0.150*	*0.125*	*0.280*	*0.270*	*0.255*
	(0.060:0.450)	*(0.070:0.420)*	*(0.060:0.390)*	*(0.095:0.580)*	*(0.070:0.650)*	*(0.070:0.730)*
HDL-C, mean (SD)	58.2 (15.0)	52.4 (16.4)	49.8 (15.4)	48.9 (14.1)	50.1 (14.8)	50.5 (15.7)
	1.509 (0.389)	*1.357 (0.426)*	*1.290 (0.399)*	*1.267 (0.365)*	*1.298 (0.383)*	*1.309 (0.407)*
Fasting TGs, median (Q1:Q3)	120.0	136.5	139.0	132.0	128.0	125.0
	(86.0:172.0)	(93.0:190.0)	(101.0:201.0)	(99.0:171.0)	(95.0:173.0)	(93.0:176.0)
	1.356	*1.542*	*1.571*	*1.492*	*1.446*	*1.413*
	(0.972:1.944)	*(1.051:2.147)*	*(1.141:2.271)*	*(1.119:1.932)*	*(1.074:1.955)*	*(1.051:1.989)*
Apo A1, mean (SD)	166.4 (26.7)	157.1 (30.4)	153.1 (29.3)	149.3 (26.5)	149.0 (27.4)	147.6 (30.6)
	1.664 (0.267)	*1.571 (0.304)*	*1.531 (0.293)*	*1.493 (0.265)*	*1.490 (0.274)*	*1.476 (0.306)*

75Q2W, 75 mg every 2 weeks (with possible dose adjustment to 150 mg every 2 weeks); 300Q4W, 300 mg every 4 weeks (with possible dose adjustment to 150 mg every 2 weeks); Apo, apolipoprotein; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; HeFH, heterozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; Lp(a), lipoprotein (a); SD, standard deviation; TGs, triglycerides; WHO, World Health Organization.

[a] Patients received statin due to randomization error.

[b] In combination with statins or not. Patients could be receiving more than one category of LLT.

3.4. Safety

The overall frequency of TEAEs ranged from 79.2 to 83.6% in the alirocumab 300Q4W group and 73.2 to 77.8% in the placebo groups, depending on statin status (Table 2). There were three deaths. The frequency of treatment-emergent serious adverse events was generally consistent across each cohort (Table 2). Among all treatment groups, 5.1–9.6% of patients prematurely discontinued study treatment because of one or more TEAE (Table 2). The frequency of TEAEs occurring within the system organ class "musculoskeletal and connective tissue disorders" was similar between patients treated with alirocumab 300Q4W and placebo, irrespective of background statin use (Supplementary Table 7). Of these patients, 3 (0.7%) discontinued study treatment due to muscle pain. A higher proportion of patients experienced injection-site reactions in the alirocumab 300Q4W group compared with placebo and alirocumab 75Q2W groups. Most of these events (92.3%) were classified as mild in intensity, and most patients (97.1%) experiencing these continued to receive study treatment (Supplementary Table 7). Overall, 12 and nine patients experienced cardiovascular and neurocognitive events, respectively, during the study (Table 2).

LDL-C levels <25 mg/dL (0.6 mmol/L) on at least two consecutive occasions (measurements ≥21 days apart) were observed in 118 alirocumab-treated patients (20.6%; 300Q4W and 75Q2W; Supplementary Table 8). The overall adverse event profile appeared similar to those patients without such low LDL-C levels.

3.5. Immunogenicity

Overall, ADA positivity was not associated with decreased

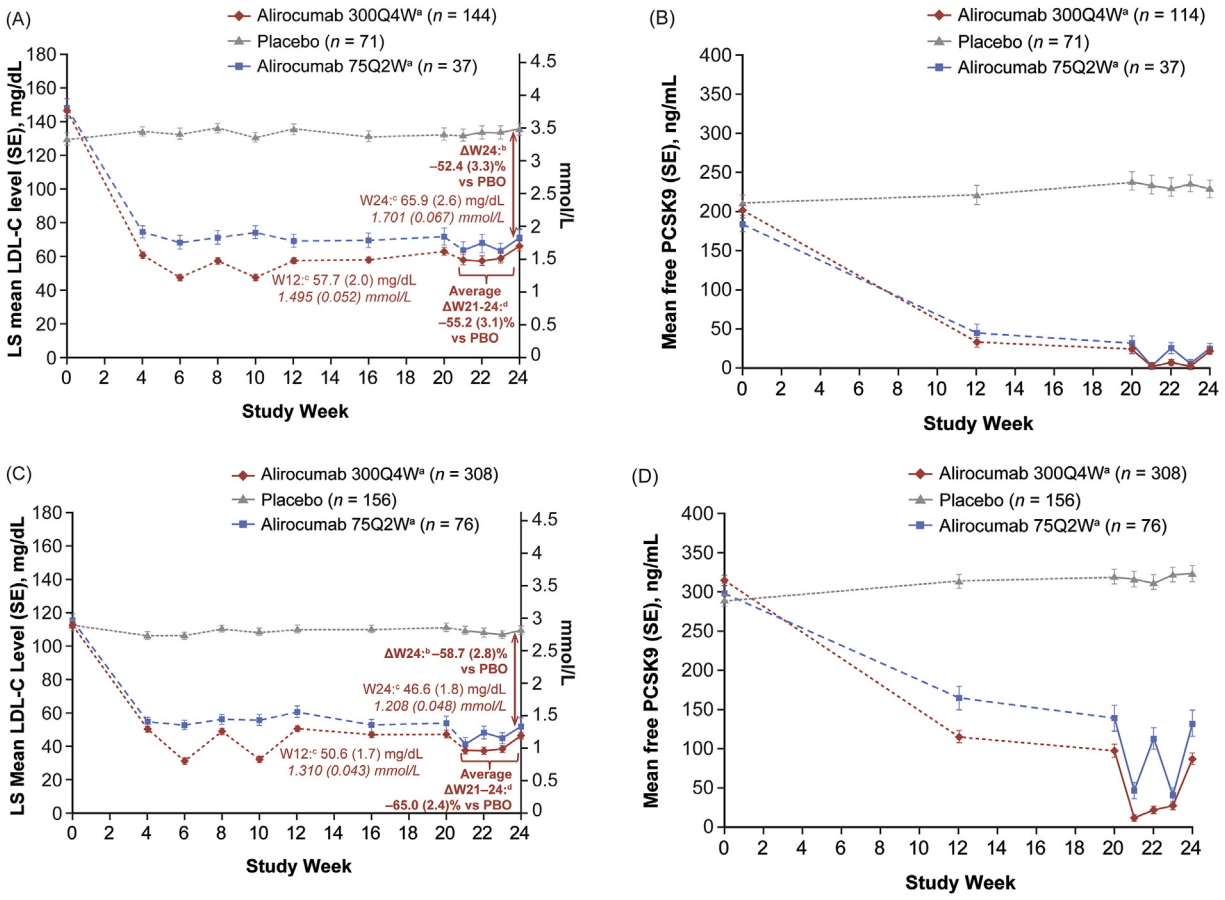

Fig. 2. Mean (SE) calculated LDL-C levels (A and C) and free PCSK9 levels (B and D) over time in patients not receiving concomitant statin therapy (A and B) and patients receiving concomitant statin therapy (C and D) (ITT population) – time profile of patients. a. At Week 12, 14.7% and 21.2% of patients in the no statin population and 19.3% and 19.7% of those in the statin population received dose adjustment to 150 mg Q2W, based on Week 8 LDL-C levels, in the alirocumab 300 mg Q4W and 75 mg Q2W groups, respectively. b. ΔW24 defined as % change in calculated LDL-C from baseline to Week 24 *vs.* placebo in the ITT population. c. Absolute LDL-C value. d. ΔW21–24 defined as % change in calculated LDL-C from baseline to averaged values from Weeks 21–24 *vs.* placebo in the ITT population. 75Q2W, 75 mg every 2 weeks (with possible dose adjustment to 150 mg every 2 weeks); 300Q4W, 300 mg every 4 weeks (with possible dose adjustment to 150 mg every 2 weeks); ITT, intent-to-treat; LDL-C, low-density lipoprotein cholesterol; LS, least-squares; PBO, placebo; PCSK9, proprotein convertase subtilisin/kexin type 9; SE, standard error; W, week.

percent change from baseline in LDL-C levels during this study (Supplementary Fig. 4). Low titer, treatment-emergent persistent positive responses in the ADA assay were observed in 4/445 (0.9%) patients in the 300Q4W group, 3/226 (1.3%) patients in the placebo group, and 2/110 (1.8%) patients in the 75Q2W group. Five patients administered alirocumab were positive in the neutralizing antibody assay.

4. Discussion

In the current study, alirocumab 300Q4W demonstrated statistically significant reductions in LDL-C *vs.* placebo both in patients receiving and not receiving concomitant statin at Week 12 (before possible dose adjustment), Week 24, averaged Weeks 21–24, and Week 48. In addition, beneficial effects were seen for all secondary lipid parameters with alirocumab 300Q4W at Week 24, notably with robust reductions in Lp(a).

Statins are known to upregulate the expression of PCSK9 [9,19]; this phenomenon has been shown to limit the effectiveness of statins through increased degradation of the LDL receptor [9]. When dosed in combination with a PCSK9 monoclonal antibody, statins may increase the magnitude of efficacy; however, statins also increase circulating PCSK9 levels [19,20], which may limit the durability of effect of a PCSK9 monoclonal antibody over a 4-week dosing interval through target-mediated clearance [5,6]. This situation is mitigated with higher doses of PCSK9 monoclonal antibody.

Our study showed a tendency for a less pronounced least-squares mean maximum reduction in LDL-C when alirocumab 300Q4W was administered without statin compared with concomitant statin. That is, both the least-squares mean LDL-C reduction from baseline to Week 24 (alirocumab 300Q4W: −52.7%; placebo: −0.3%) and the average LDL-C reduction from baseline to Weeks 21–24 (alirocumab 300Q4W: −56.9%; placebo: −1.6%) were numerically smaller in the alirocumab 300Q4W group not receiving concomitant statin compared with patients receiving concomitant statin (alirocumab 300Q4W: −58.8%; placebo: −0.1% and alirocumab 300Q4W: −65.8%; placebo: −0.8%, respectively).

In terms of durability, patients receiving concomitant statin did tend to see slightly more variation in the level of their LDL-C reduction over time compared with those who were not receiving a statin. Furthermore, this variability was more apparent in those patients who ultimately required dose adjustment at Week 12. Analysis of the dose adjustment scheme revealed that patients requiring adjustment at Week 12 had higher mean LDL-C levels at baseline (no statin: 174.3 mg/dL [4.5 mmol/L]; statin: 123.5 mg/dL [3.2 mmol/L]) and a more variable response to Q4W dosing compared with those remaining on alirocumab 300 mg Q4W (mean baseline LDL-C levels no statin: 143.6 mg/dL [3.7 mmol/L];

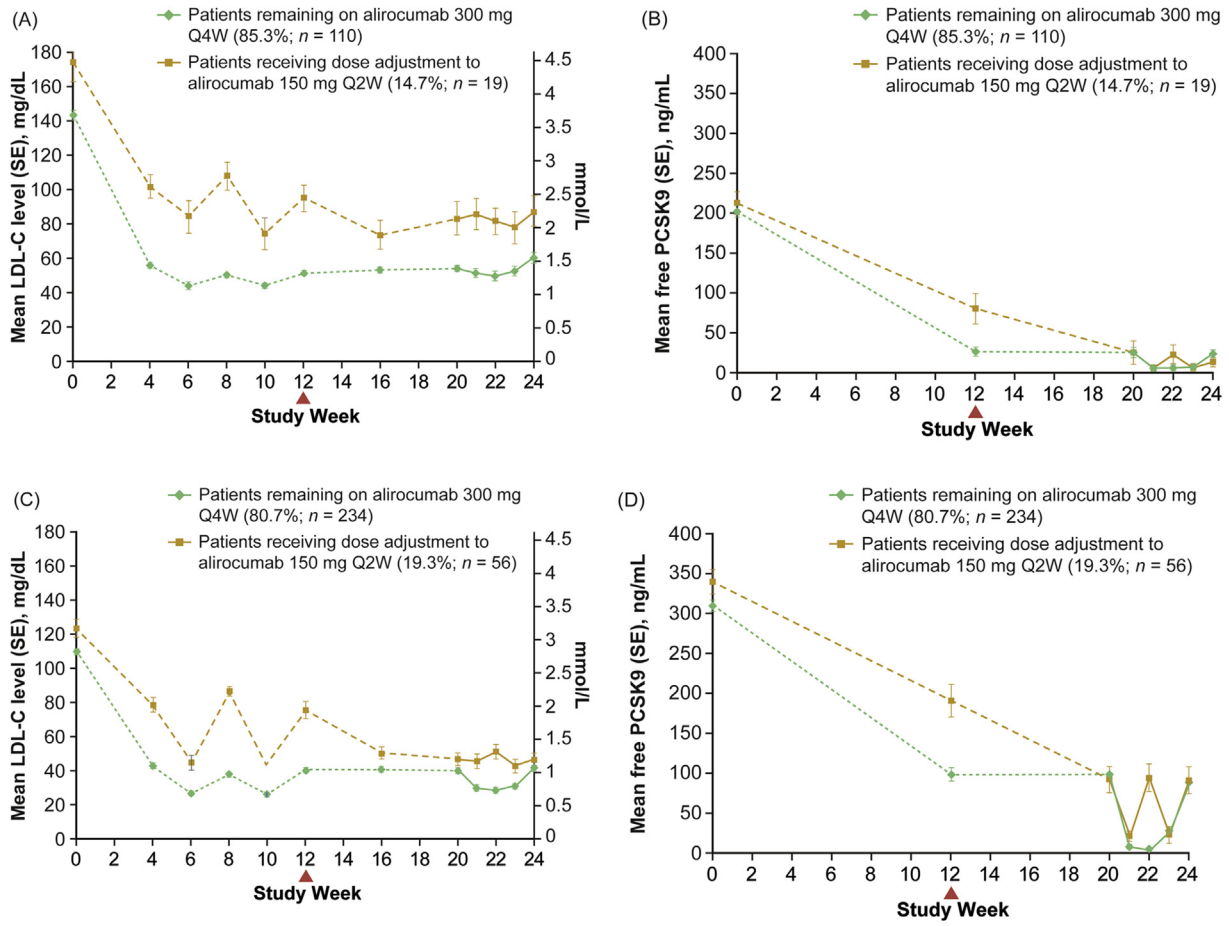

Fig. 3. Impact of dosing/frequency adjustment on LDL-C (A and C) and free PCSK9 levels (B and D) in patients in the alirocumab 300 mg Q4W group who were not receiving statin (A and B) or receiving statin (C and D) (ITT population) – time profile of patients[a]. a. Patients who received dose adjustment at Week 12 and had at least one subsequent injection. Arrows indicate time of dose adjustment. LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9; Q2W, every 2 weeks; Q4W, every 4 weeks; SE, standard error.

Table 2
Adverse events and safety laboratory values (safety population).

n (%)	Patients not receiving statin			Patients receiving statin		
	Alirocumab		Placebo ($n = 72$)	Alirocumab		Placebo ($n = 157$)
	75Q2W ($n = 37$)	300Q4W ($n = 146$)		75Q2W ($n = 78$)	300Q4W ($n = 312$)	
TEAEs	31 (83.8)	122 (83.6)	56 (77.8)	55 (70.5)	247 (79.2)	115 (73.2)
Treatment-emergent SAEs	4 (10.8)	19 (13.0)	10 (13.9)	9 (11.5)	34 (10.9)	23 (14.6)
TEAEs leading to discontinuation	3 (8.1)	14 (9.6)	4 (5.6)	4 (5.1)	17 (5.4)	13 (8.3)
TEAEs leading to death	1 (2.7)	1 (0.7)	1 (1.4)	0	0	0
Safety terms of interest						
Adjudicated cardiovascular events[a]	0	2 (1.4)	2 (2.8)	1 (1.3)	5 (1.6)	2 (1.3)
General allergic TEAE	9 (24.3)	16 (11.0)	8 (11.1)	8 (10.3)	29 (9.3)	13 (8.3)
General allergic serious (CMQ)	0	1 (0.7)	0	1 (1.3)	1 (0.3)	1 (0.6)
Neurocognitive disorders	1 (2.7)	0	0	2 (2.6)	4 (1.3)	2 (1.3)
Laboratory parameter[b]						
Alanine aminotransferase >3 times ULN	0/37	1/143 (0.7)	1/71 (1.4)	0/75	2/307 (0.7)	1/154 (0.6)
Aspartate aminotransferase >3 times ULN	0/36	1/143 (0.7)	0/71	1/75 (1.3)	4/307 (1.3)	2/154 (1.3)
Creatine kinase >3 times ULN	2/37 (5.4)	5/143 (3.5)	4/71 (5.6)	3/75 (4.0)	10/307 (3.3)	5/154 (3.2)

75Q2W, 75 mg every 2 weeks (with possible dose adjustment to 150 mg every 2 weeks); 300Q4W, 300 mg every 4 weeks (with possible dose adjustment to 150 mg every 2 weeks); CMQ, Custom Medical Dictionary of Regulatory Activities Query; SAE, serious adverse event; TEAE, treatment-emergent adverse event; ULN, upper limit of normal.

[a] Includes coronary heart disease death, non-fatal myocardial infarction, fatal and non-fatal ischemic stroke, unstable angina requiring hospitalization, congestive heart failure requiring hospitalization, and ischemia-driven coronary revascularization procedure.

[b] Regardless of baseline status.

statin: 110.0 mg/dL [2.8 mmol/L]). After dose adjustment, a more consistent level of reduction was achieved (highlighted by relatively stable LDL-C levels over Weeks 21–24), indicating that, while 300Q4W is effective for the majority of patients studied, irrespective of background statin use, the dosing strategy (i.e., Q4W *vs.* Q2W) could be tailored to suit the needs of the individual patient.

At Week 24, there was a strong and consistent response to treatment.

A similar proportion of patients receiving placebo and alirocumab with or without statin experienced treatment-emergent serious adverse events, or discontinued because of adverse events. The higher rate of injection-site reactions in the alirocumab 300Q4W groups *vs.* earlier ODYSSEY studies could potentially be attributed to patients receiving two 1 mL injections at each potential dosage administration Q2W in order to maintain the study blind (previous studies had one 1 mL injection at each administration). Of note, when examined on the basis of the number of injection-site reactions per double-blind injection, the rate of injection-site reactions observed in the current study (0.13–0.21 injection-site reactions per injection) is not dramatically different to the rates seen in other ODYSSEY studies (0.09–0.16 injection-site reactions per injection) [1,4]. There were no other specific safety findings associated with this dosing regimen. Due to the low number of patients with positive ADA responses and positive alirocumab-neutralizing antibody status, no definite conclusion can be made regarding the impact of immunogenicity on drug exposure. However, an overlapping of the reduction in LDL-C in anti-drug/neutralizing antibodies positive and negative patients was observed.

The results of this study suggest that an alirocumab 300Q4W regimen may provide an additional treatment option with or without concomitant statin for patients in need of LDL-C-lowering.

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Conflict of interest

Eli M. Roth: has received research grants, personal fees and non-financial support from Regeneron Pharmaceuticals Inc., and Sanofi.

Patrick M. Moriarty: has received grants from Amgen, Genzyme, Ionis, Regeneron Pharmaceuticals Inc., and Sanofi; personal fees from Amgen, Duke, Eliaz Therapeutics, Esperion, Genzyme, Ionis, Regeneron Pharmaceuticals Inc., and Sanofi.

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Gisle Langslet: has received personal fees from Amgen, Boehringer Ingelheim, Janssen Pharmaceuticals, and Sanofi.

Garen Manvelian: is an employee of Regeneron Pharmaceuticals, Inc.

Jian Zhao: is an employee of Regeneron Pharmaceuticals, Inc. (contractor).

Marie T. Baccara-Dinet: is an employee of Sanofi.

Daniel J. Rader: has received personal fees from Sanofi.

Clinical trial registration

NCT01926782; clinicaltrials.gov.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.atherosclerosis.2016.08.043.

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