A Phase 3 Study of Evolocumab (AMG 145) in Statin-Treated Japanese Patients at High Cardiovascular Risk

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Evolocumab (AMG 145), a fully human monoclonal antibody against PCSK9, significantly reduced low-density lipoprotein cholesterol (LDL-C) levels in phase 2 and 3 studies. This phase 3 study evaluated the efficacy and safety of evolocumab plus atorvastatin in Japanese patients with hyperlipidemia or mixed dyslipidemia and high cardiovascular risk. Patients were randomized to atorvastatin 5 or 20 mg/day for 4 weeks. Subsequently, patients underwent second randomization to evolocumab 140 mg biweekly (Q2W) or 420 mg monthly (QM) or placebo Q2W or QM. Coprimary end points were % change from baseline in LDL-C at week 12 and mean of weeks 10 and 12. Secondary end points included change and % change in other lipids and proportion of patients reaching LDL-C <70 mg/dl. Adverse events and laboratory values were recorded. Four hundred four patients were randomized to study drug. At baseline, the mean (SD) age was 61 (10) years (placebo) and 62 (11) years (evolocumab); 39% and 40% were women; 14% and 12% had cerebrovascular or peripheral arterial disease; and 51% and 47% had diabetes. At entry, mean (SD) calculated LDL-C was 128 (23) mg/dL; after stabilization on atorvastatin 5 and 20 mg/day, baseline LDL-C levels were 118 (35) and 94 (24) mg/dL, respectively. Mean LDL-C reductions at week 12 for evolocumab versus placebo ranged from 67% to 76%. No imbalances were observed in adverse events between treatment groups. Efficacy and safety for Q2W or QM evolocumab dosing were similar. In conclusion, in high-risk Japanese patients receiving stable statin therapy, evolocumab markedly reduced LDL-C and was well tolerated. **(Am J Cardiol 2016;117:40−47)**

Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a serine protease involved in the regulation of low-density lipoprotein (LDL) receptor expression. PCSK9 binds to the LDL receptor and targets it for destruction, leading to decreased LDL receptor expression and an increase in plasma LDL cholesterol (LDL-C).[1] Inhibiting PCSK9 with a monoclonal antibody reduced serum LDL-C levels in preclinical studies.[2−4] Evolocumab is a fully human monoclonal immunoglobulin G2 antibody against PCSK9 that markedly reduced serum LDL-C levels in phase 2 and 3 studies.[5−16] In the first phase 2 study reported of a PCSK9 inhibitor in patients in Japan, evolocumab plus background statin therapy reduced LDL-C levels by up to 69% from baseline versus placebo; favorable changes were seen in other lipid parameters, including lipoprotein (a) (Lp[a]) reductions of up to 51% versus placebo.[7] YUKAWA-2 (Study of LDL-Cholesterol Reduction Using a Monoclonal PCSK9 Antibody in Japanese Patients With Advanced Cardiovascular Risk; NCT01953328) is the first phase 3 and largest clinical study to date of a PCSK9 inhibitor in Japan. The primary objective of the study was to evaluate the efficacy of 12 weeks of subcutaneous evolocumab administered biweekly (Q2W) or monthly (QM) in combination with atorvastatin in Japanese patients with hyperlipidemia or mixed dyslipidemia and at high cardiovascular (CV) risk.

Methods

Eligible patients (aged ≥20 and ≤85 years) from study sites in Japan were at high risk for CV events based on Japan Atherosclerosis Society (JAS) criteria.[17] JAS criteria used for high-risk classification can be found in the Supplementary Data. Patients were required to be on a stable dose of an approved statin for ≥4 weeks before LDL-C screening without need for uptitration; use of any other lipid-lowering therapy had to be unchanged within 4 weeks before LDL-C screening. At screening (before randomization to study-specified background statin therapy), fasting LDL-C level was required to be ≥100 mg/dl (2.6 mmol/L), and fasting triglyceride level was required to be ≤400 mg/dl (4.5 mmol/L). Key exclusion criteria can be found in the Supplementary Data. Independent ethics committees at each

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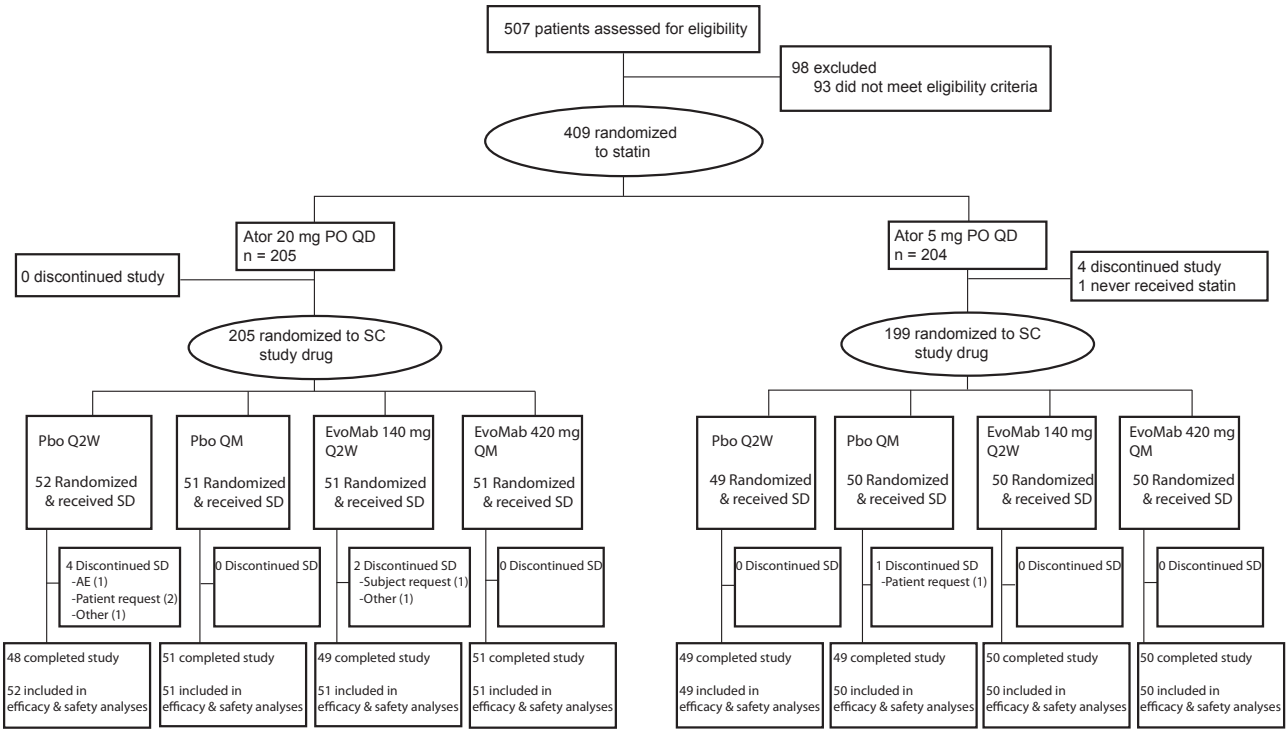

Figure 1. Patient disposition. Ator = atorvastatin; EvoMab = evolocumab; Pbo = placebo; PO = per oral; QD = daily; SC = subcutaneous; SD = study drug.

study site approved the protocol, and all patients provided written informed consent before initiation of study-specific procedures.

Before randomization, all eligible patients underwent a placebo run-in period (3 placebo injections) to confirm tolerance of subcutaneous injections. Patients were then randomized 1:1 to 1 of 2 atorvastatin treatment groups consistent with low (5 mg/day) and high (20 mg/day) statin doses used in clinical practice in participating regions. After successful completion of a 4-week lipid stabilization period, patients in each atorvastatin dose cohort were further randomized 1:1:1:1 to 1 of 4 treatment groups: placebo Q2W, placebo QM, evolocumab 140 mg Q2W, or evolocumab 420 mg QM. Patients were randomized to atorvastatin therapy in 3 strata: patients diagnosed with heterozygous familial hypercholesterolemia (HeFH); patients without HeFH receiving intensive lipid-lowering therapy (defined according to local treatment practices as atorvastatin $\geq$10 mg/day or equivalent); and patients without HeFH receiving non-intensive lipid-lowering therapy. Patients, investigators, and study site personnel were blinded to treatment.

The co-primary efficacy end points were the mean % change from baseline in LDL-C at week 12 (end of study) and the mean % change from baseline in LDL-C at weeks 10 and 12 (time-averaged reduction in LDL-C). Secondary end points included the mean change from baseline at weeks 10 and 12 and at week 12 in LDL-C; the mean % change from baseline at weeks 10 and 12 and at week 12 in other lipids, including apolipoprotein B (ApoB); achievement of LDL-C $<$70 mg/dl; and % change from baseline in Lp(a), triglycerides, high-density lipoprotein cholesterol (HDL-C), and very-low-density lipoprotein cholesterol. When calculated LDL-C was $<$40 mg/dl or triglyceride was $>$400 mg/dl, a value from the same blood sample measured through preparative ultracentrifugation was used, if available.

A sample size of 45 patients in each of the 8 treatment groups was calculated to provide $>$90% power to detect the treatment effect (30% reduction in LDL-C with a common SD of 30%) of evolocumab compared with placebo. For the coprimary end points, a repeated measures linear effects model was used for each atorvastatin dose cohort and dose frequency to compare the efficacy of evolocumab with placebo. The repeated measures model included terms for treatment group, stratification factor, scheduled visit, and interaction of treatment with scheduled visit. No imputation of missing data was performed for the repeated measures linear effects model. Analyses for the secondary end points were adjusted for multiplicity conditional on the primary end point meeting statistical significance. The secondary end point of LDL-C response at week 12 was analyzed using the Cochran−Mantel Haenszel test adjusted by stratification factor. Safety outcomes included the incidences of treatment-emergent adverse events (AEs) and serious AEs (SAEs), treatment-related AEs, AEs leading to discontinuation of investigational product, and laboratory parameters. AEs were coded using the Medical Dictionary for Regulatory Activities, version 17.0, and graded by severity using the Common Terminology for Adverse Events (CTCAE), version 4.3. Laboratory analyses were based on CTCAE, version 4, toxicity criteria.

Results

In total, 507 patients were screened for the study and 409 were randomized to 1 of 2 atorvastatin doses (5 mg/day or 20 mg/day). All patients were able to tolerate the 3 placebo

Table 1
Demographics, baseline risk factors, and lipid parameters

Variable	Placebo + Atorvastatin N = 202	Evolocumab + Atorvastatin N = 202
Age (years, mean ± SD)	61 ± 10	62 ± 11
Women	79 (39%)	81 (40%)
Coronary artery disease	22 (11%)	30 (15%)
Peripheral arterial disease or cerebrovascular disease	29 (14%)	25 (12%)
Hypertension	145 (72%)	152 (75%)
Elevated waist circumference	138 (68%)	138 (68%)
Current smoker	52 (26%)	46 (23%)
Heterozygous familial hypercholesterolemia	11 (5%)	13 (6%)
Simon-Broome	5 (3%)	3 (2%)
Other*	6 (3%)	10 (5%)
Type 2 diabetes mellitus	103 (51%)	94 (47%)
Metabolic syndrome†	57 (28%)	54 (27%)
≥ 2 cardiovascular risk factors	117 (58%)	113 (56%)
LDL-C (mg/dL, mean ± SD)‡	103 ± 28	109 ± 35
Lipoprotein (a) (nmol/L, median [Q1, Q3])‡	31 (12, 50)	34 (14, 61)
HDL-C (mg/dL,mean ± SD)‡	58 ± 14	56 ± 14
Triglycerides (mg/dL, median [Q1, Q3])‡	127 (91, 168)	118 (92,155)
Apolipoprotein B (mg/dL, mean ± SD)‡	92 ± 20	96 ± 25
PCSK9 (ng/mL, mean [SD]) ‡	356 (99)	362 (100)

All demographics and baseline risk factors are given as n (%) unless indicated otherwise.

HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; PCSK9 = proprotein convertase subtilisin/kexin type 9; Q1 = first quartile; Q3 = third quartile.

* Japanese definition based on criteria from Harada-Shiba et al 2012 (reference 43).

† Metabolic syndrome was defined as 3 or more risk factors (elevated waist circumference, elevated systolic blood pressure or diastolic blood pressure, elevated fasting glucose, elevated triglycerides, and/or low HDL-C) and without diabetes mellitus.

‡ Collected after the lipid-stabilization period and before administration of first dose of study drug.

injections given to assess tolerability (none failed to enter the study because of intolerance of placebo injections). A total of 404 patients successfully completed the 4-week lipid stabilization period and were subsequently randomized and received study drug (Figure 1). The first patient enrolled on October 7, 2013, and the last patient last visit was June 25, 2014. In general, baseline patient characteristics were balanced between the placebo and evolocumab treatment groups (Table 1). To be eligible for participation in this study, all patients were required to be at high CV risk based on local guidelines. Patients most often satisfied this criteria by having diabetes, possessing 2 or more CV risk factors (such as advanced age, hypertension, or smoking history) or by being a secondary prevention patient. At baseline, half of patients had a diagnosis of type 2 diabetes mellitus and one quarter had a diagnosis of metabolic syndrome. Twenty-eight percent of placebo-treated and 37% of evolocumab-treated patients with metabolic syndrome at baseline had elevated fasting plasma glucose (≥110 mg/dl). Study eligibility criteria required all patients to have received stable statin therapy (defined as ≥4 weeks) at home. At screening, 100% of patients were on a statin. The mean (SD) LDL-C level before the initiation of treatment with study-provided atorvastatin was 128 (23) mg/dl. In patients randomized to background atorvastatin 5 mg/day, the mean (SD) baseline LDL-C at the end of the lipid stabilization period but before study drug administration was 115 (28) mg/dl in the placebo group and 120 (41) mg/dl in the evolocumab group. In patients on background atorvastatin 20 mg/day, the corresponding values were 91 (23) mg/dl in the placebo group and 97 (25) mg/dl in the evolocumab group.

At week 12, evolocumab reduced LDL-C by ≥67% versus placebo in all evolocumab treatment groups, with mean reductions ranging from 67% to 76% (Table 2; Figure 2). Reductions in LDL-C at the time-averaged mean of weeks 10 and 12 were comparable with those observed at week 12 (data not shown). Efficacy in the 140-mg Q2W and 420-mg QM doses was comparable; reductions were also comparable between patient subgroups, including age, gender, body mass index (BMI), type 2 diabetes mellitus, and metabolic syndrome (Supplementary Figure S1).

The median (first quartile, third quartile) achieved LDL-C level at week 12 for patients receiving evolocumab plus atorvastatin was 28 (20, 40) mg/dl and for patients receiving placebo plus atorvastatin was 97 (83, 115) mg/dl. The 2012 JAS guidelines recommend LDL-C <120 or <100 mg/dl for patients at high risk or secondary prevention, respectively.[17] In patients receiving placebo plus atorvastatin, 29% on Q2W placebo plus atorvastatin 5 mg/day and 42% on QM placebo plus atorvastatin 5 mg/day reached an LDL-C <100 mg/day. Most patients receiving placebo plus atorvastatin 20 mg/day were able to achieve an LDL-C <100 mg/dl (59% placebo Q2W and 88% placebo QM). Few patients were able to achieve a more aggressive target LDL-C of <70 mg/dl on placebo plus atorvastatin therapy (0% placebo Q2W plus atorvastatin 5 mg/day and 4% placebo QM plus atorvastatin 5 mg/day; 20% placebo Q2W plus atorvastatin 20 mg/day and 20% placebo QM plus atorvastatin 20 mg/day). In contrast, 100% of patients treated with evolocumab achieved an LDL-C <100 mg/dl, and almost all achieved an LDL-C level <70 mg/dl, regardless of atorvastatin dose (Table 2, Figure 3).

Favorable changes were observed in other lipid parameters at week 12 in the evolocumab treatment groups (Table 2; Figure 4) with results being similar to the time-averaged mean of weeks 10 and 12 (data not shown). The changes were comparable between 140-mg Q2W and 420-mg QM doses. Across evolocumab treatment groups, the mean (SE) treatment differences versus placebo at week 12 ranged from −56% (2%) to −66% (2%) for apolipoprotein B; 10% (3%) to 17% (3%) for HDL-C; and −40% (5%) to −53% (6%) for Lp(a).

AEs were comparable between patients receiving placebo and those receiving evolocumab (Table 3) without notable differences seen between patients receiving 140-mg Q2W or 420-mg Q2W (data not shown). Patients demonstrated similar rates of discontinuation and AEs (including injection site reactions) across all placebo and evolocumab treatment

Table 2
Efficacy at week 12

Variable	Evolocumab + Atorvastatin 5 mg/d		Evolocumab + Atorvastatin 20 mg/d	
	Q2W (N = 50)	QM (N = 50)	Q2W (N = 51)	QM (N = 51)
LS mean (SE) treatment difference versus placebo + atorvastatin				
Low-density lipoprotein cholesterol	−74.9% (2.7)*	−69.9% (2.4)*	−75.9% (3.9)*	−66.9% (3.0)*
Apolipoprotein B	−65.6% (2.4)*	−57.2% (2.4)*	−60.4% (2.8)*	−56.2% (2.4)*
High-density lipoprotein cholesterol	13.5% (3.1)*	15.2% (2.7)*	16.9% (3.1)*	10.2% (2.7)*
Lipoprotein (a)	−50.1% (7.6)*	−48.8% (5.9)*	−52.7% (5.7)*	−40.0% (5.3)*
Triglycerides	−27.6% (9.5)†	−20.0% (5.9)*	−17.2% (5.5)†	−16.9% (7.2)‡
Apolipoprotein A1	7.3% (2.4)†	8.9% (2.2)*	9.1% (2.4)*	8.6% (2.3)*
Achieved low-density lipoprotein cholesterol				
Median (Q1, Q3) Achieved LDL-C, mg/dL	26.0 (16.0, 40.0)	36.0 (29.0, 43.0)	24.5 (18.0, 34.0)	26.0 (20.0, 38.0)
Low-density lipoprotein cholesterol < 70 mg/dL, % patients§	98.0%	96.0%	96.0%	98.0%

LDL-C = low-density lipoprotein cholesterol; LS = least squares; Q1 = first quartile; Q2W = biweekly; Q3 = third quartile; QM = monthly.
* p <0.001.
† p <0.01.
‡ p <0.05.
§ At week 12, in patients receiving 5 mg/day atorvastatin, 0% placebo Q2W and 4% placebo QM reached LDL-C < 70; in patients receiving 20 mg/day atorvastatin, 20% placebo Q2W and 20% placebo QM reached LDL-C < 70.

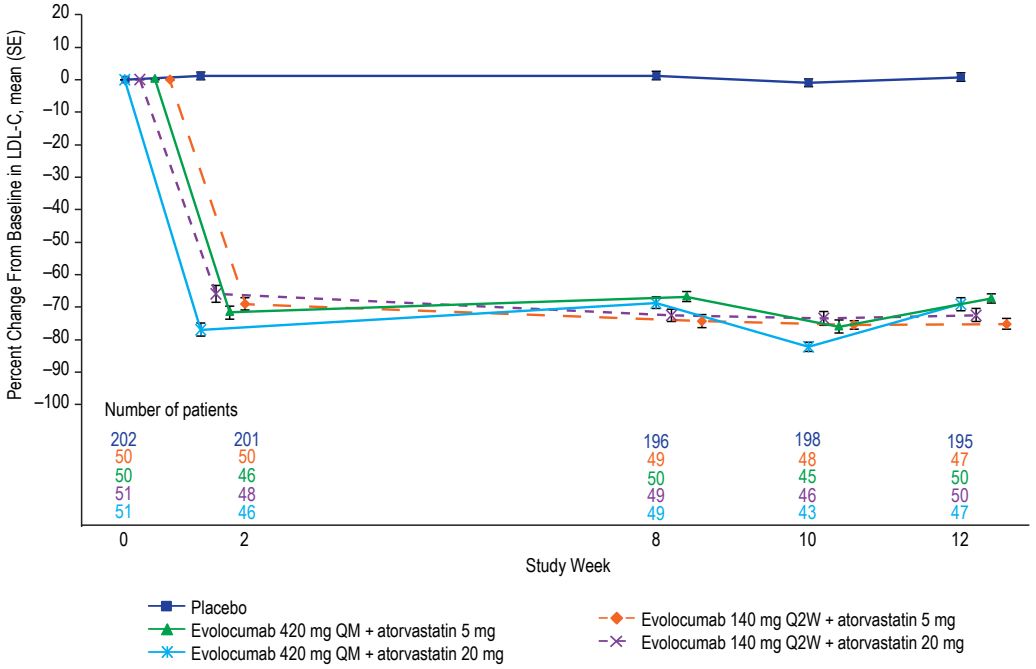

Figure 2. Mean % change from baseline to week 12 in calculated LDL-C. Results are shown for patients receiving placebo *(purple squares)*, evolocumab 420 mg QM + atorvastatin 5 mg *(green triangles)*, evolocumab 420 mg QM + atorvastatin 20 mg *(blue stars)*, evolocumab 140 mg Q2W + atorvastatin 5 mg *(orange diamonds)*, and evolocumab 140 mg Q2W + atorvastatin 20 mg *(purple crosses)*.

groups, suggesting good tolerability of both Q2W and QM dosing regimens. The most common AEs occurring in ≥2% of patients in any treatment group are listed in Table 3. SAEs were infrequent in both groups. One placebo-treated patient discontinued study drug because of an SAE (brain stem infarction). Transaminase and creatine kinase elevations were infrequent (Table 3). Few patients experienced injection site reactions; all were mild, CTCAE grade 1 (Table 3). One patient treated with evolocumab with a negative or no result at baseline was found to have an antievolocumab-binding antibody (Table 3); this patient completed the study and had 3 nonserious AEs of upper respiratory tract infection (twice) and herpes labialis (once); none was deemed related to evolocumab. No patient reported neurocognitive AEs. Changes at week 12 in fasting plasma glucose and glycated hemoglobin (HbA_{1c}) were not notably different in patients receiving evolocumab versus those receiving placebo (Supplementary Table S1). In addition, rates of AEs and laboratory abnormalities were comparable between patients with low LDL-C (<15 mg/dl, <25 mg/dl or <40 mg/dl; all patients in these groups were treated with evolocumab) and those with higher LDL-C

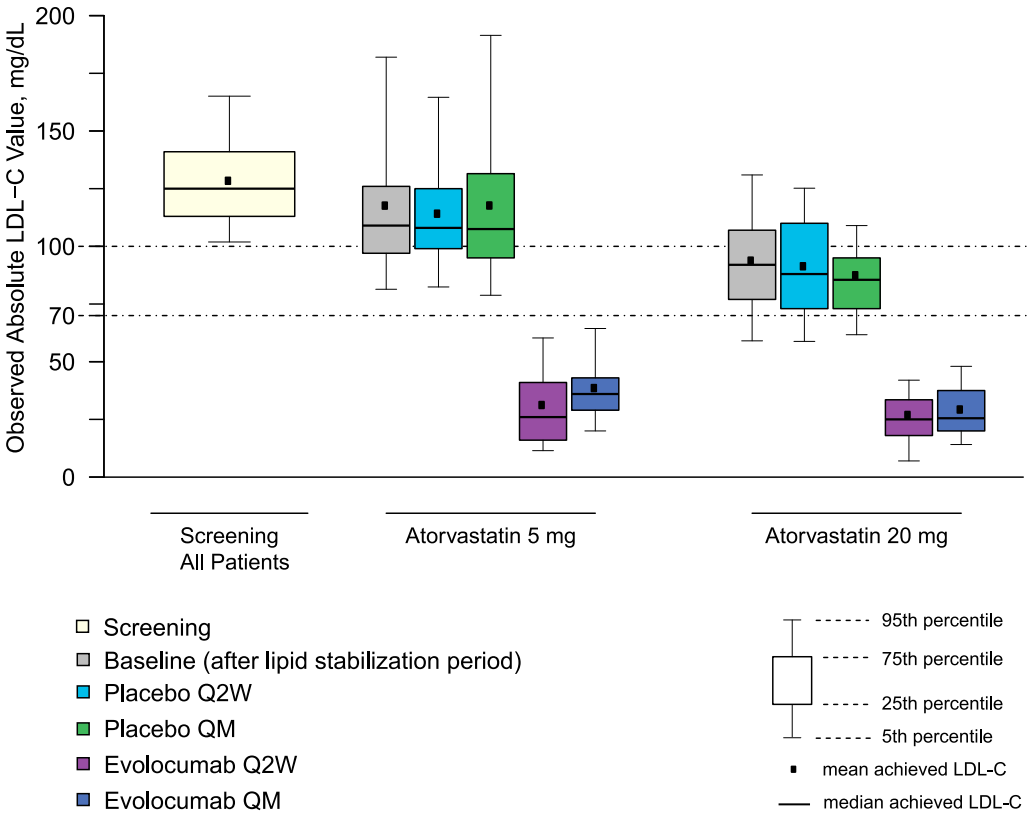

Figure 3. LDL-C at screening, baseline, and week 12 according to treatment group.

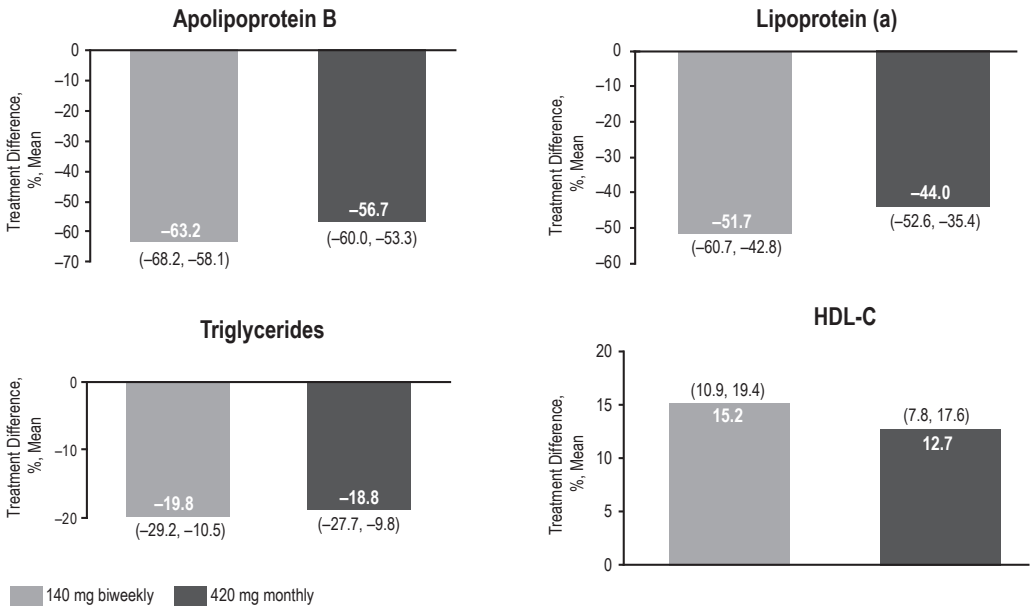

Figure 4. Mean % change from baseline versus placebo in other lipids at week 12 in patients receiving evolocumab 140-mg Q2W or 420-mg QM. Numbers in parenthesis indicate 95% confidence intervals.

(≥40 mg/dl; all placebo patients and 11 patients treated with evolocumab; Supplementary Table S2).

Discussion

In this study, Japanese patients at high risk for CV disease according to JAS criteria who were treated with Q2W or QM evolocumab in combination with background atorvastatin showed marked reductions in LDL-C at week 12 compared with patients receiving atorvastatin plus placebo. These reductions (67% to 76%) fall within the range of those observed in LAPLACE-2 (55% to 76% vs placebo in patients treated with 140 mg Q2W or 420 mg QM evolocumab)[13] and are also consistent with those observed in

Table 3
Safety

n (%)	Atorvastatin + Placebo (N = 202)	Atorvastatin + Evolocumab (N = 202)
Adverse events	103 (51.0%)	94 (46.5%)
Most common adverse events*		
Nasopharyngitis	36 (17.8%)	34 (16.8%)
Gastroenteritis	2 (1.0%)	6 (3.0%)
Pharyngitis	5 (2.5%)	5 (2.5%)
Bronchitis	3 (1.5%)	4 (2.0%)
Diabetes mellitus	4 (2.0%)†	4 (2.0%)†
Serious adverse events	5 (2.5%)	1 (0.5%)‡
Leading to study drug discontinuation	1 (0.5%)§	0
Positively adjudicated cardiovascular events	1 (0.5%)‖	0
Creatine kinase > 5 x ULN at any postbaseline visit	1 (0.5%)	0
ALT or AST > 3 x ULN at any postbaseline visit	2 (1.0%)	1 (0.5%)
Potential injection-site reactions	5 (2.5%)	5 (2.5%)
Potential muscle events	2 (1%)	1 (0.5%)
Neurocognitive adverse events¶	0	0
Binding antibodies#	0	1 (0.5%)

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal.

* Top 5 AEs reported by ≥2% of patients in any treatment group.

† All 4 patients treated with placebo and 3 patients treated with evolocumab had type 2 diabetes at baseline and reported worsening of preexisting diabetes. One patient treated with evolocumab did not have type 2 diabetes at baseline and subsequently developed type 2 diabetes.

‡ Bacterial pneumonia.

§ Brain stem infarction.

‖ Nonfatal ischemic stroke.

¶ Neurocognitive adverse events were self-reported. Searched High Level Group Terms related to cognitive function were deliria (including confusion), cognitive and attention disorders and disturbances, dementia and amnesic conditions, disturbances in thinking and perception, and mental impairment disorders.

Postbaseline binding antibody positive, with a negative or no result at baseline. No neutralizing antibodies were detected.

a phase 2 statin combination-therapy study in Japan (64% and 69% for evolocumab 140 mg Q2W and 420 mg QM, respectively).[7] The range of effect in YUKAWA-2 suggests modestly greater LDL-C reductions with less variability. The reasons for this difference is not clear; however, it does not appear to be explained by factors such as background statin use, baseline LDL-C or PCSK9 levels, or adherence to therapy while on study. The response was consistent across a number of subgroups, including in patients with type 2 diabetes mellitus and patients with metabolic syndrome, suggesting that evolocumab has a consistent effect in patient populations at high risk.

At week 12, evolocumab treatment Q2W or QM also resulted in beneficial changes in other lipids, including reductions in Lp(a) and increases in HDL-C. Lp(a) reductions (40% to 53% compared with atorvastatin + placebo) were greater than those observed in LAPLACE-2 (20% to 36% compared with control).[13] LAPLACE-2 and YUKAWA-2 demonstrated similar baseline Lp(a), LDL-C, and PCSK9 levels, but the lower LDL-C levels achieved in YUKAWA-2 could partially explain the greater Lp(a) reduction seen in this study. The mode of clearance of Lp(a)[18] and the mechanism by which PCSK9 inhibition reduces Lp(a) remain to be fully elucidated. However, a recent study suggests that plasma Lp(a) and LDL particles compete for uptake by the LDL receptor.[19] The lower achieved LDL-C levels at week 12 (31 mg/dl in YUKAWA-2 and 44 mg/dl in LAPLACE-2) would theoretically signal increased LDL receptor availability. This, in combination with increased LDL receptor availability due to PCSK9 inhibition, may partly explain the greater Lp(a) reduction observed in YUKAWA-2, as there would be fewer LDL particles to compete with Lp(a), thereby resulting in more Lp(a) clearance. This effect, a unique feature of therapies inhibiting PCSK9[20] is potentially important as elevations in Lp(a) are associated with coronary heart disease risk independent of LDL-C levels.[21]

Evolocumab also increased HDL-C by 10% to 17%. The mechanism by which PCSK9 inhibition increases HDL-C is not known, but one possible explanation is that through reduction in LDL-C, cholesteryl ester transfer protein activity is reduced, as a decrease in LDL-C levels would mean less LDL-C available to receive cholesterol from HDL particles (thus, indirectly raising the level of HDL-C). At least one study has shown that changes in HDL-C are associated with corresponding changes in HDL particle number.[22] A direct increase in ApoA1 or HDL is also possible. An increase in HDL-C may be therapeutically beneficial as HDLs have been shown to reduce the risk for CV disease, although questions remain regarding the use of HDL-C as a biomarker.[23]

Evolocumab was well tolerated, with no notable imbalances in AEs observed between treatment groups, including patients achieving very low versus higher LDL-C levels. No neurocognitive AEs were noted in YUKAWA-2, consistent with the low incidence observed in other, longer term evolocumab studies.[24] Roughly half of patients had type 2 diabetes mellitus and a quarter had metabolic syndrome (with no diabetes) at baseline; despite this, the AE profile for evolocumab was favorable, with no notable differences in AEs of diabetes, fasting glucose, or HbA_{1c} between treatment groups.

Statin therapy has been shown in global studies to reduce the incidence of CV events by 20% for every 1-mmol/L reduction in LDL-C.[25] Reduction of LDL-C can reduce CV events regardless of mechanism.[26–29] The recently completed IMPROVE-IT study, which compared simvastatin plus ezetimibe versus simvastatin alone in >18,000 patients, showed that LDL-C reduction beyond that provided by statin therapy further reduces the likelihood of CV events; this effect was not counterbalanced by safety concerns even with lower achieved LDL-C levels.[27] The potential benefits of non−statin-mediated LDL-C reduction are also supported by a recent analysis of exploratory CV end points in 4,465 patients receiving evolocumab for 1 year, which demonstrated a statistically significant reduction in adjudicated CV events in patients receiving study drug versus those receiving standard therapy.[24] Similar results have been reported for another PCSK9 inhibitor, alirocumab.[30] Thus, PCSK9 inhibition may be an effective tool for reducing LDL-C in patients at high risk receiving statin therapy who require additional LDL-C reduction. An ongoing, large, randomized, placebo-controlled study of evolocumab added to

effective statin therapy (FOURIER; NCT01764633) will evaluate the long-term effects of evolocumab treatment on patient outcomes.

Limitations of this study included the 12-week treatment duration for the assessment of safety, tolerability, and sustained duration of LDL-C reduction. In addition, this study incorporated nonintensive (atorvastatin, 5 mg/day) and intensive (atorvastatin, 20 mg/day) statin use, representative of standard practice in Japan, which is more conservative than that in other global regions. This could affect the ability to compare these results with those of global studies.

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Disclosures

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Supplementary Data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.amjcard.2015.10.021.

1. Horton JD, Cohen JC, Hobbs HH. Molecular biology of PCSK9: its role in LDL metabolism. *Trends Biochem Sci* 2007;32:71−77.
2. Chan JC, Piper DE, Cao Q, Liu D, King C, Wang W, Tang J, Liu Q, Higbee J, Xia Z, Di Y, Shetterly S, Arimura Z, Salomonis H, Romanow WG, Thibault ST, Zhang R, Cao P, Yang XP, Yu T, Lu M, Retter MW, Kwon G, Henne K, Pan O, Tsai MM, Fuchslocher B, Yang E, Zhou L, Lee KJ, Daris M, Sheng J, Wang Y, Shen WD, Yeh WC, Emery M, Walker NP, Shan B, Schwarz M, Jackson SM. A proprotein convertase subtilisin/kexin type 9 neutralizing antibody reduces serum cholesterol in mice and nonhuman primates. *Proc Natl Acad Sci U S A* 2009;106:9820−9825.
3. Ni YG, Condra JH, Orsatti L, Shen X, Di Marco S, Pandit S, Bottomley MJ, Ruggeri L, Cummings RT, Cubbon RM, Santoro JC, Ehrhardt A, Lewis D, Fisher TS, Ha S, Njimoluh L, Wood DD, Hammond HA, Wisniewski D, Volpari C, Noto A, Lo Surdo P, Hubbard B, Carfi A, Sitlani A. A proprotein convertase subtilisin-like/kexin type 9 (PCSK9) C-terminal domain antibody antigen-binding fragment inhibits PCSK9 internalization and restores low density lipoprotein uptake. *J Biol Chem* 2010;285:12882−12891.
4. Zhang L, McCabe T, Condra JH, Ni YG, Peterson LB, Wang W, Strack AM, Wang F, Pandit S, Hammond H, Wood D, Lewis D, Rosa R, Mendoza V, Cumiskey AM, Johns DG, Hansen BC, Shen X, Geoghagen N, Jensen K, Zhu L, Wietecha K, Wisniewski D, Huang L, Zhao JZ, Ernst R, Hampton R, Haytko P, Ansbro F, Chilewski S, Chin J, Mitnaul LJ, Pellacani A, Sparrow CP, An Z, Strohl W, Hubbard B, Plump AS, Blom D, Sitlani A. An anti-PCSK9 antibody reduces LDL-cholesterol on top of a statin and suppresses hepatocyte SREBP-regulated genes. *Int J Biol Sci* 2012;8:310−327.
5. Blom DJ, Hala T, Bolognese M, Lillestol MJ, Toth PD, Burgess L, Ceska R, Roth E, Koren MJ, Ballantyne CM, Monsalvo ML, Tsirtsonis K, Kim JB, Scott R, Wasserman SM, Stein EA; DESCARTES Investigators. A 52-week placebo-controlled trial of evolocumab in hyperlipidemia. *N Engl J Med* 2014;370:1809−1819.
6. Giugliano RP, Desai NR, Kohli P, Rogers WJ, Somaratne R, Huang F, Liu T, Mohanavelu S, Hoffman EB, McDonald ST, Abrahamsen TE, Wasserman SM, Scott R, Sabatine MS; LAPLACE-TIMI 57 Investigators. Efficacy, safety, and tolerability of a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 in combination with a statin in patients with hypercholesterolaemia (LAPLACE-TIMI 57): a randomised, placebo-controlled, dose-ranging, phase 2 study. *Lancet* 2012;380:2007−2017.
7. Hirayama A, Honarpour N, Yoshida M, Yamashita S, Huang F, Wasserman SM, Teramoto T. Effects of evolocumab (AMG 145), a monoclonal antibody to PCSK9, in hypercholesterolemic, statin-treated Japanese patients at high cardiovascular risk−primary results from the phase 2 YUKAWA study. *Circ J* 2014;78:1073−1082.
8. Koren MJ, Lundqvist P, Bolognese M, Neutel JM, Monsalvo ML, Yang J, Kim JB, Scott R, Wasserman SM, Bays H; MENDEL-2 Investigators. Anti-PCSK9 monotherapy for hypercholesterolemia: the MENDEL-2 randomized, controlled phase III clinical trial of evolocumab. *J Am Coll Cardiol* 2014;63:2531−2540.
9. Koren MJ, Scott R, Kim JB, Knusel B, Liu T, Lei L, Bolognese M, Wasserman SM. Efficacy, safety, and tolerability of a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 as monotherapy in patients with hypercholesterolaemia (MENDEL): a randomised, double-blind, placebo-controlled, phase 2 study. *Lancet* 2012;380:1995−2006.
10. Raal F, Scott R, Somaratne R, Bridges I, Li G, Wasserman SM, Stein EA. Low-density lipoprotein cholesterol-lowering effects of AMG 145, a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 serine protease in patients with heterozygous familial hypercholesterolemia: the Reduction of LDL-C with PCSK9 Inhibition in Heterozygous Familial Hypercholesterolemia Disorder (RUTHERFORD) randomized trial. *Circulation* 2012;126:2408−2417.
11. Raal FJ, Honarpour N, Blom DJ, Hovingh GK, Xu F, Scott R, Wasserman SM, Stein EA; TESLA Investigators. Inhibition of PCSK9 with evolocumab in homozygous familial hypercholesterolaemia

(TESLA Part B): a randomised, double-blind, placebo-controlled trial. *Lancet* 2015;385:341−350.
12. Raal FJ, Stein EA, Dufour R, Turner T, Civeira F, Burgess L, Langslet G, Scott R, Olsson AG, Sullivan D, Hovingh GK, Cariou B, Gouni-Berthold I, Somaratne R, Bridges I, Scott R, Wasserman SM, Gaudet D; RUTHERFORD-2 Investigators. PCSK9 inhibition with evolocumab (AMG 145) in heterozygous familial hypercholesterolaemia (RUTHERFORD-2): a randomised, double-blind, placebo-controlled trial. *Lancet* 2015;385:331−340.
13. Robinson JG, Nedergaard BS, Rogers WJ, Fialkow J, Neutel JM, Ramstad D, Somaratne R, Legg JC, Nelson P, Scott R, Wasserman SM, Weiss R; LAPLACE-2 Investigators. Effect of evolocumab or ezetimibe added to moderate- or high-intensity statin therapy on LDL-C lowering in patients with hypercholesterolemia: the LAPLACE-2 randomized clinical trial. *JAMA* 2014;311:1870−1882.
14. Stein EA, Honarpour N, Wasserman SM, Xu F, Scott R, Raal FJ. Effect of the proprotein convertase subtilisin/kexin 9 monoclonal antibody, AMG 145, in homozygous familial hypercholesterolemia. *Circulation* 2013;128:2113−2120.
15. Stroes E, Colquhoun D, Sullivan D, Civeira F, Rosenson RS, Watts GF, Bruckert E, Cho L, Dent R, Knusel B, Xue A, Scott R, Wasserman SM, Rocco M; GAUSS-2 Investigators. Anti-PCSK9 antibody effectively lowers cholesterol in patients with statin intolerance: the GAUSS-2 randomized, placebo-controlled phase 3 clinical trial of evolocumab. *J Am Coll Cardiol* 2014;63:2541−2548.
16. Sullivan D, Olsson AG, Scott R, Kim JB, Xue A, Gebski V, Wasserman SM, Stein EA. Effect of a monoclonal antibody to PCSK9 on low-density lipoprotein cholesterol levels in statin-intolerant patients: the GAUSS randomized trial. *JAMA* 2012;308:2497−2506.
17. Teramoto T, Sasaki J, Ishibashi S, Birou S, Daida H, Dohi S, Egusa G, Hiro T, Hirobe K, Iida M, Kihara S, Kinoshita M, Maruyama C, Ohta T, Okamura T, Yamashita S, Yokode M, Yokote K. Executive summary of the Japan Atherosclerosis Society (JAS) guidelines for the diagnosis and prevention of atherosclerotic cardiovascular diseases in Japan—2012 version. *J Atheroscler Thromb* 2013;20:517−523.
18. Nordestgaard BG, Chapman MJ, Ginsberg HN. Lipoprotein(a): EAS recommendations for screening, desirable levels and management: A Handbook for Clinicians. Warwickshire, UK: Sherborne Gibbs Ltd, 2012.
19. Romagnuolo R, Scipione C, Boffa MB, Marcovina SM, Seidah NG, Koschinsky ML. Lipoprotein(a) catabolism is regulated by proprotein convertase subtilisin/kexin type 9 through the low density lipoprotein receptor. *J Biol Chem* 2015;290:11649−11662.
20. Raal FJ, Giugliano RP, Sabatine MS, Koren MJ, Langslet G, Bays H, Blom D, Eriksson M, Dent R, Wasserman SM, Huang F, Xue A, Albizem M, Scott R, Stein EA. Reduction in lipoprotein (a) with PCSK9 monoclonal antibody evolocumab (AMG 145): a pooled analysis of more than 1,300 patients in 4 phase II trials. *J Am Coll Cardiol* 2014;63:1278−1288.
21. Sharrett AR, Ballantyne CM, Coady SA, Heiss G, Sorlie PD, Catellier D, Patsch W. Coronary heart disease prediction from lipoprotein cholesterol levels, triglycerides, lipoprotein(a), apolipoproteins A-I and B, and HDL density subfractions: the atherosclerosis risk in communities (ARIC) study. *Circulation* 2001;104:1108−1113.
22. Xu R, Peach M, Tracy M, Hamilton L, Djedjos S, Dent R, Fitzpatrick D, Scott R, Wasserman SM. Effects of evolocumab (AMG 145) as a monotherapy or in combination with statins on lipoprotein particles and subclasses. *Circulation* 2014;130:A16955.
23. Santos-Gallego CG, Badimon JJ, Rosenson RS. Beginning to understand high-density lipoproteins. *Endocrinol Metab Clin North Am* 2014;43:913−947.
24. Sabatine MS, Giugliano RP, Wiviott SD, Raal FJ, Blom DJ, Robinson J, Ballantyne CM, Somaratne R, Legg J, Wasserman SM, Scott R, Koren MJ, Stein EA; Open-Label Study of Long-Term Evaluation against LDL Cholesterol Investigators. Efficacy and safety of evolocumab in reducing lipids and cardiovascular events. *N Engl J Med* 2015;372:1500−1509.
25. Cholesterol Treatment Trialists (CTT) Collaboration. Baigent C, Blackwell L, Emberson J, Holland L, Reith C, Bhala N, Peto R, Barnes E, Keech A, Simes J, Collins R. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet* 2010;376:1670−1681.
26. Buchwald H, Varco RL, Matts JP, Long JM, Fitch LL, Campbell GS, Pearce MB, Yellin AE, Edmiston WA, Smink RD Jr, Sawin HS, Campos CT, Hansen BJ, Tuna N, Karnegis JN, Sanmarco ME, Amplatz K, Castaneda-Zuniga WR, Hunter DW, Bissett JK, Weber FJ, Stevenson JW, Leon AS, Chalmers TC; POSCH Group. Effect of partial ileal bypass surgery on mortality and morbidity from coronary heart disease in patients with hypercholesterolemia. Report of the Program on the Surgical Control of the Hyperlipidemias (POSCH). *N Engl J Med* 1990;323:946−955.
27. Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, Darius H, Lewis BS, Ophuis TO, Jukema JW, De Ferrari GM, Ruzyllo W, De Lucca P, Im K, Bohula EA, Reist C, Wiviott SD, Tershakovec AM, Musliner TA, Braunwald E, Califf RM; IMPROVE-IT Investigators. Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med* 2015;372:2387−2397.
28. US Department of Health and Human Services. Lipid Research Clinics Manual of Laboratory Operations. Lipid and Lipoprotein Analysis (Revised). Department of Health and Human Services Publication (NIH) #75−67815. Washington, DC: Government Printing Office, 1982.
29. Stone NJ, Robinson J, Lichtenstein AH, Merz CN, Blum CB, Eckel RH, Goldberg AC, Gordon D, Levy D, Lloyd-Jones DM, McBride P, Schwartz JS, Shero ST, Smith SC Jr, Watson K, Wilson PW, Eddleman KM, Jarrett NM, LaBresh K, Nevo L, Wnek J, Anderson JL, Halperin JL, Albert NM, Bozkurt B, Brindis RG, Curtis LH, DeMets D, Hochman JS, Kovacs RJ, Ohman EM, Pressler SJ, Sellke FW, Shen WK, Smith SCJ, Tomaselli GF; American College of Cardiology/American Heart AssociationTask Force on Practice Guidelines. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association task force on practice guidelines. *Circulation* 2014;125:S1−S45.
30. Robinson JG, Farnier M, Krempf M, Bergeron J, Luc G, Averna M, Stroes ES, Langslet G, Raal FJ, Shahawy ME, Koren MJ, Lepor NE, Lorenzato C, Pordy R, Chaudhari U, Kastelein JJ; ODYSSEY LONG TERM Investigators. Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. *N Engl J Med* 2015;372:1489−1499.