ORIGINAL RESEARCH

Effect of Evolocumab on Non-High-Density Lipoprotein Cholesterol, Apolipoprotein B, and Lipoprotein(a): A Pooled Analysis of Phase 2 and Phase 3 Studies

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***Background*—**Dyslipidemia guidelines recommend non-high-density lipoprotein cholesterol (non-HDL-C) and apolipoprotein B (ApoB) as additional targets of therapy and consider lipoprotein(a) a significant cardiovascular risk marker. The current analysis evaluates the effects of evolocumab on these parameters in various patient populations over time.

***Methods and Results*—**Data from 7690 patients, 4943 of whom received at least 1 dose of evolocumab, in 15 phase 2 and phase 3 studies with a duration ranging from 12 weeks to 5 years were pooled based on study length, patient population, and ezetimibe or placebo comparator groups. Patients could receive intensive statin therapy but not in the statin intolerance and monotherapy studies. The effects of evolocumab on percent change from baseline for non-HDL-C, ApoB, and lipoprotein(a) and achievement of treatment goals for non-HDL-C and ApoB were examined. Compared with placebo, evolocumab at both approved dosing regimens substantially reduced mean non-HDL-C (Q2W dose: −49% to −56%, monthly dose: −48% to −52%), mean ApoB (Q2W dose: −46% to −52%, monthly dose: −40% to −48%), and median lipoprotein(a) (Q2W dose: −22% to −38%, monthly dose: −20% to −33%) at 12 weeks. Effects on all 3 parameters persisted over 5 years. Lipid-lowering effects were consistent among the patient populations examined (hypercholesterolemia/mixed dyslipidemia, statin intolerance, heterozygous familial hypercholesterolemia, and type 2 diabetes mellitus).

***Conclusions*—**In this pooled analysis, evolocumab substantially reduced non-HDL-C, ApoB, and lipoprotein(a) compared with placebo. The effect was consistent and maintained in various patient populations over 5 years. **(*J Am Heart Assoc*. 2020;9: e014129. DOI: 10.1161/JAHA.119.014129.)**

Key Words: apolipoprotein • lipids and lipoproteins • low-density lipoprotein cholesterol

Low-density lipoprotein (LDL) is the primary lipid treatment target to reduce atherosclerotic risk.[1–4] Non-high-density lipoprotein cholesterol (non-HDL-C) is considered to be a co-primary[3] or secondary treatment target,[1,2,4] while apolipoprotein B (ApoB) can be considered as a secondary target[2,3] or an alternative to LDL cholesterol (LDL-C) as the primary measurement, and may be preferred over non-HDL-C in patients with high triglycerides, diabetes mellitus, obesity, or very low LDL-C.[1] Lipoprotein(a) (Lp(a)) is recognized as a risk factor, based on Mendelian randomization, for atherosclerotic disease[1] and cardiovascular events,[5,6] and its measurement can help improve cardiovascular risk classification under certain conditions.[1,2] Non-HDL-C levels are an estimate of the concentration of atherogenic cholesterol in low-density lipoprotein (LDL) and very-low-density lipoprotein (VLDL) particles.[7] ApoB is a direct measure of non-HDL atherogenic lipoprotein particle concentration.[8]

Both non-HDL-C and ApoB are well-validated measures of cardiovascular risk, particularly for patients with elevated triglyceride levels, diabetes mellitus, or metabolic syndrome.[1,2,8] For patients at very high total cardiovascular risk, guidelines recommend lowering of non-HDL-C (<100 mg/dL) for which treatment intensification on top of statin therapy may be needed.[1,2] A treatment goal for ApoB <80 mg/dL has also been recommended for these patients.[1] It has been suggested that in patients at cardiovascular risk with Lp(a) ≥50 mg/dL or ≥125 nmol/L, intensification of treatment

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Received July 31, 2019; accepted January 6, 2020.

Clinical Perspective

What Is New?

- Recent US and European guidelines have emphasized the role of measuring of non-high-density lipoprotein (HDL), but also ApoB and lipoprotein(a) for risk stratification.
- In this pooled analysis, evolocumab therapy consistently reduced non-HDL cholesterol (−51% to −57%, placebo-corrected), apolipoprotein B100 (−48% to −52%, placebo-corrected), and lipoprotein(a) (−21% to −33%, placebo-corrected), whether used as monotherapy or as adjuvant therapy to statins or ezetimibe.
- Reductions in these secondary targets are sustained for up to 5 years of follow-up.

What Are the Clinical Implications?

- Evolocumab increases the likelihood of attaining risk-stratified goals of therapy for ApoB and non-HDL-C in patients with primary dyslipidemia, heterozygous familial hypercholesterolemia, diabetes mellitus, or statin intolerance.
- It is reassuring that evolocumab therapy was safe and provided enduring reductions in these secondary lipoprotein-related targets for up to 5 years of continuous treatment.
- Evolocumab reduces ApoB, non-HDL-C, and lipoprotein(a) to a greater extent than any other lipid-lowering drug class currently approved for use in patients with dyslipidemia.

directed to modifiable risk factors, including LDL-C, is a reasonable strategy.[1,2] Another recommendation suggests that levels of Lp(a) >75 nmol/L are associated with an increased risk of cardiovascular events.[9]

Meta-analyses present conflicting results as to whether ApoB or non-HDL-C provide enhanced predictive value of cardiovascular risk over LDL-C, suggesting these markers be measured in complement rather than in place of LDL-C until further evidence emerges.[10,11]

Evolocumab, a monoclonal antibody that binds to proprotein convertase subtilisin/kexin type 9, substantially and consistently reduces LDL-C levels in a broad range of patients[12–17] and significantly reduces the risk of such cardiovascular events as myocardial infarction, ischemic stroke, and coronary revascularization in patients with stable atherosclerotic cardiovascular disease (ASCVD).[18] When considering the clinical outcome of major vascular events (coronary heart death, nonfatal myocardial infarction, stroke, or coronary revascularization) used by the CTTC (Cholesterol Treatment Trialists' Collaboration), each 1 mmol/L reduction in LDL-C with evolocumab treatment in the FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk) trial[18] had an associated risk reduction in major vascular events of 10% during year 1 and 17% during year 2.

The primary objective of this pooled analysis of phase 2 and phase 3 global evolocumab studies is to characterize the effects of evolocumab on non-HDL-C, ApoB, and Lp(a) across a range of patient populations and for up to 5 years of treatment.

Methods

Data from patients enrolled in 15 phase 2 and phase 3 evolocumab studies with a duration of 12 weeks to 5 years were pooled on the basis of study length, patient population, and ezetimibe or placebo comparator groups.[12–17,19] Patients were eligible to receive intensive statin therapy except for those enrolled in the GAUSS (Goal Achievement After Utilizing an Anti-PCSK9 Antibody in Statin Intolerant Subjects) [NCT01375764] and GAUSS-2 [NCT01763905] studies, who were statin intolerant, and in the MENDEL (Monoclonal Antibody Against PCSK9 to Reduce Elevated LDL-C in Adults Currently Not Receiving Drug Therapy for Easing Lipid Levels) [NCT01375777] and MENDEL-2 [NCT01763827] studies, which examined the use of evolocumab as monotherapy.

The GAUSS, GAUSS-2, MENDEL, and MENDEL-2 studies as well as the atorvastatin cohorts of the LAPLACE-2 (LDL-C Assessment With PCSK9 Monoclonal Antibody Inhibition Combined With Statin Therapy) [NCT01763866] study used ezetimibe comparators; whereas the LAPLACE [NCT01380730], LAPLACE-2, MENDEL, MENDEL-2, YUKAWA (Study of LDL-C Reduction Using a Monoclonal PCSK9 Antibody in Japanese Patients With Advanced Cardiovascular Risk) [NCT01652703], YUKAWA-2 [NCT01953328], DESCARTES (Durable Effect of PCSK9 Antibody Compared With Placebo Study) [NCT01516879], RUTHERFORD (Reduction of LDL-C with PCSK9 Inhibition in Heterozygous Familial Hypercholesterolemia Disorder) [NCT01375751] and RUTHERFORD-2 [NCT01763918] (heterozygous familial hypercholesterolemia [HeFH]), and BANTING (Evolocumab Efficacy and Safety in Type 2 Diabetes Mellitus on Background Statin Therapy) [NCT02739984] and BERSON (Evolocumab Efficacy for LDL-C Reduction in Subjects with Type 2 Diabetes Mellitus on Background Statin Study) [NCT02662569] (type 2 diabetes mellitus) studies used placebo comparators. The open-label extension studies OSLER-1 (Open-Label Study of Long-Term Evaluation Against LDL-C) [NCT01439880], with a 5-year duration, and OSLER-2 [NCT01854918], with a 3-year duration, randomized patients to evolocumab plus standard-of-care versus standard-of-care alone in the first year, after which all patients received evolocumab until end-of-study. All were 12-week duration studies except for OSLER-1, OSLER-2, and the 52-week DESCARTES trial. All of the 12-week studies and the 52-week DESCARTES trial were double-blind. Randomization was performed centrally via an interactive web-based or voice recognition system. Allocation was concealed using the centralized randomization process. Treatment assignment was

blinded to the sponsor study team, investigators, site staff, and patients throughout the study, except after the first year for the open-label extension studies, OSLER-1 and OSLER-2.

ApoB was measured by nephelometry (MedPace Reference Laboratories, Cincinnati, OH) and non-HDL-C was calculated (total cholesterol minus HDL-C) following precipitation of HDL-C on Beckman Coulter chemistry analyzers (Olympus, Beckman Coulter Instruments, Brea, CA). Lp(a) levels were measured by MedPace with an isoform-independent immunoturbidimetric assay (Randox Laboratories, Ltd., UK; Polymedco calibrators, Cortlandt Manor, NY) on a Beckman Coulter chemistry analyzer. LDL-C was calculated using the Friedewald equation, and VLDL-C was calculated using the Friedewald estimate (triglycerides/5). Individual patient data were pooled across studies within each patient population, and the analyses were descriptive in nature. Means and SDs were calculated for all lipid parameters except Lp(a), for which medians with interquartile ranges were calculated because of the skewed distribution.

All patients provided written informed consent before study participation. The individual protocols were approved by each institutional review board and the investigations were in accordance with the Declaration of Helsinki. While additional methods for each trial have been reported elsewhere, a summary of the trial design and parameters of each contributing study is provided in Table 1. Qualified researchers may request data from Amgen clinical studies. Complete details are available at the following: http://www.amgen.com/datasharing.

The primary objective of this analysis was to determine the percent change from baseline in non-HDL-C, ApoB, and Lp(a) with evolocumab treatment. Secondary objectives were to examine the achievement of treatment goals of <100 mg/dL (<2.6 mmol/L) for non-HDL-C and <80 mg/dL for ApoB. Percent change from baseline in LDL-C, VLDL-C, and triglycerides were also summarized to further characterize patient lipid profiles.

We present results for approved dosing regimens of subcutaneous evolocumab (420 mg once monthly [QM] and 140 mg every 2 weeks [Q2W]) separately as well as pooled across dosing regimens since similar efficacy has been noted between the 2.[20]

Results

A total of 7690 patients were analyzed, and 5644 received at least 1 dose of evolocumab at any time (either in the parent study, or the open label extension study, or both). Five hundred fifty-four patients were randomized to an ezetimibe comparator arm (MENDEL-1/2, LAPLACE-2, GAUSS-1/2) and received at least 1 dose of ezetimibe. Two thousand one hundred ninety-three patients were randomized to a placebo comparator arm and received at least 1 dose of subcutaneous placebo. Baseline characteristics are presented in Tables 2 and 3. Age, sex, race, presence of ASCVD or type 2 diabetes mellitus, 10-year ASCVD risk score, and lipid parameters were balanced between the pooled evolocumab dosing group and placebo or ezetimibe comparators across all 12-week randomized trials that contributed to this analysis.

Evolocumab effects on lowering non-HDL-C, ApoB, and Lp(a) were highly consistent across the patient populations studied, namely, hypercholesterolemia/mixed dyslipidemia, statin intolerance, heterozygous familial hypercholesterolemia (HeFH), and type 2 diabetes mellitus, as well as over time and up to 5 years (Table 4).

When both dosing regimens of evolocumab were pooled, non-HDL-C percent change from baseline at 12 weeks was −55% to −57% (placebo-corrected) and −32% to −35% (ezetimibe-corrected), in all corresponding subgroups considered; percent change ranged from −39% to −43% in the long-term studies (1–5 years; not control-corrected) (Table 4). Consistent reductions of ApoB with evolocumab treatment were also observed. Percent change from baseline in ApoB at 12 weeks was −48% to −52% (placebo-corrected) and −32 to −35% (ezetimibe-corrected), in all corresponding subgroups considered; percent change ranged from −39% to −42% in the long-term studies (not control-corrected) (Table 4). Across all 12-week studies, Lp(a) median percent change from baseline ranged from −21.2% to −33.3% (placebo-corrected). In long-term studies median percent change in Lp(a) ranged from −23.8% to −33.3% (not control-corrected). Both ezetimibe and placebo had median percent changes in Lp(a) of 0.0% across all 12-week studies.

When dosing regimens were examined separately, evolocumab substantially reduced mean non-HDL-C (Q2W dose: −49% to −56%, monthly dose: −48% to −52%), mean ApoB (Q2W dose: −46% to −52%, monthly dose: −40% to −48%), and median Lp(a) (Q2W dose: −22% to −38%, monthly dose: −20% to −33%) at 12 weeks compared with placebo. Results by evolocumab, ezetimibe, and placebo dosing regimens are shown for these lipid parameters in Figure 1. Treatment effect on all lipids did not notably differ between approved subcutaneous evolocumab dosing regimens.

Compared with placebo or ezetimibe, a higher percentage of patients treated with evolocumab achieved non-HDL-C and ApoB recommended treatment goals. At 12 weeks, non-HDL-C <100 mg/dL was achieved in 84.3% to 87.9% of patients with hypercholesterolemia or mixed dyslipidemia receiving evolocumab versus 28.5% receiving ezetimibe versus 11.5% receiving placebo. Of those statin-intolerant patients not receiving background intensive statin therapy, this was achieved by 43.4% of patients receiving evolocumab versus 0.8% receiving ezetimibe. In patients with HeFH or type 2 diabetes mellitus, 73.7% to 86.3% of patients receiving evolocumab versus 0.7% to 25.5% receiving placebo were within recommended levels. In the 1-year study, this was achieved by 85.0% with evolocumab versus 14.8% with

Table 1. Contributing Studies

	N Randomized	Study Design, Phase	Trial Population	Background Lipid-Lowering Therapy	Comparator(s)
Short-term (12-wk) studies					
Hypercholesterolemia/mixed dyslipidemia					
LAPLACE-TIMI 57 NCT01380730	631	Randomized, double-blind, phase 2	Ages 18–80 y with fasting LDL ≥85 mg/dL	Statin±ezetimibe	Placebo
LAPLACE-2 NCT01763866	1899	Randomized, double-blind, phase 3	Ages 18–80 y with screening LDL ≥150 mg/dL and no statin use, LDL ≥100 mg/dL with nonintensive statin use, or LDL ≥80 mg/dL with intensive statin use	Statin therapy	Placebo or ezetimibe (atorvastatin cohort)
MENDEL NCT01375777	411	Randomized, double-blind, phase 2	Ages 18–75 y with fasting LDL ≥100 and <190 mg/dL	None	Placebo & ezetimibe
MENDEL-2 NCT01763827	615	Randomized, double-blind, phase 3	Ages 18–18 y with fasting LDL ≥100 and <190 mg/dL	None	Placebo & ezetimibe
YUKAWA NCT01652703	310	Randomized, double-blind, phase 2	Ages 20–80 y (Japan) with screening LDL ≥115 mg/dL	Statin±ezetimibe	Placebo
YUKAWA-2 NCT01953328	404	Randomized, double-blind, phase 3	Ages 20–85 y (Japan) with LDL ≥100 mg/dL	Statin	Placebo
Heterozygous familial hypercholesterolemia					
RUTHERFORD NCT01375751	168	Randomized, double-blind, phase 2	Ages 18–75 y with LDL ≥100 mg/dL	Statin±ezetimibe	Placebo
RUTHERFORD-2 NCT01763918	331	Randomized, double-blind, phase 3	Ages 18–80 y with LDL ≥100 mg/dL	Statin±ezetimibe	Placebo
Statin intolerance					
GAUSS NCT01375764	160	Randomized, double-blind, phase 2	Ages 18–74 y with LDL ≥100 mg/dL with diagnosed CHD or risk equivalent per NCEP criteria, LDL ≥130 mg/dL without CHD/risk equivalent and 2+ CVD risk factors, or LDL ≥160 mg/dL without CHD/risk equivalent and 0–1 CVD risk factors	Low-dose statin permitted	Ezetimibe
GAUSS-2 NCT01763905	307	Randomized, double-blind, phase 3	Ages 18–80 y with LDL >NCEP Adult Treatment Panel III goal	Low-dose statin permitted	Ezetimibe
Type 2 diabetes mellitus					
BANTING NCT02739984	424	Randomized, double-blind, phase 3	Ages ≥18 y with LDL ≥70 mg/dL or non-HDL-C ≥100 mg/dL with CVD, or LDL ≥100 mg/dL or non-HDL-C ≥130 mg/dL without CVD, at least on moderate statin intensity	Statin	Placebo
BERSON NCT02662569	986	Randomized, double-blind, phase 3	Ages 18–80 y with LDL ≥130 mg/dL—no statin or LDL ≥100 mg/dL—statin	Statin	Placebo
Long-term (1–5-y) studies					
DESCARTES NCT01516879	905	Randomized, double-blind, phase 3	Ages 18–75 y with LDL ≥75 mg/dL (1-y duration)	Diet±statin or diet+statin+ezetimibe	Placebo
OSLER-2 NCT01854918	3681	Controlled, open-label extension, phase 3	Ages 18–85 y. Open-label extension of MENDEL-2, LAPLACE-2, GAUSS-2, RUTHERFORD-2, DESCARTES, THOMAS-1, -2 studies (3-y duration)	Standard-of-care	Standard-of-care in the first year of the study*
OSLER NCT01439880	1324	Controlled, open-label extension, phase 3	Ages 18–85 y. Open-label extension of MENDEL, LAPLACE-TIMI-57, GAUSS, RUTHERFORD, YUKAWA studies (5-y duration)	Standard-of-care	Standard-of-care in the first year of the study*

BANTING indicates Evolocumab Efficacy and Safety in Type 2 Diabetes Mellitus on Background Statin Therapy; BERSON, Evolocumab Efficacy for LDL-C Reduction in Subjects with Type 2 Diabetes Mellitus on Background Statin Study; CHD, coronary heart disease; CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; DESCARTES, Durable Effect of PCSK9 Antibody Compared With Placebo Study; GAUSS/GAUSS-2, Goal Achievement After Utilizing an Anti-PCSK9 Antibody in Statin Intolerant Subjects; LAPLACE/LAPLACE-2, LDL-C Assessment With PCSK9 Monoclonal Antibody Inhibition Combined With Statin Therapy; LDL, low-density lipoprotein; MENDEL/MENDEL-2, Monoclonal Antibody Against PCSK9 to Reduce Elevated LDL-C in Adults Currently Not Receiving Drug Therapy for Easing Lipid Levels; NCEP, National Cholesterol Education Panel; OSLER-1/OSLER-2, Open-Label Study of Long-Term Evaluation Against LDL-C; RUTHERFORD/RUTHERFORD-2, Reduction of LDL-C with PCSK9 Inhibition in Heterozygous Familial Hypercholesterolemia Disorder; YUKAWA/YUKAWA-2, Study of LDL-C Reduction Using a Monoclonal PCSK9 Antibody in Japanese Patients With Advanced Cardiovascular Risk.

*During year 1, patients were randomized to evolocumab plus standard-of-care or standard-of-care alone. After year 1, all patients received evolocumab plus standard-of-care.

DOI: 10.1161/JAHA.119.014129

Table 2. Baseline Characteristics

	Age, y, Mean (SD)	Sex, Female, %	Race, White, %	ASCVD*, %	10-year ASCVD Risk, Median (Q1, Q3)	Type 2 DM, %	Non-HDL-C, Mean (SD), mg/dL	ApoB, Mean (SD), mg/dL	Lp(a), Median (Q1, Q3), nmol/L	LDL-C, Mean (SD), mg/dL	VLDL-C, Median (Q1, Q3), mg/dL	TG, Median (Q1, Q3), mg/dL
Hypercholesterolemia/mixed dyslipidemia (LAPLACE-TIMI-57, LAPLACE-2, MENDEL-1, MENDEL-2, YUKAWA-1, YUKAWA-2)												
Evolocumab (n=1978)	58.6 (11.1)	48.8	76.7	23.9	6.8 (3.2, 13.3)	17.3	145.2 (42.4)	95.4 (25.1)	34.0 (11.0, 129.0)	118.4 (38.8)	23.0 (17.0, 31.5)	117.0 (88.0, 160.0)
Placebo (n=1261)	58.8 (10.6)	48.3	69.3	22.8	6.5 (3.2, 13.5)	18.2	144.8 (40.1)	96.0 (23.5)	34.0 (12.0, 107.0)	118.4 (36.7)	23.0 (17.0, 32.5)	118.0 (88.0, 163.0)
Evolocumab (n=835)	56.1 (11.9)	54.9	88.6	15.9	5.5 (2.6, 9.8)	8.6	151.1 (42.2)	97.3 (24.9)	28.0 (9.0, 108.0)	125.0 (38.7)	23.0 (16.5, 32.0)	114.5 (84.0, 161.0)
Ezetimibe (n=420)	56.9 (11.4)	57.1	86.2	12.9	5.9 (3.0, 11.3)	10.5	152.0 (39.7)	98.3 (23.8)	31.0 (12.0, 140.0)	125.3 (35.9)	23.5 (17.0, 32.0)	119.0 (87.0, 160.5)
Statin intolerance (GAUSS-1 & -2)												
Evolocumab (n=237)	61.5 (9.8)	47.3	93.7	34.6	11.6 (6.4, 19.4)	17.3	227.1 (60.5)	138.6 (32.8)	31.0 (9.0, 97.0)	193.6 (59.2)	30.0 (21.5, 42.5)	150.5 (108.5, 214.5)
Ezetimibe (n=134)	61.3 (8.8)	50.0	91.8	37.3	12.8 (6.4, 22.3)	22.4	227.7 (57.5)	139.5 (31.4)	37.0 (11.0, 176.0)	191.6 (53.6)	32.0 (23.0, 44.5)	166.5 (118.5, 232.0)
Heterozygous FH (RUTHERFORD-1 & -2)												
Evolocumab (n=276)	52.2 (12.3)	40.2	90.2	39.5	N/A	6.5	180.5 (50.2)	117.4 (28.0)	59.0 (20.0, 197.0)	155.2 (45.7)	22.3 (16.5, 30.0)	111.8 (84.5, 157.0)
Placebo (n=165)	49.1 (12.6)	49.1	89.1	26.7	N/A	7.3	177.9 (47.5)	116.8 (28.1)	57.0 (23.0, 178.0)	154.2 (42.4)	19.0 (14.5, 29.5)	100.5 (74.5, 151.0)
Type 2 DM (BANTING, BERSON)												
Evolocumab (n=937)	61.6 (8.5)	52.0	53.4	46.3	12.5 (6.5, 22.8)	100	128.2 (38.3)	88.9 (23.4)	30.0 (10.0, 110.0)	97.5 (34.0)	27.0 (20.0, 37.0)	134.0 (101.0, 188.0)
Placebo (n=465)	61.6 (8.7)	55.9	51.6	48.0	12.1 (5.9, 23.5)	100	127.3 (38.1)	88.0 (23.6)	31.0 (11.0, 118.0)	97.4 (33.5)	26.0 (19.0, 36.0)	130.0 (95.0, 183.0)
1-y study (DESCARTES)												
Evolocumab (n=599)	55.9 (10.8)	51.6	79.5	18.2	5.6 (2.5, 9.8)	10.4	124.2 (25.6)	87.0 (16.3)	38.0 (14.0, 137.0)	100.4 (22.3)	17.5 (13.0, 24.0)	105.0 (80.0, 140.0)
Placebo (n=302)	56.7 (10.1)	53.6	82.1	15.6	6.0 (2.7, 11.6)	13.9	125.6 (26.9)	87.5 (16.3)	40.0 (12.0, 145.0)	100.2 (21.6)	18.0 (13.0, 27.0)	110.3 (85.0, 155.0)
3-y study (OSLER-2)												
Evolocumab (n=3443)	58.7 (10.5)	46.4	83.2	26.9	6.8 (3.2, 12.8)	16.3	154.3 (56.1)	101.0 (32.3)	36.0 (12.0, 137.0)	126.8 (51.6)	23.5 (17.0, 33.0)	120.5 (89.0, 168.0)
5-y study (OSLER-1)												
Evolocumab (n=1151)	57.3 (11.2)	52.1	72.5	25.2	6.9 (3.8, 12.9)	14.4	167.9 (42.3)	111.9 (24.8)	36.0 (12.0, 124.0)	140.3 (38.5)	22.5 (16.5, 31.5)	122.5 (93.0, 169.5)

ApoB indicates apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; BANTING, Evolocumab Efficacy and Safety in Type 2 Diabetes Mellitus on Background Statin Therapy; BERSON, Evolocumab Efficacy for LDL-C Reduction in Subjects with Type 2 Diabetes Mellitus on Background Statin Study; DESCARTES, Durable Effect of PCSK9 Antibody Compared With Placebo Study; DM, diabetes mellitus; FH, familial hypercholesterolemia; GAUSS/GAUSS-2, Goal Achievement After Utilizing an Anti-PCSK9 Antibody in Statin Intolerant Subjects; LAPLACE/LAPLACE-2, LDL-C Assessment With PCSK9 Monoclonal Antibody Inhibition Combined With Statin Therapy; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); MENDEL/MENDEL-2, Monoclonal Antibody Against PCSK9 to Reduce Elevated LDL-C in Adults Currently Not Receiving Drug Therapy for Easing Lipid Levels; N/A, not applicable; non-HDL-C, nonhigh-density lipoprotein cholesterol; OSLER-1/OSLER-2, Open-Label Study of Long-Term Evaluation Against LDL-C; Q1, Q3, quartile 1, quartile 3; RUTHERFORD/RUTHERFORD-2, Reduction of LDL-C with PCSK9 Inhibition in Heterozygous Familial Hypercholesterolemia Disorder; TG, triglycerides; VLDL-C, very-low-density lipoprotein cholesterol; YUKAWA/YUKAWA-2, Study of LDL-C Reduction Using a Monoclonal PCSK9 Antibody in Japanese Patients With Advanced Cardiovascular Risk.
*ASCVD includes coronary artery disease, peripheral artery disease, angina, myocardial infarction, coronary revascularization, and stroke or transient ischemic attack. 10-year ASCVD risk scores were not calculated for those with ASCVD or FH.

DOI: 10.1161/JAHA.119.014129

placebo (Figure 2A). In longer-term (OSLER studies), 62.2% to 66.9% of patients receiving evolocumab reached goal levels. At 12 weeks, ApoB <80 mg/dL was achieved in ≈94% of patients with hypercholesterolemia or mixed dyslipidemia receiving evolocumab versus 45.4% receiving ezetimibe versus 24.4% receiving placebo, and 60.6% of statin-intolerant patients receiving evolocumab versus 4.8% receiving ezetimibe. In patients with HeFH or type 2 diabetes mellitus, 83% to 87% receiving evolocumab versus 4% to 24% receiving placebo were within recommended levels. In the 1-year study, this was achieved by 90.7% with evolocumab versus 40.7% with placebo (Figure 2B). Longer-term, 73.9% to 82.0% of patients receiving evolocumab in long-term studies achieved goal levels.

Discussion

ApoB, non-HDL-C, and Lp(a) are important measures of risk for ASCVD. The incorporation of these apoprotein and lipoprotein measures into guidelines makes risk assessment more comprehensive and helps to identify more patients likely to benefit from lipid-lowering therapies. Herein we demonstrate that evolocumab provides substantial reductions in ApoB, non-HDL-C, and Lp(a) when used either as monotherapy or when used as adjuvant therapy to statins or ezetimibe. Moreover, the administration of evolocumab in a broad range of patients at high cardiovascular risk or unable to receive high-intensity statin therapy (eg, patients with primary dyslipidemia, HeFH, diabetes mellitus, or statin intolerance) substantially increases the likelihood of attaining risk-stratified goals of therapy for ApoB and non-HDL-C in these subgroups. The reductions in ApoB, non-HDL-C, and Lp(a) are durable for up to 5 years of continuous therapy. We also demonstrate substantive reductions in VLDL-C in these patients. In total these changes represent significant, broad-spectrum incremental reductions in total atherogenic lipoprotein burden in serum that no other currently available drug class can achieve.

Lp(a) is a covalent conjugate of an LDL-like lipoprotein particle and apolipoprotein(a). Prospective longitudinal cohort

Table 3. 10-Year ASCVD Risk Score Stratification* at Baseline

	Low Risk (<5%), %	Borderline Risk (≥5% to <7.5%), %	Intermediate Risk (≥7.5% to <20%), %	High Risk (≥20%), %
Hypercholesterolemia/Mixed Dyslipidemia (LAPLACE-TIMI-57, LAPLACE-2, MENDEL-1, MENDEL-2, YUKAWA-1, YUKAWA-2)				
Evolocumab (n=1503)	38.6	14.6	34.5	12.3
Placebo (n=969)	38.8	17.0	31.7	12.5
Evolocumab (n=702)	46.2	18.1	29.3	6.4
Ezetimibe (n=366)	42.5	17.9	29.7	9.9
Statin intolerance (GAUSS-1 & -2)				
Evolocumab (n=155)	14.9	13.2	48.8	23.1
Ezetimibe (n=84)	12.9	21.0	38.7	27.4
Type 2 DM (BANTING, BERSON)				
Evolocumab (n=491)	17.6	11.6	40.4	30.4
Placebo (n=240)	16.4	16.8	34.1	32.7
1-y study (DESCARTES)				
Evolocumab (n=490)	46.2	16.2	31.6	6.0
Placebo (n=255)	42.6	17.4	34.8	5.2
3-y study (OSLER-2)				
Evolocumab (n=2289)	37.6	15.7	35.3	11.4
5-y study (OSLER-1)				
Evolocumab (n=760)	34.7	19.7	33.1	12.5

ASCVD indicates atherosclerotic cardiovascular disease; BANTING, Evolocumab Efficacy and Safety in Type 2 Diabetes Mellitus on Background Statin Therapy; BERSON, Evolocumab Efficacy for LDL-C Reduction in Subjects with Type 2 Diabetes Mellitus on Background Statin Study; DESCARTES, Durable Effect of PCSK9 Antibody Compared With Placebo Study; DM, diabetes mellitus; GAUSS/GAUSS-2, Goal Achievement After Utilizing an Anti-PCSK9 Antibody in Statin Intolerant Subjects; LAPLACE/LAPLACE-2, LDL-C Assessment With PCSK9 Monoclonal Antibody Inhibition Combined With Statin Therapy; MENDEL/MENDEL-2, Monoclonal Antibody Against PCSK9 to Reduce Elevated LDL-C in Adults Currently Not Receiving Drug Therapy for Easing Lipid Levels; OSLER-1/OSLER-2, Open-Label Study of Long-Term Evaluation Against LDL-C; RUTHERFORD/RUTHERFORD-2, Reduction of LDL-C with PCSK9 Inhibition in Heterozygous Familial Hypercholesterolemia Disorder; YUKAWA/YUKAWA-2, Study of LDL-C Reduction Using a Monoclonal PCSK9 Antibody in Japanese Patients With Advanced Cardiovascular Risk.

*Patients with ASCVD or familial hypercholesterolemia were excluded from ASCVD risk calculations.

Table 4. Effects of Evolocumab, Ezetimibe, and Placebo on Non-HDL-C, ApoB, and Lp(a)

	Non-HDL-C (mg/dL), % Change From Baseline, Mean (SD)				ApoB (mg/dL), % Change From Baseline, Mean (SD)		ApoB (mg/dL), % Change From Baseline, Mean (SD)		Lp(a) (nmol/L), % Change From Baseline, Median (Q1, Q3)			
	Ezetimibe Comparator		Placebo Comparator		Ezetimibe Comparator		Placebo Comparator		Ezetimibe Comparator		Placebo Comparator	
	EvoMab	Ezet	EvoMab	Pbo	EvoMab	Ezet	EvoMab	Pbo	EvoMab	Ezet	EvoMab	Pbo
12-wk studies												
Hypercholesterolemia/mixed dyslipidemia*	−51.8 (15.3) n=760	−16.4 (20.2) n=386	−53.9 (17.0) n=1838	2.8 (19.7) n=1173	−47.9 (15.3) n=759	−13.0 (17.4) n=386	−49.7 (16.4) n=1837	2.7 (17.4) n=1172	−22.0 (−39.4, 0.0) n=760	0.0 (−11.8, 14.6) n=387	−26.3 (−44.7, −5.0) n=1838	0.0 (−10.4, 15.4) n=1179
Statin intolerance (GAUSS-1 & -2)	−48.4 (14.2) n=226	−15.9 (12.2) n=125	…	…	−44.5 (14.7) n=223	−12.4 (13.3) n=125	…	…	−23.1 (−42.0, −3.3) n=223	0.0 (−16.7, 3.6) n=126	…	…
Heterozygous FH (RUTHERFORD-1 & -2)	…	…	−52.9 (18.3) n=262	1.7 (21.2) n=153	…	…	−46.9 (17.2) n=262	1.4 (18.4) n=150	…	…	−21.2 (−38.1, −7.0) n=263	0.0 (−4.2, 15.3) n=150
Type 2 DM (BANTING, BERSON)	…	…	−50.3 (22.9) n=838	4.7 (25.5) n=428	…	…	−45.5 (20.9) n=829	4.4 (21.3) n=421	…	…	−33.3 (−55.6, −16.7) n=833	0.0 (−16.2, 16.7) n=425
Long-term studies												
1-y study (DESCARTES)	…	…	−43.4 (26.4) n=515	7.5 (26.4) n=263	…	…	−42.4 (22.5) n=536	2.3 (22.5) n=275	…	…	−28.4 (−49.2, −6.0) n=535	−5.5 (−20.5, 0.9) n=272
3-y study†,‡ (OSLER-2)	−39.4 (32.9) n=3029	…	…	…	−38.7 (27.2) n=3083	…	…	…	−23.8 (−44.4, 0.0) n=3077	…	…	…
5-y study‡ (OSLER-1)	−43.2 (24.7) n=940	…	…	…	−39.9 (21.9) n=946	…	…	…	−33.3 (−51.3, −11.1) n=941	…	…	…

ApoB indicates apolipoprotein B; BANTING, Evolocumab Efficacy and Safety in Type 2 Diabetes Mellitus on Background Statin Therapy; BERSON, Evolocumab Efficacy for LDL-C Reduction in Subjects with Type 2 Diabetes Mellitus on Background Statin Study; DESCARTES, Durable Effect of PCSK9 Antibody Compared With Placebo Study; DM, diabetes mellitus; EvoMab, evolocumab; Ezet, ezetimibe; FH, familial hypercholesterolemia; GAUSS/GAUSS-2, Goal Achievement After Utilizing an Anti-PCSK9 Antibody in Statin Intolerant Subjects; LAPLACE/LAPLACE-2, LDL-C Assessment With PCSK9 Monoclonal Antibody Inhibition Combined With Statin Therapy; Lp(a), lipoprotein(a); MENDEL/MENDEL-2, Monoclonal Antibody Against PCSK9 to Reduce Elevated LDL-C in Adults Currently Not Receiving Drug Therapy for Easing Lipid Levels; non-HDL-C, non-high-density lipoprotein cholesterol; OSLER-1/OSLER-2, Open-Label Study of Long-Term Evaluation Against LDL-C; Pbo, placebo; Q1, Q3, quartile 1, quartile 3; RUTHERFORD/RUTHERFORD-2, Reduction of LDL-C with PCSK9 Inhibition in Heterozygous Familial Hypercholesterolemia Disorder; YUKAWA/YUKAWA-2, Study of LDL-C Reduction Using a Monoclonal PCSK9 Antibody in Japanese Patients With Advanced Cardiovascular Risk.

*LAPLACE-TIMI-57, LAPLACE-2, MENDEL-1, MENDEL-2, YUKAWA-1, and YUKAWA-2 had placebo comparators. MENDEL-1, MENDEL-2, and LAPLACE-2 atorvastatin cohorts had ezetimibe comparators.

†OSLER-2 was a 152-week study; however, data for ApoB and Lp(a) were available up to 104 weeks and are presented as such.

‡OSLER-1 and OSLER-2 were open label extension studies with no comparator groups. Evolocumab and placebo groups were pooled for once-monthly and every-2-week dosing; ezetimibe dosing was 10 mg orally once daily.

DOI: 10.1161/JAHA.119.014129

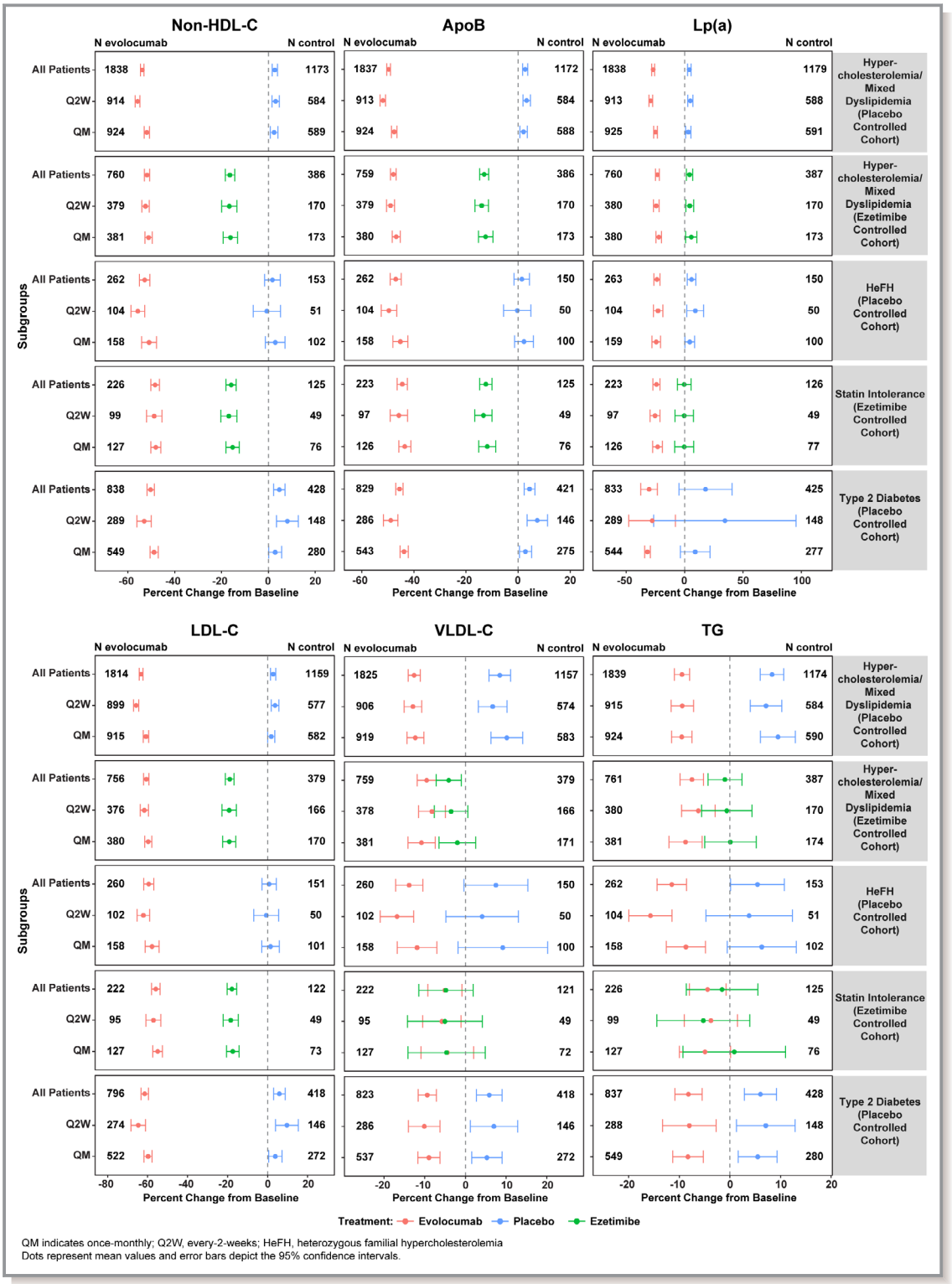

Figure 1. Percent change in non-HDL-C, ApoB, Lp(a), LDL-C, VLDL-C, and TG from baseline. Forest plots highlight the percent change in non-HDL-C, ApoB, Lp(a), VLDL-C, and TG from baseline with evolocumab, placebo, and ezetimibe for all 12-week studies by patient population. Individual patient data were pooled across studies within each patient population. The dots represent mean values, and the error bars depict the 95% CIs. ApoB indicates apolipoprotein B; HeFH, heterozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); non-HDL-C, non-high-density lipoprotein cholesterol; N, number of patients within each group with a nonmissing percent change from baseline at week 12; Q2W, every-2-week, QM, once monthly; TG, triglycerides; VLDL-C, very-low-density lipoprotein cholesterol.

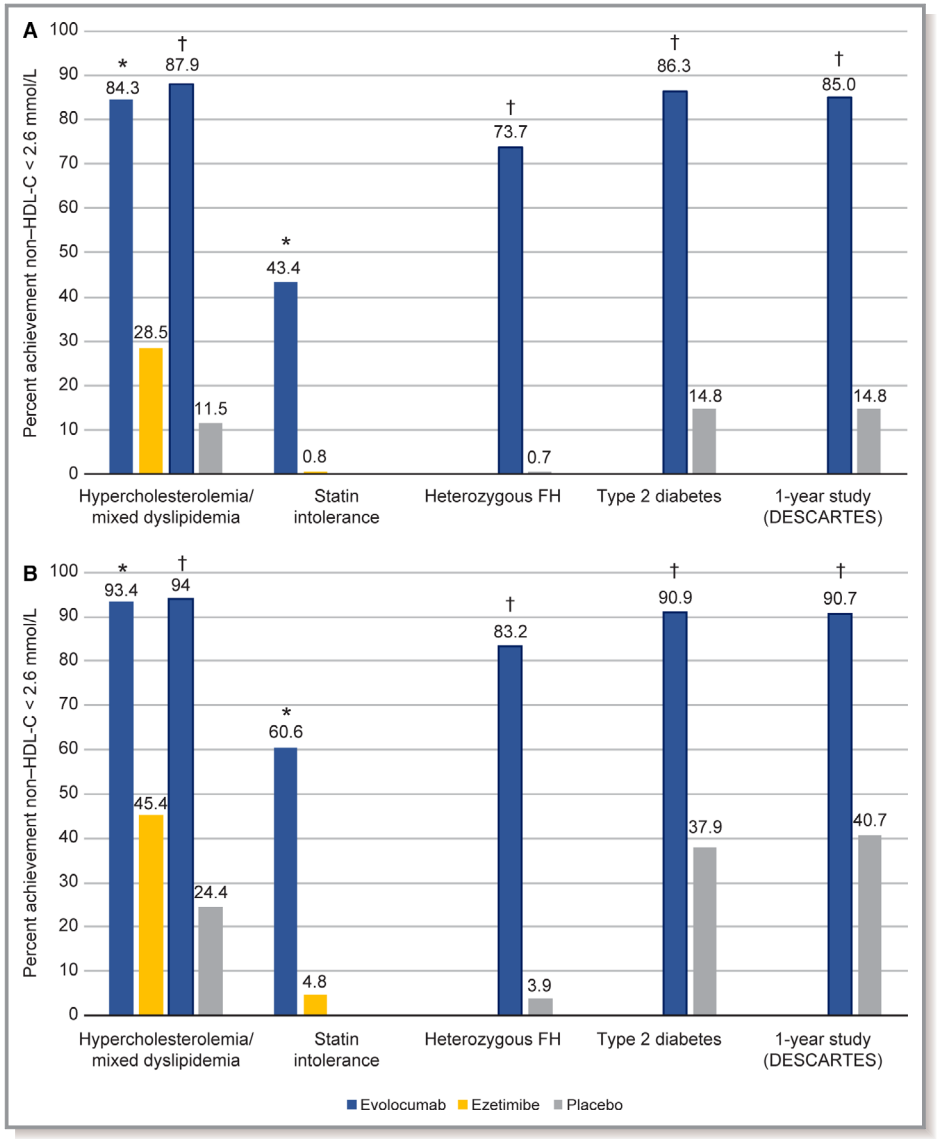

Figure 2. Percent achievement in placebo or ezetimibe-controlled phase 2 and phase 3 evolocumab studies of (**A**) Non-HDL-C <100 mg/dL (2.6 mmol/L) and (**B**) ApoB <80 mg/dL. The percentages of patients who achieved non-HDL-C <100 mg/dL (**A**) and ApoB <80 mg/dL (**B**) with evolocumab, ezetimibe, or placebo are depicted in this plot for all studies with a placebo or ezetimibe comparator. Results are shown separately for each patient population examined (hypercholesterolemia/mixed dyslipidemia, type 2 diabetes mellitus, heterozygous FH, and statin intolerance), all 12 weeks in duration, as well as for the 1-year study (DESCARTES). ApoB indicates apolipoprotein B; FH, familial hypercholesterolemia; non-HDL-C, non-high-density lipoprotein cholesterol. *Evolocumab-treated patients with ezetimibe comparator arm; †Evolocumab-treated patients with placebo comparator arm.

and Mendelian randomization studies confirm that elevated levels of Lp(a) are causally associated with risk for ASCVD-related events.[1,5,6,21,22] Neither statins nor ezetimibe impact serum levels of Lp(a). Nicotinic acid was long heralded as a therapy that reduced Lp(a).[23] In a post hoc analysis of the AIM HIGH (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes) trial, there was no demonstrable impact of the limited extent of Lp(a) lowering with nicotinic acid on risk for cardiovascular events.[24] In a recent kinetic analysis by Watts et al, it was shown that evolocumab therapy decreases hepatic production of Lp(a) when used as monotherapy and increases the clearance of Lp(a) when used in combination with a statin,[25] likely via a LDL receptor–dependent pathway.[26,27] In the FOURIER trial, evolocumab reduced Lp(a) by a median of 26.9%, consistent with our findings herein.[28] This analysis of FOURIER also demonstrated that higher baseline Lp(a) concentration helped to identify individuals with greater

clinical efficacy with evolocumab, raising the possibility that in addition to LDL lowering, concurrent reduction in Lp(a) by evolocumab may have provided incremental risk reduction.

Substantial arguments have been advanced that ApoB is the optimal lipid-related ASCVD risk marker.[29,30] All atherogenic lipoproteins (VLDL remnants, intermediate-density lipoprotein, LDL, and Lp(a)) contain ApoB. The capacity of evolocumab to reduce ApoB is significantly larger than that of statins and ezetimibe; in addition, the effect of evolocumab on ApoB is additive to that of statins and ezetimibe in patients with primary dyslipidemia or HeFH. In patients in whom evolocumab is indicated, the ability of evolocumab to further reduce ApoB when added to statins, ezetimibe, or the combination of the 2 affords clinicians therapeutic opportunity to target a potential contributor to residual ASCVD risk. This is especially important in patients such as those with statin intolerance or HeFH, where substantial atherogenic lipoprotein reductions can be difficult to achieve.[31] Our findings are particularly relevant now that the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) lipid guidelines recommend measuring ApoB (especially in patients with high triglycerides, obesity, diabetes mellitus, and metabolic syndrome) and Lp(a), the latter at least once in each adult person's lifetime.

Historically, risk-stratified goal attainment rates for such measures as LDL-C, non-HDL-C, and ApoB have been relatively low, especially among high-risk patients and those with statin intolerance.[32,33] Evolocumab dramatically increases the percentage of patients reaching their non-HDL-C and ApoB goals compared with both placebo and ezetimibe, with or without a statin background. This has important direct consequences on risk for ASCVD events and their associated economic burden in terms of long-term physical and physiological function, poorer quality of life, and costs because of myocardial infarction, stroke, and need for revascularization procedures.[34,35]

In the FOURIER trial, evolocumab was shown to provide stable reductions in atherogenic lipoprotein for a median of 26 months.[18] We extend these findings with results from the Open-Label Study of Long-Term Evaluation against LDL Cholesterol (OSLER) -2 and -1 trials. These trials demonstrate that the therapeutic effect of evolocumab is durable over 3 and 5 years of follow-up, respectively. The lack of attenuation in lipid-lowering efficacy suggests there is no tachyphylaxis with chronic, long-term use of this monoclonal antibody. Stable reductions were observed with ApoB, non-HDL-C, and Lp(a).

Also, of note, diabetic dyslipidemia is multifactorial and is frequently accompanied by elevated VLDL and triglycerides. In patients with diabetes mellitus and impaired triglyceride clearance, remnant lipoprotein levels (small VLDLs and intermediate-density lipoproteins) are increased. It is now widely accepted that remnant lipoproteins are atherogenic and proinflammatory.[36–38] In previous work, we have demonstrated reduction in remnant lipoproteins by evolocumab.[39] Herein we demonstrate a substantial reduction of VLDL-C, the direct precursor to remnant lipoprotein formation. For diabetic patients with hypertriglyceridemia, ApoB and non-HDL-C reductions are important. The diabetic patients in this analysis experienced marked reductions in both ApoB and non-HDL-C, with notable improvements in goal attainment for these risk markers when compared with either placebo or ezetimibe, with or without a statin background.

Limitations of the analysis include the 12-week duration of most studies and the between-study heterogeneity, which was minimized by the use of highly consistent procedures across studies for randomization, blinding, and lipid measurement. Additionally, LDL-C and VLDL-C were calculated by the Friedewald equation and not directly measured, with VLDL-C estimated as the difference between LDL-C and non-HDL-C. As such, LDL may have been underestimated at low LDL levels and higher triglyceride levels.

In this pooled analysis of 15 studies, evolocumab treatment demonstrated consistent and stable reductions in non-HDL-C, ApoB, and Lp(a) across all patient populations studied.

Acknowledgments

The authors thank Maya Shehayeb, of Amgen Inc., for medical writing and editorial support and Ben Wang and Joshua Givens, on behalf of Amgen Inc., for statistical support.

Sources of Funding

This work was supported by Amgen Inc.

Disclosures

Toth is a member of the speaker's bureau for Amarin, Amgen, Kowa, Merck, Novo-Nordisk, Regeneron, and Sanofi; he is a consultant to Amarin, Amgen, Novo-Nordisk, Resverlogix, and Theravance. Jones receives grant support from the David and June Trone Family Foundation (significant). Monsalvo, Elliott-Davey, and López are employees of and stockholders in Amgen Inc (significant). Banach has received research grant (s)/support from Sanofi and Valeant and has served as a consultant for Mylan (modest), Amgen (significant), KRKA (modest), Polfarmex (significant), Polpharma (modest), Sanofi-Aventis (significant), Servier (modest), and Esperion (modest).

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