Cardiometabolic Risk

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

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Objectives   The purpose of this study was assess the effect of evolocumab (AMG 145) on lipoprotein (Lp)(a) from a pooled analysis of 4 phase II trials.

Background   Lp(a), a low-density lipoprotein (LDL) particle linked to the plasminogen-like glycoprotein apolipoprotein(a), shows a consistent and independent positive association with cardiovascular disease risk in epidemiological studies. Current therapeutic options to reduce Lp(a) are limited.

Methods   A pooled analysis of data from 1,359 patients in 4 phase II trials assessed the effects of evolocumab, a fully human monoclonal antibody to PCSK9, on Lp(a), the relationship between Lp(a) and lowering of low-density lipoprotein cholesterol (LDL-C) and apolipoprotein B, and the influence of background statin therapy. Lp(a) was measured using a standardized isoform-independent method.

Results   Evolocumab treatment for 12 weeks resulted in significant ($p < 0.001$) mean (95% confidence interval) dose-related reductions in Lp(a) compared to control: 29.5% (23.3% to 35.7%) and 24.5% (20.4% to 28.7%) with 140 mg and 420 mg, dosed every 2 and 4 weeks, respectively, with no plateau of effect. Lp(a) reductions were significantly correlated with percentages of reductions in LDL-C (Spearman correlation coefficient, 0.5134; $p < 0.001$) and apolipoprotein B (Spearman correlation coefficient, 0.5203; $p < 0.001$). Mean percentage reductions did not differ based on age or sex but the trend was greater in those patients taking statins.

Conclusions   Inhibition of PCSK9 with evolocumab resulted in significant dose-related reductions in Lp(a). While the mean percentage of reduction was significantly greater in those patients with baseline Lp(a) of ≤125 nmol/l, the absolute reduction was substantially larger in those with levels >125 nmol/l.   (J Am Coll Cardiol 2014;63:1278–88) © 2014 by the American College of Cardiology Foundation

Lipoprotein(Lp)(a) is a low-density lipoprotein (LDL)-like particle consisting of hepatically synthesized apolipoprotein B_{100} that is noncovalently bound to the plasminogen-like glycoprotein apolipoprotein(a) (1). The biological role of Lp(a) is uncertain, but it is present only in humans, hedgehogs, primates, and old-world monkeys (2). Lp(a) is recognized as an independent risk factor for myocardial infarction, stroke, and peripheral arterial disease and is believed to increase the risk for cardiovascular disease (CVD) via its atherogenic LDL moiety and its prothrombotic, proinflammatory apolipoprotein(a) moiety (3,4). Levels of Lp(a) >125 nmol/l (approximately 50 mg/dl), the 80th percentile for most populations, have shown a consistent and independent positive association with CVD risk in epidemiological studies (5,6). Recently, a large Mendelian randomization study demonstrated that a genetically determined doubling of Lp(a) was associated with a 22% increase in CVD risk, suggesting a causal link (7). In addition, elevated Lp(a) is an independent CVD risk factor in patients with familial hypercholesterolemia (8).

Lp(a) levels are primarily genetically determined and are dependent mainly on the rate of hepatic synthesis. Formation of Lp(a) appears to take place at the hepatic cell surface, where an apolipoprotein(a) kringle moiety is noncovalently linked to LDL apolipoprotein B (9). The lower the number of kringle IV type 2 repeats in the apolipoprotein(a) gene, the higher the plasma level of Lp(a) (10). Clearance of circulating Lp(a) is not well understood but is thought to occur primarily by hepatic and renal pathways, although these metabolic routes do not appear to govern plasma Lp(a) levels. The LDL receptor does not appear to participate in Lp(a) clearance, reinforced by the fact that statins, which act mainly by upregulating LDL receptor activity, do not lower Lp(a) (11,12).

Lp(a) is relatively refractory to both lifestyle and drug intervention, with current therapeutic options limited to nicotinic acid, which shows consistent reductions of 15% to 25% (13,14). Studies using monoclonal antibody inhibition of the proprotein convertase subtilisin/kexin type 9 (PCSK9) have demonstrated reductions in Lp(a) levels, but the studies have been of short duration with small numbers of subjects; and relationships to dose, sex, and background lipid therapy have not been fully established (15–17). PROFICIO (Program to Reduce LDL-C and Cardiovascular Outcomes Following

Inhibition of PCSK9 In Different Populations), a pooled analysis of 1,359 patients from 4 phase II trials, provided the ability to robustly assess the effects of evolocumab (AMG 145), a fully human monoclonal antibody to PCSK9, on Lp(a), the relationship between Lp(a) and the lowering of LDL-C and apolipoprotein B, and the influence of factors such as sex, baseline Lp(a), and background statin therapy. In addition, the open-label extension of these trials allowed for evaluation of the maintenance or discontinuation of evolocumab therapy on Lp(a) levels.

Abbreviations and Acronyms

CVD = cardiovascular disease

LDL = low-density lipoprotein

PCSK9 = proprotein convertase subtilisin/kexin type 9

Q2W = every 2 weeks

Q4W = every 4 weeks

SC = subcutaneous

UC LDL-C = low-density lipoprotein cholesterol measured by ultracentrifugation

Methods

Study design and participants. This analysis included patients who participated in 4 randomized, double-blind, controlled phase II studies of evolocumab (15,18–20). The patient populations, background lipid therapy, and treatment arms in these studies were described previously and are summarized in Table 1. All studies were of 12-week durations and examined a range of evolocumab doses and dose frequencies administered subcutaneously (SC): 70 mg, 105 mg, or 140 mg every 2 weeks (Q2W) or 280 mg, 350 mg, or 420 mg every 4 weeks (Q4W) and were compared with placebo (Q2W or Q4W, respectively); in 2 trials, ezetimibe was administered, either alone or concomitantly with evolocumab or placebo (Fig. 1). The primary endpoint for all 4 trials was the percentage change from baseline in LDL-C at week 12, measured by ultracentrifugation (UC LDL-C); pooled results for this endpoint and other lipid analyses, as well as pooled safety data, were reported separately (21). This analysis focuses on Lp(a), including the percentage of change from baseline at week 12 in Lp(a) by dose group and for the patient subgroup considered to be at highest risk as indicated by baseline Lp(a) values that exceeded 125 nmol/l (approximately 50 mg/dl). Additional analyses included the relationship between Lp(a) lowering and lowering of UC LDL-C and apolipoprotein B and the effects of sex, age, baseline LDL-C and statin therapy on Lp(a) lowering. In addition, the phase II open-label extension study (NCT01439880) allowed for evaluation of evolocumab maintenance or discontinuation on Lp(a) levels during the first 12 weeks of follow-up for patients re-randomized to receive either evolocumab, 420 mg Q4W, or to continue with background lipid-lowering standard of care (SOC) therapy.

Lp(a) was measured using an isoform-independent immunoturbidometric assay (Denka Seiken Co. Ltd., Lp(a) assay, Polymedco, Cortlandt Manor, New York) with a AU5400 analyzer (Olympus, Beckman Coulter Instruments, Brea, California) (22).

Table 1	Characteristics of the 4 Evolocumab Phase II Studies			
Study (Ref. #) (Method)	**n***	**Patient Profile and Background Lipid-Lowering Therapy**	**Treatments and Doses**	**Key Efficacy Results After 12 Weeks of Treatment**
MENDEL (1) (monotherapy)†	406	LDL-C ≥100 and <190 mg/dl (≥2.6 and <4.9 mmol/l) No background antilipid therapy Patients with CAD were excluded.	9 treatment groups: Evolocumab 70 mg, 105 mg, or 140 mg or placebo Q2W OR Evolocumab 280 mg, 350 mg, or 420 mg or placebo Q4W OR Daily ezetimibe 10 mg	LDL-C (UC) mean % change from baseline vs. placebo: −37.3% to −52.5% vs. ezetimibe: −26.7% to −34.1% p < 0.001 for all doses Lp(a) mean % change from baseline vs. placebo: −11.1% (p = 0.0437) to −29.2% (p < 0.001 for all doses) vs. ezetimibe: −7.8% (p = 0.13) to −26.0% (p < 0.001 for all doses)
LAPLACE-TIMI 57 (2,3) (combination therapy) †	629	LDL-C ≥85 mg/dl (≥2.2 mmol/l) Statin ± ezetimibe CAD at baseline: Evolocumab: n = 145 (31%) Placebo: n = 42 (27%)	8 treatment groups: Evolocumab 70 mg, 105 mg, 140 mg, or placebo Q2W OR Evolocumab 280 mg, 350 mg, 420 mg, or placebo Q4W	LDL-C (UC) mean % change from baseline vs. placebo: 41.8% to 66.1% (p < 0.001 for all doses) Lp(a) mean % change from baseline vs. placebo: −18.0% to −32.3% (p < 0.001 for all doses)
RUTHERFORD (4) (heterozygous FH) †	167	Heterozygous FH with LDL-C ≥100 mg/dl (≥2.6 mmol/l) Statin ± ezetimibe CAD at baseline: Evolocumab: n = 25 (23%) Placebo: n = 10 (18%)	3 treatment groups: Evolocumab 350 mg, 420 mg, or placebo Q4W	LDL-C (UC) mean % change from baseline vs. placebo: −43.8% to −56.4% (p < 0.001 for all doses) Lp(a) mean % change from baseline vs. placebo: −23.1% to −31.5% (p < 0.001 for all doses)
GAUSS (5) (statin intolerance) †	157	Statin-intolerant patients LDL-C ≥100 mg/dl (≥2.6 mmol/l) No/low-dose statin CAD at baseline: Evolocumab: n = 11 (12%) Placebo: n = 10 (31%)	5 treatment groups: Evolocumab 280 mg, 350 mg, or 420 mg Q4W OR Ezetimibe 10 mg plus SC placebo Q4W OR Ezetimibe 10 mg plus evolocumab 420 mg Q4W	LDL-C (UC) mean % change from baseline vs. ezetimibe: −26.0% to −47.3%, p < 0.001 for all doses Lp(a) mean % change from baseline vs. ezetimibe: −19.1% to −33.1%

*The number of patients who were randomized and received at least 1 dose of investigational product. †The primary endpoint for each trial was percent reduction in LDL-C from baseline at week 12.

CAD = coronary artery disease, based on the presence of angina, myocardial infarction, coronary artery bypass graft, or percutaneous coronary intervention; FH = familial hypercholesterolemia; GAUSS = Goal Achievement After Utilizing an Anti-PCSK9 Antibody in Statin-Intolerant Subjects; LDL-C = low-density lipoprotein cholesterol; LAPLACE-TIMI 57 = LDL-C Assessment With PCSK9 Monoclonal Antibody Inhibition Combined With Statin Therapy; MENDEL = Monoclonal Antibody Against PCSK9 to Reduce Elevated LDL-C in Patients Currently Not Receiving Drug Therapy for Easing Lipid Levels; Q2W = every 2 weeks; Q4W = every 4 weeks; PBO = placebo; RUTHERFORD = Reduction of LDL-C With PCSK9 Inhibition in Heterozygous Familial Hypercholesterolemia Disorder; SC = subcutaneous.

Data extraction and statistical analysis. A total of 1,359 patients were enrolled, and the pooled analyses included all randomly assigned patients who received at least 1 dose of investigational product or placebo in the 4 phase II studies (Fig. 1). In the Lp(a) analyses, patients randomized to receive either ezetimibe or placebo therapy were included in the control groups. Analyses for Lp(a), UC LDL-C, and apolipoprotein B were performed using the analysis of covariance model in each dosing regimen (Q2W or Q4W), with the last observation carried forward imputation for missing data, to compare the efficacy of evolocumab doses to those of the control. Analyses were not controlled for multiplicity. The correlations between Lp(a) and UC LDL-C or apolipoprotein B for patients randomized to evolocumab and placebo combined were assessed using the Spearman correlation coefficient for patients with Lp(a) ≥5 nmol/l (the lower limit of detection) at week 12. All analyses were done with SAS/STAT version 9.2 software (SAS Institute, Cary, North Carolina).

Results

In a population with an age of 56.4 ± 11.7 years, 56.2% women, and 60.3% patients taking statin therapy, the median baseline Lp(a) concentration was 40.0 nmol/l (interquartile range [IQR]: 13.0 to 144.0 nmol/l), and the mean baseline UC LDL-C concentration was 140.6 ± 38.9 mg/dl Table 2. Evolocumab treatment resulted in significant (p < 0.001) dose-related mean reductions in Lp(a) for all treatment groups compared with control (Fig. 2, Table 3). Lp(a) reductions were accompanied by significant reductions from baseline in UC LDL-C and apolipoprotein B (Table 3). Significant correlations were observed between percentages of reductions in Lp(a) and UC LDL-C (Spearman correlation coefficient, 0.5134; p < 0.001) (Fig. 3A) and between reductions in Lp(a) and apolipoprotein B (Spearman correlation coefficient, 0.5203; p < 0.001) (Fig. 3B).

Results were also analyzed according to consensus-based "high-risk" Lp(a) levels >125 nmol/l (approximately 50 mg/dl, or the 80th percentile of the population) (6) (Table 4). There were significantly more patients in the high-risk Lp(a) group with coronary artery disease and hypertension and who were taking statins or ezetimibe at baseline and who were black (Table 4). Baseline UC LDL-C was 141.6 ± 39.1 mg/dl and 138.2 ± 38.8 mg/dl in the low- and high-risk groups, respectively, and
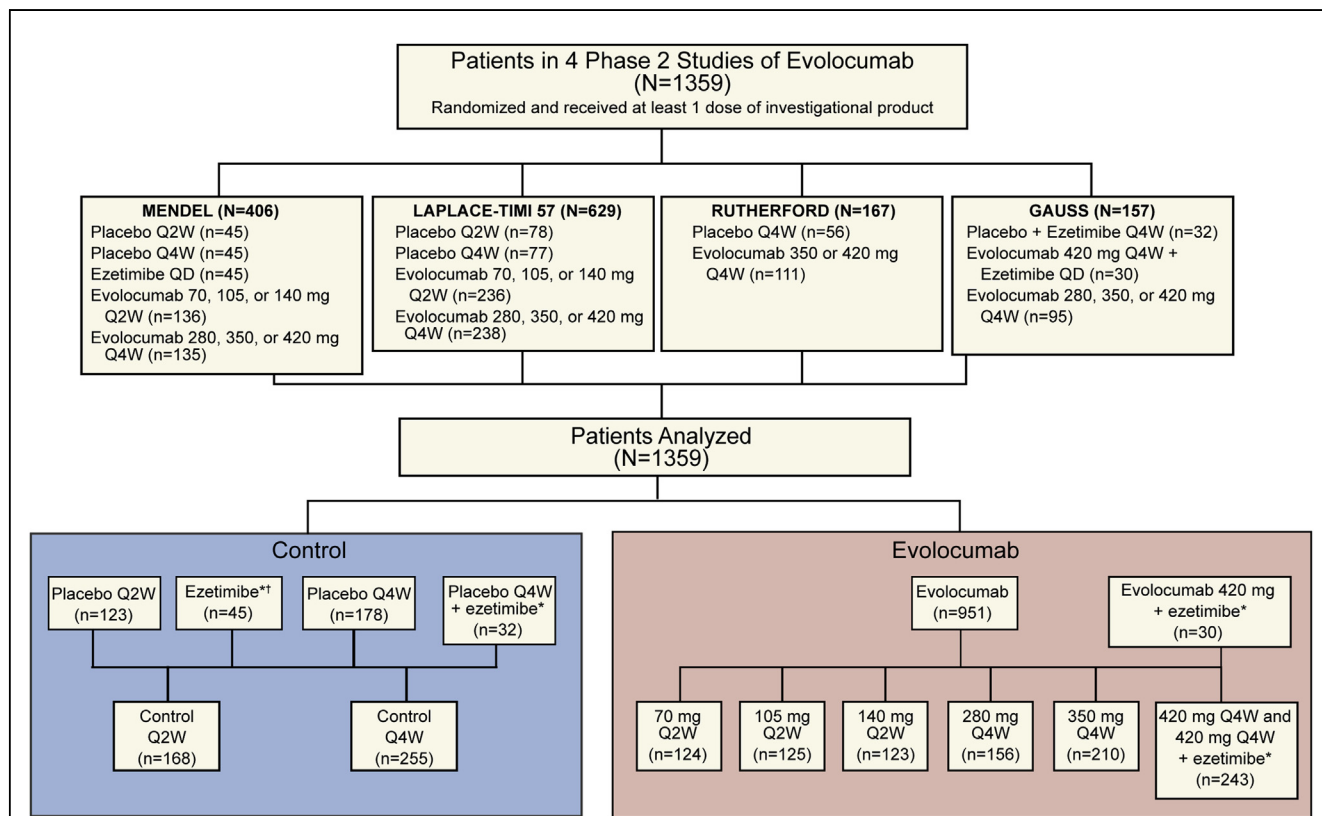
Figure 1   PROFICIO Analysis Schema

The PROFICIO analysis included pooled patient data from 4 phase II studies of evolocumab in patients receiving various background therapies. Q2W = every 2 weeks; Q4W = every 4 weeks. *In the Lp(a) analysis, patients who received ezetimibe or placebo were analyzed in the control groups; the ezetimibe group was analyzed with both the Q2W and Q4W control groups. Patients who received evolocumab, 420 mg Q4W, plus ezetimibe were included in the evolocumab 420-mg group. In the LDL-C and apolipoprotein B analyses, patients who received ezetimibe or ezetimibe plus placebo or evolocumab, 420 mg Q4W, plus ezetimibe were excluded. LDL-C = low-density lipoprotein cholesterol.

apolipoprotein B was 110.8 ± 25.2 mg/dl and 110.7 ± 25.9 mg/dl in the 2 groups.

Statistically significant reductions (p < 0.001) in Lp(a), UC LDL-C, and apolipoprotein B were observed with evolocumab, regardless of patients' baseline Lp(a) levels (Table 5). Patients with baseline Lp(a) levels ≤125 nmol/L had greater percentage reductions than controls in Lp(a) compared to those in the high-risk group (for 140 mg Q2W: −33.2% vs. −20.0%, respectively; for 420 mg Q4W: −28.7% vs. −16.1%, respectively), whereas the absolute reductions compared to those of control were substantially greater in the high-risk Lp(a) group (for 140 mg Q2W: 34.1 nmol/l vs. 8.9 nmol/l, respectively; for 420 mg Q4W: 38.6 nmol/l vs. 9.7 nmol/l, respectively). Baseline Lp(a) also appeared to have an impact on both the percentages and absolute reductions versus placebo in LDL-C and apolipoprotein B, with those with baseline Lp(a) >125 nmol/l experiencing a lower percent reduction of approximately 6% to 8% and a modestly smaller absolute reduction (Table 5).

There were no differences in Lp(a) responses based on sex, age (below and at or above 65 years), or LDL-C (below and at or above median baseline levels) (Online Fig. S1). Reductions in Lp(a) were numerically greater in patients on background statin therapy than in those not on statin therapy and were statistically significant compared to controls at all doses except 70 mg Q2W. The treatment differences between those taking statins and those not taking statins within evolocumab doses were numerically greater, but the interaction effects were not statistically significant except in the 105-mg-Q2W group (interaction, p = 0.0112) (Online Fig. S2).

For patients who were randomized to receive SOC and stopped evolocumab therapy in the open-label extension study, Lp(a) values returned to their pre-treatment levels. Patients who were taking evolocumab, 420 mg Q4W, and continued with this dosage during the open-label extension maintained the reduction in Lp(a) as shown in Figure 4.

Overall, adverse events were reported in 56.8% and 49.2% of patients in the combined evolocumab and combined placebo groups, respectively, with no relationship to dose or frequency. Serious adverse events were reported in 2.0% and 1.2% of patients in the evolocumab and placebo groups,

| Table 2 | Patient Demographics, Lipoprotein(a), Apolipoprotein B, and Related Lipid Parameters at Baseline | | | | | | | |

		Evolocumab						
	Control* (n = 378)	70 mg Q2W (n = 124)	105 mg Q2W (n = 125)	140 mg Q2W (n = 123)	280 mg Q4W (n = 156)	350 mg Q4W (n = 210)	420 mg Q4W* (n = 243)	Total (N = 1,359)
Age, yrs	55.5 (11.4)	56.3 (11.8)	54.9 (11.6)	58.9 (11.7)	57.5 (10.7)	55.9 (13.0)	56.8 (11.8)	56.4 (11.7)
Women	214 (56.6)	74 (59.7)	58 (46.4)	81 (65.9)	86 (55.1)	117 (55.7)	134 (55.1)	764 (56.2)
Race								
White	328 (86.8)	105 (84.7)	104 (83.2)	106 (86.2)	127 (81.4)	185 (88.1)	209 (86.0)	1164 (85.7)
Black	32 (8.5)	13 (10.5)	13 (10.4)	13 (10.6)	18 (11.5)	15 (7.1)	22 (9.1)	126 (9.3)
Other†	18 (4.8)	6 (4.8)	8 (6.4)	4 (3.3)	11 (7.1)	10 (4.8)	13 (5.3)	70 (5.2)
Statin use	217 (57.4)	78 (62.9)	78 (62.4)	78 (63.4)	84 (53.8)	139 (66.2)	145 (59.7)	819 (60.3)
Ezetimibe use	46 (12.2)	6 (4.8)	8 (6.4)	7 (5.7)	7 (4.5)	44 (21.0)	42 (17.3)	160 (11.8)
Lipid parameters								
Lipoprotein(a) nmol/l	42.0 (14.0–144.0)	49.0 (14.0–154.0)	40.0 (12.0–151.0)	43.5 (14.0–141.0)	37.0 (12.0–130.0)	36.0 (10.0–127.0)	41.0 (14.0–160.0)	40.0 (13.0–144.0)
UC LDL-C, mg/dl	141.6 (35.6)	129.3 (25.6)	132.6 (29.6)	127.8 (25.3)	142.4 (42.4)	144.8 (42.2)	150.8 (49.4)	140.6 (38.9)
Calc LDL-C, mg/dl	140.2 (36.4)	128.1 (27.1)	130.4 (30.4)	125.5 (25.5)	140.1 (42.6)	142.7 (43.8)	148.6 (50.2)	138.7 (39.8)
Apolipoprotein B, mg/dl	111.1 (23.5)	103.1 (16.9)	105.4 (20.1)	101.9 (16.9)	112.1 (27.3)	114.3 (28.1)	117.8 (30.7)	110.8 (25.4)
Non-HDL-C, mg/dl	167.1 (41.0)	153.9 (30.2)	157.8 (34.0)	152.0 (26.8)	168.3 (47.6)	170.5 (46.9)	176.9 (54.8)	166.1 (43.7)
HDL-C, mg/dl	53.8 (16.8)	54.5 (17.1)	53.6 (17.7)	54.7 (15.1)	54.7 (17.8)	51.7 (15.3)	52.9 (17.3)	53.6 (16.7)
Triglycerides, mg/dl	136.0 (70.1)	129.1 (54.8)	137.4 (63.8)	132.7 (56.3)	140.3 (63.8)	141.8 (72.1)	141.4 (70.4)	137.6 (66.8)

Values are n (%), mean ± SD, or median (interquartile range). n = number of subjects randomized and dosed. *The control group includes placebo Q2W and Q4W, placebo plus ezetimibe, and ezetimibe alone. The Q4W 420 mg group includes Q4W 420 mg plus ezetimibe. †Other race included American Indian or Alaskan native, Asian, Native Hawaiian or other Pacific Islander, mixed race, and all others not specified.

calc = calculated; HDL-C = high-density lipoprotein cholesterol; IQR = interquartile range; LDL-C = low-density lipoprotein cholesterol; Q2W = every 2 weeks; Q4W = every 4 weeks; SD = standard deviation; UC = ultracentrifugation.

respectively; none of these adverse events were considered by the investigators to be treatment related. Anti-evolocumab binding antibodies were observed in 1 patient taking evolocumab and in 1 patient in the placebo group; no neutralizing antibodies were detected.

| Figure 2 | Lipoprotein(a) Mean Percentage Change (95% CI) From Baseline at Week 12 |

Statistically significant mean reductions in Lp(a) were observed with all doses of evolocumab compared with those of control. Least-squares mean differences (95% CI) from ANCOVA model are shown with last observation carried forward (LOCF) imputation. Treatment difference within each dose frequency group used control in the same frequency group as the reference. *p < 0.001. Within each dose frequency, the p value of the linear trend test is <0.001. ANCOVA = analysis of covariance; CI = confidence interval; Q2W = every 2 weeks; Q4W = every 4 weeks.

Discussion

PROFICIO analysis confirms some observations and shows contrasts with other observations in a smaller individual trial with a PCSK9 monoclonal antibody (17) and provides additional insights into responses by sex, age, baseline Lp(a), and background lipid therapy. In this pooled analysis of more than 1,300 patients, evolocumab treatment resulted in highly significant dose-related reductions in Lp(a). Unlike the analysis from the trial of evolocumab in patients with dyslipidemia treated with statins included in this pooled analysis (17), we demonstrate that, overall, within each dosing regimen, either 2- or 4-week dosing, there were continued reductions in Lp(a) as the dose increased, with no plateau effect. Furthermore, PROFICIO was differentiated in that it included a large number of patients not taking background statin treatment, and, although numerical reductions in treatment differences for Lp(a) appeared to be greater with statin therapy in all dose groups, these reductions were only statistically significant (p < 0.02) for the 105-mg-Q2W dosage. Significant reductions in Lp(a) compared to control were observed with all evolocumab doses (except the lowest dosage of 70 mg Q2W), regardless of background therapy. In addition, we show for the first time that the reductions in Lp(a) were both related to treatment with evolocumab and reversible upon discontinuation of evolocumab or maintained with continued therapy. The PROFICIO data pool was also large enough to provide meaningful analysis based on the consensus high-risk
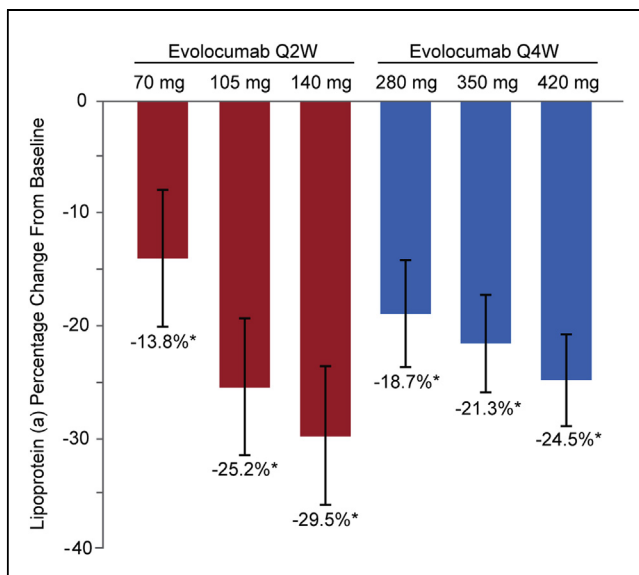
Table 3	Summary of Efficacy Outcomes at Week 12							
		Evolocumab					Evolocumab	
	Control Q2W (n = 168)	70 mg Q2W (n = 124)	105 mg Q2W (n = 125)	140 mg Q2W (n = 123)	Control Q4W (n = 255)	280 mg Q4W (n = 156)	350 mg Q4W (n = 210)	420 mg Q4W (n = 243)
Lipoprotein(a)*†								
Absolute change from baseline, nmol/l	−2.3 (−7.7 to 3.2)	−9.5 (−15.4 to −3.6)	−20.0 (−25.9 to −14.1)	−18.6 (−24.6 to −12.5)	−5.6 (−10.2 to −1.0)	−16.6 (−22.0 to −11.1)	−17.7 (−22.5 to −12.9)	−23.2 (−27.8 to −18.6)
% change from baseline	1.7 (−3.2 to 6.7)	−12.1 (−17.5 to −6.7)	−23.5 (−28.9 to −18.1)	−27.8 (−33.3 to −22.3)	0.1 (−3.8 to 3.9)	−18.6 (−23.2 to −14.0)	−21.3 (−25.3 to −17.2)	−24.5 (−28.4 to −20.6)
% change vs. control	—	−13.8 (−19.9 to −7.7) <0.001	−25.2 (−31.3 to −19.1) <0.001	−29.5 (−35.7 to −23.3) <0.001	—	−18.7 (−23.4 to −13.9) <0.001	−21.3 (−25.6 to −17.0) <0.001	−24.5 (−28.7 to −20.4) <0.001
Other related lipid parameters								
UC LDL-C*†	(n = 123)	(n = 124)	(n = 125)	(n = 123)	(n = 178)	(n = 156)	(n = 210)	(n = 213)
% change from baseline	0.0 (−3.7 to 3.7)	−40.3 (−43.9 to −36.6)	−53.0 (−56.6 to −49.3)	−59.4 (−63.1 to −55.7)	2.0 (−1.7 to 5.7)	−40.7 (−44.5 to −36.9)	−45.2 (−48.6 to −41.8)	−50.9 (−54.3 to −47.5)
% change vs. control	–	−40.2 (−44.6 to −35.8) <0.001	−52.9 (−57.3 to −48.5) <0.001	−59.4 (−63.8 to −55.0) <0.001	—	−42.8 (−46.9 to −38.6) <0.001	−47.3 (−51.0 to −43.5) <0.001	−52.9 (−56.6 to −49.2) <0.001
Apolipoprotein B*†	(n = 123)	(n = 124)	(n = 125)	(n = 123)	(n = 178)	(n = 156)	(n = 210)	(n = 213)
% change from baseline	3.2 (0.0 to 6.4)	−30.7 (−33.9 to −27.5)	−41.8 (−45.0 to −38.6)	−49.0 (−52.2 to −45.7)	2.7 (−0.6 to 6.0)	−31.6 (−35.0 to −28.2)	−35.3 (−38.3 to −32.2)	−40.8 (−43.9 to −37.8)
% change vs. control	—	−33.9 (−37.7 to −30.1) <0.001	−44.9 (−48.8 to −41.1) <0.001	−52.1 (−56.0 to −48.3) <0.001	—	−34.2 (−37.9 to −30.5) <0.001	−37.9 (−41.2 to −34.6) <0.001	−43.5 (−46.8 to −40.2) <0.001

n = number of subjects randomized and dosed. *Least squares mean (95% confidence interval) is from the analysis of covariance model, which includes the study/stratification-combined variable and treatment as covariates. Missing values at week 12 are imputed using last observation carried forward (LOCF) and, for UC LDL-C, calculated LDL-C. Percentage of change from baseline is the treatment difference versus control. Treatment difference within each dose frequency group uses control in the same frequency group as the reference. Note that 1 trial (GAUSS) (20) did not have a true placebo-only group. †In the lipoprotein(a) analysis, patients who received ezetimibe or placebo were analyzed in the control group, and patients who received evolocumab 420 mg Q4W plus ezetimibe were analyzed in the evolocumab 420 mg group. In the LDL-C and apolipoprotein B analyses, patients who received ezetimibe or ezetimibe plus placebo or evolocumab 420 mg Q4W plus ezetimibe were excluded.

UC LDL-C = low-density lipoprotein cholesterol measured by preparative ultracentrifugation; other abbreviations as in Table 2.

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Figure 3   Correlation of Lipoprotein(a) With LDL-C and Apolipoprotein B

Correlation of Lp(a) percentage reductions at week 12 with percentage reductions in LDL-C **(A)** and apolipoprotein B **(B)** at week 12, including evolocumab and placebo groups combined, were statistically significant (Spearman correlation coefficients, p < 0.001). LDL-C = low-density lipoprotein cholesterol.

cut point above 125 mmol/l (approximately 50 mg/dl) and that for subjects with Lp(a) above this level, evolocumab produced absolute reductions of 35 to 40 nmol/l at the highest doses administered, either every 2 or 4 weeks. PROFICIO also demonstrated that baseline Lp(a) appears to have an impact on LDL-C and apolipoprotein B response in patients with levels >125 nmol/l experiencing approximately 6% to 8% less LDL-C and apolipoprotein B reduction.

The statistically significant (p < 0.001) associations between reductions in Lp(a) and those in LDL-C and apolipoprotein B may provide some insight into the potential mechanism(s) by which PCSK9 inhibition results in Lp(a) reduction. Lp(a) reduction could result from decreased production or assembly, increased clearance, or a combination of both mechanisms.

As shown by Tsimikas et al. (23), Koschinsky et al. (24), and Koschinsky and Marcovina (25), there is a strong inverse relationship between triglyceride and Lp(a) levels, consistent with the requirement for delipidation of triglyceride-rich forms of apolipoprotein B in the circulation as a prerequisite for Lp(a) assembly, which likely occurs at the cell surface and not intracellularly. Patients with defects in very low-density lipoprotein clearance or, alternatively, those with abetalipoproteinemia who have mutations in the microsomal triglyceride transfer protein (MTP) gene required for lipoprotein assembly, have very low plasma levels of all apolipoprotein B containing lipoproteins, including Lp(a), supporting this hypothesis (26). Further evidence of the critical role of apolipoprotein B availability and LDL in the formation of Lp(a) comes from reductions in Lp(a) seen when apolipoprotein B synthesis is downregulated with an antisense drug (27). While a direct effect on reducing apolipoprotein B synthesis by inhibition of PCSK9 has not been established, the converse has been

Table 4	Baseline Characteristics, Lipoprotein(a) ≤ and >125 nmol/l		
	≤125 nmol/l (n = 971)	>125 nmol/l (n = 382)	p Value*
Age, yrs	56.1 (11.9)	57.1 (11.3)	0.12
Women	552 (56.8)	209 (54.7)	0.48
Race			<0.001
White	862 (88.8)	296 (77.5)	
Black	57 (5.9)	69 (18.1)	
Other	52 (5.4)	17 (4.5)	
Lipid medication	568 (58.5)	262 (68.6)	
Statin	558 (57.5)	258 (67.5)	<0.001
Ezetimibe	90 (9.3)	70 (18.3)	<0.001
Coronary artery disease	151 (15.6)	93 (24.3)	<0.001
Type 2 diabetes mellitus	88 (9.1)	43 (11.3)	0.22
Hypertension	460 (47.4)	216 (56.5)	0.002
Lipid parameters			
Lipoprotein(a), nmol/l	22.0 (9.0–49.0)	196.0 (165.0–253.0)	
UC LDL-C, mg/dl	141.6 (39.1)	138.2 (38.8)	0.16
Apolipoprotein B, mg/dl	110.8 (25.2)	110.7 (25.9)	0.94
HDL-C, mg/dl	52.8 (16.2)	55.6 (18.0)	0.006
Triglycerides, mg/dl	141.7 (70.2)	126.2 (55.1)	0.001
PCSK9, ng/mL	421.2 (137.7)	444.1 (154.8)	0.009

Values are (%), mean ± SD, or median (interquartile range). n = number of subjects randomized and dosed in respective subgroup. *p values were assessed as univariate predictors of baseline Lp(a) >125 nmol/l.

PCSK9 = proprotein convertase subtilisin/kexin type 9; other abbreviations as in Table 2.

shown in animal models where excess circulating PCSK9 increases apolipoprotein B synthesis independently of the decreased uptake of LDL/apolipoprotein B by the LDL

| Figure 4 | Longer-term Effects of Evolocumab Maintenance or Discontinuation |

Longer-term effect of evolocumab maintenance or discontinuation on Lp(a) changes are shown during 12 weeks of the phase II open-label extension, median, and IQR values. EOS = end of original study; IQR = interquartile range; Q2W = every 2 weeks; Q4W = every 4 weeks; SOC = standard of care.

receptor. These findings may lend support to the notion that either reduced apolipoprotein B synthesis or decreased LDL-apolipoprotein B availability, or both, could lead to reduced Lp(a) formation (28–30).

It is known that apolipoprotein(a), once cleaved from LDL-apolipoprotein B, is degraded by elastases and proteases, and the resultant fragments are excreted in urine, where they can be measured (9). As patients with advanced renal failure have increased Lp(a) levels, usually made up of large isoforms, there does appear to be a significant role for the kidney in Lp(a) clearance (9). Thus, if there were a reduction in Lp(a) formation due to decreased LDL-apolipoprotein B availability subsequent to the marked fall in LDL associated with PCSK9 inhibition with evolocumab, an increase in "free" apolipoprotein(a) would occur if apolipoprotein(a) synthesis rates remained constant, resulting in increased urinary excretion of intact apolipoprotein(a) or its fragments. Future studies with PCSK9 inhibitors should assess this by measurements in pre- and post-treated patients.

Mechanisms for clearance of Lp(a) are not well established, and no known specific receptors or pathways have been validated. Studies assessing clearance of radiolabeled Lp(a) in both rodents and humans with LDL receptor defects do not support a significant role for the LDL receptor (12). Clinical evidence for the role of the LDL receptor is, however, conflicting as patients with heterozygous and especially homozygous familial hypercholesterolemia (FH) have higher levels of Lp(a) than non-FH populations and their relatives with similar Lp(a) isoforms (31). Numerous trials with drugs that upregulate LDL receptor activity, especially statins, have shown no or minimal reduction in Lp(a) (13). Approximately 10% to 15% of Lp(a) is converted to LDL when apolipoprotein(a) is cleaved, and this LDL could then be cleared more rapidly with PCSK9 inhibition as LDLR activity is markedly enhanced (13). This may contribute to the reduction in Lp(a) when LDL levels are very low.

There are currently no approved pharmacological agents to specifically lower plasma Lp(a) levels without affecting other lipoproteins. Of the lipid-altering drugs approved for LDL-C reduction in the general population, only nicotinic acid has been shown to consistently reduce Lp(a) (14,32). Reductions in Lp(a) were reported with therapeutic agents recently approved under very strict prescribing guidelines for the sole indication of treating homozygous familial hypercholesterolemia (33,34), such as antisense oligonucleotides to apolipoprotein B (mipomersen), and MTP inhibitors (lomitapide). However, the effect with lomitapide appeared to be lost after 78 weeks. Drugs that inhibit cholesteryl ester transfer protein (CETP), either in development or terminated due to toxicity or lack of efficacy on cardiovascular endpoints, such as torcetrapib, dalcetrapib, anacetrapib and evacetrapib (35), have also been shown to reduce Lp(a). The hepatic thyroid analog eprotirome also reduced Lp(a), but development was recently terminated due to toxicity (36). For both drug classes, the mechanism for Lp(a) reduction remains unclear (37).
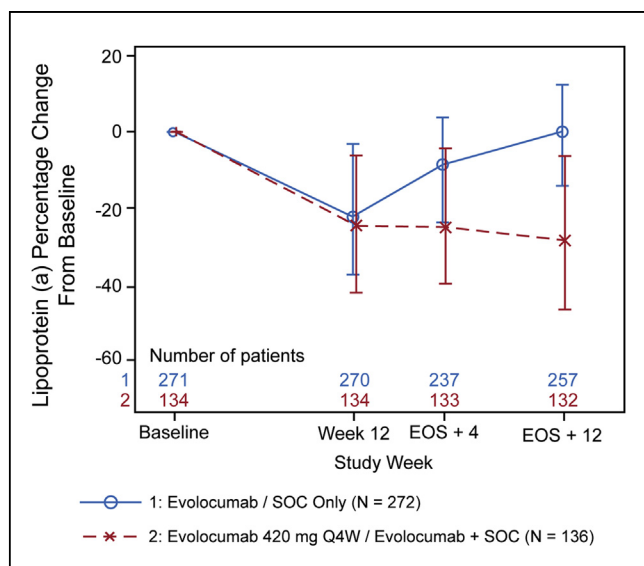
Table 5 Lipoprotein(a), UC LDL-C, and Apolipoprotein B Response by Specific Lipoprotein(a) Cut-Points at Week 12, Change and Percentage of Change Versus Control*

Dose Frequency		Evolocumab Q2W			Evolocumab Q4W		
	Dose	70 mg	105 mg	140 mg	280 mg	350 mg	420 mg
Lipoprotein(a)†							
Baseline Lp(a), ≤125 nmol/l	Absolute change from baseline vs. control‡	−5.2 (−9.0 to −1.4) <0.001	−9.0 (−12.7 to −5.2) <0.001	−8.9 (−12.7 to −5.0) <0.001	−7.0 (−9.9 to −4.0) <0.001	−8.0 (−10.7 to −5.4) <0.001	−9.7 (−12.3 to −7.0) <0.001
	% change from baseline vs. control	−16.1 (−23.8 to −8.5) <0.001	−27.6 (−35.2 to −20.0) <0.001	−33.2 (−40.9 to −25.4) <0.001	−21.0 (−27.0 to −15.1) <0.001	−25.3 (−30.6 to −20.0) <0.001	−28.7 (−34.0 to −23.5) <0.001
Baseline Lp(a), >125 nmol/l	Absolute change from baseline vs. control‡	−16.0 (−36.5 to 4.5) 0.12	−39.6 (−60.6 to −18.5) <0.001	−34.1 (−54.9 to −13.3) 0.002	−25.3 (−43.4 to −7.3) 0.006	−26.1 (−42.5 to −9.6) 0.002	−38.7 (−53.9 to −23. <0.001
	% change from baseline vs. control	−7.5 (−16.7 to 1.8) 0.11	−17.4 (−26.9 to −7.9) <0.001	−20.0 (−29.4 to −10.6) <0.001	−11.8 (−18.9 to −4.6) 0.001	−11.1 (−17.6 to −4.6) <0.001	−16.1 (−22.1 to −10.0) <0.001
	Interaction p value for % change by baseline lipoprotein(a) >125 or ≤125 nmol/l¶		0.247			0.006	
LDL-C							
Baseline Lp(a), ≤125 nmol/l	Absolute change from baseline vs. control‡	−52.4 (−60.4 to −44.3) <0.001	−71.2 (−79.2 to −63.1) <0.001	−77.9 (−86.0 to −69.8) <0.001	−61.5 (−69.4 to −53.5) <0.001	−64.2 (−71.22 to −57.1) <0.001	−75.1 (−82.3 to −67.8) <0.001
	% change from baseline vs. control	−41.1 (−46.6 to −35.5) <0.001	−53.7 (−59.3 to −48.2) <0.001	−61.7 (−67.2 to −56.1) <0.001	−46.8 (−51.7 to −42.0) <0.001	−48.6 (−52.9 to −44.2) <0.001	−54.7 (−59.1 to −50.3) <0.001
Baseline Lp(a), >125 nmol/l	Absolute change from baseline vs. control‡	−48.7 (−58.6 to −38.8) <0.001	−68.4 (−78.4 to −58.4) <0.001	−67.0 (−76.9 to −57.0) <0.001	−45.9 (−58.7 to −33.2) <0.001	−59.0 (−70.7 to −47.2) <0.001	−65.9 (−77.1 to −54.8) <0.001
	% change from baseline vs. control	−38.3 (−45.3 to −31.2) <0.001	−54.0 (−61.1 to −46.8) <0.001	−56.2 (−63.2 to −49.1) <0.001	−34.8 (−42.9 to −26.7) <0.001	−43.4 (−50.8 to −35.9) <0.001	−48.2 (−55.3 to −41.2) <0.001
	Interaction p value for % change by baseline lipoprotein(a) >125 or ≤125 nmol/l¶		0.554			0.113	

Table 5   Continued

Dose	Evolocumab Q2W			Evolocumab Q4W		
	70 mg	105 mg	140 mg	280 mg	350 mg	420 mg
Apolipoprotein B						
Baseline Lp(a), ≤125 nmol/l						
Absolute change from baseline vs. control‡	−35.6 (−40.9 to −30.3) <0.001	−48.1 (−53.3 to −42.8) <0.001	−55.7 (−61.0 to −50.3) <0.001	−39.7 (−45.0 to −34.4) <0.001	−41.7 (−46.4 to −37.0) <0.001	−50.9 (−55.7 to −46.1) <0.001
% change from baseline vs. control	−34.7 (−39.3 to −30.1) <0.001	−45.6 (−50.2 to −41.0) <0.001	−54.5 (−59.1 to −49.8) <0.001	−38.1 (−42.3 to −33.9) <0.001	−39.4 (−43.1 to −35.7) <0.001	−46.2 (−50.0 to −42.4) <0.001
Baseline Lp(a), >125 nmol/l						
Absolute change from baseline vs. control‡	−32.0 (−39.4 to −24.5) <0.001	−48.0 (−55. to −40.3) <0.001	−46.6 (−54.2 to −39.1) <0.001	−27.9 (−37.0 to −18.8) <0.001	−37.4 (−45.9 to −29.0) <0.001	−41.9 (−49.8 to −33.9) <0.001
% change from baseline vs. control	−31.7 (−38.4 to −25.0) <0.001	−45. 4 (−52.3 to −38.6) <0.001	−48.3 (−55.1 to −41.6) <0.001	−27.2 (−34.7 to −19.8) <0.001	−34.4 (−41.2 to −27.5) <0.001	−37.8 (−44.3 to −31.3) <0.001
Interaction p value for % change by baseline lipoprotein(a) >125 or ≤125 nmol/l¶		0.337			0.026	

‡In the lipoprotein(a) analysis, patients who received ezetimibe or placebo were analyzed in the control group, and patients who received evolocumab 420 mg Q4W plus ezetimibe were included in the evolocumab 420 mg group. In the LDL-C and apolipoprotein B analyses, patients who received ezetimibe or ezetimibe plus placebo or evolocumab 420 mg Q4W plus ezetimibe were excluded. *Least squares mean difference compared to control (95% confidence interval) is from the analysis of covariance model, which includes the study/stratification variable and treatment as covariates. Missing values at week 12 were imputed using the last observation carried forward method. ‡Lipoprotein(a) change from baseline is in nmol/l. LDL-C change from baseline is in mg/dl. Apolipoprotein B change from baseline is in mg/dl. ¶Analysis models include all treatment groups within the dose frequencies (Q2W and Q4W). Interaction results provided are for all doses within each dose frequency by baseline lipoprotein(a) (>125 or ≤125 nmol/l). Interaction p values are for the percentages of change from baseline analyses only and not for the absolute change. Abbreviations are as in Table 2.

Study limitations. It remains unknown whether lowering Lp(a) will yield clinical benefit and reduce cardiovascular mortality. Nevertheless, the strong epidemiologic and genetic evidence suggesting that Lp(a) is an independent causal risk factor for CVD makes it a valid interventional target for therapy when attempting to further reduce CVD risk. Definitive outcome trials are likely to be very difficult as all current drug strategies do not reduce Lp(a) selectively but affect multiple other lipoprotein classes. In addition to the marked reduction in LDL-C, the reduction in Lp(a) seen with evolocumab may be of greater benefit to patients with increased levels of this risk factor. However the apparent 6% to 8% less LDL-C and apolipoprotein B reduction seen in patients with elevated Lp(a) will make it very difficult to isolate the impact on CVD risk of Lp(a) reduction by PCSK9 inhibitors in any clinical trial.

Conclusions

Inhibition of PCSK9 with evolocumab yielded significant dose-related reductions in Lp(a) with both 2- and 4-week dosing. The reductions were both reversible upon discontinuation of evolocumab and sustained during longer-term therapy. The reductions were independent of age, sex and baseline LDL-C and tended to be greater in those on statin background therapy than those on diet alone. Although percentage reductions from baseline were greater in those with lower starting Lp(a) levels, the absolute reductions were substantially greater in those considered at higher risk, with baseline Lp(a) >125 nmol/l. Those with higher baseline Lp(a) levels had 6% to 8% less LDL-C and apolipoprotein B reduction than those with Lp(a) in the normal range. The reductions in Lp(a) demonstrated strong correlation with reductions in LDL-C and apolipoprotein B, but the mechanism by which PCSK9 reduces Lp(a) remains to be elucidated.

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Key Words: dyslipidemia ▪ evolocumab ▪ lipoprotein(a) ▪ PCSK9 inhibition.

▶ **APPENDIX**

For supplemental figures, please see the online version of this article.