AMG145, a Monoclonal Antibody Against Proprotein Convertase Subtilisin Kexin Type 9, Significantly Reduces Lipoprotein(a) in Hypercholesterolemic Patients Receiving Statin Therapy

An Analysis From the LDL-C Assessment With Proprotein Convertase Subtilisin Kexin Type 9 Monoclonal Antibody Inhibition Combined With Statin Therapy (LAPLACE)–Thrombolysis in Myocardial Infarction (TIMI) 57 Trial

Nihar R. Desai, MD, MPH; Payal Kohli, MD; Robert P. Giugliano, MD, SM; Michelle L. O'Donoghue, MD, MPH; Ransi Somaratne, MD; Jing Zhou, MS; Elaine B. Hoffman, PhD; Fannie Huang, MS; William J. Rogers, MD; Scott M. Wasserman, MD; Robert Scott, MD; Marc S. Sabatine, MD, MPH

Background—Lipoprotein(a) [Lp(a)] is an emerging risk factor for cardiovascular disease. Currently, there are few available therapies to lower Lp(a). We sought to evaluate the impact of AMG145, a monoclonal antibody against proprotein convertase subtilisin kexin type 9 (PCSK9), on Lp(a).

Methods and Results—As part of the LDL-C Assessment With PCSK9 Monoclonal Antibody Inhibition Combined With Statin Therapy (LAPLACE)–Thrombolysis in Myocardial Infarction (TIMI) 57 trial, 631 patients with hypercholesterolemia receiving statin therapy were randomized to receive AMG145 at 1 of 3 different doses every 2 weeks or 1 of 3 different doses every 4 weeks versus placebo. Lp(a) and other lipid parameters were measured at baseline and at week 12. Compared with placebo, AMG145 70 mg, 105 mg, and 140 mg every 2 weeks reduced Lp(a) at 12 weeks by 18%, 32%, and 32%, respectively (P<0.001 for each dose versus placebo). Likewise, AMG145 280 mg, 350 mg, and 420 mg every 4 weeks reduced Lp(a) by 18%, 23%, and 23%, respectively (P<0.001 for each dose versus placebo). The reduction in Lp(a) correlated with the reduction in low-density lipoprotein cholesterol (ρ=0.33, P<0.001). The effect of AMG145 on Lp(a) was consistent regardless of age, sex, race, history of diabetes mellitus, and background statin regimen. Patients with higher levels of Lp(a) at baseline had larger absolute reductions but comparatively smaller percent reductions in Lp(a) with AMG145 compared with those with lower baseline Lp(a) values.

Conclusions—AMG145 significantly reduces Lp(a), by up to 32%, among subjects with hypercholesterolemia receiving statin therapy, offering an additional, complementary benefit beyond robust low-density lipoprotein cholesterol reduction with regard to a patient's atherogenic lipid profile.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT01380730.

(*Circulation*. 2013;128:962-969.)

Key Words: biomarker ■ lipids ■ lipoproteins ■ PCSK9 protein, human

Lipoprotein(a) [Lp(a)] is a circulating lipoprotein composed of an apolipoprotein B100 (ApoB) molecule covalently bound to a liver-derived glycoprotein, apolipoprotein(a) [Apo(a)].[1] Apo(a) is encoded by the *LPA* gene on chromosome 6 and shares structural homology with plasminogen.[2] Lp(a) is postulated to play a role in tissue healing and innate immunity, but its precise physiological role remains undefined.[3] It is increasingly recognized as having both proatherosclerotic and prothrombotic

Continuing medical education (CME) credit is available for this article. Go to http://cme.ahajournals.org to take the quiz.

Received March 1, 2013; accepted July 12, 2013.

From the TIMI Study Group, Division of Cardiovascular Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA (N.R.D., P.K., R.P.G., M.L.O'D., J.Z., E.B.H., M.S.S.); Amgen, Inc, Thousand Oaks, CA (R. Somaratne, F.H., S.M.W., R. Scott); and University of Alabama at Birmingham (W.J.R.).

Guest Editor for this article was Robert H. Eckel, MD.

The online-only Data Supplement is available with this article at http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIRCULATIONAHA.113.001969/-/DC1.

Correspondence to Marc S. Sabatine, MD, MPH, TIMI Study Group, 350 Longwood Ave, Boston, MA 02115. E-mail msabatine@partners.org

Circulation **is available at http://circ.ahajournals.org** **DOI: 10.1161/CIRCULATIONAHA.113.001969**

effects.[3] Specifically, Lp(a) promotes smooth muscle cell proliferation, endothelial cell adhesion molecule expression, foam cell generation, and endothelial dysfunction. Moreover, given its structural similarity to plasminogen, it acts as a competitive inhibitor for plasminogen and has antifibrinolytic effects.

Clinical Perspective on p 969

In epidemiological and genetic analyses, Lp(a) has emerged as an important risk factor for the development of cardiovascular disease (CVD).[4–6] On the basis of these data, the 2010 European Society of Atherosclerosis issued a consensus statement recommending assessment of Lp(a) in individuals with premature CVD, familial hypercholesterolemia, a family history of premature CVD or elevated Lp(a), or recurrent CVD despite statin therapy.[7] The 2011 European Society of Cardiology/European Society of Atherosclerosis guidelines are also consistent with this approach, recommending screening for elevated Lp(a) in people at high risk for CVD or with a strong family history of premature atherothrombotic disease.[8]

There are limited therapeutic options for lowering Lp(a) levels. Beyond niacin, which at daily doses of 2 to 4 g reduces Lp(a) by ≈30%, other therapies such aspirin, fibrates, and thyroid hormone supplementation offer modest reductions in Lp(a).[9–13] The impact of statins on Lp(a) remains a point of controversy, but most analyses suggest a neutral effect or an increase in Lp(a) levels.[14,15]

AMG145 is a fully human monoclonal antibody to proprotein convertase subtilisin kexin type 9 (PCSK9), a protein synthesized and secreted by the hepatocyte, that binds to the low-density lipoprotein (LDL) receptor, targeting it for lysosomal degradation. In the LDL-C Assessment with PCSK9 Monoclonal Antibody Inhibition Combined With Statin Therapy (LAPLACE)–Thrombolysis in Myocardial Infarction (TIMI) 57 trial, AMG145 compared with placebo led to significant, dose-dependent reductions in LDL cholesterol (LDL-C) of up to 66% at week 12 in patients with hypercholesterolemia receiving statin therapy with or without ezetimibe.[16] We sought to evaluate the impact of PCSK9 inhibition with AMG145 on Lp(a) in this patient population.

Methods

Study Population and Treatment

The design, rationale, and primary findings of the LAPLACE–TIMI 57 trial were published previously.[16,17] In brief, the study was a phase 2, double-blind, placebo-controlled, dose-ranging study of AMG145 versus placebo in 631 subjects with hypercholesterolemia and LDL-C ≥85 mg/dL on a stable dose of statin therapy with or without ezetimibe. At baseline, 30% of subjects were receiving intensive statin therapy, defined as daily simvastatin 80 mg, atorvastatin ≥40 mg, rosuvastatin ≥20 mg, or any statin in combination with ezetimibe. Subjects were randomized equally across 8 treatment arms: AMG145 70 mg, 105 mg, 140 mg, or matching placebo every 2 weeks or AMG145 280 mg, 350 mg, 420 mg, or matching placebo every 4 weeks. Blood samples for Lp(a) assessment were collected at baseline (on the day of randomization but before the first dose of study drug) and at week 12 as part of this prespecified analysis. Lp(a) was measured with the use of a Polymedco immunoturbidimetric assay that is independent of Lp(a) particle size (Cortlandt Manor, NY; intra-assay coefficient of variation ≤4.1%; interassay coefficient of variation ≤8.5%; limit of detection 5 nmol/L) at a Medpace Reference Laboratory (see the online-only Data Supplement for further details). The baseline and week-12 LDL-C was measured by preparative ultracentrifugation at the Lipid Core Laboratory (Cincinnati, OH).

Statistical Analysis

Normality of the distribution of baseline Lp(a) and Lp(a) at week 12 and the absolute and percent changes in Lp(a) from baseline to week 12 were evaluated with the Shapiro-Wilk test of normality. Because of nonnormality of Lp(a) at baseline and week 12 even after log-transformation, median (interquartile range [IQR]) values are reported, and nonparametric tests were used for statistical inference. The absolute and percent changes in Lp(a) from baseline to week 12 were approximately normally distributed. The correlation between baseline, absolute change, and percent change in Lp(a) and similar assessments of LDL-C and other lipid parameters were evaluated with the Spearman correlation coefficient. Baseline clinical factors, demographic characteristics, and lipid parameters were assessed as univariate predictors of baseline Lp(a) greater than or equal to the median. Multivariable logistic regression models were developed with the use of a backward selection method applied to all factors that achieved $P<0.25$ on univariate testing to identify independent factors associated with baseline Lp(a) greater than or equal to the median. The least squares mean percent change in Lp(a) from baseline to week 12 for each treatment arm compared with placebo was calculated with the use of ANCOVA models with covariates for treatment group, LDL-C at study entry (<130 versus ≥130 mg/dL), and baseline use of ezetimibe (yes versus no). Formal interaction testing was performed to assess for heterogeneity across binary subgroups for subjects receiving AMG145 140 mg every 2 weeks or 420 mg every 4 weeks compared with placebo with the use of ANCOVA models. A linear trend interaction test was performed when assessing for heterogeneity across quartile of baseline Lp(a) (excluding subjects with nonquantifiable level) and baseline LDL-C. The absolute difference in Lp(a) from baseline to week 12 for each AMG145 dose versus placebo was compared with the Wilcoxon rank sum test. For all analyses of the change in Lp(a) from baseline to week 12, only subjects who had Lp(a) assessed at both time points were included. For all analyses, $P<0.05$ was considered significant. All analyses were performed by the TIMI Study Group with the use of an independent copy of the complete clinical trial database. The authors wrote all drafts of the article and take responsibility for its content.

Results

Of the 631 randomized subjects in the LAPLACE–TIMI 57 trial, 626 subjects (99%) had Lp(a) assessed at baseline, and 612 (97%) had Lp(a) assessed at both baseline and week 12. The distribution of Lp(a) at baseline is shown in Figure I in the online-only Data Supplement. The distribution was positively skewed with a long right tail: the mean was 95 nmol/L, and the median (IQR) was 43 (13–161) nmol/L. The distribution of baseline Lp(a) stratified by race demonstrated significant heterogeneity, with higher levels among blacks than among whites ($P<0.0001$; Figure IIA and IIB in the online-only Data Supplement). There was no correlation between baseline Lp(a) and baseline LDL-C ($\rho=0.005$, $P=0.89$) or other related lipid parameters (Table I in the online-only Data Supplement). There were weak correlations, some statistically significant, between baseline Lp(a) levels and baseline levels of high-density lipoprotein cholesterol ($\rho=0.09$, $P=0.02$), apolipoprotein A1 ($\rho=0.08$, $P=0.06$), triglycerides ($\rho=-0.13$, $P=0.001$), and PCSK9 ($\rho=0.09$, $P=0.03$) (Table I in the online-only Data Supplement).

Baseline characteristics for the cohort overall and for subjects with baseline Lp(a) less than versus greater than or equal to the median are shown in Table 1. Overall, the mean age was 61 years, 51% were female, 89% were white, 29% had a prior history of coronary artery disease, and 16% had diabetes mellitus. The mean (SD) baseline LDL-C by ultracentrifugation was 123 (28) mg/dL. Subjects with a Lp(a) greater than or equal to the median at baseline were more likely to be black and to have a prior history of

Table 1. Baseline Characteristics for Subjects With Baseline Lp(a) Less Than Median or Greater Than or Equal to Median (43 nmol/L)

Characteristic	Total (n=626)	Baseline Lp(a)		*P* Value
		Less Than Median (n=309)	Greater Than or Equal to Median (n=317)	
Age, mean (SD), y	61 (9.5)	60 (9.5)	61 (9.6)	0.18
Female, n (%)	318 (51)	147 (48)	171 (54)	0.11
Race, n (%)				<0.001
White	555 (89)	295 (95)	260 (82)	
Black	50 (8)	3 (1)	47 (15)	
Other	21 (3)	11 (4)	10 (3)	
Body mass index, mean (SD), kg/m^2	30.0 (5.6)	30.2 (5.7)	29.8 (5.6)	0.44
History of coronary artery disease, n (%)	184 (29)	79 (26)	105 (33)	0.04
History of diabetes mellitus, n (%)	102 (16)	51 (17)	51 (16)	0.89
History of hypertension, n (%)	434 (69)	198 (64)	236 (74)	0.005
History of stroke, n (%)	20 (3)	8 (3)	12 (4)	0.39
Current smoking, n (%)	100 (16)	50 (16)	50 (16)	0.89
Baseline creatinine clearance, mean (SD), mL/min	85 (18.9)	83 (17.4)	86 (20.2)	0.18
Baseline UC-LDL-C, mean (SD), mg/dL	123 (27.8)	122 (26.7)	124 (28.8)	0.29
Baseline total cholesterol, mean (SD), mg/dL	202 (33.5)	200 (32.3)	203 (34.6)	0.27
Baseline non-HDL cholesterol, mean (SD), mg/dL	147 (31.8)	148 (31.3)	147 (32.4)	0.89
Baseline HDL cholesterol, mean (SD), mg/dL	54 (16.9)	52 (16.2)	56 (17.4)	0.01
Baseline apolipoprotein B, mean (SD), mg/dL	101 (19.0)	101 (18.8)	101 (19.2)	0.68
Baseline triglycerides, mean (SD), mg/dL	137 (60.7)	146 (66.3)	129 (53.6)	<0.001

HDL indicates high-density lipoprotein; Lp(a), lipoprotein(a); and UC-LDL-C, ultracentrifugation low-density lipoprotein cholesterol.

coronary artery disease and hypertension as well as higher high-density lipoprotein and lower triglycerides. The median (IQR) Lp(a) values at baseline in patients with and without a history of coronary artery disease were 63 (15–181 nmol/L) and 40 (12–152 nmol/L), respectively (P=0.03). In a multivariable model, race, history of hypertension, history of coronary artery disease, higher baseline high-density lipoprotein, and lower baseline triglycerides were significant independent predictors of Lp(a) greater than or equal to the median at baseline (Table 2).

Among patients who had Lp(a) measured at both baseline and week 12 (n=612), all doses of AMG145 significantly reduced Lp(a) from baseline to week 12 compared with placebo (P<0.001 for each AMG145 dose compared with placebo; Figure 1). Compared with placebo, the mean percent reduction in Lp(a) from baseline to week 12 was 18.0%, 32.1%, and 32.3% for subjects receiving AMG145 70 mg, 105 mg, and 140 mg, respectively, and 18.2%, 22.8%, and 23.1% for subjects receiving AMG145 280 mg, 350 mg, and 420 mg every 4 weeks, respectively. In sensitivity analyses restricted to patients who had an Lp(a) level above the limit of detection at baseline (n=554), the effect of AMG145 compared with placebo on Lp(a) levels from baseline to week 12 was similar, with reductions of 20% to 36% and reductions of 21% to 26% for subjects receiving AMG145 every 2 and every 4 weeks, respectively (P<0.001 for each AMG145 dose compared with placebo; Figure III in the online-only Data Supplement). Reductions in ultracentrifugation LDL-C and ApoB for each AMG145 dose compared with placebo are shown side by side in Figure 2. The median (IQR) absolute changes in Lp(a) and achieved Lp(a) levels at week 12 across the different dose regimens are shown in Table 3.

Table 2. Multivariable Logistic Regression Model for Baseline Lipoprotein(a) Greater Than or Equal to Median (43 nmol/L)

Predictor	Odds Ratio	95% Confidence Interval	*P* Value
Race			
Black vs white	16.87	5.14–55.31	<0.0001
Other vs white	1.14	0.47–2.78	0.77
History of hypertension	1.48	1.03–2.14	0.036
History of coronary artery disease	1.55	1.05–2.28	0.026
Baseline HDL (per 1-SD increase)	1.26	1.04–1.52	0.017
Baseline triglycerides (per 1-SD increase)	0.82	0.68–0.99	0.036

HDL indicates high-density lipoprotein.

Among subjects who were allocated to and completed treatment with AMG145 and had an Lp(a) level above the limit of detection at baseline (n=405), there was only a moderate positive correlation between the percent change in Lp(a) and the percent change in LDL-C from baseline to week 12 (ρ=0.33, P<0.001; Figure 3).[18] The correlation with the percent change in ApoB was similar (ρ=0.36, P<0.001; Figure IV in the online-only Data Supplement), whereas the correlation with the percent change in PCSK9 was weak (ρ=0.12, P=0.013). The correlations with the percent change in other lipid parameters are shown in Table II in the online-only Data Supplement. In addition, there was

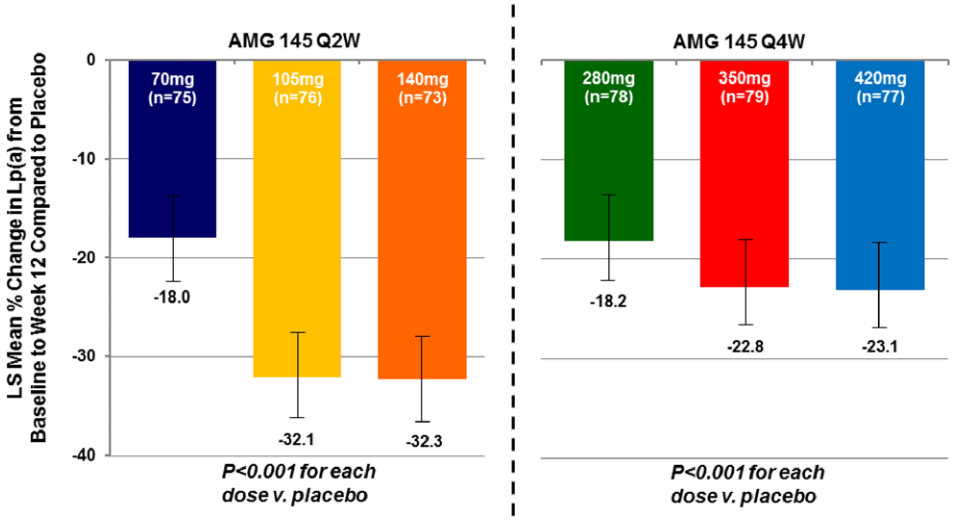

Figure 1. Least squares (LS) mean percent change in lipoprotein(a) [Lp(a)] from baseline to week 12 among subjects with Lp(a) assessed at both of those time points (n=612). The mean percent change was +3.4% for placebo every 2 weeks (Q2W) and −0.08% for placebo every 4 weeks (Q4W). The bars show the mean percent change by AMG145 treatment arm compared with the corresponding placebo. Error bars depict the standard error.

only a moderate correlation between LDL-C achieved at week 12 and percent change in Lp(a) (ρ=0.30, P<0.001).

Figure 4 demonstrates the percent reduction in Lp(a) among subjects receiving AMG145 140 mg every 2 weeks or 420 mg every 4 weeks across key subgroups. The percent change in Lp(a) was consistent regardless of age, sex, race, history of diabetes mellitus, intensity of background statin therapy, and LDL-C at study entry for AMG145 140 mg every 2 weeks and 420 mg every 4 weeks. There was a significant treatment interaction for the mean percent change in Lp(a) based on baseline Lp(a). Specifically, there were lesser percent reductions in Lp(a) across progressively higher quartiles of baseline Lp(a) for AMG145 140 mg every 2 weeks and 420 mg every 4 weeks (P_{int}<0.001 for both AMG145 doses versus placebo; Figure 4). Conversely, there were greater absolute reductions in Lp(a) from baseline to week 12 across higher quartiles of baseline Lp(a) for AMG145 140 mg every 2 weeks (P_{int}=0.003), with a similar appearance for AMG145 420 mg every 4 weeks (P_{int}=0.32) (Figure 5). In terms of correlations, for baseline Lp(a) and the percent reduction in Lp(a), the correlation coefficient was −0.24 (P<0.001), whereas for baseline Lp(a) and the absolute decrease in Lp(a), the correlation coefficient was 0.49 (P<0.001) (Figure VA and VB in the online-only Data Supplement).

Discussion

Several prior studies have suggested that Lp(a) is an important risk factor for the development of CVD.[4–6] In a meta-analysis of 36 studies including 126 634 individuals, there was a significant, curvilinear association between Lp(a) and the risk of coronary death, nonfatal myocardial infarction, and ischemic stroke.[4] After adjustment for age, sex, systolic blood pressure, smoking status, history of diabetes mellitus, body mass index, and total cholesterol, the risk ratio (95% confidence interval) per 3.5-fold (1-SD) higher Lp(a) level was 1.13 (1.09–1.18) for coronary heart disease and 1.10 (1.02–1.18) for ischemic stroke. Mendelian randomization data from 42 000 subjects in the Copenhagen City Heart Study suggested a significant causal association between elevated Lp(a) levels and the risk of myocardial infarction.[5] Another genetic analysis identified 2 common variants in the *LPA* gene that were strongly associated with both increased levels of Lp(a) and an increased risk of coronary disease, further supporting a causal role of Lp(a) in coronary disease.[6] Supporting the association between Lp(a) and CAD, in our study we found that

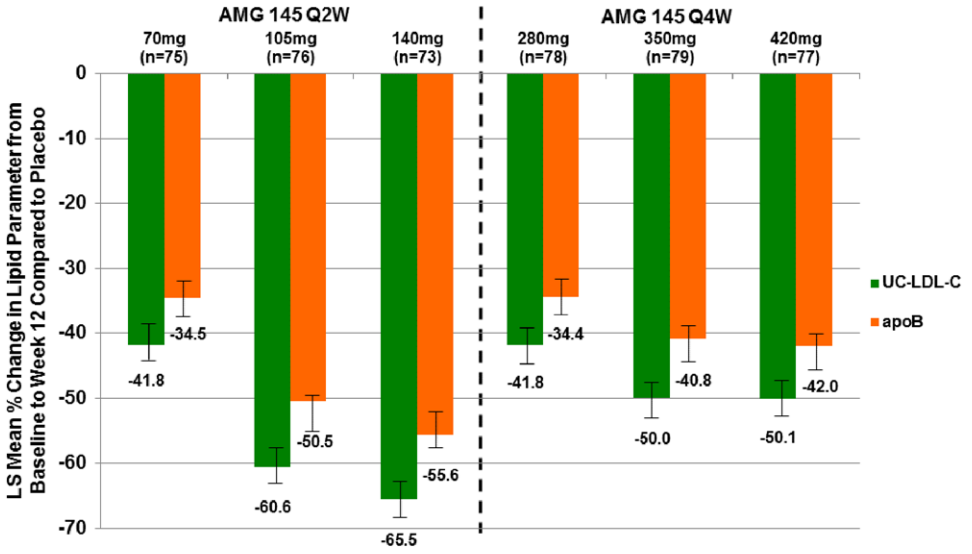

Figure 2. Least squares (LS) mean percent change in ultracentrifugation low-density lipoprotein cholesterol (UC-LDL-C) and apolipoprotein B (apoB) from baseline to week 12 by AMG145 treatment arm compared with placebo. Error bars depict the standard error. Q2W indicates every 2 weeks; and Q4W, every 4 weeks.

Table 3. Median (Interquartile Range) Lp(a) at Baseline and Week 12 and Median (Interquartile Range) Absolute Change in Lp(a) From Baseline to Week 12 Across Treatment Arm

Parameter	Placebo Q2W (n=77)	AMG145 70 mg Q2W (n=75)	AMG145 105 mg Q2W (n=76)	AMG145 140 mg Q2W (n=73)	Placebo Q4W (n=77)	AMG145 280 mg Q4W (n=78)	AMG145 350 mg Q4W (n=79)	AMG145 420 mg Q4W (n=77)
Lp(a) at baseline, nmol/L	41 (11, 178)	40 (10, 128)	46 (19, 178)	59 (15, 148)	45 (14, 130)	38 (10, 151)	29 (10, 174)	59 (20, 182)
Lp(a) at week 12, nmol/L	37 (14, 181)	30 (9, 116)	27 (7, 148)	29 (7, 97)	45 (16, 119)	22 (7, 125)	17 (7, 155)	40 (9, 167)
Absolute change in Lp(a) from baseline to week 12, nmol/L	0 (−5, 4)	−6 (−18, 0)	−13 (−32, −2.5)	−9 (−41, −2)	0 (−14, 4)	−7 (-23, −1)	−5 (−22, −1)	−13 (−30, 0)
P value*	…	<0.001	<0.001	<0.001	…	<0.001	<0.001	<0.001

Values are median (interquartile range). Lp(a) indicates lipoprotein(a); Q2W, every 2 weeks; and Q4W, every 4 weeks.
**P* value was calculated with the use of the Wilcoxon rank sum test for each AMG145 dose vs placebo.

a prior history of coronary artery disease was independently associated with higher levels of Lp(a) at baseline.

We found that compared with placebo, AMG145 significantly lowers Lp(a) in subjects with hypercholesterolemia receiving background therapy with statin with or without ezetimibe. In addition, we observed dose-response relationships at both dosing frequencies, with progressively more robust reductions in Lp(a), up to 32%, from baseline to week 12. However, similar to observations for ultracentrifugation LDL-C and ApoB, there appeared to be a plateau effect, which is consistent with the biology of PCSK9 inhibition with AMG145. When our analysis was restricted to subjects with an Lp(a) level above the limit of detection at baseline, AMG145 reduced Lp(a) by up to 36%. Of note, these measurements were made at the end of the AMG145 dosing intervals, and therefore, akin to our observations for LDL-C,[16] they likely underestimate the magnitude of reduction. Importantly, we found that the reduction in Lp(a) with AMG145 was consistent across several important subgroups including age, sex, race, history of diabetes mellitus, and background statin regimen. We found a significant interaction in the percent change in Lp(a) from baseline to week 12 based on baseline Lp(a). There were lesser percent reductions in Lp(a) from baseline to week 12 with progressively higher quartiles of baseline Lp(a). Conversely, there were greater absolute reductions in Lp(a) from baseline to week 12 with progressively higher quartiles of baseline Lp(a). These observations likely reflect, at the lower end of the baseline Lp(a) distribution, the mathematical inability to effect large absolute reductions, and, at the higher end of the markedly positively skewed baseline Lp(a) distribution, subjects who enjoyed larger absolute but comparatively smaller percent reductions in Lp(a).

The precise mechanism by which AMG145 lowers Lp(a) is unknown and warrants further research but is presumed to be a consequence of either decreased production or increased clearance. Given the close homology between Lp(a) and LDL-C and the dramatic reductions in LDL-C with AMG145, it is possible that Lp(a) could be cleared via the LDL receptor or the very-low-density lipoprotein receptor. Interestingly, patients with homozygous familial hypercholesterolemia have higher levels of Lp(a) than relatives with similar Lp(a) isoforms.[19] However, cell culture and animal studies have yielded mixed results, with some supporting and others casting doubt on the potential relevance of the LDL receptor for clearance of Lp(a).[20–25] Moreover, it remains unknown whether increased clearance of Lp(a) via the LDL receptor might be triggered in the setting of very low circulating levels of LDL-C, as existed for our patients. Alternatively,

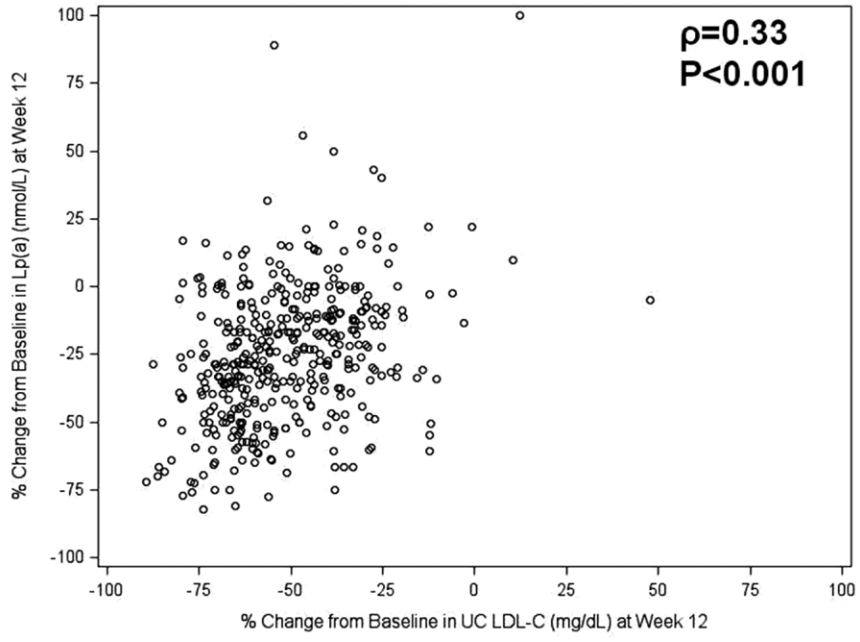

Figure 3. Spearman correlation between the percent change in lipoprotein(a) [Lp(a)] and the percent change in ultracentrifugation low-density lipoprotein cholesterol (UC-LDL-C) from baseline to week 12 among AMG145-treated subjects with quantifiable Lp(a) at baseline (n=405). Results were similar (ρ=0.25, *P*<0.001) when we corrected LDL-C levels for estimated Lp(a) cholesterol.

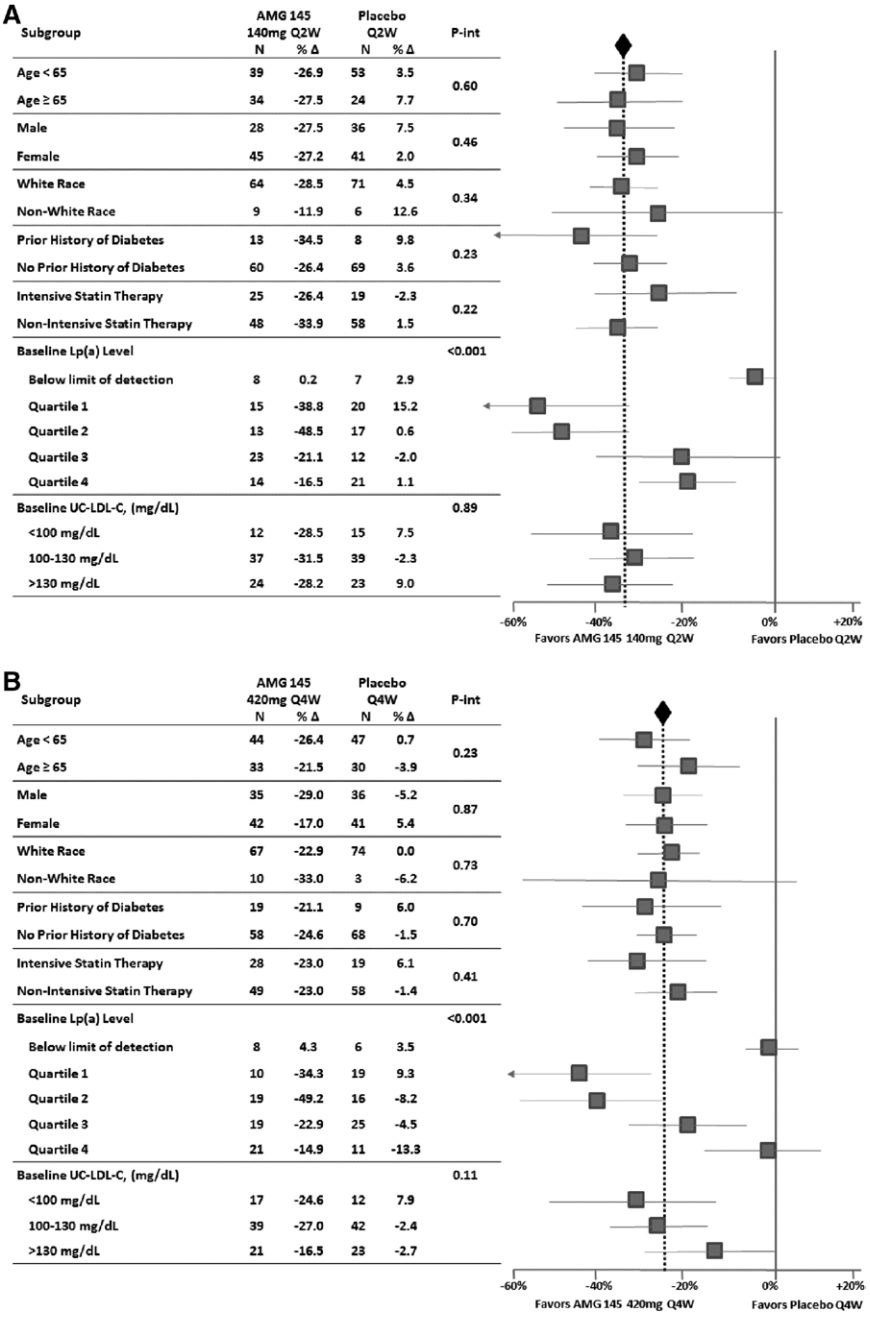

Figure 4. Forest plot of the mean percent change in lipoprotein(a) [Lp(a)] from baseline to week 12 for AMG145 140 mg every 2 weeks (Q2W; **A**) and AMG145 420 mg every 4 weeks (Q4W; **B**) across key subgroups. Boxes represent placebo-adjusted point estimates, and the horizontal bars represent 95% confidence intervals. The diamond and vertical dashed lines represent the effect observed in overall cohort. UC-LDL-C indicates ultracentrifugation low-density lipoprotein cholesterol.

lower levels of LDL-C and hence ApoB may limit substrate availability for the synthesis of Lp(a). We found only a moderate correlation between the percent change in Lp(a) and both the percent change in and achieved levels of LDL-C, but because AMG145 reduced both LDL-C and Lp(a) in a dose-dependent manner, it is not possible to disentangle the 2 effects. Finally, whatever the exact mechanism of Lp(a) reduction, this appears to be a class effect of PCSK9 inhibitors rather than a unique property of AMG145 because similar reductions were observed with the monoclonal antibody SAR236553/REGN727.[26]

In terms of other options to lower Lp(a), treatment with niacin lowers levels, but large clinical trials of niacin in patients with dyslipidemia [not specifically selected for Lp(a) levels] have failed to show any clinical benefit.[27,28] Other therapies offer modest reductions in Lp(a),[11–13] and statins appear, if anything, to increase Lp(a).[14,15] Trials of varying size are now ongoing with novel therapies that, in addition to other lipid-modifying effects, also reduce Lp(a), such as the cholesteryl ester transfer protein inhibitor anacetrapib[29] and mipomersen.[30] A specific antisense oligonucleotide targeted to Apo(a) has been shown to substantially lower Lp(a) in animal models.[31]

Several analytical points in regard to our study are worth noting. First, the distribution of Lp(a) was heavily positively skewed at baseline, similar to observations in other epidemiological studies. For that reason, we reported median (IQR) values and used nonparametric tests for statistical inference. Second, our findings are similar to those of other epidemiological studies that demonstrated heterogeneity of baseline Lp(a) by race. This observation has important implications for comparisons across studies drawing from different populations. Third, our assay had a limit of detection of 5 nmol/L such that 58 subjects (9%) had Lp(a) levels at or below the limit of detection at

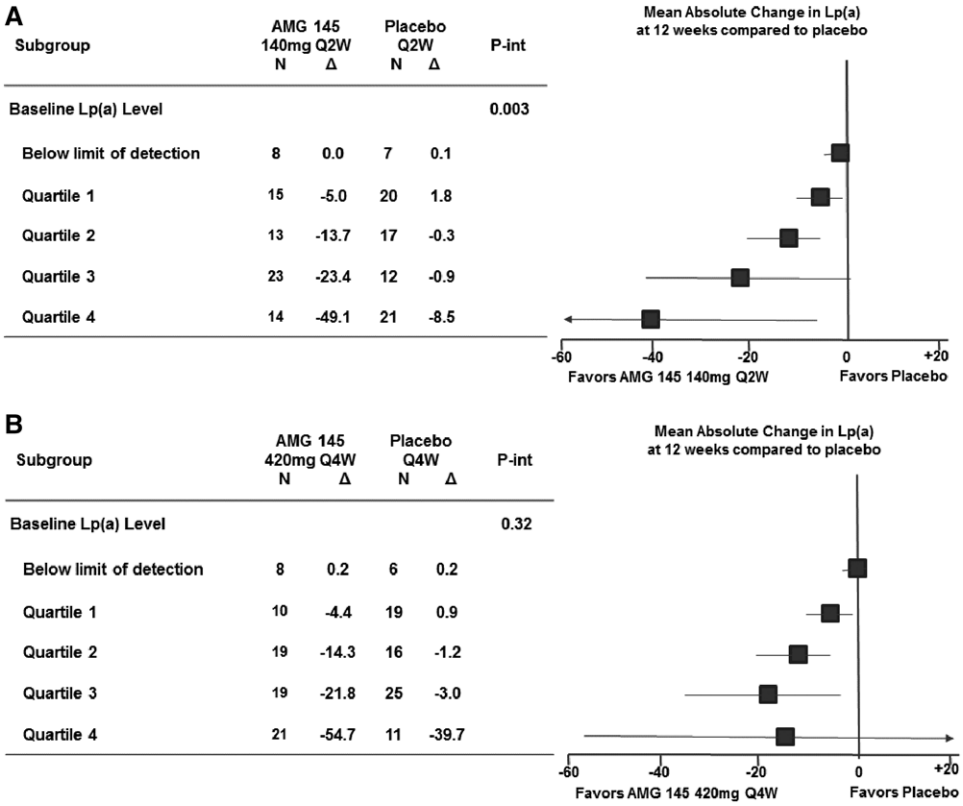

Figure 5. Forest plot of the mean absolute change in lipoprotein(a) [Lp(a)] from baseline to week 12 for AMG145 140 mg every 2 weeks (Q2W; **A**) and AMG145 420 mg every 4 weeks (Q4W; **B**) across quartiles of baseline Lp(a).

baseline. However, we used an immunoturbidometric assay that is independent of Apo(a) isoform and is preferred over alternative assays that rely on a measurement of the entire mass of Lp(a) and are more vulnerable to bias.[14] In addition, we performed sensitivity analyses excluding patients with Lp(a) levels below the limit of detection. Although we did not detect statistically significant interactions between baseline clinical characteristics and the effect of AMG145 on Lp(a) levels, this study was not powered to do so, and confirmation from data being gathered in larger ongoing trials will be important. Finally, our estimates of the change in Lp(a) are based on measurements at week 12, which is at the end of the dosing interval, and likely underestimate the true biological effect. Furthermore, the kinetics of Lp(a) reduction may differ from those observed for LDL-C, and further analyses of samples during the dosing interval may offer additional insights to both the timing and extent of Lp(a) reduction with AMG145.

In conclusion, the reduction in Lp(a) with AMG145, a monoclonal antibody to PCSK9, offers an additional, complementary benefit beyond robust LDL-C reductions with regard to a patient's atherogenic lipid profile. Although the clinical benefit of Lp(a) reduction remains undefined, these data lend further support to studying the impact of PCSK9 inhibition with AMG145 in a phase 3 clinical outcomes trial.

Sources of Funding

The LAPLACE–TIMI 57 Trial was supported by a research grant from Amgen, Inc, to the TIMI Study Group, Brigham and Women's Hospital.

Disclosures

Dr Giugliano reports receiving research grant support through Brigham and Women's Hospital from Daiichi-Sanyo and Merck and having received honoraria for consulting and/or CME lectures from Amgen, Daiichi-Sanyo, and Merck. Dr O'Donoghue reports receiving research grant support through Brigham and Women's Hospital from AstraZeneca and GlaxoSmithKline and having received honoraria for consulting from Aegerion. F. Huang and Drs Somaratne, Scott, and Wasserman are employees of Amgen and own Amgen stock. Dr Sabatine reports receiving research grant support through Brigham and Women's Hospital from Abbott Laboratories, Accumetrics, Amgen, AstraZeneca, AstraZeneca/Bristol-Myers Squibb Alliance, Bristol-Myers Squibb/Sanofi-Aventis Joint Venture, Critical Diagnostics, Daiichi-Sankyo, Eisai, Genzyme, GlaxoSmithKline, Intarcia, Merck, Nanosphere, Roche Diagnostics, Sanofi-Aventis, and Takeda and received honoraria for consulting from Aegerion, Amgen, AstraZeneca/Bristol-Myers Squibb Alliance, GlaxoSmithKline, Intarcia, Merck, Pfizer, Sanofi-Aventis, and Vertex. Dr Rogers reports receiving research grant support from Amgen and Sanofi-Aventis. The other authors report no conflicts.

References

1. Kathiresan S. Lp(a) lipoprotein redux: from curious molecule to causal risk factor. *N Engl J Med*. 2009;361:2573–2574.
2. McLean JW, Tomlinson JE, Kuang WJ, Eaton DL, Chen EY, Fless GM, Scanu AM, Lawn RM. cDNA sequence of human apolipoprotein(a) is homologous to plasminogen. *Nature*. 1987;330:132–137.
3. Kiechl S, Willeit J. The mysteries of lipoprotein(a) and cardiovascular disease revisited. *J Am Coll Cardiol*. 2010;55:2168–2170.
4. Erqou S, Kaptoge S, Perry PL, Di Angelantonio E, Thompson A, White IR, Marcovina SM, Collins R, Thompson SG, Danesh J. Lipoprotein(a) concentration and the risk of coronary heart disease, stroke, and nonvascular mortality. *JAMA*. 2009;302:412–423.
5. Kamstrup PR, Tybjaerg-Hansen A, Steffensen R, Nordestgaard BG. Genetically elevated lipoprotein(a) and increased risk of myocardial infarction. *JAMA*. 2009;301:2331–2339.
6. Clarke R, Peden JF, Hopewell JC, Kyriakou T, Goel A, Heath SC, Parish S, Barlera S, Franzosi MG, Rust S, Bennett D, Silveira A, Malarstig A, Green FR, Lathrop M, Gigante B, Leander K, de Faire U, Seedorf U, Hamsten A, Collins R, Watkins H, Farrall M; PROCARDIS Consortium. Genetic variants associated with Lp(a) lipoprotein level and coronary disease. *N Engl J Med*. 2009;361:2518–2528.

7. Nordestgaard BG, Chapman MJ, Ray K, Borén J, Andreotti F, Watts GF, Ginsberg H, Amarenco P, Catapano A, Descamps OS, Fisher E, Kovanen PT, Kuivenhoven JA, Lesnik P, Masana L, Reiner Z, Taskinen MR, Tokgözoglu L, Tybjærg-Hansen A; European Atherosclerosis Society Consensus Panel. Lipoprotein(a) as a cardiovascular risk factor: current status. *Eur Heart J*. 2010;31:2844–2853.
8. Chapman MJ, Ginsberg HN, Amarenco P, Andreotti F, Borén J, Catapano AL, Descamps OS, Fisher E, Kovanen PT, Kuivenhoven JA, Lesnik P, Masana L, Nordestgaard BG, Ray KK, Reiner Z, Taskinen MR, Tokgözoglu L, Tybjærg-Hansen A, Watts GF; European Atherosclerosis Society Consensus Panel. Triglyceride-rich lipoproteins and high-density lipoprotein cholesterol in patients at high risk of cardiovascular disease: evidence and guidance for management. *Eur Heart J*. 2011;32:1345–1361.
9. Guyton JR, Blazing MA, Hagar J, Kashyap ML, Knopp RH, McKenney JM, Nash DT, Nash SD; Niaspan-Gemfibrozil Study Group. Extended-release niacin vs gemfibrozil for the treatment of low levels of high-density lipoprotein cholesterol. *Arch Intern Med*. 2000;160:1177–1184.
10. Carlson LA, Hamsten A, Asplund A. Pronounced lowering of serum levels of lipoprotein Lp(a) in hyperlipidaemic subjects treated with nicotinic acid. *J Intern Med*. 1989;226:271–276.
11. Kolski B, Tsimikas S. Emerging therapeutic agents to lower lipoprotein (a) levels. *Curr Opin Lipidol*. 2012;23:560–568.
12. Jones PH, Pownall HJ, Patsch W, Herd JA, Farmer JA, Payton-Ross C, Kimball KT, Gotto AM, Morrisett JD. Effect of gemfibrozil on levels of lipoprotein[a] in type II hyperlipoproteinemic subjects. *J Lipid Res*. 1996;37:1298–1308.
13. Brown WV, Ballantyne CM, Jones PH, Marcovina S. Management of Lp(a). *J Clin Lipidol*. 2010;4:240–247.
14. Tsimikas S, Hall JL. Lipoprotein(a) as a potential causal genetic risk factor of cardiovascular disease: a rationale for increased efforts to understand its pathophysiology and develop targeted therapies. *J Am Coll Cardiol*. 2012;60:716–721.
15. Tsimikas S, Witztum JL, Miller ER, Sasiela WJ, Szarek M, Olsson AG, Schwartz GG; Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) Study Investigators. High-dose atorvastatin reduces total plasma levels of oxidized phospholipids and immune complexes present on apolipoprotein B-100 in patients with acute coronary syndromes in the MIRACL trial. *Circulation*. 2004;110:1406–1412.
16. 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. 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.
17. Kohli P, Desai NR, Giugliano RP, Kim JB, Somaratne R, Huang F, Knusel B, McDonald S, Abrahamsen T, Wasserman SM, Scott R, Sabatine MS. Design and rationale of the LAPLACE-TIMI 57 trial: a phase II, double-blind, placebo-controlled study of the efficacy and tolerability of a monoclonal antibody inhibitor of PCSK9 in subjects with hypercholesterolemia on background statin therapy. *Clin Cardiol*. 2012;35:385–391.
18. Tate JR, Rifai N, Berg K, Couderc R, Dati F, Kostner GM, Sakurabayashi I, Steinmetz A. International Federation of Clinical Chemistry standardization project for the measurement of lipoprotein(a), phase I: evaluation of the analytical performance of lipoprotein(a) assay systems and commercial calibrators. *Clin Chem*. 1998;44(pt 1):1629–1640.
19. Kraft HG, Lingenhel A, Raal FJ, Hohenegger M, Utermann G. Lipoprotein(a) in homozygous familial hypercholesterolemia. *Arterioscler Thromb Vasc Biol*. 2000;20:522–528.
20. Rader DJ, Mann WA, Cain W, Kraft HG, Usher D, Zech LA, Hoeg JM, Davignon J, Lupien P, Grossman M. The low density lipoprotein receptor is not required for normal catabolism of Lp(a) in humans. *J Clin Invest*. 1995;95:1403–1408.
21. Knight BL, Perombelon YF, Soutar AK, Wade DP, Seed M. Catabolism of lipoprotein(a) in familial hypercholesterolaemic subjects. *Atherosclerosis*. 1991;87:227–237.
22. Reblin T, Niemeier A, Meyer N, Willnow TE, Kronenberg F, Dieplinger H, Greten H, Beisiegel U. Cellular uptake of lipoprotein[a] by mouse embryonic fibroblasts via the LDL receptor and the LDL receptor-related protein. *J Lipid Res*. 1997;38:2103–2110.
23. Fan J, Challah M, Shimoyamada H, Shiomi M, Marcovina S, Watanabe T. Defects of the LDL receptor in WHHL transgenic rabbits lead to a marked accumulation of plasma lipoprotein[a]. *J Lipid Res*. 2000;41:1004–1012.
24. Cain WJ, Millar JS, Himebauch AS, Tietge UJ, Maugeais C, Usher D, Rader DJ. Lipoprotein [a] is cleared from the plasma primarily by the liver in a process mediated by apolipoprotein [a]. *J Lipid Res*. 2005;46:2681–2691.
25. Snyder ML, Hay RV, Whitington PF, Scanu AM, Fless GM. Binding and degradation of lipoprotein(a) and LDL by primary cultures of human hepatocytes: comparison with cultured human monocyte-macrophages and fibroblasts. *Arterioscler Thromb*. 1994;14:770–779.
26. McKenney JM, Koren MJ, Kereiakes DJ, Hanotin C, Ferrand AC, Stein EA. Safety and efficacy of a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 serine protease, SAR236553/REGN727, in patients with primary hypercholesterolemia receiving ongoing stable atorvastatin therapy. *J Am Coll Cardiol*. 2012;59:2344–2353.
27. Preliminary results of the Heart Protection Study 2. http://www.thrivestudy.org. Accessed February 6, 2013.
28. Boden WE, Probstfield JL, Anderson T, Chaitman BR, Desvignes-Nickens P, Koprowicz K, McBride R, Teo K, Weintraub W. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. *N Engl J Med*. 2011;365:2255–2267.
29. Cannon CP, Shah S, Dansky HM, Davidson M, Brinton EA, Gotto AM, Stepanavage M, Liu SX, Gibbons P, Ashraf TB, Zafarino J, Mitchel Y, Barter P; Determining the Efficacy and Tolerability Investigators. Safety of anacetrapib in patients with or at high risk for coronary heart disease. *N Engl J Med*. 2010;363:2406–2415.
30. Tsimikas S, Witztum J, Catapano A. Effect of mipomersen on lipoprotein(a) in patients with hypercholesterolemia across four phase iii studies [abstract]. *J Am Coll Cardiol*. 2012;59:E1494.
31. Merki E, Graham M, Taleb A, Leibundgut G, Yang X, Miller ER, Fu W, Mullick AE, Lee R, Willeit P, Crooke RM, Witztum JL, Tsimikas S. Antisense oligonucleotide lowers plasma levels of apolipoprotein (a) and lipoprotein (a) in transgenic mice. *J Am Coll Cardiol*. 2011;57:1611–1621.

CLINICAL PERSPECTIVE

Lipoprotein(a) [Lp(a)] is a circulating lipoprotein composed of an apolipoprotein B100 molecule covalently bound to a liver-derived glycoprotein, apolipoprotein(a). In epidemiological and genetic analyses, Lp(a) has emerged as an important risk factor for the development of cardiovascular disease. The 2011 European Society of Cardiology/European Atheroscloerosis Society guidelines recommend screening for elevated Lp(a) in people at high risk for cardiovascular disease or with a strong family history of premature atherothrombotic disease. There are limited therapeutic options for lowering Lp(a) levels. We sought to evaluate the impact of AMG145, a monoclonal antibody against proprotein convertase subtilisin kexin type 9 (PCSK9), on Lp(a) levels in the LDL-C Assessment With PCSK9 Monoclonal Antibody Inhibition Combined With Statin Therapy (LAPLACE)–Thrombolysis in Myocardial Infarction (TIMI) 57 trial, a randomized, phase 2 trial of AMG145 versus placebo. We found that compared with placebo, AMG145 significantly lowers Lp(a) in subjects with hypercholesterolemia receiving background therapy with statin with or without ezetimibe. Specifically, we observed dose-response relationships at both dosing frequencies, with progressively more robust reductions in Lp(a), up to 32%, from baseline to week 12. We found that the reduction in Lp(a) with AMG145 was consistent across several important subgroups including age, sex, race, history of diabetes mellitus, and background statin regimen. Although the clinical benefit of Lp(a) reduction remains undefined, these data lend further support to studying the impact of PCSK9 inhibition with AMG145 in a phase 3 clinical outcomes trial.