Effect of PCSK9 Inhibition by Alirocumab on Lipoprotein Particle Concentrations Determined by Nuclear Magnetic Resonance Spectroscopy

Michael J. Koren, MD; Dean Kereiakes, MD; Ray Pourfarzib, PhD; Deborah Winegar, PhD; Pouabi Banerjee, PhD; Sara Hamon, PhD; Corinne Hanotin, MD; James M. McKenney, Pharm D

Background—In patients with discordance between low-density lipoprotein (LDL) cholesterol and LDL particle (LDL-P) concentrations, cardiovascular risk more closely correlates with LDL-P.

Methods and Results—We investigated the effect of alirocumab, a fully human monoclonal antibody to proprotein convertase subtilisin/kexin type 9, on lipoprotein particle concentration and size in hypercholesterolemic patients, using nuclear magnetic resonance spectroscopy. Plasma samples were collected from patients receiving alirocumab 150 mg every 2 weeks (n=26) or placebo (n=31) during a phase II, double-blind, placebo-controlled trial in patients (LDL cholesterol ≥100 mg/dL) on a stable atorvastatin dose. In this post hoc analysis, percentage change in concentrations of LDL-P, very-low-density lipoprotein particles, and high-density lipoprotein particles from baseline to week 12 was determined by nuclear magnetic resonance. Alirocumab significantly reduced mean concentrations of total LDL-P (−63.3% versus −1.0% with placebo) and large (−71.3% versus −21.8%) and small (−54.0% versus +17.8%) LDL-P subfractions and total very-low-density lipoprotein particle concentrations (−36.4% versus +33.4%; all P<0.01). Total high-density lipoprotein particles increased with alirocumab (+11.2% versus +1.4% with placebo; P<0.01). There were greater increases in large (44.6%) versus medium (17.7%) or small high-density lipoprotein particles (2.8%) with alirocumab. LDL-P size remained relatively unchanged in both groups; however, very-low-density and high-density lipoprotein particle sizes increased to a significantly greater extent with alirocumab.

Conclusions—Alirocumab significantly reduced LDL-C and LDL-P concentrations in hypercholesterolemic patients receiving stable atorvastatin therapy. These findings may be of particular relevance to patients with discordant LDL-C and LDL-P concentrations.

Clinical Trial Registration—URL: https://clinicaltrials.gov. Unique identifier: NCT01288443. (J Am Heart Assoc. 2015;4: e002224 doi: 10.1161/JAHA.115.002224)

Key Words: alirocumab • lipoprotein particle number • lipoprotein subfractions • nuclear magnetic resonance spectroscopy • proprotein convertase subtilisin/kexin type 9 inhibitor

Low-density lipoprotein (LDL) is most commonly quantified by its cholesterol content (LDL cholesterol [LDL-C]) using indirect (Friedewald) calculation based on measurements of total cholesterol, total triglycerides, and high-density lipoprotein (HDL) cholesterol. LDL-C can also be determined by ultracentrifugation. The cholesterol content of LDL particles (LDL-P), can vary between individuals. This variation sometimes results in discordance between measures of LDL-C and the actual number of LDL-P.

Although there is a well-established relationship between risk of atherosclerotic cardiovascular disease and LDL-C levels, several studies have suggested that cardiovascular disease risk more closely correlates with LDL-P than LDL-C level. The discordance between LDL-P and LDL-C levels may be particularly prominent in certain patient populations, for example, those with elevated triglycerides and/or low HDL cholesterol, diabetes, or metabolic syndrome.

LDL-P concentration can be estimated indirectly by measuring serum concentrations of apolipoprotein (apo) B or measured directly by nuclear magnetic resonance (NMR)
spectroscopy or ion mobility. NMR spectroscopy has been validated as an accurate measurement of the number, size, and subclass distribution of circulating lipoprotein particles.

Inhibition of proprotein convertase subtilisin/kexin type 9 (PCSK9) is a novel mechanism for reducing levels of LDL-C. PCSK9 is a circulating protease which binds to and promotes the degradation of the LDL receptor on hepatocytes. Alirocumab is a fully human, highly specific monoclonal antibody directed against PCSK9. Treatment with alirocumab resulted in significant reductions in levels of LDL-C and other apoB-containing lipoproteins in clinical trials with a safety and tolerability profile generally comparable with controls.

In the current analysis, we examined the impact of alirocumab 150 mg Q2W on lipoprotein particle concentration and size using NMR spectroscopy as part of a post hoc substudy of a phase II dose-ranging trial in hypercholesterolemic patients receiving stable atorvastatin therapy.

### Methods

#### Study Design and Patients

The design of the phase II dose-ranging trial (study 11565; ClinicalTrials.gov identifier NCT01288443) has been described previously. This multicenter, randomized, double-blind, parallel-group, placebo-controlled study was conducted in 182 patients (aged 18–75 years) with hypercholesterolemia (nonfamilial) and LDL-C levels ≥100 mg/dL (2.59 mmol/L) receiving stable atorvastatin therapy (10, 20, or 40 mg daily) for ≥6 weeks. Key exclusion criteria included type 1 or 2 diabetes requiring insulin or glycated hemoglobin ≥8.5%, blood pressure >150/95 mm Hg, history of a major coronary event within 6 months of screening, or a triglyceride level >350 mg/dL.

Patients were randomized to receive subcutaneous placebo every 2 weeks; alirocumab 50, 100, or 150 mg Q2W; or alirocumab 200 or 300 mg Q4W, alternating with placebo. This analysis is focused on patients who received alirocumab 150 mg Q2W, a dose chosen for evaluation in late stage trials (other doses are not included in this analysis). The total treatment period was 12 weeks. The protocol was approved by the institutional review board at each study center, and written informed consent was obtained from all participants.

A total of 31 patients were randomized to receive alirocumab 150 mg Q2W, and 31 patients were randomized to receive placebo every 2 weeks. Four patients randomized to the alirocumab group did not complete the original trial; 1 patient discontinued due to an adverse event (fatigue), and 3 patients discontinued for other reasons.

#### Lipoprotein Analysis

Lipid and lipoprotein analyses were performed on frozen EDTA plasma samples collected after a 12–hour overnight fast at baseline and week 12. Lipoprotein particle concentrations were measured by NMR spectroscopy at LipoScience, Inc, using the LipoProfile-3 algorithm. Samples from 1 of the 27 patients randomized to alirocumab who completed the trial were not evaluable by NMR.

As described previously, LDL and HDL subclasses were quantified from the amplitudes of their spectroscopically distinct lipid methyl group NMR signals, and weighted-average LDL and HDL sizes were derived from the sum of the diameter of each subclass multiplied by its relative mass percentage. The diameter range for each LDL-P and HDL particle (HDL-P) subclass was described previously. End points for the analysis were percentage change in the concentration of LDL—P, very-low-density lipoprotein particles (vLDL-P), and HDL-P from baseline to week 12.

Lipoprotein(a), or Lp(a), was not analyzed by NMR because this method does not distinguish LDL-P with an attached apo(a) from LDL-P without apo(a). The methyl signals of apo are broader than the lipid methyl signals and do not contribute to the bulk lipid signal used for quantitation of lipoproteins. In the parent study, Lp(a) was reduced from baseline to week 12 by 28.6% with alirocumab versus 0% with placebo (P<0.001). Each vLDL-P, LDL-P, and intermediate-density lipoprotein particle contains a single apoB-100 molecule. Chylomicrons and chylomicron remnants contain a single apoB-48. Most commercial immunoassays measure both forms of apoB; however, >95% of apoB in plasma from fasting persons is apoB-100, associated mostly with LDL. To compare apoB measurements with lipoprotein particle measurements, add vLDL-P and LDL-P (both nmol/L) and convert to apoB equivalents (mg/dL) by multiplying by the factor 0.055 based on the molecular weight of apoB, which is about 550 000 Da.

#### Safety

Safety data, including information on treatment-emergent adverse events and serious treatment-emergent adverse events, were collected throughout the study. The treatment-emergent adverse event reporting period spanned the time from first dose of study treatment up to 70 days after the last dose.

#### Statistical Analyses

Data were checked for normality and mean. Standard deviations were reported for continuous normally distributed variables, and medians (with interquartile ranges for quartiles 1 to 3) were reported for non-normally distributed values. To determine whether there was a significant difference in
percentage change for each of the variables between the alirocumab 150 mg Q2W and placebo treatment groups, ANCOVA was performed in which the treatment groups were the fixed effects and the corresponding baseline value of the variable was the covariate. For parameters known to be non-normally distributed, a rank-based ANCOVA was performed. $P$ values were provided for descriptive purposes only and were not adjusted for multiple testing. A $P$ value of $<0.05$ was nominally set as a significance threshold.

Analyses were run with and without adjustments for baseline factors such as age, sex, diabetes, and smoking and with atorvastatin dose and the significance of primary results did not change. The covariates were also nonsignificant in the model, so they were not included in the final analysis.

All statistical analyses were performed in R version 3.0.2 (R Foundation for Statistical Computing).

Results

Patients and Baseline Lipoprotein Levels

Data for lipoprotein analysis were available for 26 of the 27 patients who received alirocumab and completed the trial and for all patients ($n=31$) who received placebo. Patient baseline characteristics were similar in both treatment groups (Table 1). Minor between-group differences in age, sex distribution, and prevalence of diabetes were noted but considered to be a random consequence of sample size, with no statistically significant difference between groups.

Mean baseline LDL-C levels were 123.9 mg/dL in the alirocumab group and 130.2 mg/dL in the placebo group. Mean LDL-P concentrations were similar between alirocumab and placebo groups, and LDL-P was distributed nearly equally between small and large particles (Table 2). Mean baseline HDL cholesterol levels were 53.3 and 49.0 mg/dL in the alirocumab and placebo groups, respectively; median baseline triglyceride levels were 140.5 and 124.0 mg/dL, respectively. In contrast to LDL-P, the majority of baseline HDL-P and vLDL-P were small particles (Table 2). There were no marked differences in lipoprotein particle subclass concentrations at baseline between treatment groups (Table 2).

Effects on Lipoprotein Particle Concentration

At week 12, mean total LDL-P concentrations were reduced by 63.3% from baseline with alirocumab compared with a 1.0% reduction in the placebo group ($P<0.001$) (Table 2). Significant reductions were observed in all LDL-P subclass concentrations in the alirocumab group (intermediate-density lipoprotein particles, $-52.8\%$ versus $-15.0\%$ with placebo; large LDL-P, $-71.3\%$ versus $-21.8\%$; and small LDL-P, $-54.0\%$ versus $+17.8\%$; $P<0.05$).

Mean total HDL-P concentrations were increased from baseline to week 12 by 11.2% in the alirocumab group compared with a 1.4% increase in the placebo group at week 12 ($P<0.01$) (Table 2). Notably, HDL-P in the alirocumab group increased substantially more for large HDL-P ($44.6\%$) compared with medium ($17.7\%$) or small HDL-P ($2.8\%$) and reached statistical significance versus placebo for large HDL-P ($44.6\%$ versus $7.0\%$; $P<0.01$) (Table 2).

By week 12, alirocumab reduced total vLDL-P and chylomicron concentrations by 36.4% compared with an increase of 33.4% in the placebo group ($P<0.001$) (Table 2). The reduction in vLDL-P concentration in the alirocumab group largely reflected a reduction in medium and small vLDL-P subclasses ($P<0.01$ versus placebo) (Table 2).

With the exception of large vLDL-P, changes in concentrations of lipoprotein particle subclasses in the alirocumab group were directionally similar to the changes in total particle concentrations (Table 2).

Changes in levels of LDL-C and other lipid parameters as measured by conventional methods are shown for comparison in Table 2.

Figure shows individual patient responses for LDL-P, HDL-P, and vLDL-P (and chylomicrons) for alirocumab and placebo-treated patients at baseline and week 12. All alirocumab-treated patients experienced a reduction in LDL-P from baseline (Figure – Panel A).

Effects on Lipoprotein Size

At 12 weeks, mean LDL-P size did not differ from baseline in either the alirocumab or placebo group, and there was no difference between groups ($P$ not significant) (Table 2). In contrast, mean HDL-P and vLDL-P sizes increased to a greater extent in the alirocumab group compared with placebo ($2.8\%$ versus $0.2\%$ and $10.1\%$ versus $0.8\%$, respectively; both $P<0.01$) (Table 2).

Table 1. Patient Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo ($n=31$)</th>
<th>Alirocumab 150 mg Q2W ($n=26$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, mean (SD)</td>
<td>53.3 (8.5)</td>
<td>59.9 (10.7)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>15 (48)</td>
<td>16 (62)</td>
</tr>
<tr>
<td>BMI, kg/m², mean (SD)</td>
<td>27.9 (4.8)</td>
<td>28.3 (4.4)</td>
</tr>
<tr>
<td>Type 2 diabetes, n (%)</td>
<td>1 (3)</td>
<td>3 (12)</td>
</tr>
<tr>
<td>Smoker, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>8 (26)</td>
<td>9 (35)</td>
</tr>
<tr>
<td>Former</td>
<td>4 (13)</td>
<td>5 (19)</td>
</tr>
<tr>
<td>Never</td>
<td>19 (61)</td>
<td>12 (46)</td>
</tr>
</tbody>
</table>

All comparisons between placebo and alirocumab are not significant. BMI indicates body mass index.
Table 2. Lipid and NMR-Determined Lipoprotein Variables at Week 12 and Percent Change From Baseline to Week 12

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Alirocumab 150 mg Q2W</th>
<th>P Value vs Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=31</td>
<td>n=29</td>
<td></td>
</tr>
<tr>
<td><strong>Lipid parameters, mean (SD) or median (IQR)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL-C, mg/dL</td>
<td>130.2 (27.3)</td>
<td>120.5 (27.0)</td>
<td>5.1 (3.1)</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>124.0 (92.0–157.0)</td>
<td>127.0 (88.0–197.0)</td>
<td>9.7 (15.0 to 30.7)</td>
</tr>
<tr>
<td>HDL-C, mg/dL</td>
<td>49.0 (10.3)</td>
<td>48.9 (13.2)</td>
<td>-1.0 (2.3)</td>
</tr>
<tr>
<td><strong>Lipoprotein particle concentrations, mean (SD) or median (IQR)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total LDL-P, nmol/L</td>
<td>1423 (321)</td>
<td>1384 (328)</td>
<td>-1.04 (20.0)</td>
</tr>
<tr>
<td>IDL-P</td>
<td>110 (51–167)</td>
<td>57 (24.5–145)</td>
<td>-15.0 (–81.2 to 111.6)</td>
</tr>
<tr>
<td>Large LDL-P</td>
<td>547 (205)</td>
<td>432 (217)</td>
<td>-21.8 (34.1)</td>
</tr>
<tr>
<td>Small LDL-P</td>
<td>755 (305)</td>
<td>848 (375)</td>
<td>17.8 (50.3)</td>
</tr>
<tr>
<td>Total HDL-P, μmol/L</td>
<td>32.9 (6.4)</td>
<td>33.2 (7.4)</td>
<td>1.4 (16.5)</td>
</tr>
<tr>
<td>Large HDL-P</td>
<td>3.8 (2.0)</td>
<td>3.9 (2.2)</td>
<td>7.0 (52.8)</td>
</tr>
<tr>
<td>Medium HDL-P</td>
<td>9.2 (5.9–14.4)</td>
<td>8 (5.4–10.2)</td>
<td>-13.9 (–39.9 to 7.5)</td>
</tr>
<tr>
<td>Small HDL-P</td>
<td>18.5 (5.3)</td>
<td>21.3 (5.83)</td>
<td>18.4 (37.2)</td>
</tr>
<tr>
<td>Total vLDL-P and chylomicron, mmol/L</td>
<td>61.9 (47.8–95.6)</td>
<td>83.9 (45.0–102.0)</td>
<td>33.4 (–23.4 to 66.6)</td>
</tr>
<tr>
<td>Large vLDL-P and chylomicron</td>
<td>3.5 (2.1–8.5)</td>
<td>4.3 (1.8–9.4)</td>
<td>14.3 (–23.9 to 80.3)</td>
</tr>
<tr>
<td>Medium vLDL-P</td>
<td>19.3 (13.1–33.9)</td>
<td>33.1 (13.1–51.9)</td>
<td>24.0 (–10.9 to 79.9)</td>
</tr>
<tr>
<td>Small vLDL-P</td>
<td>35.3 (28.2–47.8)</td>
<td>37.3 (25.4–56.3)</td>
<td>21.4 (–32.2 to 70.3)</td>
</tr>
<tr>
<td><strong>Lipoprotein particle size, mean (SD)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL-P, nm</td>
<td>20.8 (0.6)</td>
<td>20.5 (0.6)</td>
<td>-1.3 (2.0)</td>
</tr>
<tr>
<td>HDL-P, nm</td>
<td>8.8 (0.4)</td>
<td>8.8 (0.4)</td>
<td>0.2 (4.6)</td>
</tr>
<tr>
<td>vLDL-P, nm</td>
<td>49.8 (6.4)</td>
<td>49.9 (7.6)</td>
<td>0.8 (12.1)</td>
</tr>
</tbody>
</table>

HDL-C indicates high-density lipoprotein cholesterol; HDL-P, high-density lipoprotein particle; IDL-P, intermediate-density lipoprotein particles; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; LDL-P, low-density lipoprotein particle; NMR, nuclear magnetic resonance; vLDL-P, very-low-density lipoprotein particle.

*As assessed by conventional methods (data previously reported17). Mean (SD) is reported for continuous normally distributed variables, and median (IQR) is reported for any non-normally distributed variables.

†As assessed by NMR analysis.
Of the 31 patients randomized to alirocumab 150 mg Q2W, 19 patients (61.3%) experienced a treatment-emergent adverse event compared with 14 patients (45.2%) in the placebo group. Permanent discontinuation of alirocumab due to fatigue was reported for 1 patient. The most common treatment-emergent adverse events with alirocumab 150 mg...
Q2W were injection-site reactions, which were reported in 4 patients (12.9%) and were typically of mild intensity and short duration.

**Discussion**

Treatment for 12 weeks with alirocumab 150 mg Q2W (in patients receiving stable background atorvastatin therapy) resulted in significantly reduced concentrations of LDL-P and vLDL-P versus placebo and significantly raised total HDL-P. Standard deviations associated with the LDL-P reductions in the alirocumab group were approximately half of the corresponding standard deviation values observed in the placebo group, indicating a consistent response with alirocumab. Alirocumab treatment also shifted the HDL-P profile from small to large size. The observed 63% reduction in total LDL-P concentration after 12 weeks of treatment with alirocumab in this substudy approximately matched the magnitude of previously reported reductions in serum measures of LDL-C (72%) and apoB (56%). Total HDL-P increased by 11% with alirocumab treatment compared with increases of 5.5% and 1.4% in HDL cholesterol and apoA1, respectively. Total vLDL-P and chylomicrons were reduced by 36% compared with a 19% reduction in triglyceride levels. These observed effects of alirocumab on lipoprotein particles compared with standard lipid measurements add to evidence of previous NMR analyses showing that circulating levels of free PCSK9 correlate with vLDL-P and LDL-P concentration.

Although comparisons between studies should be interpreted cautiously, the effects of alirocumab on lipoprotein particle subfractions reported in this study differ somewhat from the effects of statins reported in the literature, which vary by dose and type of statin. Reported changes related to statin therapy have ranged from −10% to −61% in large LDL-P and from +15% to −55% in small LDL-P. Statins were also reported to produce changes of −16% to −72% in large vLDL-P and −17% to −71% in small vLDL-P and changes of 0% to +57% in large HDL-P and −9% to +17% in small HDL-P. In these studies, statin treatment had minimal effects on the size profile of LDL-P, vLDL-P, and HDL-P.

Because there may be discordance between LDL-P and LDL-C levels, some high-risk patients may achieve currently recommended LDL-C levels but still remain at risk of cardiovascular events due to elevated LDL-P levels. In an observational study of high-risk patients, those who received LDL-P assessments and achieved LDL-P concentrations <1000 nmol/L were found to have received higher dose statin therapy and experienced a 22%–25% reduction in cardiovascular event risk over a 3-year period compared with patients who did not have LDL-P measurements and achieved an LDL-C level of <100 mg/dL. Two guidelines committees have incorporated LDL-P targets as part of their recommendations: The American Association of Clinical Chemistry advocates LDL-P targets (estimated by apoB measurement) of <1100 nmol/L for high-risk patients with near-normal LDL-C (100 mg/dL), and the American Association of Clinical Endocrinologists recommends goals of <1000 nmol/L for LDL-P and <70 mg/dL for LDL-C among diabetic patients at high risk of cardiovascular disease. Based on results from the current study, alirocumab treatment enabled the majority of patients to achieve these goals.

Although some groups have supported the measurement and quantification of lipid particle subclasses in certain clinical circumstances, not all experts agree. In 2011, the National Lipid Association expert panel reviewed data on lipid particle analyses and concluded that there is insufficient evidence to support LDL or HDL subfraction measurement for initial patient assessments or management while on therapy. The same guidelines, however, support (total) LDL-P measurement for certain high-risk patients, such as those with metabolic syndrome or diabetes, who often demonstrate discordance between LDL-C levels and LDL-P concentrations. The finding of robust and consistent reductions in both LDL-C and LDL-P concentrations with alirocumab provides some reassurance that populations with LDL-C and LDL-P discordance should benefit to a similar degree as other hypercholesterolemic patients. An ongoing large clinical outcomes study of alirocumab (ODYSSEY OUTCOMES; ClinicalTrials.gov identifier NCT01663402) will provide a more definitive analysis of the effects of alirocumab for secondary prevention of cardiovascular complications and will include patients with metabolic syndrome and others who may have LDL-C and LDL-P discordance.

Alirocumab lowered total vLDL and chylomicrons by a median of 36.4% (P<0.0001 compared with placebo). The mechanism by which alirocumab reduces these lipoproteins is unclear. Although the catabolism of these particles is primarily mediated by their conversion into small particles by lipoprotein lipase, the recent finding of reductions in these particles using PSCK9 inhibitors has raised the possibility of a role of the LDL receptor.

Limitations of this study include the small sample size. Although the principal findings of the analysis regarding LDL-P appear robust, a larger trial might uncover more subtle differences in particle size and concentration attributable to treatment with alirocumab. Furthermore, the changes decision to measure lipid particles in the alirocumab 150 mg Q2W group occurred after completion of the original phase II study analysis and determination of this dose for further study in the phase III clinical trial program. Consequently, the current study should be viewed as a post hoc analysis best suited for hypothesis generation. Future studies should focus on the clinical populations most likely to experience LDL-C and LDL-P discordance.
In summary, PCSK9 inhibition with alirocumab in hypercholesterolemic patients receiving stable background atorvastatin therapy produced substantial reductions in LDL, as determined by measurement of both LDL-C and LDL-P concentrations. This finding suggests a potential benefit of alirocumab in patients with discordant LDL-C and LDL-P concentrations. Alirocumab is currently being evaluated for both LDL-C and cardiovascular event reductions in the ODYSSEY phase III program involving 14 clinical trials and >23 500 patients.

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