Carriers of the PCSK9 R46L Variant Are Characterized by an Antiatherogenic Lipoprotein Profile Assessed by Nuclear Magnetic Resonance Spectroscopy—Brief Report

Rutger Verbeek, Marjorie Boyer, S. Matthijs Boekholdt, G. Kees Hovingh, John J.P. Kastelein, Nicholas Wareham, Kay-Tee Khaw, Benoit J. Arsenault

Objective—Carriers of the PCSK9 (proprotein convertase subtilisin/kexin 9) R46L genetic variant (rs11591147) are characterized by low levels of low-density lipoprotein cholesterol and a decreased risk of cardiovascular disease. We studied the impact of the R46L variant on lipoprotein size and composition.

Approach and Results—Lipoprotein size and composition were measured by nuclear magnetic resonance spectroscopy in 2373 participants of the EPIC (European Prospective Investigation into Cancer and Nutrition)-Norfolk study. After adjusting for age, sex, and cardiovascular disease status, carriers of the R46L variant (n=77) were characterized by lower concentrations of very low–density lipoprotein particles (85.8±26.2 versus 99.0±33.3 nmol/L; P<0.001), low-density lipoprotein particles (1479.7±396.8 versus 1662.9±458.3 nmol/L; P<0.001), and lipoprotein(a) (11.1 [7.2–28.6] versus 12.4 [6.7–29.1] mg/dL; P<0.001) compared with noncarriers. Total high-density lipoprotein particle and very low–density lipoprotein, low-density lipoprotein, and high-density lipoprotein particle sizes were comparable in carriers and noncarriers. Carriers were characterized by lower secretory phospholipase A2 (4.2±0.9 versus 4.6±1.3 nmol/mL/min; P=0.02) and lipoprotein-associated phospholipase A2 activity (47.5±14.1 versus 52.4±16.2 nmol/mL/min; P=0.02) compared with noncarriers.

Conclusions—Results of this study suggest that carriers of the PCSK9 R46L genetic variant have lower very low–density lipoprotein and low-density lipoprotein particle concentrations, lower lipoprotein(a) levels, and lower secretory phospholipase A2 activity compared with noncarriers. (Arterioscler Thromb Vasc Biol. 2017;37:43-48. DOI: 10.1161/ATVBAHA.116.307995.)

Key Words: lipoprotein(a) ■ lipoproteins ■ nuclear magnetic resonance spectroscopy ■ PCSK9 ■ R46L
compared with noncarriers. The heterozygous carriers showed a trend toward a lower CVD risk with an odds ratio (95% confidence interval) of 0.72 (0.50–1.04). Because this cohort was age and sex matched, the age- and sex-adjusted odds ratios were identical. We measured serum levels of cholesteryl ester transfer protein; lecithin–cholesterol acyltransferase; lipoprotein lipase; oxidized phospholipids; lipoprotein(a) [Lp(a)]; C-reactive protein; apolipoproteins A-I, A-II, A-V, and B; and NMR-measured lipoproteins (Table 2). Cholesteryl ester transfer protein, lecithin–cholesterol acyltransferase, lipoprotein lipase, oxidized phospholipids, C-reactive protein, apolipoprotein A-I, apolipoprotein A-II, and high-density lipoprotein particle levels, as well as high-density lipoprotein size, LDL size, and very low–density lipoprotein (VLDL) size were not different in carriers compared with noncarriers. Apolipoprotein B; Lp(a); VLDL-P (total, medium, and small); intermediate-density lipoprotein particles (IDL-P); and LDL particle (LDL-P) levels; and secretory phospholipase A2 and lipoprotein-associated phospholipase A2 (Lp-PLA2) activity were lower in carriers compared with noncarriers.

**Table 1. Baseline Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Noncarriers</th>
<th>Carriers</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>65.1±7.8</td>
<td>66.2±7.3</td>
<td>0.25</td>
</tr>
<tr>
<td>Male sex</td>
<td>67.7% (1554)</td>
<td>62.3% (48)</td>
<td>0.33</td>
</tr>
<tr>
<td>Current smoker</td>
<td>11.1% (251)</td>
<td>12.0% (9)</td>
<td>0.35</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>26.7±3.7</td>
<td>26.4±3.6</td>
<td>0.52</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>3.9% (89)</td>
<td>3.9% (3)</td>
<td>0.99</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>140.5±18.2</td>
<td>140.0±17.1</td>
<td>0.79</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>84.3±11.4</td>
<td>83.8±11.2</td>
<td>0.79</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>6.4±1.2</td>
<td>5.8±0.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>4.2±1.0</td>
<td>3.7±0.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.3±0.4</td>
<td>1.4±0.4</td>
<td>0.49</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>2.0±1.1</td>
<td>1.8±0.9</td>
<td>0.08</td>
</tr>
</tbody>
</table>

The baseline characteristics were based on variables from participants whose NMR data were available. Data are presented as mean±SD and percentage number for categorical variables. HDL indicates high-density lipoprotein; LDL, low-density lipoprotein; and NMR, nuclear magnetic resonance.

**Discussion**

Our study shows that carriers of the PCSK9 R46L variant are characterized by lower levels of NMR-measured atherogenic lipoproteins and subfractions compared with noncarriers. The most prominent differences based on percentage change between carriers and noncarriers were observed with IDL-P (−18%) and medium VLDL-P (−16%; Figure). The most prominent differences based on change in SD between carriers and noncarriers were observed with apolipoprotein B (−0.44 SD), LDL-C (−0.41 SD), VLDL-P (−0.40 SD), and LDL-P (−0.40 SD). Our results extend those of Cohen et al, who have reported a 15% reduction in LDL-C in carriers of the PCSK9 R46L variant in the ARIC study (Atherosclerosis Risk in Communities). The effect on other parameters of the lipoprotein–lipid profile was comparable, with in both studies significant lower levels of total cholesterol and no effect on high-density lipoprotein cholesterol.

In a cross-sectional study of 52 healthy subjects, PCSK9 levels were found to correlate with total cholesterol, non–high-density lipoprotein cholesterol, LDL-C, triglycerides, and VLDL-P and LDL-P concentrations. In a subsequent multivariable regression analysis, PCSK9 levels were only related to LDL-P concentration. Interestingly, in an analysis that included the 3 LDL subfractions, PCSK9 was only associated with IDL-P. The R46L variant examined in our study has been shown to be associated with lower levels of PCSK9, and therefore, we expected a similar effect on NMR lipoprotein subfractions. Our study suggests that there is not only an association between PCSK9 and IDL-P but also with other lipoprotein particles. The effect of the R46L variant on lipoproteins in our study seemed to be comparable with the results of Chasman et al, who showed a significant effect of the single-nucleotide polymorphism on large LDL-P, total LDL-P, small LDL-P, IDL-P, LDL-C, total VLDL-P, and small VLDL-P. Other groups also documented the effect of different single-nucleotide polymorphisms on lipoprotein particle levels. However, our study is the first to show a significant effect of the R46L variant on intermediate-density lipoprotein particle levels.

**Nonstandard Abbreviations and Acronyms**

CVD: cardiovascular disease
EPIC-Norfolk: European Prospective Investigation into Cancer and Nutrition (EPIC)-Norfolk
IDL: intermediate-density lipoprotein
LDL: low-density lipoprotein
Lp-PLA2: lipoprotein-associated phospholipase A2
NMR: nuclear magnetic resonance
PCSK9: proprotein convertase subtilisin/kexin 9
VLDL: very low–density lipoprotein
A recent analysis of the Copenhagen general population study showed that carriers of the R46L variant had lower Lp(a) than noncarriers.9 Recently, Koren et al10 documented the impact of the PCSK9 inhibitor alirocumab on NMR lipoprotein subfractions in 60 patients with hypercholesterolemia. Alirocumab therapy resulted in a 63.3% decrease of LDL-P concentration, whereas IDL-P concentration fell by 52.8%. Although the effect of alirocumab on Lp(a) was not determined by Koren et al,10 Lp(a) reductions ≤30% Table 2. CETP, LCAT, LPL, OxPL, Apolipoproteins, and Nuclear Magnetic Resonance Spectroscopy–Measured Lipid Levels and Size of Participants of the EPIC-Norfolk Study Classified on the Basis of PCSK9 R46L Carrier Status

<table>
<thead>
<tr>
<th></th>
<th>Noncarriers</th>
<th>N</th>
<th>Carriers</th>
<th>N</th>
<th>D, %</th>
<th>D (SD)</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td>CETP, mg/L</td>
<td>2.9 (2.2–3.8)</td>
<td>2099</td>
<td>2.9 (1.9–4.0)</td>
<td>71</td>
<td>0.3</td>
<td>0.00</td>
<td>1.00</td>
</tr>
<tr>
<td>LCAT, µg/mL</td>
<td>8.9±2.2</td>
<td>2071</td>
<td>8.7±2.3</td>
<td>68</td>
<td>−2.2</td>
<td>−0.09</td>
<td>0.47</td>
</tr>
<tr>
<td>LPL, ng/mL</td>
<td>62.5 (44.1–88.8)</td>
<td>2239</td>
<td>61.4 (51.8–81.2)</td>
<td>76</td>
<td>−1.7</td>
<td>0.04</td>
<td>0.95</td>
</tr>
<tr>
<td>OxPL, RLU</td>
<td>1694.0 (1167.0–2670.0)</td>
<td>1997</td>
<td>1573.5 (1093.0–3128.0)</td>
<td>66</td>
<td>−7.1</td>
<td>−0.04</td>
<td>0.83</td>
</tr>
<tr>
<td>CRP, mg/L</td>
<td>1.7 (0.8–14.0)</td>
<td>2296</td>
<td>1.9 (0.8–14.2)</td>
<td>77</td>
<td>11.8</td>
<td>0.03</td>
<td>0.72</td>
</tr>
<tr>
<td>WBC, 10^3/µL</td>
<td>6.7±1.9</td>
<td>2852</td>
<td>6.3±2.0</td>
<td>96</td>
<td>2.9</td>
<td>0.10</td>
<td>0.20</td>
</tr>
<tr>
<td>sPLA2, nmol/mL/min*</td>
<td>4.6±1.3</td>
<td>2373</td>
<td>4.2±0.9</td>
<td>77</td>
<td>−8.7</td>
<td>−0.33</td>
<td>0.0036</td>
</tr>
<tr>
<td>Apolipoprotein B, mg/dL*</td>
<td>133.9±32.5</td>
<td>2105</td>
<td>119.6±31.9</td>
<td>75</td>
<td>−10.7</td>
<td>−0.44</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Apolipoprotein A-I, mg/dL</td>
<td>158.6±28.4</td>
<td>1971</td>
<td>160.2±27.5</td>
<td>73</td>
<td>1.1</td>
<td>0.06</td>
<td>0.79</td>
</tr>
<tr>
<td>Apolipoprotein A-II, mg/L</td>
<td>35.2±6.1</td>
<td>2280</td>
<td>34.5±5.3</td>
<td>77</td>
<td>−2.1</td>
<td>−0.12</td>
<td>0.22</td>
</tr>
<tr>
<td>Apolipoprotein A-V, ng/mL</td>
<td>180.0 (141.6–235.6)</td>
<td>2236</td>
<td>193.7 (159.2–266.5)</td>
<td>76</td>
<td>7.6</td>
<td>0.17</td>
<td>0.15</td>
</tr>
<tr>
<td>Lipoprotein(a), mg/dL*</td>
<td>12.4 (6.7–29.1)</td>
<td>2296</td>
<td>11.1 (7.2–28.6)</td>
<td>77</td>
<td>−10.3</td>
<td>−0.04</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>VLDL size, nm</td>
<td>51.8±8.7</td>
<td>2296</td>
<td>52.6±10.0</td>
<td>77</td>
<td>1.4</td>
<td>0.09</td>
<td>0.30</td>
</tr>
<tr>
<td>HDL size, nm</td>
<td>8.9±0.5</td>
<td>2296</td>
<td>9.0±0.4</td>
<td>77</td>
<td>1.3</td>
<td>0.24</td>
<td>0.12</td>
</tr>
<tr>
<td>NMR LDL-P (total), nmol/L*</td>
<td>99.0±33.3</td>
<td>2296</td>
<td>85.8±26.2</td>
<td>77</td>
<td>−13.3</td>
<td>−0.40</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Large VLDL/Chylomicrons, nmol/L</td>
<td>4.7 (1.8–7.8)</td>
<td>2296</td>
<td>3.6 (1.7–6.9)</td>
<td>77</td>
<td>−22.1</td>
<td>−0.21</td>
<td>0.11</td>
</tr>
<tr>
<td>Medium VLDL, nmol/L*</td>
<td>34.6±17.7</td>
<td>2296</td>
<td>29.0±14.6</td>
<td>77</td>
<td>−16.4</td>
<td>−0.32</td>
<td>0.0082</td>
</tr>
<tr>
<td>Small VLDL, nmol/L*</td>
<td>59.1±18.7</td>
<td>2296</td>
<td>52.4±18.7</td>
<td>77</td>
<td>−11.2</td>
<td>−0.35</td>
<td>0.0021</td>
</tr>
<tr>
<td>NMR HDL-P, µmol/L</td>
<td>33.8±5.6</td>
<td>2296</td>
<td>34.3±4.7</td>
<td>77</td>
<td>1.6</td>
<td>0.10</td>
<td>0.51</td>
</tr>
<tr>
<td>Large HDL, µmol/L</td>
<td>5.0 (2.8–7.7)</td>
<td>2296</td>
<td>6.1 (3.9–8.3)</td>
<td>77</td>
<td>23.2</td>
<td>0.24</td>
<td>0.11</td>
</tr>
<tr>
<td>Medium HDL, µmol/L</td>
<td>2.6 (1.1–4.9)</td>
<td>2296</td>
<td>3.4 (1.4–5.0)</td>
<td>77</td>
<td>29.5</td>
<td>0.05</td>
<td>0.64</td>
</tr>
<tr>
<td>Small HDL, µmol/L</td>
<td>24.9±5.0</td>
<td>2296</td>
<td>24.4±4.3</td>
<td>77</td>
<td>−1.8</td>
<td>−0.09</td>
<td>0.54</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L*</td>
<td>4.2±1.0</td>
<td>3446</td>
<td>3.8±1.0</td>
<td>113</td>
<td>−9.9</td>
<td>−0.41</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are presented as mean±SD for variables with a normal distribution and median with interquartile range for variables with a non-normal distribution. CETP indicates cholesteryl ester transfer; CRP, C-reactive protein; CVD, cardiovascular disease; D, difference; D (SD), difference as proportion of SD; HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; LCAT, lecithin–cholesterol acyltransferase; LDL, low-density lipoprotein; LPL, lipoprotein lipase; Lp-PLA2, lipoprotein-associated phospholipase A2; N, number; NMR, nuclear magnetic resonance; OxPL, oxidized phospholipids; RLU, relative light units; sPLA2, secretory phospholipase A2; VLDL, very low-density lipoprotein; and WBC, white blood cells.

†Significant difference.

*Significant difference. 

†P values calculated with a linear regression model, adjusted for age, sex, and CVD status.

polymorphisms at the PCSK9 locus on plasma lipids.7,8 A recent analysis of the Copenhagen general population study showed that carriers of the R46L variant had lower Lp(a) than noncarriers.9 Recently, Koren et al10 documented the impact of the PCSK9 inhibitor alirocumab on NMR lipoprotein subfractions in 60 patients with hypercholesterolemia. Alirocumab therapy resulted in a 63.3% decrease of LDL-P concentration, whereas IDL-P concentration fell by 52.8%. Although the effect of alirocumab on Lp(a) was not determined by Koren et al,10 Lp(a) reductions ≤30%
Figure. Data are presented as percentage change. For variables that differ significantly (P<0.05), the bars are filled black. P values adjusted for age, sex, and cardiovascular disease status. Apo indicates apolipoprotein; CETP, cholesteryl ester transfer; CRP, C-reactive protein; HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; LCAT, lecithin–cholesterol acyltransferase; LDL, low-density lipoprotein; Lp(a), lipoprotein(a); LPL, lipoprotein lipase; Lp-PLA2, lipoprotein-associated phospholipase A2; OxPL, oxidized phospholipids; P, particle; sPLA2, secretory phospholipase A2; VLDL, very low–density lipoprotein; and WBC, white blood cells.
were demonstrated in phase 2 trials. The effect of alirocumab on cholesterol ester transfer, lecithin–cholesterol acyltransferase, lipoprotein lipase, oxidized phospholipids, sPLA2, and Lp-PLA2 has not been reported. Our study extends the results of Koren et al by showing that PCSK9 inhibition could be associated with lower LDL-P and Lp(a) in patients without hypercholesterolemia.

The relationship between LDL-C and CVD risk is strong and consistent, but evidence suggests that LDL-P concentrations could be more closely associated with CVD risk than LDL-C. Because of a possible discordance between LDL-C and LDL-P concentrations, patients with LDL-C levels on target could be at increased CVD risk attributable to high LDL-P levels. The American Association of Clinical Chemistry has suggested to strive for a LDL-P concentration treatment goal of <1100 nmol/L or an equivalent LDL-C level of <100 mg/dL in patients at high CVD risk according to the National Cholesterol Education Program Adult Treatment Panel III.

As was shown by Ference et al, a lifelong exposition to lower LDL-C levels resulted in a 3-fold greater reduction in CHD per millimoles per liter than in the statin trials. Also, it was recently shown that plasma Lp-PLA2 are inversely correlated with PCSK9 levels. This enzyme is positively associated with the development of CHD, stroke, and aortic stenosis. R46L carriers had both lower levels of secretory phospholipase A2 and Lp-PLA2 than noncarriers, which could be an additional explanation of the lower CHD risk in R46L carriers. Results of our genetic association study are, however, more likely to imply a causal role for PCSK9 in Lp-PLA2 than an association between blood levels of both factors based on correlations.

In conclusion, our results suggest that carriers of the PCSK9 R46L genetic variant have a lifelong lower exposure to all atherogenic lipoproteins, including Lp(a), secretory phospholipase A2, and Lp-PLA2, which presumably explains their reduced CHD risk.

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We would like to thank participants, general practitioners, and staff of the EPIC-Norfolk study.

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Disclosures

None.

References


**Highlights**

- Carriers of the PCSK9 (proprotein convertase subtilisin/kexin 9) R46L genetic variant have, compared with noncarriers, the following: lower apolipoprotein B concentrations; lower very low-density lipoprotein and low-density lipoprotein particle concentrations; lower lipoprotein(a) concentrations; lower secretory phospholipase A2 and Lp-PLA2 activity.
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Methods

Study design
The EPIC-Norfolk prospective cohort consists of 25,633 individuals recruited from general practises in the Norfolk area, United Kingdom. Study participants aged between 39 and 79 were enrolled between 1993 and 1997. This cohort study was originally developed to investigate the relation between diet, lifestyle and cancer, but additional variables were collected to study the pathogenesis of other chronic diseases. At baseline, patients completed general health questionnaires about their medical and family history and dietary and lifestyle parameters. Also, a panel of measurements was performed at baseline, including blood pressure, weight, waist circumference and non-fasting lipid parameters.

During follow up, all participants were flagged for mortality at the UK Office of National Statistics, and vital status was ascertained for the entire cohort. Data on hospital admissions in England and Wales were obtained using National Health Service numbers through linkage with the East Norfolk Health Authority (ENCORE) database. Data from hospital records and death certificates were coded by trained nosologists and participants were categorized by International Classification of Disease (ICD) 10th revision codes. The study protocol was approved by the Norwich District Health Authority Ethics Committee. All participants gave written informed consent.

For the current analysis, data was used of a case-control study designed by Boekholdt et al in 2004. Originally designed as a 1:2 sex and age matched case-control cohort, later in time more cases were added to come to an approximate ratio of 1:1. All individuals have been flagged for mortality at the UK Office of National Statistics, with vital status ascertained for the entire cohort. Death certificates for all decedents were coded by trained nosologists according to the International Classification of Diseases (ICD) 9th revision. Death was considered due to CHD if the underlying cause was coded as ICD 410 to 414. These codes encompass the clinical spectrum of CHD, i.e. unstable angina, stable angina, and myocardial infarction. In addition, participants admitted to hospital were identified by their unique National Health Service number by data linkage with ENCORE (East Norfolk Health Authority database), which identifies all hospital contacts throughout England and Wales for Norfolk residents. Participants were identified as having CHD during follow-up if they had a hospital admission and/or died with CHD as an underlying cause. For the current analysis, participants were excluded if their PCSK9 R46L status was unknown.

Biochemical analysis
Custom TaqMan® SNP Genotyping Assays (Applied Biosystems, Warrington, UK) was used for genotyping the PCSK9 R46L (or rs11591147). Non-fasting blood samples were drawn from the
participants at baseline, and levels of total cholesterol (TC), high density lipoprotein (HDL) cholesterol and triglycerides were analyzed on a RA-1000 analyzer (Bayer Diagnostics, Basingstoke, UK). LDL-cholesterol levels were subsequently calculated with the Friedewald formula.\(^3\) \(Lp(a)\) levels were determined with an immunoturbidimetric method on a Olympos AU640 analyzer with Randox reagents (Randox laboratories Ltd. Crumlin, County Antrim, United Kingdom). Serum concentrations of apolipoprotein A-I (apoA-I) and apolipoprotein B (apoB) levels were measured by using rate immunophlelometry (Behring Nephelometer BNII, Marburg, Germany) as previously described.\(^4\) Serum concentrations of apolipoprotein A-II (apoA-II) were measured with a commercially available immunoturbidimetric assay (Wako Pure Chemicals Industries, Ltd, Osaka, Japan) on a CobasMira autoanalyzer (Roche, Basel, Switzerland) as previously described.\(^4\) Serum apoA-V levels were measured using a sandwich ELISA as previously described.\(^5\) Proton NMR spectroscopy was performed to measure very low density lipoprotein (VLDL), intermediate density lipoprotein (IDL), LDL and HDL particle concentration using a 400 megahertz proton NMR analyzer at Liposcience, Inc. (Raleigh, NC) as previously described.\(^6\) Lipoprotein information was obtained with the NMR LipoProfile-2 analysis procedure. Briefly, particle concentrations of lipoprotein subclasses of different sizes were obtained directly from the measured amplitudes of their spectroscopically distinct lipid methyl group NMR signals. A validated 2-antibody sandwich-type ELISA was used to measure CETP concentrations.\(^7\) LPL concentration were measured with a commercially available ELISA (Dainippon).\(^8\) LCAT concentration were measured with a commercially available sandwich type ELISA (Daiichi, Japan).\(^8\) OxPL levels were measured with the use of biotinylated murine monoclonal antibodies as previously described.\(^9\) Serum sPLA2 activity was measured by a selective fluorometric assay by using fluorescent substrate 1-hexadecanoyl-2-(1-pyrenedecanoyl)-sn-glycerol-3-phosphomethanol, sodium salt (Interchim, Montlucon, France) as previously described.\(^10\) \(Lp-PLA2\) activity was measured in duplicate from ethylenediamine tetraacetic acid plasma stored at -80°C by the trichloroacetic acid precipitation procedure as previously described.\(^11\)

**Statistical analysis**

Due to an insufficient amount of plasma available for some participants, not all markers were determined in each participant. Participants with missing variables other than their R46L status, were nevertheless included in this analysis, but they were not taken into account for the missing variables. Baseline characteristics were evaluated for participants, stratified accordingly with their PCSK9 R46L status. The baseline characteristics were based on participants with NMR data available. Data are presented as mean (± standard deviation) for continuous variables with a normal distribution or as median (interquartile range) for data with a non-normal distribution.
The difference between carriers and non-carriers was determined as percentages and as proportion of the standard deviation. Between group comparison was performed by using a linear regression model, adjusted for age, sex and CVD status. All statistical analyses were performed using SPSS statistical software (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp).

References


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Change (%)