HHS Public Access

Author manuscript

Circ Cardiovasc Genet. Author manuscript; available in PMC 2018 August 01.

Published in final edited form as:

Circ Cardiovasc Genet. 2017 August ; 10(4): e001632. doi:10.1161/CIRCGENETICS.116.001632.

PCSK9 Loss-of-Function Variants, Low-Density Lipoprotein Cholesterol, and Risk of Coronary Heart Disease and Stroke: Data from Nine Studies of African Americans and Whites

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Abstract

Background—*PCSK9* loss-of-function (LOF) variants allow for the examination of the effects of lifetime low low-density lipoprotein cholesterol (LDL-C) on cardiovascular events. We examined the association of *PCSK9* LOF variants with LDL-C and incident coronary heart disease (CHD) and stroke through a meta-analysis of data from eight observational cohorts and one randomized trial of statin therapy.

Methods and Results—These nine studies together included 17,459 African Americans (AAs) with 403 (2.3%) having at least one Y142X or C679X variant, and 31,306 whites with 955 (3.1%) having at least one R46L variant. Unadjusted odds ratios (ORs) for associations between *PCSK9* LOF variants and incident CHD (851 events in AAs and 2,662 events in whites) and stroke (523 events in AAs and 1,660 events in whites) were calculated using pooled Mantel-Haenszel estimates with continuity correction factors. Pooling results across studies using inverse-variance weighted fixed-effects, *PCSK9* LOF variants were associated with 35 mg/dL (95% confidence interval [CI]: 32, 39) lower LDL-C in AAs and 13 mg/dL (95% CI: 11, 16) lower LDL-C in whites. *PCSK9* LOF variants were associated with a pooled OR for CHD of 0.51 (95% CI: 0.28, 0.92) in AAs and 0.82 (95% CI: 0.63, 1.06) in whites. *PCSK9* LOF variants were not associated with incident stroke (OR = 0.84 [95% CI: 0.48, 1.47] in AAs and OR = 1.06 [95% CI: 0.80, 1.41] in whites).

Conclusions—*PCSK9* LOF variants were associated with lower LDL-C and CHD incidence. *PCSK9* LOF variants were not associated with stroke risk.

Keywords

lipids and lipoproteins; genetics; association studies; stroke; myocardial infarction; meta-analysis

Journal Subject Terms

Genetic; Association Studies; Lipids and Cholesterol; Meta Analysis; Cerebrovascular Disease/ Stroke; Myocardial Infarction

Introduction

Gain-of-function variants in the proprotein convertase subtilisin/kexin type 9 (*PCSK9*) gene lead to high levels of low-density lipoprotein cholesterol (LDL-C), whereas loss-of-function (LOF) variants are associated with lower LDL-C levels.[1–4] While gain-of-function mutations are rare and occur in less than 0.1% of the general population, LOF variants in *PCSK9* are present in 1% to 3% of adults.[1–5] *PCSK9* LOF variants serve as a model to examine whether a lifetime with low LDL-C is associated with reduced risk for cardiovascular disease events.[2]

African Americans (AAs) more commonly manifest Y142X and C679X nonsense *PCSK9* LOF variants, which are associated with larger reductions in LDL-C than the missense R46L variant that is more common in whites.[2, 3] However, most currently published studies have relied on a small number of participants with *PCSK9* LOF variants and larger studies have not included AAs.[2, 3, 6] In addition, while there is some evidence that LOF variants in *PCSK9* are associated with lower coronary heart disease (CHD) incidence, there are few data on the association between *PCSK9* LOF variants and stroke risk.[2, 4] Therefore, the goal of the current analysis was to examine the associations between *PCSK9* LOF variants with LDL-C and incident CHD and stroke events in AAs and whites enrolled in nine studies. In addition to assessing the overall associations, we performed analyses stratified by statin use.

Methods

Data Sources

Analyses were performed by combining data from eight population-based cohort studies and one randomized controlled trial of statin therapy. Descriptions, methods, and acknowledgments for each study are included in the Supplemental Appendices. Eight of the nine studies are in the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium. The primary goal of the CHARGE Consortium is to provide high-quality, reliable, and valid estimates of associations between genotypes with cardiovascular and aging phenotypes across multiple studies.[7] Studies participating in CHARGE were conducted in the US and Europe and include genome-wide data. Each study has its own administrative structure and set of investigators. For the current analyses, we included seven observational cohorts from CHARGE: the Age, Gene, Environment, Susceptibility Study – Reykjavik (AGES), Atherosclerosis Risk in Communities (ARIC) Study, Cardiovascular Health Study (CHS), Framingham Heart Study (FHS), Health, Aging, and Body Composition (Health ABC) Study, Jackson Heart Study (JHS), and Multi-Ethnic Study of Atherosclerosis (MESA). We also included a statin trial participating in CHARGE, the PROspective Study of Pravastatin in the Elderly at Risk for vascular disease (PROSPER) Study. In addition to data from these eight participating CHARGE studies, meta-analyses included data from the observational REasons for Geographic And Racial Differences in Stroke (REGARDS) study.[8]

PCSK9 LOF variants Y142X (rs67608943) and C679X (rs28362286) were genotyped for 17,459 AAs in 6 studies (ARIC, CHS, Health ABC, JHS, MESA, and REGARDS). *PCSK9* LOF variant R46L (rs11591147) was genotyped for 31,306 whites in 8 studies (AGES, ARIC, CHS, FHS, Health ABC, MESA, PROSPER, and REGARDS). FHS, PROSPER, and AGES consisted only of white participants and JHS consisted only of AA participants. For the purposes of this analysis, participants were considered to have a *PCSK9* LOF variant if they carried at least one minor allele at Y142X or C679X (in AAs) or at least one minor allele at R46L (in whites); this nomenclature indicates the amino acid change not the nucleotide change.

To provide a larger number of participants taking statins while maximizing follow-up time and the number of outcomes that occurred, studies selected their participants' first available visit date after January 1st, 1995 for assessment of LDL-C levels and as the baseline to

initiate follow-up for CHD and stroke outcomes. The Institutional Review Boards of participating institutions for all nine studies approved this research. All participants gave written informed consent, including for genetic research.

Statistical Analyses

All analyses were performed separately for AAs and whites. For each study, mean age, the percentage of participants who were male, and the prevalence of diabetes, history of CHD, history of stroke, current smoking, and statin use were calculated by *PCSK9* LOF variant status. Linear regression models were used to calculate average differences in fasting LDL-C levels by *PCSK9* LOF variant status, after adjustment for age, gender, study center (for multi-center studies), region of residence (for REGARDS), and statin use. Regression model results from each study were pooled using fixed-effect inverse variance weighted models. Cochran's Q was calculated to assess homogeneity of estimates.

Incident CHD and stroke (any subtype) during follow-up were studied after excluding participants with a history of each respective condition at their baseline study visit. In some studies, no CHD or stroke events occurred among participants with *PCSK9* LOF variants. In order to avoid bias created when omitting these studies, unadjusted pooled Mantel-Haenszel odds ratios (ORs) for CHD and stroke were calculated using inverse-treatment arm weighted continuity correction factors.[9] The Breslow-Day test was calculated to assess homogeneity of estimates.

In secondary analyses, we calculated participant characteristics and examined the associations between *PCSK9* LOF variants and LDL-C and incident CHD and stroke stratified by statin use at baseline. We also conducted separate sensitivity analyses examining whether results from individual studies differed by analysis method. For these analyses, Cox regression models were performed to estimate the hazard ratios (HRs) for associations between the presence of a *PCSK9* LOF variant and incident CHD and stroke, adjusted for age, gender, study center (for multi-center studies), region (for REGARDS), and statin use. HRs could not be calculated for studies where no CHD or stroke events occurred among participants with *PCSK9* LOF variants. Therefore, these studies were not included in this sensitivity analysis. We performed an additional sensitivity analysis in the REGARDS study cohort calculating the OR for the association of *PCSK9* LOF variants and ischemic stroke events, while censoring follow-up when hemorrhagic stroke events occurred. Meta-analyses were performed in SAS 9.3 (Cary, NC, USA) and STATA 13.1 (College Station, TX, USA). P-values < 0.05 were considered statistically significant.

Results

Participant characteristics

Among 17,459 AAs, 403 (2.3%) had a Y142X or C679X *PCSK9* LOF variant and among 31,306 whites, 955 (3.1%) had an R46L *PCSK9* LOF variant. The mean age ranged from 47.9 years among white participants in FHS without *PCSK9* LOF variants to 79.0 years among white participants in CHS with *PCSK9* LOF variants (Table 1). Differences in characteristics across *PCSK9* status were larger in studies with smaller numbers of

participants. In all studies except PROSPER (a randomized trial), participants with *PCSK9* LOF variants were less likely to be taking statins than those without *PCSK9* LOF variants.

PCSK9 LOF variants, LDL-C, CHD and stroke

Among AAs, *PCSK9* LOF variants were associated with lower LDL-C levels in each study (Figure 1). In a pooled analysis of 6 studies with AAs that included adjustment for age, gender, and statin use, *PCSK9* LOF variants were associated with 35 mg/dL (95% confidence intervals [CI]: 32, 39) lower LDL-C levels. Among whites, having the *PCSK9* LOF variant was associated with lower LDL-C levels in each study except REGARDS. In pooled analyses among whites in 8 studies and adjusted for age, gender, and statin use, the *PCSK9* LOF variant was associated with 13 mg/dL (95% CI: 11, 16) lower LDL-C levels.

No CHD events occurred among AA participants with *PCSK9* LOF variants in CHS or JHS (Figure 2). In pooled analyses of 6 studies with AAs, *PCSK9* LOF variants were associated with an OR for CHD of 0.51 (95% CI: 0.28, 0.92). Among whites, the *PCSK9* LOF variant was associated with a statistically significant lower CHD risk in only REGARDS (OR = 0.20; [95% CI 0.05, 0.85]). Pooling white participants in 8 studies, the OR for CHD associated with having the *PCSK9* LOF variant was 0.82 (95% CI: 0.63, 1.06).

Among AAs, no stroke events occurred among participants with *PCSK9* LOF variants in CHS, JHS, or MESA (Figure 3). In pooled analyses of 6 studies with AAs, *PCSK9* LOF variants were associated with an OR for stroke of 0.84 (95% CI: 0.48, 1.47). Pooling 8 studies with white participants, the *PCSK9* LOF variant was associated with an OR for stroke of 1.06 (95% CI: 0.80, 1.41). Cochran's Q and Breslow-Day tests did not detect heterogeneous study results for any LDL-C, CHD, or stroke models ($p>0.05$).

Results stratified by statin use

Characteristics of participants not taking and taking statins are provided by *PCSK9* LOF variant status in Tables S1 and S2. The associations of *PCSK9* LOF variants with LDL-C, CHD, and stroke among participants not taking statins were similar to associations in the overall population (Table S3). In pooled analyses of participants taking statins, *PCSK9* LOF variants were associated lower LDL-C levels in AAs, but were not associated with LDL-C levels in whites (Table S4). Among participants taking statins, no AAs with a *PCSK9* LOF variant had a CHD event. The OR for CHD associated with having a PCSK9 LOF variant was 1.46 (95% CI: 0.77, 2.79) among whites. The pooled OR for stroke among those taking statins was 4.53 (95% CI: 1.35, 15.24) for AAs and 0.91 (95% CI: 0.39, 2.11) for whites.

Sensitivity analyses

When using Cox regression models to calculate hazard ratios, the associations of PCSK9 LOF variants and incident CHD and stroke were similar to the primary analyses (Tables S5–S7). In the REGARDS study, the OR for ischemic stroke was 1.42 (95% CI: 0.67, 3.03) for AAs and 1.67 (95% CI: 0.79, 3.52) for whites.

Discussion

In this meta-analysis of 17,459 AAs and 31,306 whites, *PCSK9* LOF genetic variants were associated with lower LDL-C. Y142X and C679X variants were associated with large reductions in LDL-C and lower CHD risk among AAs. The R46L variant was associated with smaller reductions in LDL-C and correspondingly smaller, non-statistically significant reduced CHD risk among whites. These results support a dose-response association for LDL-C and CHD. *PCSK9* LOF variants were not associated with stroke risk among either AAs or whites.

The *PCSK9* gene encodes a protease that binds to the low-density lipoprotein receptor and leads to its degradation. *PCSK9* gain-of-function variants result in decreased low-density lipoprotein receptor activity, leading to a rare form of autosomal dominant familial hypercholesterolemia.[10] Conversely, the more common *PCSK9* LOF variants result in preserved low-density lipoprotein receptor activity and lower circulating LDL-C levels.[2, 10] The current analyses confirm previous observational studies which found *PCSK9* LOF variants to be associated with lower LDL-C levels. Y142X and C679X nonsense variants are more common in AAs and have been consistently associated with ≥ 30 mg/dL lower LDL-C levels.[2, 3, 11] The current analyses found similar reductions in LDL-C levels attributable to the Y142X and C679X variants as previously reported. The R46L missense variant is more common in whites and has been associated with ≥15 mg/dL lower LDL-C levels in previous reports.[2–4, 12–14] The pooled estimated from the current analyses found the R46L variant was associated with 13 mg/dL lower LDL-C.

Prior studies have found *PCSK9* LOF variants to be associated with a lower risk for CHD in AAs and whites.[2, 4] In a prior meta-analysis of 55,359 individuals in the US and Europe, the R46L variant was associated with an OR of 0.72 (95% CI: 0.62, 0.84) for ischemic heart disease.[4] In a previous report from the ARIC Study, the R46L variant was associated with a HR for CHD of 0.11 (95% CI: 0.02, 0.81) in 3,363 AA participants and 0.50 (95% CI: 0.32, 0.79) in 9,524 white participants.[2] A multinational study of whites comparing 1,454 early-onset myocardial infarction cases to 1,617 myocardial infarction-free controls found the R46L gene to be associated with an OR for myocardial infarction of 0.40 (95% CI: 0.26, 0.61).[15] Differences in these estimates from the current analyses may have occurred because most previous studies did not exclude participants with prevalent heart disease. Additionally, the current analyses used post-1995 study visits as the baseline in order to have larger numbers of participants taking statins for secondary analyses. A recent analysis of REGARDS, ARIC, and Kaiser Permanente Southern California data found that the preferential use of statins by high-risk individuals (e.g., patients with diabetes) in more contemporary cohorts may lead to bias that attenuates the association between lipids and CHD.[16] In the current meta-analyses, a protective association between *PCSK9* LOF variants and incident CHD events was present, which was statistically significant among AAs. These results provide evidence that the larger differences in lifetime LDL-C levels associated with the Y142X and C679X variants in AAs, compared to R46L variants in whites, are associated with larger differences in CHD risk. Previous meta-analyses of ezetimibe and other non-statin LDL-C lowering medication trials have also found greater LDL-C lowering to be associated with larger CHD risk reduction.[17, 18]

The association between *PCSK9* LOF variants and stroke has not been extensively studied.[2] A previous analysis of the ARIC Study, which included 6 strokes among AAs with a Y142X or C679X variant in and 9 strokes among whites with a R46L variant, reported no difference in stroke rates by *PCSK9* LOF variant status.[2] The current analyses, which included 13 strokes among AAs with a Y142X or C679X variant and 58 strokes among whites with a R46L variant, are consistent with the ARIC results and with previous observational studies wherein LDL-C was not associated with stroke risk.[2, 19, 20] A recent pooled analyses of observational studies found that R46L and other *PCSK9* LOF variants associated with smaller differences in LDL-C were not associated with stroke.[6] Among 6,276 FHS participants, LDL-C was not associated with ischemic stroke risk (HR = 1.08 [95% CI: 0.85, 1.36] per standard deviation increase in log-transformed LDL-C).[19] This result in FHS confirmed previous reports that lower LDL-C was not associated with reduced ischemic stroke risk.[21, 22] However, strokes have varying etiologies and LDL-C has different associations with different stroke subtypes.[21] It has been noted that hypertension and diabetes are the dominant risk factors for strokes originating from lipohyalinosis, but that serum lipids may contribute to strokes associated with carotid arthrosclerosis.[21] Additionally, a meta-analysis of 23 studies with 1,430,141 participants found that low LDL-C levels were associated with increased hemorrhagic stroke risk.[23] It is not clear if this association is causal or reflects high hemorrhagic stroke risk in individuals with general poor health status.[24] In the current study, no association was present between PCSK9 LOF variants and strokes of all sub-types or ischemic strokes. We could not examine associations between PCSK9 LOF variants and hemorrhagic stroke, since this outcome is too rare.

Clinical trials of lipid-lowering medications have also given inconsistent results on whether lower LDL-C levels lead to lower stroke risk. A 2013 Cochrane Collaboration meta-analysis of randomized trials indicated that statin treatment reduces stroke risk (relative risk = 0.78 [95% CI: 0.68, 0.89]), and a 2015 meta-analysis of 27 statin trials including 174,000 participants found that more intensive statin treatment further reduces stroke risk.[25, 26] It has been hypothesized that the lower stroke risk may not be directly related to the LDL-C lowering effects of statins, but rather from pleiotropic effects such as the lowering of triglyceride levels and reduction of inflammation.[20, 27, 28] However, a 2015 meta-analysis of 7 trials containing 31,048 patients found that ezetimibe, which is prescribed primarily due to its role in lowering LDL-C levels, was associated with a relative risk of 0.84 (95% CI: 0.74, 0.95) for stroke.[18] Randomized trials of pharmacologic *PCSK9* inhibitors where stroke is evaluated as a secondary endpoint will provide more clarity on this association.[29, 30]

In the current analyses of AAs taking statins, *PCSK9* LOF variants were associated with an increased risk for stroke. However, the sample for the stroke analyses in AAs taking statins had only 30 participants with PCSK9 LOF variants, 3 of whom had stroke events. Therefore, it is possible that the higher stroke risk for participants with PCSK9 LOF variants was due to chance. In addition, 28 of the 30 participants with PCSK9 LOF variants, including all 3 stroke events, were from a single study (REGARDS). Confounding by indication may have affected analyses among REGARDS participants taking statins. Specifically, individuals with *PCSK9* LOF variants have lower LDL-C levels and those who are prescribed statins are more likely to have a higher prevalence of cardiovascular disease risk factors.[31] Among AA participants in the REGARDS study taking statins, those with a PCSK9 LOF variant had a

higher prevalence of diabetes, history of CHD, and were smokers. Due to the small number of AAs taking statins in REGARDS who had a stroke, we could not further explore possible confounding. However, there was no association between the presence of a *PCSK9* LOF variant and stroke among whites taking statins. In the current analysis, 90 (66%) of the 136 white participants taking statins with a PCSK9 LOF variant were in PROSPER, a randomized statin trial. Among whites in PROSPER, participants with a PCSK9 LOF variant did not have a higher prevalence of diabetes, a history of CHD, or smoking.

The current analyses have a number of strengths including the availability of data on *PCSK9* LOF variants, LDL-C and cardiovascular outcomes from nine studies. The populations included a large number of AAs and whites from the United States and Europe. Additionally, the contemporary data examined in this study facilitated analyses stratified by statin use. Results should be considered in the context of known and potential limitations. Methods varied between studies, including event retrieval methods and event definitions. Another potential limitation of these analyses is the introduction of survivor bias through the exclusion of individuals with previous CHD and stroke events. However, the prevalence of previous CHD and stroke at baseline was not consistently higher among participants with PCSK9 LOF variants across cohorts. As no events occurred among participants with *PCSK9* LOF variants in some studies, the associations of *PCSK9* LOF variants and CHD and stroke in primary analyses were calculated unadjusted. However, in sensitivity analyses unadjusted ORs and adjusted HRs were similar in the studies in which both could be calculated. Although we combined data from nine studies, the numbers of CHD and stroke events were low among participants with *PCSK9* LOF variants, particularly in models stratified by statin use, and limited the ability to adjust for confounders. The low number of events resulted in high variability in the estimates for an association between each of the individual studies. Larger studies are needed determine the replicability of the pooled estimates of this analysis.[32] Also, statin use was defined at a single time point, and race was self-reported without incorporating any measures of genetic admixture.

In conclusion, this meta-analysis consisting of 17,459 AAs and 31,306 white participants from nine studies in the United States and Europe confirmed that *PCSK9* LOF variants are associated with lower LDL-C among AAs and whites. *PCSK9* Y142X or C679X variants genotyped in AAs, compared to the *PCSK9* R46L variant genotyped in whites, were associated with larger reductions in LDL-C and CHD incidence. *PCSK9* LOF variants were not associated with stroke risk. These results suggest that lifetime lower LDL-C levels are associated with lower CHD risk and support a dose-response association between LDL-C and CHD, corroborating the results from meta-analyses of ezetimibe and other LDL-C lowering medication trials.[17, 18] The current report supports recent analyses of clinical trials that found a 50% reduction in the risk for cardiovascular events in participants randomized to LDL-lowering monoclonal antibody *PCSK9* inhibitors, compared with their counterparts randomized to placebo.[10, 29, 30, 33] The results of the current analyses were less clear on stroke. Future studies of *PCSK9* inhibitors and other lipid-lowering medications should be designed and adequately powered to examine the association between LDL-C and stroke, separate from other cardiovascular events.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Sources of Funding: *Age, Gene, Environment, Susceptibility Study – Reykjavik (AGES):* This study has been funded by National Institutes of Health (NIH) contracts N01-AG-1-2100 and HHSN27120120022C, the National Institutes on Aging (NIA) Intramural Research Program, Hjartavernd (the Icelandic Heart Association), and the Althingi (the Icelandic Parliament). The study is approved by the Icelandic National Bioethics Committee, VSN: 00-063. The researchers are indebted to the participants for their willingness to participate in the study. *Atherosclerosis Risk in Communities (ARIC) Study:* The Atherosclerosis Risk in Communities Study is carried out as a collaborative study supported by National Heart, Lung, and Blood Institute (NHLBI) contracts (HHSN268201100005C, HHSN268201100006C, HHSN268201100007C, HHSN268201100008C, HHSN268201100009C, HHSN268201100010C, HHSN268201100011C, and HHSN268201100012C), R01HL087641, R01HL59367 and R01HL086694; National Human Genome Research Institute (NHGRI) contract U01HG004402; and NIH contract HHSN268200625226C. The authors thank the staff and participants of the ARIC study for their important contributions. Infrastructure was partly supported by Grant Number UL1RR025005, a component of the NIH and NIH Roadmap for Medical Research. *Cardiovascular Health Study (CHS):* This CHS research was supported by NHLBI contracts HHSN268201200036C, HHSN268200800007C, N01HC55222, N01HC85079, N01HC85080, N01HC85081, N01HC85082, N01HC85083, N01HC85086; and NHLBI grants R01HL085251, U01HL080295, R01HL087652, R01HL105756, R01HL103612, R01HL130114, and R01HL120393 with additional contribution from the National Institute of Neurological Disorders and Stroke (NINDS). Additional support was provided through R01AG023629 from the National Institute on Aging (NIA). A full list of principal CHS investigators and institutions can be found at CHS-NHLBI.org. The provision of genotyping data was supported in part by the National Center for Advancing Translational Sciences, Clinical and Translational Science Institute (CTSI) grant UL1TR000124, and the National Institute of Diabetes and Digestive and Kidney Disease (NIDDK) Diabetes Research Center (DRC) grant DK063491 to the Southern California Diabetes Endocrinology Research Center. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. *Framingham Heart Study (FHS)*: This research was conducted in part using data and resources from the Framingham Heart Study of the NHLBI and Boston University School of Medicine. The analyses reflect intellectual input and resource development from the Framingham Heart Study investigators participating in the SNP Health Association Resource (SHARe) project. This work was partially supported by the National Heart, Lung and Blood Institute's Framingham Heart Study (Contract No. N01-HC-25195 and HHSN268201500001I) and an NHLBI contract with Affymetrix, Inc for genotyping services (Contract No. N02-HL-6-4278). A portion of this research utilized the Linux Cluster for Genetic Analysis (LinGA-II) funded by the Robert Dawson Evans Endowment of the Department of Medicine at Boston University School of Medicine and Boston Medical Center. Additional support for these analyses was provided by R01HL103612 (PI Psaty, subcontract PI, Vasan). *Health Aging and Body Composition (Health ABC) Study*: The Health ABC study was supported by NIA contracts N01AG62101, N01AG62103, and N01AG62106. The genome-wide association study was funded by National Institute on Aging grant 1R01AG032098- 01A1 to Wake Forest University Health Sciences and genotyping services were provided by the Center for Inherited Disease Research (CIDR). CIDR is fully funded through a federal contract from the NIH to The Johns Hopkins University, contract number HHSN268200782096C. This research was supported in part by the Intramural Research Program of the NIH, NIA. *Jackson Heart Study*: The Jackson Heart Study is supported by contracts HHSN268201300046C, HHSN268201300047C, HHSN268201300048C, HHSN268201300049C, and HHSN268201300050C from the NHLBI and the National Institute on Minority Health and Health Disparities (NIMHD). *Multi-Ethnic Study of Atherosclerosis (MESA)*: MESA is supported by the NHLBI in collaboration with MESA investigators. Support for MESA is provided by contracts N01-HC-95159, N01-HC-95160, N01-HC-95161, N01-HC-95162, N01-HC-95163, N01-HC-95164, N01-HC-95165, N01-HC-95166, N01-HC-95167, N01-HC-95168, N01-HC-95169 and by grants UL1-TR-000040 and UL1-TR-001079 from NCRR. UL1-RR-024156. The provision of genotyping data was supported in part by the National Center for Advancing Translational Sciences, CTSI grant UL1TR000124, and the National Institute of Diabetes and Digestive and Kidney Disease Diabetes Research Center (DRC) grant DK063491 to the Southern California Diabetes Endocrinology Research Center. The authors thank the other investigators, the staff, and the participants of the MESA study for their valuable contributions. A full list of participating MESA investigators and institutions can be found at http://www.mesa-nhlbi.org<http://www.mesa-nhlbi.org/. *PROspective Study of Pravastatin in the Elderly at Risk for vascular disease (PROSPER)*: PROSPER was supported by an investigator initiated grant obtained from Bristol-Myers Squibb. Prof. Dr. J. W. Jukema is an Established Clinical Investigator of the Netherlands Heart Foundation (grant 2001 D 032). Support for genotyping was provided by the seventh framework program of the European commission (grant 223004) and by the Netherlands Genomics Initiative (Netherlands Consortium for Healthy Aging grant 050-060-810). *REasons for Geographic And Racial Differences in Stroke (REGARDS) Study*: The REGARDS Study is supported by a cooperative agreement U01 NS041588 from the National Institute of Neurological Disorders and Stroke, National Institutes of Health, Department of Health and Human Service. The content is solely the responsibility of the authors and does not

necessarily represent the official views of the National Institute of Neurological Disorders and Stroke or the National Institutes of Health. Additional REGARDS Study funding was provided by grants R01-HL80477 and K24-HL111154 from the National, Heart, Lung and Blood Institute to Dr. Safford. The authors thank the other investigators, the staff, and the participants of the REGARDS Study for their valuable contributions. A full list of participating REGARDS Study investigators and institutions can be found at http://www.regardsstudy.org. The genotyping of *PCSK9* variants in the REGARDS study was funded by an academic/industry collaboration between UAB, Mount Sinai School of Medicine and Amgen Inc.

Disclosures: Amgen provided funding to ST Kent, RS Rosenson, EB Levitan, MM Safford, and P Muntner for this work, and JM Woolley was an Amgen employee during this work. RS Rosenson also received research funding from Astra Zeneca, Sanofi, Aegerion, and was consulting for Amgen, Astra Zeneca, Genzyme, Eli Lilly, GSK, Kowa, Novartis, Regeneron, Sanofi, and UpToDate, Inc. M Cushman received funding from diaDexus. JW Jukema received funding from Bristol-Myers Squibb. EB Levitan consulted for Calcagnie Robinson Shapiro Davis. BM received funding from Johnson & Johnson and consulted for Zoll LikeCor.

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Clinical Perspective

Previous research has established that *PCSK9* loss-of-function variants are associated with lower low-density lipoprotein cholesterol (LDL-C). African Americans more commonly manifest Y142X and C679X nonsense *PCSK9* LOF variants, which are associated with larger reductions in LDL-C than the missense R46L variant that is more common in whites. In the current meta-analysis that included 9 studies (n=17,459 African Americans and 31,306 whites), the Y142X or C679X variants genotyped in African Americans were associated with larger reductions in LDL-C and coronary heart disease (CHD) incidence compared with the *PCSK9* R46L variant genotyped in whites. These results suggest that lifetime lower LDL-C levels are associated with lower CHD risk and support a dose-response association between LDL-C and CHD, supporting the results from meta-analyses of previous LDL-C lowering medication trials. *PCSK9* LOF variants were not associated with stroke risk. Future studies of PCSK9 inhibitors and other lipid-lowering medications should be designed and adequately powered to examine the association between LDL-C and stroke, separate from other cardiovascular events.

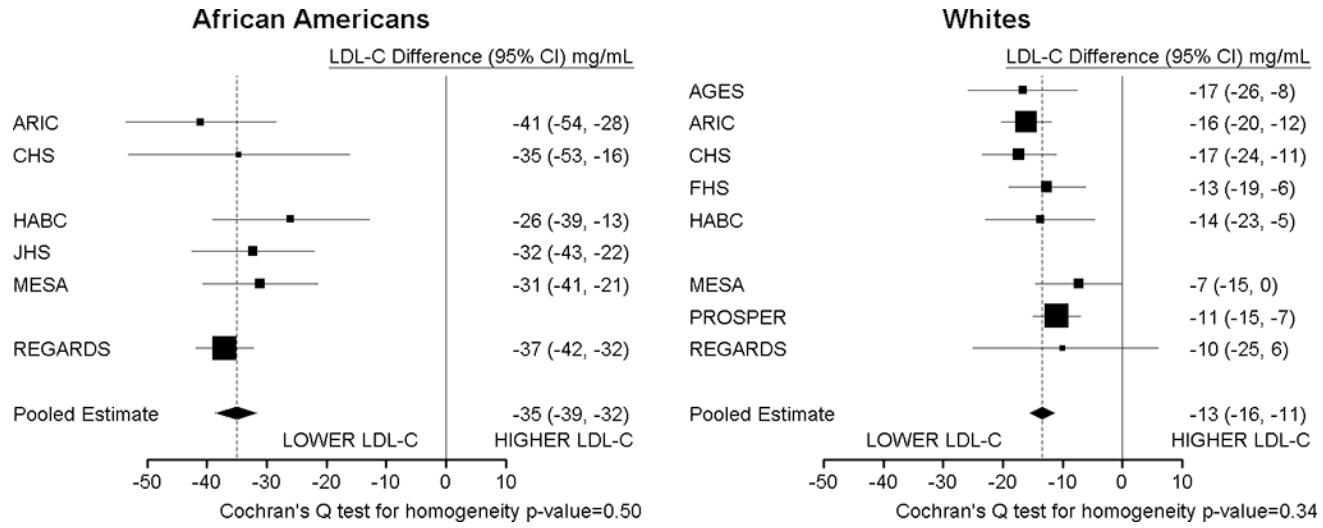

Figure 1.

Difference in low-density lipoprotein cholesterol (LDL-C) among participants with versus without *PCSK9* LOF variants in individual studies and pooled analyses. AGES = Age, Gene, Environment, Susceptibility Study – Reykjavik; ARIC = Atherosclerosis Risk in Communities Study; CHS = Cardiovascular Health Study; CI = Confidence interval; FHS = Framingham Heart Study; Health ABC = Health, Aging, and Body Composition Study; JHS = Jackson Heart Study; LDL-C = Low-density lipoprotein cholesterol; MESA = Multi-Ethnic Study of Atherosclerosis; PROSPER = PROspective Study of Pravastatin in the Elderly at Risk for vascular disease; REGARDS = REasons for Geographic and Racial Differences in Stroke Study. LDL-C differences are comparing participants with *PCSK9* LOF variants to those without *PCSK9* LOF variants (*PCSK9* LOF variant minus no *PCSK9* LOF variant). Models for each participating study include adjustment for age, gender, region/center, and statin use. Pooled analyses are performed using inverse-variance weighted fixed-effect models.

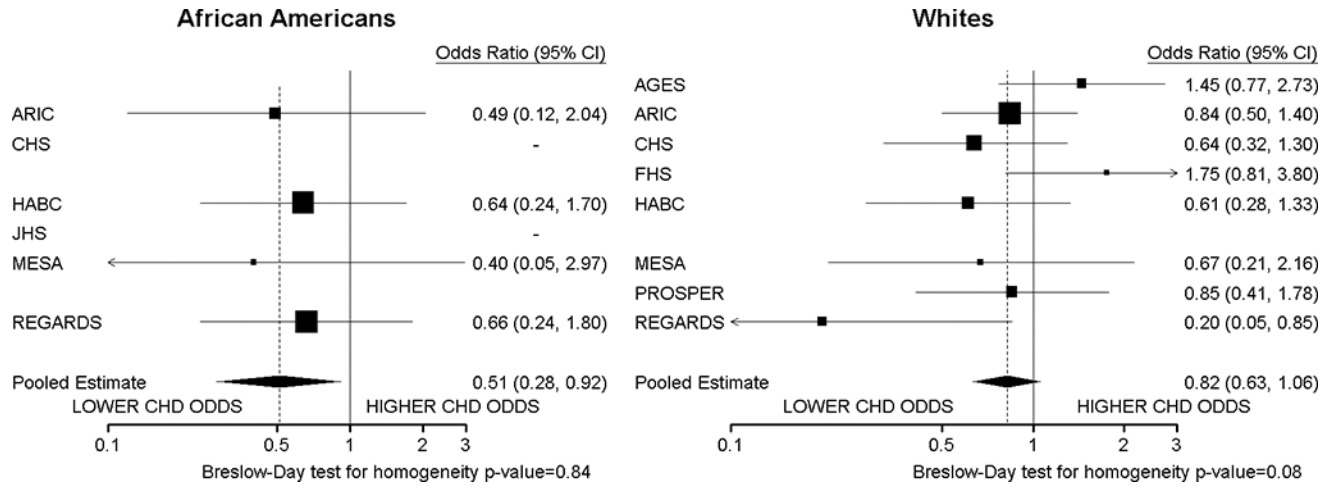

Figure 2.

Odds ratios for coronary heart disease (CHD) among participants with versus without *PCSK9* LOF variants in individual studies and pooled analyses. AGES = Age, Gene, Environment, Susceptibility Study – Reykjavik; ARIC = Atherosclerosis Risk in Communities Study; CHS = Cardiovascular Health Study; CI = Confidence interval; FHS = Framingham Heart Study; Health ABC = Health, Aging, and Body Composition Study Study; JHS = Jackson Heart Study; LDL-C = Low-density lipoprotein cholesterol; MESA = Multi-Ethnic Study of Atherosclerosis; PROSPER = PROspective Study of Pravastatin in the Elderly at Risk for vascular disease; REGARDS = REasons for Geographic and Racial Differences in Stroke Study. Pooled results are unadjusted Mantel-Haenszel ORs. Studies with no events among *PCSK9* LOF variants were included in the analyses using inverse-treatment arm continuity correction factors.

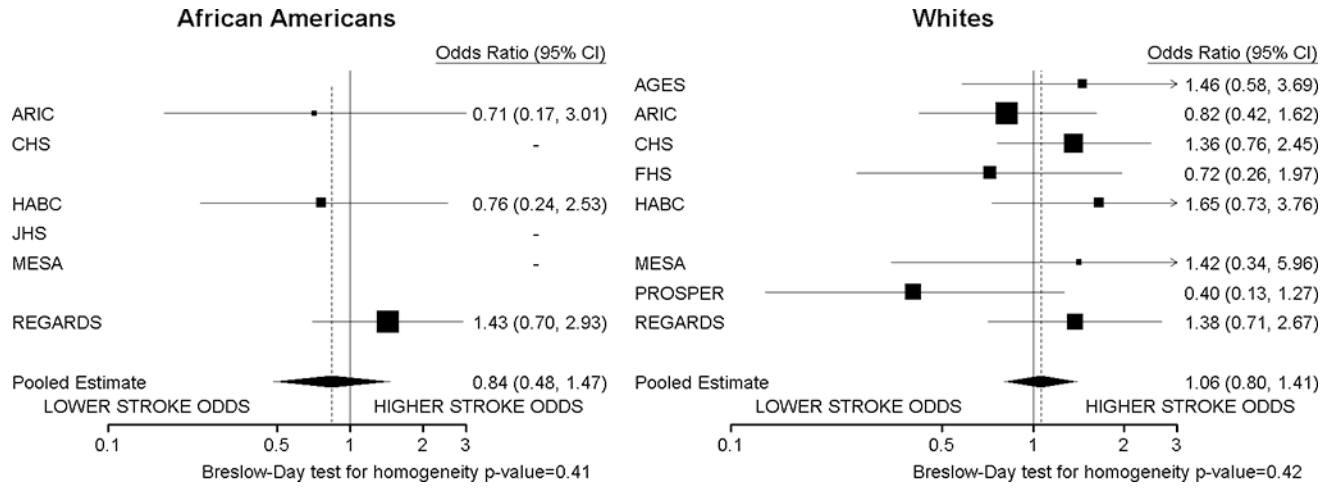

Figure 3.

Odds ratios for stroke among participants with versus without *PCSK9* LOF variants in individual studies and pooled analyses. AGES = Age, Gene, Environment, Susceptibility Study – Reykjavik; ARIC = Atherosclerosis Risk in Communities Study; CHS = Cardiovascular Health Study; CI = Confidence interval; FHS = Framingham Heart Study; Health ABC = Health, Aging, and Body Composition Study; JHS = Jackson Heart Study; LDL-C = Low-density lipoprotein cholesterol; MESA = Multi-Ethnic Study of Atherosclerosis; PROSPER = PROspective Study of Pravastatin in the Elderly at Risk for vascular disease; REGARDS = REasons for Geographic and Racial Differences in Stroke Study. Pooled results are unadjusted Mantel-Haenszel ORs. Studies with no events among *PCSK9* LOF variants were included in the analyses using inverse-treatment arm continuity correction factors.

Table 1

Baseline characteristics of African-American and white study participants included in the low-density lipoprotein analyses

African American								
Study	**N**	**Age, years**	**Male**	**Diabetes**	**History of CHD**	**History of stroke**	**Smoking**	**Statin use**
ARIC								
No *PCSK9* LOF variant	1472	60.9 (5.9)	35.9%	22.2%	7.4%	3.5%	21.9%	4.6%
PCSK9 LOF variant	30	60.9 (5.9)	26.7%	13.3%	3.3%	3.3%	23.3%	0%
CHS								
No *PCSK9* LOF variant	595	76.8 (5.5)	33.6%	21.5%	8.7%	8.9%	12.1%	7.2%
PCSK9 LOF variant	11	76.6 (3.9)	54.5%	18.2%	18.2%	81.8%	9.1%	0.0%
Health ABC								
No *PCSK9* LOF variant	1066	73.4 (2.9)	42.6%	25.8%	21.5%	10.8%	16.3%	11.8%
PCSK9 LOF variant	32	73.7 (2.9)	50.0%	18.8%	12.5%	9.4%	15.6%	0.0%
JHS								
No *PCSK9* LOF variant	1763	49.6 (11.7)	38.3%	16.6%	6.5%	3.4%	14.3%	7.5%
PCSK9 LOF variant	43	49.1 (11.8)	32.6%	12.5%	7.0%	4.7%	31.0%	2.3%
MESA								
No *PCSK9* LOF variant	1487	62.2 (10.1)	46.0%	17.1%	0.0%	0.0%	8.8%	15.1%
PCSK9 LOF variant	44	62.6 (10.6)	61.4%	13.6%	0.0%	0.0%	15.9%	2.3%
REGARDS								
No *PCSK9* LOF variant	10673	64.1 (9.2)	38.4%	29.6%	15.5%	7.9%	17.2%	29.5%
PCSK9 LOF variant	243	63.7 (9.1)	38.3%	35.1%	11.3%	4.9%	20.3%	13.2%
White								
Study	**N**	**Age, years**	**Male**	**Diabetes**	**History of CHD**	**History of stroke**	**Smoking**	**Statin use**
AGES								
No *PCSK9* LOF variant	2911	76.4 (5.5)	42.2%	11.4%	22.5%	4.5%	12.7%	22.5%
PCSK9 LOF variant	72	76.6 (5.5)	45.8%	15.3%	20.0%	8.6%	13.9%	15.3%
ARIC								
No *PCSK9* LOF variant	8206	62.0 (5.9)	46.5%	11.9%	8.3%	1.9%	14.8%	10.1%
PCSK9 LOF variant	260	62.2 (5.7)	43.8%	11.5%	7.7%	1.5%	17.3%	3.1%

CHS								
No *PCSK9* LOF variant	2875	78.8 (5.0)	39.7%	12.1%	11.6%	7.3%	6.3%	9.8%
PCSK9 LOF variant	90	79.0 (5.0)	37.8%	16.7%	15.6%	11.1%	12.2%	4.4%
FHS								
No *PCSK9* LOF variant	6448	47.9 (12.8)	46.3%	5.4%	1.7%	0.8%	32.4%	8.0%
PCSK9 LOF variant	199	48.5 (13.6)	41.2%	6.0%	2.0%	2.5%	33.2%	4.5%
Health ABC								
No *PCSK9* LOF variant	1592	73.8 (2.8)	52.8%	14.1%	21.3%	8.9%	6.3%	14.9%
PCSK9 LOF variant	52	73.9 (2.7)	51.9%	23.1%	15.4%	9.6%	5.8%	7.7%
MESA								
No *PCSK9* LOF variant	2274	62.6 (10.2)	48.0%	5.8%	0.0%	0.0%	14.9%	17.0%
PCSK9 LOF variant	66	63.6 (10.5)	59.1%	3.0%	0.0%	0.0%	15.2%	9.1%
PROPSER								
No *PCSK9* LOF variant	5052	75.3 (3.3)	48.4%	10.5%	44.7%	11.3%	26.5%	49.7%
PCSK9 LOF variant	185	75.2 (3.5)	40.0%	8.6%	41.1%	8.6%	27.6%	48.6%
REGARDS								
No *PCSK9* LOF variant	993	65.6 (0.2)	50.0%	16.5%	18.5%	4.8%	11.9%	35.3%
PCSK9 LOF variant	31	65.6 (1.5)	48.1%	19.2%	19.2%	13.3%	21.6%	13.2%

AGES = Age, Gene, Environment, Susceptibility Study – Reykjavik; ARIC = Atherosclerosis Risk in Communities Study; CHS = Cardiovascular Health Study; FHS = Framingham Heart Study; PROSPER = PROspective Study of Pravastatin in the Elderly at Risk for vascular disease; Health ABC = Health, Aging, and Body Composition Study; JHS = Jackson Heart Study; MESA = Multi-Ethnic Study of Atherosclerosis; REGARDS = REasons for Geographic and Racial Differences in Stroke Study.

PCSK9 LOF variants including Y142X and C679X in AAs and R46L in whites.
For whites in REGARDS, the total number of participants is unweighted, but the remaining characteristics are weighted to represent their proportions in the full white cohort.
Age is presented as mean (standard deviation), except for among whites in REGARDS which displays mean (standard error) because characteristics are weighted. Remaining characteristics are presented as percentages.