# Supplementary Online Content

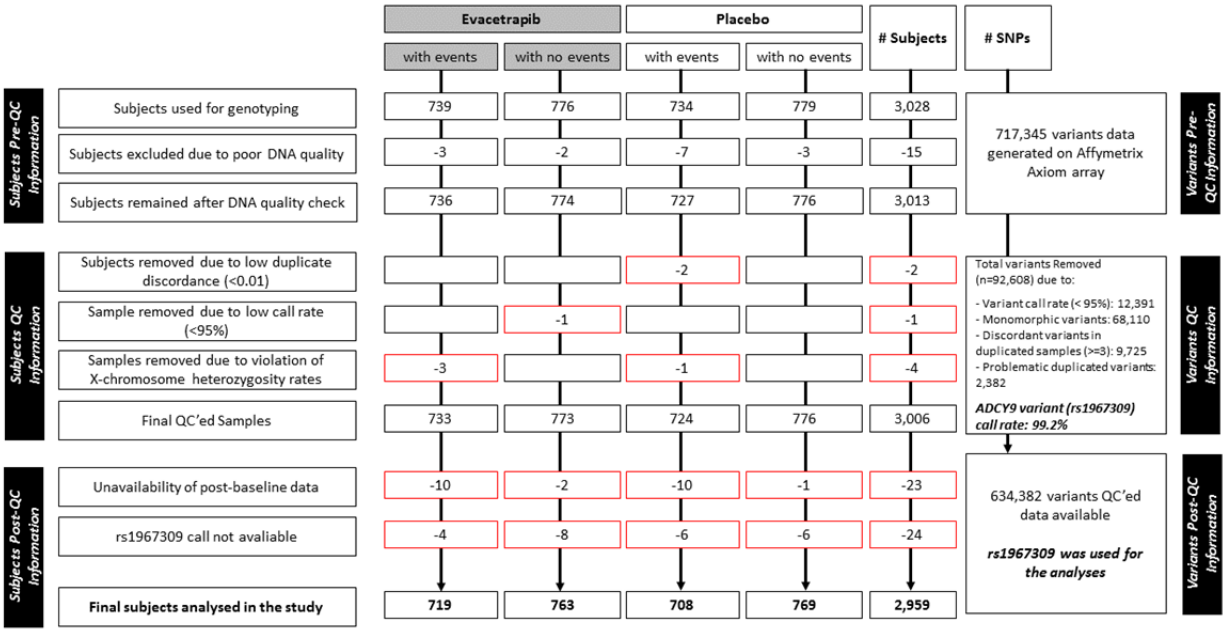
Nissen SE, Pillai SG, Nicholls SJ, et al. *ADCY9* genetic variants and cardiovascular outcome with evacetrapib in patients with high-risk vascular disease: a nested case-control study. *JAMA Cardiol*. Published online March 11, 2018. doi:10.1001/jamacardio.2018.0569



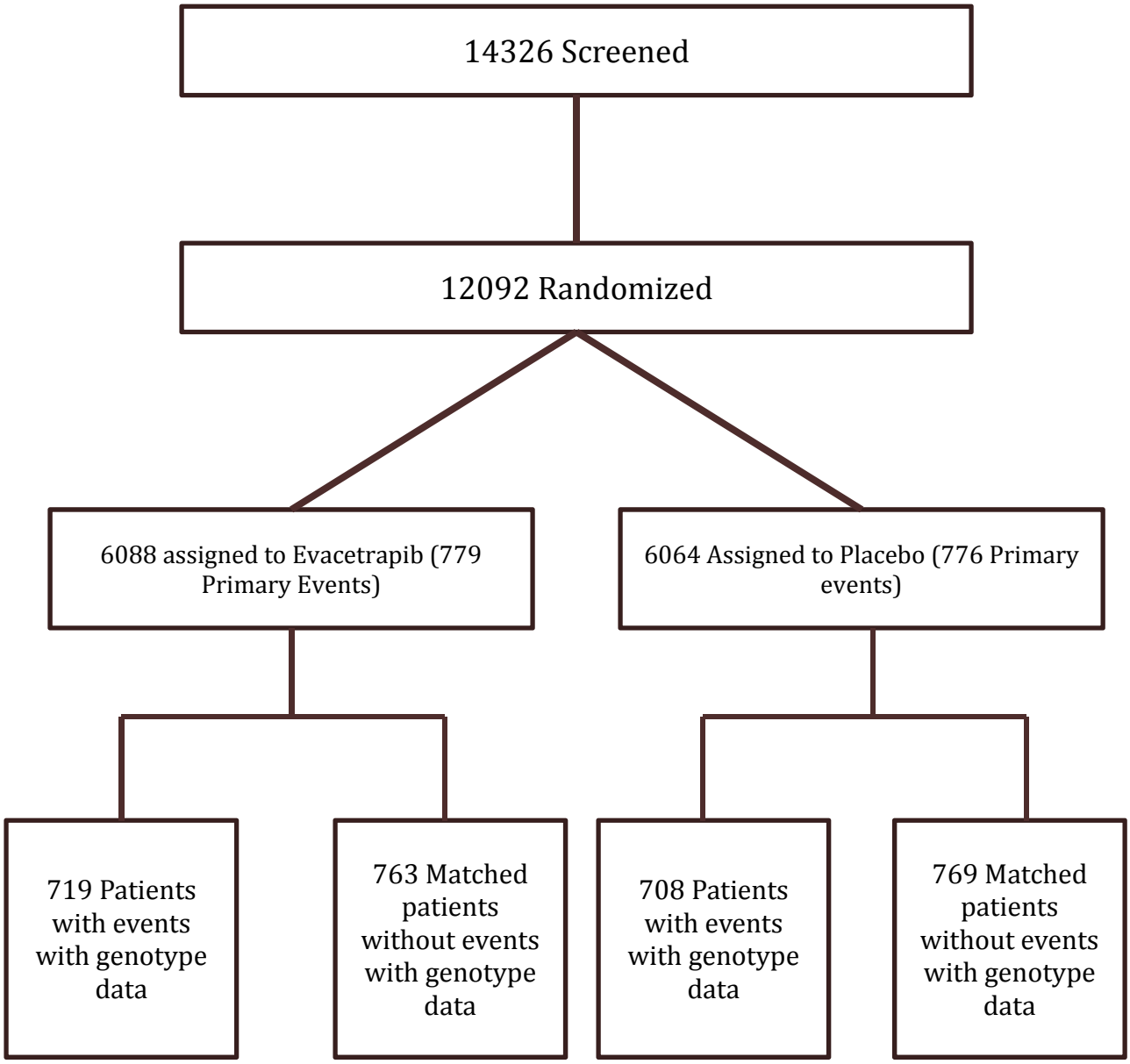
This supplementary material has been provided by the authors to give readers additional information about their work.

**eFigure 1: Flowchart Summarizing the Subject- and Variant-Levels Quality Control (QC) Information**

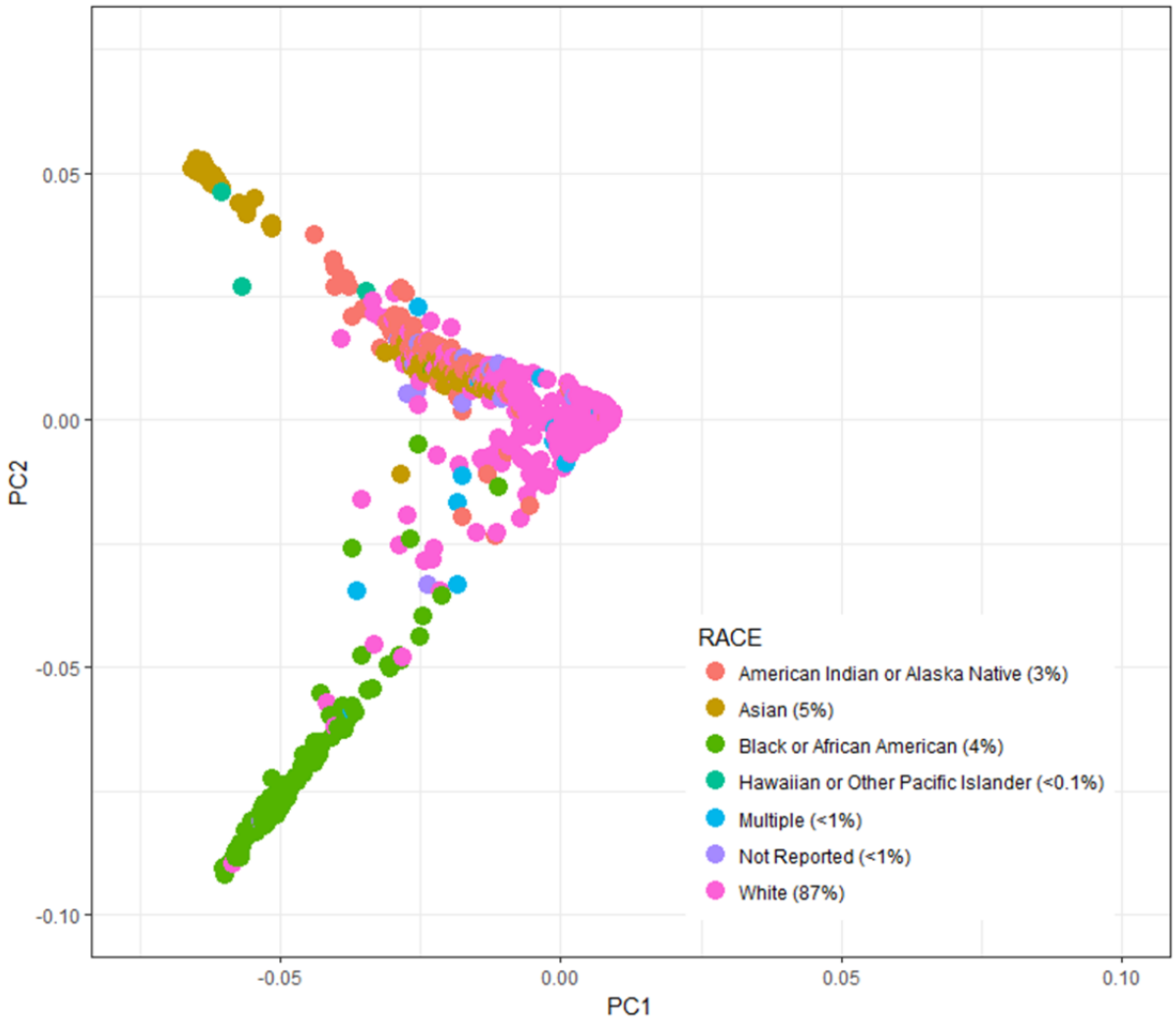
A total of 3,028 patient DNA samples were used for genotyping, including 1,473 cases with events (Evacetrapib group cases: 739; Placebo group cases: 734) and 1,555 controls with no events (Evacetrapib group controls: 776; Placebo group controls: 779). Twenty-four International HapMap consortium controls along with 43 duplicates were also genotyped as a quality control measure. Average call rate for the study samples and HapMap control were 99.28 and 99.56%, respectively. The average concordance across all the duplicate samples were >99.6%. Seven samples were excluded during genotype QC process (low sample call rate, n=1; X-chromosome heterozygosity violation, n=4; and duplicate discordance, 98.6% and 98.9%, n=2), and 3,006 patients (99.27%) passed QC. Of these, 23 did not have complete post-baseline clinical data available, thus further excluded from the analysis. The genotype call rate for rs1967309 was >99.2%, and 24 patients did not generate genotype data for this SNP, thus resulted 2,959 patients for the subsequent analysis



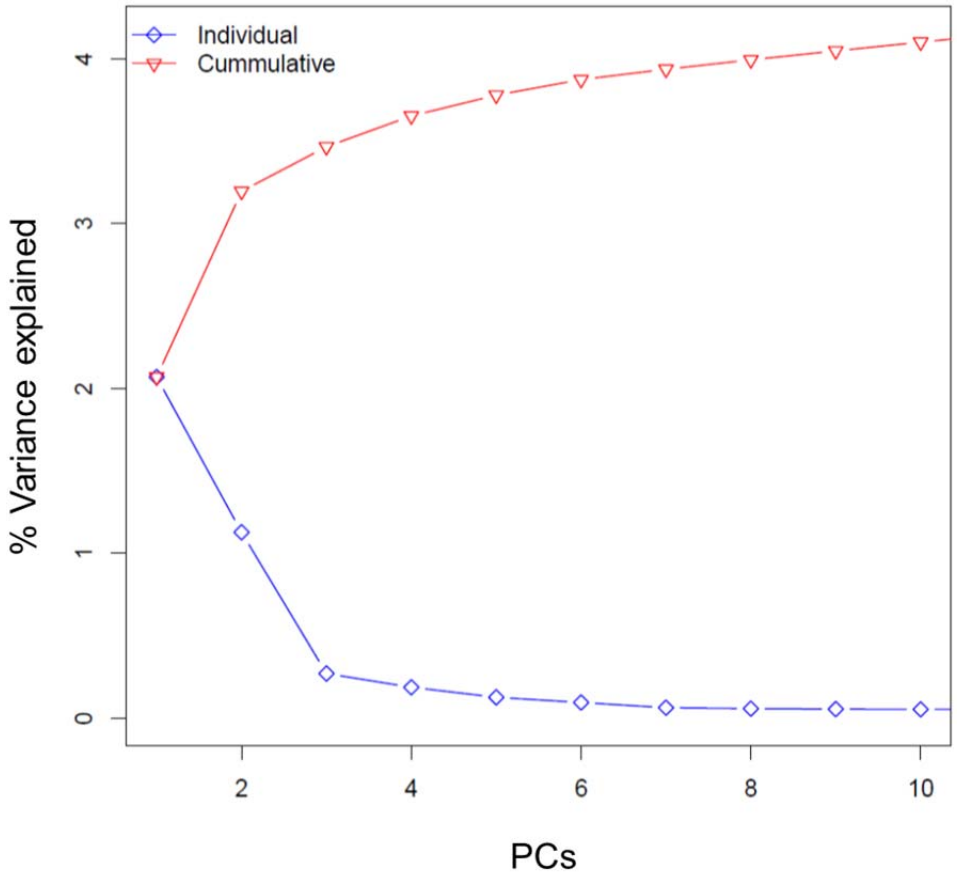
**eFigure 2. Flow of Patients Through the Pharmacogenetic Analysis**



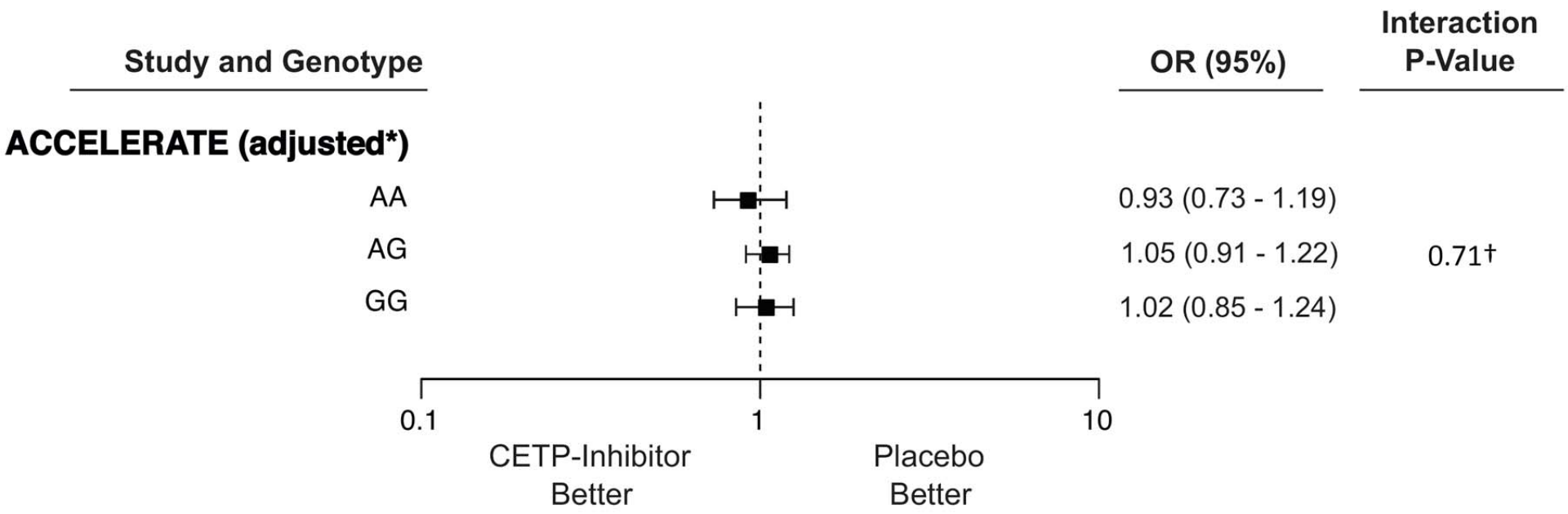
**eFigure 3. Principal Components Analysis Results for Top 2 Components (PC1 vs PC2) Based on the Quality-Controlled Data (each dot representing one individual).**



**eFigure 4: Scree Plot Showing Individual and Cumulative Percent Genomic Variance Explained by Top 10 Principal Components**



**eFigure 5.Treatment Effects of CETP Inhibition Compared with Placebo for 5 Component MACE (rs1967309 SNP)**




*Adjusted for sex, top five principal components, and risk factors including baseline apolipoprotein B, history of cerebral vascular disease, history of peripheral arterial disease, history of prior percutaneous coronary intervention, history of prior mycoardial infarction, region, race, and smoking status in an interaction model with treatment and SNP main effects and treatment-by-SNP interaction effect. CETP = cholesteryl Ester Transfer Protein. OR = odds ratio.
†P value for trend across genotypes = 0.59

**eTable 1. Baseline Characteristics for Patients Who Underwent Genotyping and All Patients Enrolled in the ACCLERATE Trial**

| Characteristic | Genomic Substudy | | All Enrolled Patients | |
|---|---|---|---|---|
| | Evacetrapib | Placebo | Evacetrapib | Placebo |
| | N=1482 | N=1477 | N=6038 | N=6054 |
| Age, years | 65.4±9.1 | 65.9±8.8 | 64.3±9.4 | 64.6±9.5 |
| Female gender | 324 (21.9) | 357 (24.2) | 1390 (23.0) | 1394 (23.0) |
| Caucasian | 1262 (85.2) | 1303 (88.2) | 4933 (81.7) | 4971 (82.1) |
| Geographic region | | | | |
| North America | 1085 (73.2) | 1090 (73.8) | 2861 (47.4) | 2859 (47.2) |
| Europe | 233 (15.7) | 232 (15.7) | 1683 (27.9) | 1695 (28.0) |
| Asia | 51 (3.4) | 53 (3.6) | 592 (9.8) | 598 (9.9) |
| Other | 113 (7.6) | 102 (6.9) | 902 (14.9) | 902 (14.9) |
| BMI | 31.5±6.4 | 31.3±5.9 | 30.3±5.8 | 30.2±5.6 |
| Hypertension | 1370 (92.4) | 1375 (93.1) | 5272 (87.3) | 5301 (87.6) |
| Diabetes mellitus | 1074 (72.5) | 1101 (74.5) | 4032 (66.8) | 4041 (66.7) |
| Current smoker | 456 (30.8) | 464 (31.4) | 1936 (32.1) | 1920 (31.7) |
| ACS | 862 (58.2) | 843 (57.1) | 3670 (60.8) | 3696 (61.1) |
| PAD | 305 (20.6) | 280 (19.0) | 1214 (20.1) | 1141 (18.8) |
| Previous MI | 890 (60.2) | 866 (58.6) | 3625 (60.0) | 3641 (60.1) |
| Previous PCI | 1033 (69.7) | 1004 (68.0) | 3849 (63.7) | 3914 (64.7) |
| Previous CABG | 508 (34.3) | 517 (35.0) | 1614 (26.8) | 1572 (26.0) |
| Any statin | 1396 (94.2) | 1410 (95.5) | 5819 (96.4) | 5846 (96.6) |
| HDL cholesterol | 44.2±11.4 | 44.1±11.4 | 45.4±11.7 | 45.4±11.7 |
| LDL cholesterol | 82.1±27.8 | 82.2±27.8 | 81.6±28.4 | 81.1±27.8 |
| ApoB/ApoA | 1.84±0.58 | 1.84±0.57 | 1.90±0.60 | 1.90±0.60 |
| hs-CRP | 4.3±11 | 3.6±8 | 3.8±11 | 3.3±8 |

BMI=Body mass index. ACS=acute coronary syndrome. PAD=peripheral arterial disease. MI=myocardial infarction. PCI=percutaneous coronary intervention. CABG= coronary artery bypass grafting. HDL-C=high density lipoprotein cholesterol. LDL-C=low density lipoprotein cholesterol. ApoB=apolipoprotein B. ApoA=apolipoprotein A. hsCRP=high sensitivity C reactive protein.

**eTable 2. Baseline Characteristics of Patients Selected for Pharmacogenetic Analysis in the dal-OUTCOMES Trial**

| Characteristic | Patients with events | | Patients without events | |
|---|---|---|---|---|
| | Dalcetrapib-treated | Dalcetrapib placebo | Dalcetrapib treated | Dalcetrapib placebo |
| | N=390 | N=398 | N=2455 | N=2506 |
| Age (years) | 61.8±9.3 | 61.5±9.3 | 60.3±9.0 | 60.4±8.9 |
| Female gender -N (%) | 74 (19.0) | 73 (18.3) | 513 (20.9) | 490 (19.5) |
| Caucasian – N (%) | 390 (100) | 398 (100) | 2450 (99.8) | 2501 (99.8) |
| Geographic region- N (%) | | | | |
| North America | 200 (51.3) | 218 (54.7) | 1187 (48.3) | 1216 (48.5) |
| Europe | 190 (48.7) | 180 (45.2) | 1268 (51.6) | 1290 (51.5) |
| Asia | 0 | 0 | 0 | 0 |
| Other | 0 | 0 | 0 | 0 |
| BMI ($kg/m^2$) | 29.7±5.1 | 29.9±5.8 | 29.1±5.1 | 29.1±5.0 |
| Hypertension – N (%) | 302 (77.4) | 312 (78.3) | 1622 (66.0) | 1689 (67.4) |
| Diabetes -N (%) | 134 (34.3) | 128 (32.1) | 495 (20.1) | 503 (20.0) |
| Current smoker-N (%) | 88 (22.5) | 81 (20.3) | 473 (19.2) | 497 (19.8) |
| ACS – N (%) | 390 (100) | 398 (100) | 2455 (100) | 2506 (100) |
| PAD – N (%) | 61 (15.6) | 49 (12.3) | 189 (7.7) | 171 (6.8) |
| Previous MI – N (%) | 109 (27.9) | 114 (28.6) | 361 (14.7) | 333 (13.2) |
| Previous PCI– N (%) | 111 (28.4) | 111 (27.8) | 338 (13.7) | 352 (14.0) |
| Previous CABG-N (%) | 57 (14.6) | 65 (16.3) | 120 (4.8) | 142 (5.6) |
| Any statin – N (%) | 375 (96.2) | 382 (96.0) | 2399 (97.7) | 2452 (97.8) |
| HDL-C (mg/dL) | 43.1±11.8 | 42.8±12.1 | 43.2±11.7 | 42.9±11.7 |
| LDL-C (mg/dL) | 79.6±27.7 | 80.9±28.4 | 76.1±25.0 | 75.2±24.9 |
| ApoB/ApoA ratio | 0.62±0.18 | 0.63±0.19 | 0.59±0.18 | 0.60±0.32 |
| hs-CRP (mg/L) | 4.5±11 | 4.3±9 | 3.5±9 | 3.3±7 |

BMI=Body mass index. ACS=acute coronary syndrome. PAD=peripheral arterial disease. MI=myocardial infarction. PCI=percutaneous coronary intervention. CABG= coronary artery bypass grafting. HDL-C=high density lipoprotein cholesterol. LDL-C=low density lipoprotein cholesterol. ApoB=apolipoprotein B. ApoA=apolipoprotein A. hsCRP=high sensitivity C reactive protein.

**eTable 3. Genotype frequencies for the (rs1967309) SNP for the ACCELERATE and Dal-OUTCOMES Trials**

| Genotype | ACCELERATE N= 2959 | Dal-OUTCOMES N = 5749 | P value* |
|---|---|---|---|
| | All Patients | | |
| AA | 527 (17.8%) | 961 (16.7%) | 0.22 |
| AG | 1459 (49.3%) | 2796 (48.7%) | |
| GG | 973 (32.9%) | 1984 (34.6%) | |
| Placebo-treatment group without cardiovascular events | | | |
| | N = 769 | N = 2506 | |
| AA | 129 (16.7%) | 417 (16.6%) | 0.99 |
| AG | 378 (49.2%) | 1225 (49%) | |
| GG | 262 (34.1%) | 860 (34.4%) | |
| Placebo treatment group with cardiovascular events | | | |
| | N = 708 | N = 398 | |
| AA | 143 (20.2%) | 59 (14.8%) | 0.02 |
| AG | 353 (49.9%) | 192 (48.2%) | |
| GG | 212 (29.9%) | 146 (36.7%) | |
| CETP treatment group without cardiovascular events | | | |
| | N =763 | N= 2455 | |
| AA | 130 (17%) | 447 (18.2%) | 0.75 |
| AG | 379 (49.7%) | 1203 (49%) | |
| GG | 254 (33.3%) | 802 (32.7%) | |
| CETP treatment group with cardiovascular events | | | |
| | N =719 | N =390 | |
| AA | 125 (17.4%) | 38 (9.7%) | <0.001 |
| AG | 349 (48.5%) | 176 (45.1%) | |
| GG | 245 (34.1%) | 176 (45.1%) | |

ACCELERATE = Assessment of Clinical Effects of Cholesteryl Ester Transfer Protein Inhibition with Evacetrapib in Patients at a High Risk for Vascular Outcomes. CETP = Cholesteryl Ester Transfer Protein. *P value is from the Chi-square test of association

**eTable 4. Treatment Effects for Dalcetrapib Compared With Placebo Within Each Genotype of rs1967309**

| Genotype | Dalcetrapib (5 component MACE vs. placebo | |
|---|---|---|
| | Cox Proportional Hazards | |
| | HR (95% CI) | P value |
| AA | 0.61 (0.41-0.92) | 0.02 |
| AG | 0.94 (0.77-1.16) | 0.56 |
| GG | 1.27 (1.02- 1.58) | 0.03 |

**eTable 5. Results From the Conditional Logistic Regression Analyses Within Treatment Group for the Additive Genetic Effect of the Minor Allele of rs1967309 in Caucasian-specific Analyses.**

| 5 Component MACE | | | | | |
|---|---|---|---|---|---|
| Treatment | Genotype | OR (95% CI) | P-value | OR (95% CI) | P-value |
| | | Unadjusted | | Adjusted* | |
| Evacetrapib | AA | 1.04 (0.92-1.18) | 0.53 | 1.07 (0.95-1.21) | 0.25 |
| | AG | | | | |
| | GG | | | | |
| Placebo | AA | 1.19 (1.06-1.34) | 0.004 | 1.09 (0.96-1.23) | 0.18 |
| | AG | | | | |
| | GG | | | | |
| **3 Component MACE** | | | | | |
| | | Unadjusted | | Adjusted* | |
| Evacetrapib | AA | 1.11 (0.94-1.31) | 0.21 | 1.1 (0.94-1.30) | 0.23 |
| | AG | | | | |
| | GG | | | | |
| Placebo | AA | 1.01 (0.86-1.18) | 0.90 | 0.86 (0.73-1.01) | 0.06 |
| | AG | | | | |
| | GG | | | | |

*Adjusted for sex, top five principal components, and risk factors including baseline apolipoprotein B, history of cerebral vascular disease, history of peripheral arterial disease, history of prior percutaneous coronary intervention, history of prior myocardial infarction, region, race, and smoking status in an interaction model with treatment and SNP main effects and treatment-by-SNP interaction effect.

**eTable 6: ADCY9 Variant (rs1967309) Allele Frequencies Across Different Ethnic Groups**

| gnomAD Populations | Allele "A" Frequencies | Allele "A" ACCELERATE | Allele "A" Dalcetrapib |
|---|---|---|---|
| Ashkenazi Jewish | 36% | | |
| European (Finnish) | 37% | | |
| European (Non-Finnish) | 42% | 41% | 41% |
| East Asian | 43% | | |
| Other | 46% | | |
| Latino | 57% | | |
| African | 66% | | |

The rs1967309 allele frequencies shown above are based on the Genome Aggregation Database (gnomAD). This aggregated and harmonized population genetic resource includes sequencing data of 123,136 exomes and 15,496 genomes from unrelated individuals

**eTable 7. Genetic Association Summary of rs1967309 from United Kingdom Biobank (UKB) and Other Consortia Datasets (European Ancestry Where P value was <.05)**

| Trait | Ref. Allele | Beta | p-value | PMID or URL |
|---|---|---|---|---|
| **UK Biobank (Phenome-wide association analysis)** | | | | |
| Monocyte percentage | G | -0.03 | 1.33E-06 | www.ukbiobank.ac.uk |
| Monocyte count | G | -0.0021 | 2.47E-06 | www.ukbiobank.ac.uk |
| Lymphocyte percentage | G | 0.067 | 8.73E-06 | www.ukbiobank.ac.uk |
| Number in household | G | -0.0086 | 0.001 | www.ukbiobank.ac.uk |
| Other disorders of ear (H90-H95) | G | -0.00078 | 0.001 | www.ukbiobank.ac.uk |
| Conductive and sensorineural hearing loss (H90) | G | -0.00034 | 0.002 | www.ukbiobank.ac.uk |
| Urolithiasis (N20-N23) | G | 0.00084 | 0.003 | www.ukbiobank.ac.uk |
| Eosinophill count | G | -0.00080 | 0.004 | www.ukbiobank.ac.uk |
| Muscle or soft tissue injuries | G | -0.00051 | 0.008 | www.ukbiobank.ac.uk |
| Muscle/soft tissue problem | G | -0.00086 | 0.008 | www.ukbiobank.ac.uk |
| Mean platelet (thrombocyte) volume | G | 0.0053 | 0.009 | www.ukbiobank.ac.uk |
| Neoplasm of uncertain or unknown behaviour of urinary organs (D41) | G | -0.00024 | 0.01 | www.ukbiobank.ac.uk |
| Other diseases of pleura (J90-J94) | G | -0.00074 | 0.01 | www.ukbiobank.ac.uk |
| Calculus of kidney and ureter (N20) | G | 0.00061 | 0.01 | www.ukbiobank.ac.uk |
| Waist circumference / Hip circumference | G | -0.00035 | 0.01 | www.ukbiobank.ac.uk |
| Red blood cell (erythrocyte) count | G | 0.0018 | 0.01 | www.ukbiobank.ac.uk |
| Perforation of tympanic membrane (H72) | G | -0.00027 | 0.01 | www.ukbiobank.ac.uk |
| Pneumonia | G | 0.00066 | 0.01 | www.ukbiobank.ac.uk |
| Other hearing loss (H91) | G | -0.00046 | 0.02 | www.ukbiobank.ac.uk |
| Arthrosis (M15-M19) | G | -0.0016 | 0.02 | www.ukbiobank.ac.uk |
| Maternal care related to the fetus and amniotic cavity and possible delivery problems (O30-O48) | G | -0.0011 | 0.02 | www.ukbiobank.ac.uk |
| Other disorders of nervous system in diseases classified elsewhere (G99) | G | 0.00028 | 0.02 | www.ukbiobank.ac.uk |
| Gonarthrosis [arthrosis of knee] (M17) | G | -0.0011 | 0.02 | www.ukbiobank.ac.uk |
| Other joint disorders (M20-M25) | G | -0.0015 | 0.02 | www.ukbiobank.ac.uk |
| Respiratory infection | G | 0.00063 | 0.02 | www.ukbiobank.ac.uk |
| Kidney stone/ureter stone/bladder stone | G | 0.00045 | 0.02 | www.ukbiobank.ac.uk |
| Allergy or anaphylactic reaction to food | G | -0.00034 | 0.02 | www.ukbiobank.ac.uk |
| Female infertility (N97) | G | -0.00046 | 0.02 | www.ukbiobank.ac.uk |
| Infection of nervous system | G | 0.00036 | 0.02 | www.ukbiobank.ac.uk |
| Other forms of heart disease (I30-I52) | G | -0.0013 | 0.023 | www.ukbiobank.ac.uk |
| Benign neoplasms (D10-D36) | G | 0.00021 | 0.03 | www.ukbiobank.ac.uk |
| Other chronic obstructive pulmonary disease (J44) | G | -0.00070 | 0.03 | www.ukbiobank.ac.uk |

| | | | | |
|---|---|---|---|---|
| Other joint disorders, not elsewhere classified (M25) | G | -0.00088 | 0.03 | www.ukbiobank.ac.uk |
| Pleural effusion, not elsewhere classified (J90) | G | -0.00055 | 0.03 | www.ukbiobank.ac.uk |
| Other disorders of bone density and structure (M85) | G | 0.00025 | 0.03 | www.ukbiobank.ac.uk |
| Lymphocyte count | G | 0.0055 | 0.03 | www.ukbiobank.ac.uk |
| Other disorders of nose and nasal sinuses (J34) | G | -0.00061 | 0.03 | www.ukbiobank.ac.uk |
| Chronic/degenerative neurological problem | G | 0.00039 | 0.03 | www.ukbiobank.ac.uk |
| Coffee intake | G | -0.0098 | 0.04 | www.ukbiobank.ac.uk |
| Viral and other specified intestinal infections (A08) | G | 0.00021 | 0.04 | www.ukbiobank.ac.uk |
| Rheumatoid arthritis | G | -0.00049 | 0.04 | www.ukbiobank.ac.uk |
| Unspecified acute lower respiratory infection (J22) | G | -0.00062 | 0.04 | www.ukbiobank.ac.uk |
| Diseases of middle ear and mastoid (H65-H75) | G | -0.00040 | 0.05 | www.ukbiobank.ac.uk |
| Unspecified renal colic (N23) | G | 0.00031 | 0.05 | www.ukbiobank.ac.uk |
| Other non-infective disorders of lymphatic vessels and lymph nodes (I89) | G | -0.00018 | 0.05 | www.ukbiobank.ac.uk |
| Emphysema/chronic bronchitis | G | -0.00065 | 0.05 | www.ukbiobank.ac.uk |
| Other acute lower respiratory infections (J20-J22) | G | -0.00061 | 0.05 | www.ukbiobank.ac.uk |
| Eosinophill percentage | G | -0.0075 | 0.05 | www.ukbiobank.ac.uk |
| Neutrophill percentage | G | -0.03 | 0.05 | www.ukbiobank.ac.uk |
| Spondylosis (M47) | G | 0.00060 | 0.05 | www.ukbiobank.ac.uk |
| Long labour (O63) | G | -0.00054 | 0.05 | www.ukbiobank.ac.uk |
| **Publically available consortia datasets** | | | | |
| Response to Dalcetrapib treatment in acute coronary syndrome | G | NA | 2.00E-08 | 25583994 |
| Irritible bowel syndrome | G | NA | 0.0018 | 18587394 |
| Crohns disease | G | 0.0657 | 0.0079 | 26192919 |
| Inflammatory bowel disease | G | 0.043 | 0.015 | 26192919 |
| Years of educational attainment in females | G | 0.008 | 0.023 | 27225129 |
| Crohns disease | G | NA | 0.031 | 23128233 |
| Serum urate | G | 0.013 | 0.043 | 23263486 |