Plasma Aldosterone Levels Are Not Associated With Cardiovascular Events Among Patients With High-Risk Vascular Disease: Insights From the ACCELERATE Trial

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Background—The failure of cholesteryl ester transfer protein inhibitor torcetrapib was associated with an off-target increase in plasma aldosterone. We sought to evaluate the impact of evacetrapib on plasma aldosterone level and determine the association between plasma aldosterone level and major adverse cardiovascular events among patients with stable high-risk vascular disease enrolled in the ACCELERATE (Assessment of Clinical Effects of Cholesteryl Ester Transfer Protein Inhibition With Evacetrapib in Patients at a High Risk for Vascular Outcomes) trial.

Methods and Results—We included all patients with a plasma aldosterone level (N=1624) and determined the impact of evacetrapib exposure compared with placebo on plasma aldosterone levels after 12 months of treatment. Using baseline and postexposure aldosterone levels, hazard ratios for major adverse cardiovascular events (cardiovascular death, nonfatal myocardial infarction, cerebrovascular accident, hospitalization for unstable angina, and revascularization) with increasing quartile of baseline and percentage change in plasma aldosterone level at follow-up were calculated. The average age was 65.2 years, 75.7% were men, 93.7% were hypertensive, 73.3% were diabetic, and 57.6% had a prior myocardial infarction. Baseline plasma aldosterone level (85.2 [43, 150] versus 86.8 [43, 155] pmol/L; \(P=0.81\)) and follow-up percentage change (13.6% [−29, 88] versus 17.9% [−24, 87]; \(P=0.23\)) were similar between those who received evacetrapib and placebo. During median follow-up of 28 months, major adverse cardiovascular events occurred in 263 patients (16.2%). The hazard ratios for increasing quartile of baseline or percentage change in plasma aldosterone level at follow-up were not significant for major adverse cardiovascular events. These findings remained consistent when adjusting for significant characteristics.

Conclusions—Exposure to evacetrapib did not result in significant change in plasma aldosterone levels compared with placebo. Among patients with stable high-risk vascular disease, plasma aldosterone levels were not a predictor for future cardiovascular events.

Clinical Trial Registration—URL: http://www.ClinicalTrials.gov. Unique identifier: NCT01687998. (J Am Heart Assoc. 2019;8:e013790. DOI: 10.1161/JAHA.119.013790.)

Key Words: aldosterone • cholesteryl transfer protein inhibitors • major adverse cardiovascular events

The cholesteryl transfer protein (CETP) inhibitors were a much anticipated drug class that were shown in early-phase studies to significantly increase serum high-density lipoprotein (HDL) while lowering low-density lipoprotein. Despite this, they failed to show a reduction in cardiovascular events in several recent randomized controlled trials.\(^1\)\(^-\)\(^4\) The reasons for this remain unclear, with possible mechanisms including an adverse effect of CETP inhibition, such as

From the Heart and Vascular Institute, Cleveland Clinic Foundation, Cleveland, OH (A.K., D.R.P., D.M.B., K.E.W., A.M.L., E.M., S.E.N., V.M.); Eli Lilly and Company, Indianapolis, IN (G.R., G.W., J.S.R.); and Monash Cardiovascular Research Centre, Monash University, Melbourne, Australia (S.J.N.).
Accompanying Tables S1 through S6 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.013790
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Received July 1, 2019; accepted October 23, 2019.
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DOI: 10.1161/JAHA.119.013790
Aldosterone Is Not Associated With Cardiac Events  
Kumar et al

**Clinical Perspective**

**What Is New?**
- Exposure to torcetrapib was associated with an off-target increase in plasma aldosterone levels, which was presumed to be its mechanism of failure.
- The failure of evacetrapib was not associated with an increase in plasma aldosterone.
- Among patients with stable high-risk vascular disease, plasma aldosterone does not predict future cardiovascular events.

**What Are the Clinical Implications?**
- This is an important mechanistic study that may be relevant to future clinical trials that investigate cholesteryl transfer protein inhibitors or use plasma aldosterone levels for risk stratification and patient selection.

Methods

The authors declare that all supporting data are available within the article and its online supplementary files. The study protocol was approved by the Cleveland Clinic Foundation institutional review board; need for informed consent was waived.

The design of the ACCELERATE trial has previously been described. Briefly, ≈12 000 patients with stable high-risk vascular disease, including those with previous acute coronary syndrome, peripheral arterial disease, cerebrovascular disease, and diabetes mellitus with known history of coronary artery disease, were randomized in a 1:1 manner to evacetrapib, 130 mg, versus placebo. The trial was event driven, with a primary end point of MACE, which included cardiovascular death, myocardial infarction, cerebrovascular accident, coronary revascularization, or hospitalization for unstable angina. Because of clinical futility for the primary composite end point, the trial was terminated prematurely after accrual of 1363 of the planned 1670 primary end point events and a median of 26 months study drug therapy. End of study visit was completed by 98.8% of patients. End points were identified and prospectively adjudicated by an independent clinical end points committee blinded to treatment assignment.

The aldosterone substudy was restricted to ACCELERATE trial sites enrolling patients in the United States. The study collected samples from 1624 patients enrolled at 79 clinical sites. Serum samples were collected using a 3.5 serum-separating tube, locally spun, placed in a plain tube, frozen (−20°C) on site, and transferred to a central laboratory. Aldosterone was measured using a liquid chromatography–tandem mass spectrometry method on the AB Sciex by QLab. A follow-up aldosterone level was similarly drawn at 12 months. No patients were excluded. We determined the impact of evacetrapib exposure compared with placebo on plasma aldosterone levels after 12 months of exposure. Baseline patient characteristics, medications, and laboratory data were summarized across quartiles of plasma aldosterone level as percentages for categorical variables and means±SDs or medians and 25th and 75th percentiles for continuous variables. Categorical variables were compared using the χ² test, whereas continuous variables were analyzed using the Student t test or the Mann-Whitney U test, when appropriate. Kaplan-Meier methods were used to estimate risk of end point for each quartile of baseline and percentage change in plasma aldosterone. Time to event was defined as the time from randomization to the onset of the end point. When used as a continuous measurement, plasma aldosterone was natural log transformed because of its nonnormal distribution. Hazard ratios with 95% CIs for the risk of end point with increasing quartile of baseline plasma aldosterone level as percentages for categorical variables and means±SDs or medians and 25th and 75th percentiles for continuous variables.
level and percentage change in plasma aldosterone level at follow-up were calculated using Cox proportional hazards models. Multivariable regression was also performed, adjusting for potential confounders of MACE. Stepwise selection methods were used to determine significant predictors of MACE; variables with a P<0.05 remained in the final model. These variables included sex, peripheral arterial disease, prior percutaneous coronary intervention, current smoking, baseline CRP (C-reactive protein) and low-density lipoprotein, angiotensin-converting enzyme inhibitor or angiotensin receptor II antagonist use, and baseline systolic blood pressure. P<0.05 was considered statistically significant. All analyses were performed using SAS System, version 9.4 (SAS Institute, Cary, NC).

Results
Among 12 092 patients enrolled in the ACCELERATE trial, 1624 had a plasma aldosterone level drawn at baseline; of these patients, 1554 also had a level drawn at 12-month

Table 1. Baseline Characteristics of the Study Population

| Baseline Characteristics | Baseline Plasma Aldosterone Level, pmol/L |
|--------------------------|------------------------------------------|
|                          | 27.7–43 (N=406) | 43–86 (N=407) | 86–152.3 (N=405) | 152.3–3471 (N=406) | P Value |
| Age, y                   | 65.7±8.9        | 64.8±9.8      | 65.0±9.8         | 65.2±9.4          | 0.49    |
| Men                      | 340 (83.7)      | 326 (80.1)    | 297 (73.3)       | 267 (65.8)        | <0.001 |
| White                    | 386 (95.1)      | 370 (91.6)    | 378 (93.6)       | 382 (94.8)        | 0.16    |
| Body mass index, kg/m²   | 31.5±6.1        | 31.7±6.0      | 32.3±6.3         | 32.0±6.4          | 0.15    |
| Systolic blood pressure, mmHg | 130.2±16.7    | 130.2±16.2    | 127.5±16.1       | 125.6±16.5        | <0.001 |
| Diastolic blood pressure, mmHg | 74.0±8.8       | 75.4±9.8      | 74.7±9.3         | 74.0±9.6          | 0.80    |
| Current smoker           | 62 (15.3)       | 62 (15.2)     | 64 (15.8)        | 49 (12.1)         | 0.25    |
| Hypertension             | 381 (93.8)      | 374 (91.9)    | 386 (95.3)       | 381 (93.8)        | 0.53    |
| Coronary artery disease  | 391 (96.3)      | 387 (95.1)    | 391 (96.5)       | 382 (94.1)        | 0.26    |
| Prior myocardial infarction | 231 (59.1)    | 217 (56.1)    | 223 (57.0)       | 223 (58.4)        | 0.91    |
| Prior percutaneous coronary intervention | 277 (70.8) | 294 (76.0) | 285 (72.9) | 279 (73.0) | 0.72 |
| Prior coronary artery bypass grafting | 159 (40.7) | 158 (40.8) | 149 (38.1) | 150 (39.3) | 0.53 |
| Congestive heart failure | 74 (18.2)       | 69 (17.0)     | 61 (15.1)        | 82 (20.1)         | 0.63    |
| Peripheral artery disease | 70 (17.2)       | 63 (15.5)    | 70 (17.3)        | 81 (20.0)         | 0.24    |
| Cerebrovascular disease  | 134 (33.0)      | 132 (32.4)    | 125 (30.9)       | 132 (32.5)        | 0.77    |
| Renal insufficiency      | 53 (13.1)       | 59 (14.5)     | 38 (9.4)         | 61 (15.0)         | 0.91    |
| Chronic obstructive pulmonary disease | 64 (15.8) | 66 (16.2) | 59 (14.6) | 68 (16.7) | 0.87 |

| Baseline medical therapy |
|--------------------------|
| Statins                  | 385 (94.8)      | 387 (95.1)    | 376 (92.8)       | 383 (94.3)        | 0.47    |
| Angiotensin-converting enzyme inhibitor/ angiotensin II receptor blocker | 330 (81.3) | 313 (76.9) | 313 (77.3) | 278 (68.5) | <0.001 |
| Aspirin                  | 361 (88.9)      | 356 (87.5)    | 357 (88.1)       | 360 (88.7)        | 0.99    |

| Baseline laboratory parameters |
|--------------------------------|
| Low-density lipoprotein cholesterol, mg/dL | 81.5±25.9 | 80.6±26.6 | 82.1±28.9 | 82.5±27.3 | 0.44 |
| High-density lipoprotein cholesterol, mg/dL | 43.4±11.4 | 43.4±10.3 | 43.1±11.4 | 44.3±11.2 | 0.17 |
| Triglycerides, mg/dL | 141.1±71.8 | 156.2±82.8 | 155.4±83.6 | 154.6±75.4 | 0.03 |
| Lipoprotein(a), mmol/L | 75.9±89.3 | 85.9±101.0 | 72.4±86.5 | 86.5±107.1 | 0.43 |
| High-sensitivity CRP, mg/L | 3.7±7.6 | 3.9±10.5 | 5.0±15.6 | 3.6±5.9 | 0.71 |
| Sodium, mmol/L | 142.1±2.9 | 141.8±2.7 | 141.3±2.5 | 141.3±2.8 | <0.001 |
| Potassium, mmol/L | 4.6±0.4 | 4.6±0.4 | 4.5±0.4 | 4.5±0.4 | 0.05 |
| Creatinine, mg/dL | 1.1±0.3 | 1.1±0.3 | 1.1±0.3 | 1.1±0.3 | 0.89 |

Data are given as mean±SD or number (percentage). CRP indicates C-reactive protein.
Aldosterone Is Not Associated With Cardiac Events  

Kumar et al

Discussion

Despite substantial improvements in both low-density lipoprotein cholesterol and HDL cholesterol lipid profiles, evacetrapib had essentially no effect on the frequency of cardiovascular events in comparison to placebo. The reasons for the failure of evacetrapib have remained unclear. Possible considerations include off-target adverse effects, such as an increase in aldosterone and blood pressure, as demonstrated by torcetrapib, or on-target adverse effects, including production of dysfunctional or larger HDL cholesterol cholesterol-rich particles, an increase in blood viscosity, or an increase in apolipoprotein CIII and E levels, which have been associated with increased cardiovascular risk. Albeit of questionable clinical relevance, both systolic blood pressure (1.2 mm Hg) and diastolic blood pressure (0.4 mm Hg) were significantly increased among patients randomized to use of evacetrapib in the ACCELERATE trial. However, we demonstrate that this difference was not associated with an increase in plasma aldosterone level at follow-up attributable to evacetrapib exposure.

In the current data set, baseline and percentage change in plasma aldosterone levels at follow-up were not associated with an increased risk for cardiovascular events. Aldosterone has been linked to the development of ventricular remodeling and tissue fibrosis in animal models. It has also been implicated to have a directly deleterious effect on blood vessels, as mediated by vascular and perivascular inflammation. In the FOS (Framingham Offspring Study), normotensive patients with plasma aldosterone levels at the upper limit of normal were at high risk for subsequent development of hypertension. In addition, patients with primary aldosteronism have been shown to have a greater rate of cardiovascular disease than age-matched controls with hypertension, suggesting a mechanism of disease progression that is independent of blood pressure. Moreover, aldosterone has also been associated with insulin resistance and the development of metabolic syndrome in both patients with obesity and primary aldosteronism.

However, although there have been several previously published reports detailing an association between plasma aldosterone levels and cardiovascular events and mortality, the mechanism implicating aldosterone remains ambiguous. The populations from which these data...
arise are composed of patients in varied degrees of decompensated states and chronic illness (namely, acute coronary syndromes and heart failure). In these conditions, it is unclear as to whether plasma aldosterone has a directly deleterious effect or is rather a marker of excess renin-angiotensin system activation, catecholamine surges, and is not associated with cardiac events.

Table 2. Kaplan-Meier Estimates for Risk of MACEs (Cardiovascular Death, Nonfatal MI, CVA, Hospitalization for UA, and Revascularization) With Increasing Quartile of Baseline Plasma Aldosterone Level

| Outcome                        | Baseline Plasma Aldosterone Level, pmol/L* | Hazard Ratio† | P Value |
|--------------------------------|------------------------------------------|---------------|---------|
| Composite MACE                 | 27.7–43                                  | 1.03 (0.90–1.19) | 0.66    |
| Cardiovascular death, MI, or CVA| 43–86                                    | 1.03 (0.85–1.25) | 0.78    |
| All-cause mortality            | 86–152.3                                 | 1.14 (0.88–1.46) | 0.32    |
| Revascularization              | 152.3–347.1                              | 0.97 (0.82–1.15) | 0.73    |
| Hospitalization for UA         | 43 (10.6)                                | 0.98 (0.71–1.34) | 0.89    |

Data are given as number (percentage), unless otherwise indicated. CVA indicates cerebrovascular accident; MACE, major adverse cardiovascular event; MI, myocardial infarction; UA, unstable angina.
*Natural log transformed.
†Unadjusted hazard ratio.

DOI: 10.1161/JAHA.119.013790
Aldosterone Is Not Associated With Cardiac Events  

Kumar et al

DOI: 10.1161/JAHA.119.013790

Journal of the American Heart Association

Table 3. Kaplan-Meier Estimates for Risk of MACEs (Cardiovascular Death, Nonfatal MI, CVA, Hospitalization for UA, and Revascularization) With Increasing Quartile of Percentage Change in Plasma Aldosterone Level at Follow-Up Compared With Baseline

| Outcome                          | % Change in Plasma Aldosterone Level at Follow-Up* |
|----------------------------------|--------------------------------------------------|
| Composite MACE, n (%)            | <26% (N=388) 26% to 16% (N=389) 16% to 87% (N=389) >87% (N=389) |
|                                  | 40 (10.3) 42 (10.8) 43 (11.1) 57 (14.7) |
|                                 | Hazard ratio 1.03 (0.67–1.59) 1.05 (0.69–1.62) 1.40 (0.93–2.09) |
|                                 | P value 0.91 0.81 0.10 |
| Cardiovascular death, MI, or CVA, n (%) | 22 (5.7) 28 (7.2) 27 (7.0) 40 (10.3) |
|                                 | Hazard ratio 1.26 (0.72–2.20) 1.20 (0.68–2.11) 1.44 (0.91–2.85) |
|                                 | P value 0.42 0.52 0.11 |
| All-cause mortality, n (%)       | 22 (5.7) 19 (4.9) 18 (4.7) 23 (5.9) |
|                                 | Hazard ratio 0.86 (0.46–1.58) 0.80 (0.43–1.49) 1.00 (0.56–1.79) |
|                                 | P value 0.61 0.48 0.97 |
| Revascularization, n (%)         | 26 (7.0) 26 (6.9) 26 (6.9) 32 (8.7) |
|                                 | Hazard ratio 0.96 (0.56–1.65) 0.95 (0.55–1.63) 1.20 (0.72–2.02) |
|                                 | P value 0.86 0.83 0.49 |
| Hospitalization for UA, n (%)    | 8 (2.1) 6 (1.6) 8 (2.1) 9 (2.4) |
|                                 | Hazard ratio 0.74 (0.26–2.12) 0.97 (0.37–2.59) 1.05 (0.41–2.73) |
|                                 | P value 0.57 0.95 0.90 |

CVA indicates cerebrovascular accident; MACE, major adverse cardiovascular event; MI, myocardial infarction; UA, unstable angina.

*Unadjusted hazard ratio.

Discussion

Exposure to evacetrapib did not result in significant change in plasma aldosterone levels compared with placebo. Among patients with high-risk vascular disease, plasma aldosterone level was not a predictor for cardiovascular events.

Conclusions

Exposure to evacetrapib did not result in significant change in plasma aldosterone levels compared with placebo. Among patients with high-risk vascular disease, plasma aldosterone level was not a predictor for cardiovascular events.

Sources of Funding

The trial was sponsored by Eli Lilly and was coordinated by the Cleveland Clinic Coordinating Center for Clinical Research and Covance (Princeton, NJ).

Disclosures

None.

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Aldosterone Is Not Associated With Cardiac Events  
Kumar et al

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Supplemental Material
Table S1. Baseline characteristics of the study population by treatment.

| Baseline Characteristics                      | Placebo N = 811 | Evacetrapib N = 813 | P-Value |
|-----------------------------------------------|-----------------|---------------------|---------|
| Age (years)                                   | 65.3 ± 9.6      | 65.1 ± 9.4          | 0.69    |
| Male (%)                                      | 615 (75.8)      | 615 (75.6)          | 0.93    |
| Caucasian (%)                                 | 756 (93.4)      | 760 (94.1)          | 0.96    |
| Body Mass Index                               | 31.8 ± 6.1      | 32.0 ± 6.3          | 0.56    |
| Systolic Blood Pressure (mmHg)                | 128.5 ± 16.6    | 128.3 ± 16.4        | 0.77    |
| Diastolic Blood Pressure (mmHg)               | 74.5 ± 9.4      | 74.5 ± 9.3          | 0.89    |
| Current Smoker (%)                            | 113 (13.9)      | 124 (15.3)          | 0.45    |
| Hypertension (%)                              | 760 (93.7)      | 762 (93.7)          | 0.99    |
| Coronary Artery Disease (%)                   | 770 (94.9)      | 781 (96.1)          | 0.28    |
| Prior Myocardial Infarction (%)               | 449 (58.3)      | 445 (57.0)          | 0.60    |
| Prior Percutaneous Coronary Intervention (%)  | 564 (73.2)      | 571 (73.1)          | 0.95    |
| Prior Coronary Artery Bypass Grafting (%)     | 292 (37.9)      | 324 (41.5)          | 0.15    |
| Congestive Heart Failure (%)                  | 151 (18.6)      | 135 (16.6)          | 0.29    |
| Peripheral Artery Disease (%)                 | 135 (16.6)      | 149 (18.3)          | 0.37    |
| Cerebrovascular Disease (%)                   | 273 (33.7)      | 250 (30.8)          | 0.21    |
| Renal Insufficiency (%)                       | 113 (13.9)      | 98 (12.1)           | 0.26    |
| Chronic Obstructive Pulmonary Disease (%)     | 119 (14.7)      | 138 (17.0)          | 0.20    |
| **Baseline Medical Therapy**                  |                 |                     |         |
| Statins (%)                                   | 768 (94.7)      | 763 (93.8)          | 0.46    |
| Angiotensin-Converting Enzyme Inhibitor/Angiotensin-II Receptor Blocker (%) | 617 (76.1) | 617 (75.9) | 0.93 |
| Aspirin (%)                                   | 710 (87.5)      | 724 (89.1)          | 0.35    |
| **Baseline Laboratory Parameters**            |                 |                     |         |
| Low-Density Lipoprotein Cholesterol (mg/dL)   | 80.5 ± 25.4     | 82.9 ± 28.8         | 0.07    |
| High-Density Lipoprotein Cholesterol (mg/dL)  | 43.3 ± 11.0     | 43.2 ± 11.2         | 0.85    |
| Triglycerides (mg/dL)                         | 152.7 ± 77.0    | 150.9 ± 80.4        | 0.65    |
| Lipoprotein(a) (nmol/L)                       | 76.4 ± 95.6     | 83.9 ± 97.1         | 0.125   |
| High-Sensitivity C-Reactive Protein (mg/L)     | 3.9 ± 8.6       | 4.2 ± 12.3          | 0.59    |
Table S2. Baseline characteristics of the study population in comparison to that of the overall trial population.

| Baseline Characteristics                          | Aldosterone Subgroup N = 1,624 | ACCELERATE Population N = 12,092 |
|---------------------------------------------------|-------------------------------|----------------------------------|
| Age (years)                                       | 65.2 ± 9.5                    | 64.4 ± 9.4                       |
| Male (%)                                          | 1230 (75.7)                   | 9308 (77.0)                      |
| Caucasian (%)                                     | 1516 (93.8)                   | 9904 (82.3)                      |
| Body Mass Index                                   | 31.9 ± 6.2                    | 30.2 ± 5.7                       |
| Systolic Blood Pressure (mmHg)                    | 128.4 ± 16.5                  | 130.9 ± 16.4                     |
| Diastolic Blood Pressure (mmHg)                   | 74.5 ± 9.4                    | 75.5 ± 9.4                       |
| Current Smoker (%)                                | 237 (14.6)                    | 1957 (16.2)                      |
| Hypertension (%)                                  | 1522 (93.7)                   | 10573 (87.4)                     |
| Coronary Artery Disease (%)                       | 1551 (95.5)                   | 10877 (90.0)                     |
| Prior Myocardial Infarction (%)                   | 894 (57.6)                    | 7266 (66.7)                      |
| Prior Percutaneous Coronary Intervention (%)      | 1135 (73.2)                   | 7763 (71.4)                      |
| Prior Coronary Artery Bypass Grafting (%)         | 616 (39.7)                    | 3186 (29.3)                      |
| Congestive Heart Failure (%)                      | 286 (17.6)                    | 1689 (14.0)                      |
| Peripheral Artery Disease (%)                     | 284 (17.5)                    | 2355 (19.5)                      |
| Cerebrovascular Disease (%)                       | 523 (32.2)                    | 2727 (22.6)                      |
| Renal Insufficiency (%)                           | 211 (13.0)                    | 1060 (8.8)                       |
| Chronic Obstructive Pulmonary Disease (%)         | 257 (15.8)                    | 1265 (10.5)                      |
| **Baseline Medical Therapy**                      |                               |                                  |
| Statins (%)                                       | 1531 (94.3)                   | 11665 (96.5)                     |
| Angiotensin-Converting Enzyme Inhibitor/Angiotensin-II Receptor Blocker (%) | 1234 (76.0)                   | 9415 (77.9)                      |
| Aspirin (%)                                       | 1434 (88.3)                   | 10007 (82.8)                     |
| **Baseline Laboratory Parameters**                |                               |                                  |
| Low-Density Lipoprotein Cholesterol (mg/dL)       | 81.7 ± 27.2                   | 81.3 ± 28.1                      |
| High-Density Lipoprotein Cholesterol (mg/dL)      | 43.3 ± 11.1                   | 45.4 ± 11.7                      |
| Triglycerides (mg/dL)                             | 151.8 ± 78.7                  | 147.4 ± 78.9                     |
| Lipoprotein(a) (nmol/L)                           | 80.2 ± 96.4                   | 71.5 ± 89.8                      |
| High-Sensitivity C-Reactive Protein (mg/L)        | 4.1 ± 10.6                    | 3.5 ± 9.3                        |
Table S3. Breakdown of patient treatment group by quartile of baseline plasma aldosterone level.

| Treatment Group | Baseline Plasma Aldosterone Level (pmol/L) | P-Value |
|-----------------|------------------------------------------|---------|
| Placebo (%)     | 202 (49.8) | 199 (48.9) | 202 (49.9) | 208 (51.2) | 0.63     |
| Evacetrapib (%) | 204 (50.2) | 208 (51.1) | 203 (50.1) | 198 (48.8) |          |
Table S4. Differences in clinical outcomes* by treatment group.

| Clinical Outcomes                  | Placebo N = 811 | Evacetrapib N = 813 | Hazard Ratio | P-Value |
|-----------------------------------|-----------------|---------------------|--------------|---------|
| Composite MACE (%)                | 100 (14.3)      | 85 (18.0)           | 0.84 (0.63-1.12) | 0.22    |
| CV Death, MI, or CVA (%)          | 68 (9.8)        | 49 (7.4)            | 0.71 (0.49-1.02) | 0.07    |
| All-Cause Mortality (%)           | 49 (7.2)        | 33 (4.6)            | 0.67 (0.43-1.04) | 0.07    |
| Revascularization (%)             | 55 (8.1)        | 58 (14.3)           | 1.05 (0.73-1.52) | 0.79    |
| Hospitalization for UA (%)        | 16 (2.7)        | 15 (2.8)            | 0.92 (0.46-1.87) | 0.83    |

* MACE (cardiovascular [CV] death, non-fatal myocardial infarction [MI], cerebrovascular accident [CVA], hospitalization for unstable angina [UA], and revascularization)
Table S5. Kaplan-Meier estimates for risk of MACE (cardiovascular [CV] death, non-fatal myocardial infarction [MI], cerebrovascular accident [CVA], hospitalization for unstable angina [UA], and revascularization) with increasing quartile of baseline plasma aldosterone level amongst patients randomized to placebo.

| Outcome                          | 27.7 - 43 | 43 – 86 | 86 – 152.3 | 152.3 - 3471 | P-Value |
|----------------------------------|-----------|---------|------------|--------------|---------|
| Composite MACE (%)               | 37 (18.3) | 28 (14.1)| 35 (17.3)  | 34 (16.3)    | 0.73    |
| CV Death, MI, or CVA (%)         | 21 (10.4) | 15 (7.5 )| 22 (10.9)  | 22 (10.6)    | 0.66    |
| All-Cause Mortality (%)          | 10 (5.0)  | 9 (4.5)  | 11 (5.4)   | 15 (7.2)     | 0.56    |
| Revascularization (%)            | 26 (12.9) | 23 (11.6)| 20 (9.9)   | 14 (6.7)     | 0.25    |
| Hospitalization for UA (%)       | 10 (5.0)  | 6 (3.0)  | 4 (2.0)    | 4 (1.9)      | 0.25    |

*Natural log-transformed
Table S6. Kaplan-Meier estimates for risk of MACE (cardiovascular [CV] death, non-fatal myocardial infarction [MI], cerebrovascular accident [CVA], hospitalization for unstable angina [UA], and revascularization) with increasing quartile of baseline plasma aldosterone level amongst patients randomized to evacetrapib.

| Outcome                          | Baseline Plasma Aldosterone Level (pmol/L)* |
|---------------------------------|---------------------------------------------|
|                                 | 27.7 - 43 | 43 – 86 | 86 – 152.3 | 152.3 - 3471 | P-Value |
| Composite MACE (%)              | 27 (13.2) | 30 (14.4) | 40 (19.7) | 32 (16.2) | 0.30 |
| CV Death, MI, or CVA (%)        | 16 (7.8) | 12 (5.8) | 18 (8.9) | 16 (8.1) | 0.68 |
| All-Cause Mortality (%)         | 6 (2.9) | 10 (4.8) | 10 (4.9) | 7 (3.5) | 0.67 |
| Revascularization (%)           | 17 (8.3) | 24 (11.5) | 27 (13.3) | 26 (13.1) | 0.33 |
| Hospitalization for UA (%)      | 5 (2.5) | 8 (3.8) | 7 (3.4) | 9 (4.5) | 0.70 |

*Natural log-transformed