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# 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

T he 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

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## 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.

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generation of dysfunctional or proatherogenic HDL cholesterol, or off-target drug effects. Specifically, torcetrapib was associated with an increase in plasma aldosterone levels that was presumed to be its mechanism of failure.[1] The mechanism by which CETP inhibition may increase aldosterone levels is unknown, with suggestion that it might stimulate aldosterone production within adipocytes.[5] Whether the failure of the potent CETP inhibitor evacetrapib was also associated with an increase in plasma aldosterone levels remains unclear.

Aldosterone, a mineralocorticoid hormone, has been linked to the development of ventricular remodeling and tissue fibrosis in animal models and elevated plasma levels have been associated with adverse clinical outcomes among patients with acute coronary syndromes and chronic heart failure.[6–11] In addition, several randomized controlled trials have demonstrated a mortality benefit with the use of aldosterone antagonists in patients with acute myocardial infarction and ejection fraction <40%, with possibly some benefit among those with an acute coronary syndrome and preserved ejection fraction.[12–15] The association between plasma aldosterone level and outcomes in patients with stable high-risk vascular disease has not been previously evaluated.

The ACCELERATE (Assessment of Clinical Effects of Cholesteryl Ester Transfer Protein Inhibition With Evacetrapib in Patients at a High Risk for Vascular Outcomes) trial was a multicenter, randomized, double-blinded, placebo-controlled trial at 543 sites in 36 countries investigating the use of evacetrapib on patients with stable high-risk vascular disease.[3] We sought to evaluate the impact of evacetrapib on plasma aldosterone levels and determine the association between plasma aldosterone levels and major adverse cardiovascular events (MACEs) among patients with stable high-risk vascular disease.

## 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.[16] 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 $\chi^2$ 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

**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/m$^2$ | 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), nmol/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.

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. $P\leq0.05$ 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
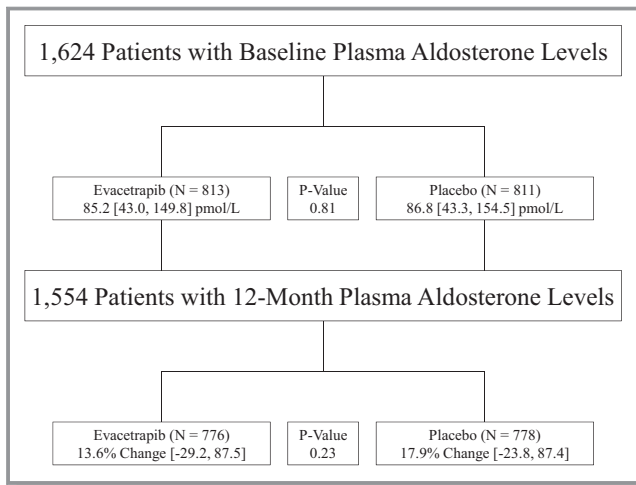
**Figure 1.** Differences in plasma aldosterone levels at baseline and 12-month follow-up by treatment group.

follow-up. Median follow-up was 28 months. The average age of the study population was 65.2 years, 75.7% were men, and the mean body mass index was 31.9 kg/m$^2$. Overall, 93.7% were hypertensive, 73.3% were diabetic, 17.3% had metabolic syndrome, 57.6% had a prior myocardial infarction, 17.5% had peripheral arterial disease, and 14.6% were current tobacco users. At baseline, 94.3% of patients were taking a statin, 76.0% were taking an angiotensin-converting enzyme inhibitor or angiotensin receptor II antagonist, and 88.3% were taking aspirin. Baseline low-density lipoprotein cholesterol was 81.7 mg/dL, HDL cholesterol was 43.4 mg/dL, and triglycerides were 151.8 mg/dL. Increasing quartile of baseline plasma aldosterone level was significantly associated with a lower prevalence of men, lower systolic blood pressure, less use of angiotensin-converting enzyme inhibitor or angiotensin receptor antagonist, and greater triglyceride levels at baseline; there were no other significant differences in baseline characteristics (Table 1). There were no significant differences in baseline characteristics of patients randomized to placebo or evacetrapib or the study population in comparison to the overall ACCELERATE trial population (Tables S1 through S6).

Baseline plasma aldosterone level (85.2 [43.0, 149.8] versus 86.8 [43.3, 154.5] pmol/L; *P*=0.81) and follow-up percentage change (13.6% [−29.2, 87.5] versus 17.9% [−23.8, 87.4]; *P*=0.23) were similar between those who received evacetrapib and placebo (Figure 1). During follow-up, MACE occurred in 263 patients (16.2%), with all-cause mortality occurring in 78 patients (4.8%). The hazard ratio for the log of baseline plasma aldosterone level (hazard ratio, 1.03; 95% CI, 0.90–1.19; *P*=0.66; Figure 2) or percentage change in plasma aldosterone level at follow-up was not significant for MACE or subcomponents of MACE, including the triple end point (cardiovascular death, myocardial

infarction, or cerebrovascular accident), all-cause mortality, revascularization, and hospitalization for unstable angina (Tables 2 and 3). These findings remained consistent when adjusting for the significant baseline characteristics mentioned above (hazard ratio of the log of baseline plasma aldosterone for MACE, 1.01; 95% CI, 0.85–1.20; *P*=0.91) and when analyzing only the placebo group.

## 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,[1] or on-target adverse effects, including production of dysfunctional or larger HDL cholesterol cholesterol-rich particles,[17,18] an increase in blood viscosity,[19] or an increase in apolipoprotein CIII and E levels,[20,21] 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.[6] It has also been implicated to have a directly deleterious effect on blood vessels, as mediated by vascular and perivascular inflammation.[22] 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.[23] 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.[24,25] Moreover, aldosterone has also been associated with insulin resistance and the development of metabolic syndrome in both patients with obesity and primary aldosteronism.[26,27]

However, although there have been several previously published reports detailing an association between plasma aldosterone levels and cardiovascular events and mortality,[6–11] the mechanism implicating aldosterone remains ambiguous. The populations from which these data
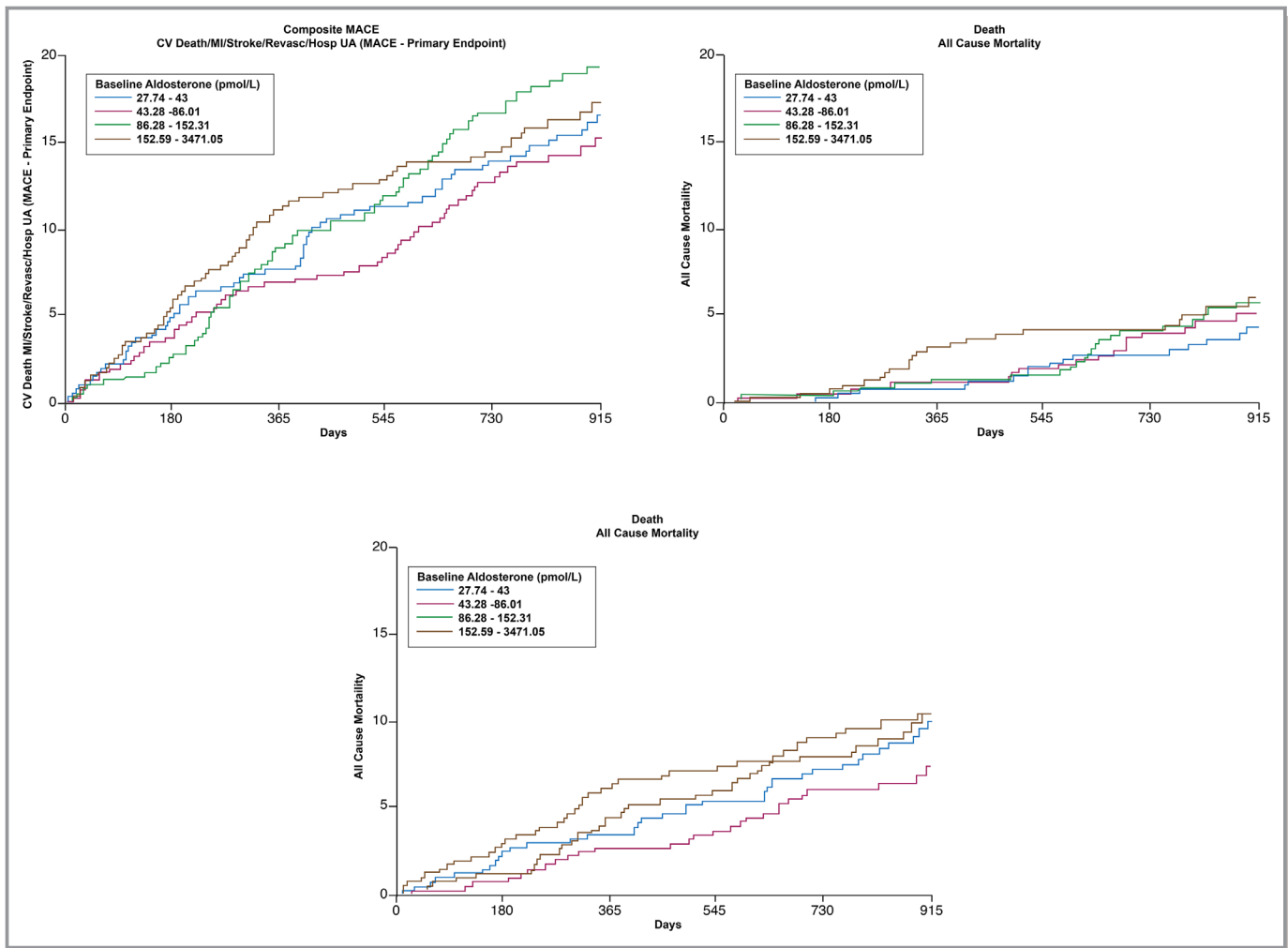
**Figure 2.** Kaplan-Meier curves for major adverse cardiovascular events (MACEs; cardiovascular [CV] death, nonfatal myocardial infarction [MI], cerebrovascular accident, hospitalization for unstable angina [UA], and revascularization), all-cause mortality, and the triple end point by quartile of baseline plasma aldosterone level.

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

**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 |
|---|---|---|---|---|---|---|
| | 27.7–43 | 43–86 | 86–152.3 | 152.3–3471 | | |
| Composite MACE | 64 (15.8) | 58 (14.3) | 75 (18.5) | 66 (16.3) | 1.03 (0.90–1.19) | 0.66 |
| Cardiovascular death, MI, or CVA | 37 (9.1) | 27 (6.6) | 40 (9.9) | 38 (9.4) | 1.03 (0.85–1.25) | 0.78 |
| All-cause mortality | 16 (3.9) | 19 (4.7) | 21 (5.2) | 22 (5.4) | 1.14 (0.88–1.46) | 0.32 |
| Revascularization | 43 (10.6) | 47 (11.5) | 47 (11.6) | 40 (9.9) | 0.97 (0.82–1.15) | 0.73 |
| Hospitalization for UA | 15 (3.7) | 14 (3.4) | 11 (2.7) | 13 (3.2) | 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.

**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* | | | |
| --- | --- | --- | --- | --- | --- |
| | | <−26% (N=388) | −26% to 16% (N=389) | 16% to 87% (N=389) | >87% (N=388) |
| Composite MACE, n (%) | | 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.

hemodynamic decompensation. The association between plasma aldosterone level and outcomes in patients with stable high-risk vascular disease has not been previously studied and in our study was not shown to have an association. Our findings are consistent with those reported with a less potent CETP inhibitor, dalcetrapib, among patients with a recent acute coronary syndrome.[28] An important limitation of this study is lack of data on the number, dosage, and type of antihypertensive agents, with the exception of angiotensin-converting enzyme inhibitors or angiotensin receptor II antagonists. We also did not have use data on mineralocorticoid receptor antagonists. This is an important mechanistic study that may be relevant to future clinical trials that investigate CETP inhibitors or use plasma aldosterone levels for risk stratification and patient selection. Future studies on the utility of plasma aldosterone in prediction of cardiovascular events in clinically stable patients with risk factors for vascular disease are needed.

## 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

## Disclosures

None.

## References

1. Barter PJ, Caulfield M, Eriksson M, Grundy SM, Kastelein JJ, Komajda M, Lopez-Sendon J, Mosca L, Tardif JC, Waters DD, Shear CL, Revkin JH, Buhr KA, Fisher MR, Tall AR, Brewer B; ILLUMINATE Investigators. Effects of torcetrapib in patients at high risk for coronary events. *N Engl J Med*. 2007;357: 2109–2122.

2. Schwartz GG, Olsson AG, Abt M, Ballantyne CM, Barter PJ, Brumm J, Chaitman BR, Holme IM, Kallend D, Leiter LA, Leitersdorf E, McMurray JJ, Mundl H, Nicholls SJ, Shah PK, Tardif JC, Wright RS; dal-OUTCOMES Investigators. Effects of dalcetrapib in patients with a recent acute coronary syndrome. *N Engl J Med*. 2012;367:2089–2099.

3. Lincoff AM, Nicholls SJ, Riesmeyer JS, Barter PJ, Brewer HB, Fox KAA, Gibson CM, Granger C, Menon V, Montalescot G, Rader D, Tall AR, McErlean E, Wolski K, Ruotolo G, Vangerow B, Weerakkody G, Goodman SG, Conde D, McGuire DK, Nicolau JC, Leiva-Pons JL, Pesant Y, Li W, Kandath D, Kouz S, Tahirkheli N, Mason D, Nissen SE; ACCELERATE Investigators. Evacetrapib and cardiovascular outcomes in high-risk vascular disease. *N Engl J Med*. 2017;376:1933–1942.

4. REVEAL Collaborative Group, Bowman L, Hopewell JC, Chen F, Wallendszus K, Stevens W, Collins R, Wiviott SD, Cannon CP, Braunwald E, Sammons E, Landray MJ. Effects of anacetrapib in patients with atherosclerotic vascular disease. *N Engl J Med*. 2017;377:1217–1227.

5. Rios FJ, Neves KB, Nguyen Dinh Cat A, Even S, Palacios R, Montezano AC, Touyz RM. Cholesteryl ester-transfer protein inhibitors stimulate aldosterone biosynthesis in adipocytes through Nox-dependent processes. *J Pharmacol Exp Ther*. 2015;353:27–34.

6. Silvestre JS, Heymes C, Oubenaissa A, Robert V, Aupetit-Faisant B, Carayon A, Swynghedauw B, Delcayre C. Activation of cardiac aldosterone production in rat myocardial infarction: effect of angiotensin II receptor blockade and role in cardiac fibrosis. *Circulation*. 1999;99:2694–2701.

7. Beygui F, Collet JP, Benoliel JJ, Vignolles N, Dumaine R, Barthelemy O, Montalescot G. High plasma aldosterone levels on admission are associated with death in patients presenting with acute ST-elevation myocardial infarction. *Circulation*. 2006;114:2604–2610.

8. Beygui F, Montalescot G, Vicaut E, Rouanet S, Van Belle E, Baulac C, Degrandsart A, Dallongeville J; OPERA Investigators. Aldosterone and long-term outcome after myocardial infarction: a substudy of the French nationwide OPERA study. *Am Heart J*. 2009;157:680–687.

9. Calhoun DA. Aldosterone and cardiovascular disease: smoke and fire. *Circulation*. 2006;114:2572–2574.

10. Palmer BR, Pilbrow AP, Frampton CM, Yandle TG, Skelton L, Nicholls MG, Richards AM. Plasma aldosterone levels during hospitalization are predictive of survival post-myocardial infarction. *Eur Heart J*. 2008;29:2489–2496.

11. Tomaschitz A, Pilz S, Ritz E, Meinitzer A, Boehm BO, Marz W. Plasma aldosterone levels are associated with increased cardiovascular mortality: the Ludwigshafen Risk and Cardiovascular Health (LURIC) Study. *Eur Heart J*. 2010;31:1237–1247.

12. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J, Wittes J. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *N Engl J Med*. 1999;341:709–717.

13. Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, Bittman R, Hurley S, Kleiman J, Gatlin M; Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study Investigators. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med*. 2003;348:1309–1321.

14. Di Pasquale P, Cannizzaro S, Scalzo S, Parrinello G, Fasullo S, Giambanco F, Fatta A, Paterna S. Effects of canrenoate plus angiotensin-converting enzyme inhibitors versus angiotensin-converting enzyme inhibitors alone on systolic and diastolic function in patients with acute anterior myocardial infarction. *Am Heart J*. 2005;150:919.

15. Montalescot G, Pitt B, Lopez de Sa E, Hamm CW, Flather M, Verheugt F, Shi H, Turgonyi E, Orri M, Vincent J, Zannad F; REMINDER Investigators. Early eplerenone treatment in patients with acute ST-elevation myocardial infarction without heart failure: the Randomized Double-Blind REMINDER Study. *Eur Heart J*. 2014;35:2295–2302.

16. Nicholls SJ, Lincoff AM, Barter PJ, Brewer HB, Fox KA, Gibson CM, Granger C, Menon V, Montalescot G, Rader D, Tall AR, McErlean E, Riesmeyer J, Vangerow B, Ruotolo G, Weerakkody GJ, Nissen SE. Assessment of the clinical effects of cholesteryl ester transfer protein inhibition with evacetrapib in patients at high-risk for vascular outcomes: rationale and design of the ACCELERATE trial. *Am Heart J*. 2015;170:1061–1069.

17. Ishigami M, Yamashita S, Sakai N, Arai T, Hirano K, Hiraoka H, Kameda-Takemura K, Matsuzawa Y. Large and cholesteryl ester-rich high-density lipoproteins in cholesteryl ester transfer protein (CETP) deficiency cannot protect macrophages from cholesterol accumulation induced by acetylated low-density lipoproteins. *J Biochem*. 1994;116:257–262.

18. Camont L, Chapman MJ, Kontush A. Biological activities of HDL subpopulations and their relevance to cardiovascular disease. *Trends Mol Med*. 2011;17:594–603.

19. Sloop GD, Weidman JJ, St Cyr JA. The failure of cholesteryl ester transfer protein inhibitors: is it due to increased blood viscosity? *Ther Adv Cardiovasc Dis*. 2015;9:32–35.

20. van Capelleveen JC, Bernelot Moens SJ, Yang X, Kastelein JJP, Wareham NJ, Zwinderman AH, Stroes ESG, Witztum JL, Hovingh GK, Khaw KT, Boekholdt SM, Tsimikas S. Apolipoprotein C-III levels and incident coronary artery disease risk: the EPIC-Norfolk prospective population study. *Arterioscler Thromb Vasc Biol*. 2017;37:1206–1212.

21. Jørgensen AB, Frikke-Schmidt R, Nordestgaard BG, Tybjærg-Hansen A. Loss-of-function mutations in APOC3 and risk of ischemic vascular disease. *N Engl J Med*. 2014;371:32–41.

22. Rossi G, Boscaro M, Ronconi V, Funder JW. Aldosterone as a cardiovascular risk factor. *Trends Endocrinol Metab*. 2005;16:104–107.

23. Vasan RS, Evans JC, Larson MG, Wilson PW, Meigs JB, Rifai N, Benjamin EJ, Levy D. Serum aldosterone and the incidence of hypertension in nonhypertensive persons. *N Engl J Med*. 2004;351:33–41.

24. Ohno Y, Sone M, Inagaki N, Yamasaki T, Ogawa O, Takeda Y, Kurihara I, Itoh H, Umakoshi H, Tsuiki M, Ichijo T, Katabami T, Tanaka Y, Wada N, Shibayama Y, Yoshimoto T, Ogawa Y, Kawashima J, Takahashi K, Fujita M, Watanabe M, Matsuda Y, Kobayashi H, Shibata H, Kamemura K, Otsuki M, Fujii Y, Yamamoto K, Ogo A, Okamura S, Miyauchi S, Fukuoka T, Izawa S, Yoneda T, Hashimoto S, Yanase T, Suzuki T, Kawamura T, Tabara Y, Matsuda F, Naruse M; Nagahama Study. Prevalence of cardiovascular disease and its risk factors in primary aldosteronism: a multicenter study in Japan. *Hypertension*. 2018;71:530–537.

25. Monticone S, Burrello J, Tizzani D, Berello C, Viola A, Buffolo F, Gabetti L, Mengozzi G, Williams TA, Rabbia F, Veglio F, Mulatero P. Prevalence and clinical manifestations of primary aldosteronism encountered in primary care practice. *J Am Coll Cardiol*. 2017;69:1811–1820.

26. Catena C, Lapenna R, Baroselli S, Nadalini E, Colussi G, Novello M, Favret G, Melis A, Cavarape A, Sechi LA. Insulin sensitivity in patients with primary aldosteronism: a follow-up study. *J Clin Endocrinol Metab*. 2006;91:3457–3463.

27. Colussi G, Catena C, Lapenna R, Nadalini E, Chiuch A, Sechi LA. Insulin resistance and hyperinsulinemia are related to plasma aldosterone levels in hypertensive patients. *Diabetes Care*. 2007;30:2349–2354.

28. Pitts R, Gunzburger E, Ballantyne CM, Barter PJ, Kallend D, Leiter LA, Leitersdorf E, Nicholls SJ, Shah PK, Tardif JC, Olsson AG, McMurray JJ, Kittelson J, Schwartz GG. Aldosterone does not predict cardiovascular events following acute coronary syndrome in patients initially without heart failure. *J Am Heart Assoc*. 2017;6:e004119. DOI: 10.1161/JAHA.116.004119.

# Supplemental Material

**Table S1**. **Baseline characteristics of the study population by treatment.**

| Baseline Characteristics | Placebo<br>N = 811 | Evacetrapib<br>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 |
|---|---|---|---|---|---|
| | **27.7 - 43** | **43 – 86** | **86 – 152.3** | **152.3 - 3471** | |
| 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<br>N = 811 | Evacetrapib<br>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 | Baseline Plasma Aldosterone Level (pmol/L)[*] | | | | P-Value |
|---|---|---|---|---|---|
| | 27.7 - 43 | 43 – 86 | 86 – 152.3 | 152.3 - 3471 | |
| 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)[*] | | | | P-Value |
|---|---|---|---|---|---|
| | 27.7 - 43 | 43 – 86 | 86 – 152.3 | 152.3 - 3471 | |
| 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