Inhibition of the Renin-Angiotensin System Reduces the Rise in Serum Aldosterone in Acute Coronary Syndrome Patients with Preserved Left Ventricular Function: Observations from the AVANT GARDE-TIMI 43 Trial

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BACKGROUND: Acute coronary syndrome (ACS) activates neurohormonal pathways, including elevations in circulating aldosterone, with deleterious cardiovascular effects. We aimed to determine if early, more complete renin-angiotensin-aldosterone system inhibition (RAASI) in post-ACS patients without ventricular dysfunction or heart failure would result in a graded reduction in aldosterone concentrations.

METHODS: We performed serial measurement of serum aldosterone within the Aliskiren and Valsartan to Reduce NT-proBNP via Renin-Angiotensin-Aldosterone-System Blockade (AVANT GARDE)–Thrombolysis in Myocardial Infarction (TIMI) 43 trial, a randomized double-blind, placebo controlled trial of RAASI by valsartan, aliskiren, or both in post-ACS patients with preserved ventricular function but increased natriuretic peptides. Aldosterone was measured at randomization and week 8.

RESULTS: Median aldosterone concentrations were comparable across treatment arms at baseline (9.26 ng/dL; interquartile range 7.12–12.76; n = 1073). In the placebo group, there was a significant increase in aldosterone over 8 weeks (19.7% rise, 2.20 (0.36) ng/dL, P = 0.0001) that was significantly reduced across active RAASI therapies (1.36 (0.39) ng/dL with aliskiren; 1.02 (0.37) ng/dL with valsartan; and 0.85 (0.37) ng/dL with combination therapy, P trend = 0.008). Compared to placebo, RAASI monotherapy resulted in a pooled relative absolute aldosterone change of −1.01 (0.45) ng/dL (P = 0.026 vs placebo), and combination therapy resulted in a relative absolute aldosterone change of −1.35 (0.52) ng/dL (P = 0.01 vs placebo). No significant difference in aldosterone concentrations was achieved between dual vs single RAASI (P = 0.47).

CONCLUSIONS: In ACS patients with preserved ventricular function but increased natriuretic peptides, serum aldosterone rises over time and is blunted by more complete RAASI. The clinical implications and role for RAASI in this population warrant further investigation.

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In patients presenting with acute coronary syndrome (ACS),9 increased markers of neurohormonal activation, including serum aldosterone, are associated with early and late adverse cardiovascular events, such as heart failure, arrhythmia, and mortality (1–3). An association between serum aldosterone and outcomes has been observed across the spectrum of patients with ACS, with and without left ventricular systolic dysfunction (LVSD) (3). Although serum aldosterone concentration after ACS is known to be a marker of adverse prognosis, important areas of uncertainty remain.

Inhibition of the renin-angiotensin-aldosterone system (RAAS) improves survival in patients with...
chronic advanced heart failure (4–6) and in high-risk patients after myocardial infarction (MI) (6–8). Captopril monotherapy in post-MI patients with LVSD demonstrated a reduction of aldosterone over time in the Survival and Ventricular Enlargement (SAVE) study (9); however, no trial testing early, more complete RAAS inhibition in post-ACS patients with preserved LV ejection fraction (LVEF) has examined whether treatment may modify temporal aldosterone concentrations as a potential mechanism for improved outcomes (4, 5, 9, 10).

The Aliskiren and Valsartan to Reduce NT-proBNP via Renin-Angiotensin-Aldosterone-System Blockade (AVANT GARDE)/Thrombolysis in Myocardial Infarction (TIMI) 43 Trial randomized patients to aliskiren (a direct renin inhibitor), valsartan, their combination, or placebo (see Supplemental Fig. 1, which accompanies the online version of this article). In brief, 1101 patients with ACS, without left ventricular systolic dysfunction or clinical heart failure but increased concentration of a natriuretic peptide (NP) after 8 weeks of therapy. In this analysis, we tested the hypothesis that early, more complete RAAS inhibition would result in a graded reduction in aldosterone concentrations after ACS in patients without heart failure or LVSD, a group in which a benefit of inhibition of RAAS remains uncertain.

Materials and Methods

STUDY POPULATION

The AVANT GARDE-TIMI 43 Trial (NCT00409578) was a randomized, multicenter, double-blind, placebo controlled trial for which the methods and results have been published previously (11). In brief, 1101 patients with ACS, without left ventricular systolic dysfunction or clinical heart failure but increased concentration of a natriuretic peptide measured within 3–10 days after their qualifying event (≥80 ng/L for B-type NP (BNP) or ≥400 ng/L for N-terminal pro-B-type NP (NT-proBNP)], were randomized to aliskiren, valsartan, their combination, or placebo (see Supplemental Fig. 1, which accompanies the online version of this article at http://www.clinchem.org/content/vol59/issue6). Patients were excluded if they had a history of known heart failure or LVEF ≤40%; planned revascularization; prior angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) therapy that could not be discontinued; renal insufficiency (creatinine clearance <45 mL/min); mechanical complications of myocardial infarction before randomization; or inability or unwillingness to provide informed consent.

STUDY PROCEDURES

Patients were randomized in a double-blind, double-dummy design to 4 arms: aliskiren, valsartan, their combination, or placebo. The study drug was titrated up over the 8-week study duration to a goal dose of aliskiren 300 mg daily, valsartan 320 mg daily, a combination dose of aliskiren 300 mg/valsartan 320 mg daily, or matching placebo. Combination therapy started at week 4 when aliskiren was added to valsartan and titrated up over the next 4 weeks (11). Patients were continued on the highest tolerated dose according to a standard treatment algorithm and were not to be treated with open-label RAAS inhibitor or diuretic therapy (11). We measured serum aldosterone at baseline and then again at the end of study or last available visit.

MEASUREMENTS OF ALDOSTERONE

Blood samples were collected in serum separator tubes, centrifuged, and stored frozen in aliquots at −20 °C to −80 °C at the enrolling site. After being shipped to the TIMI Biomarker Core Laboratory (Boston, MA), the samples were maintained at −70 °C or colder. We measured aldosterone concentrations with an immunofluorescence RIA (Coat-A-Count Aldosterone, Diagnostic Products) (12) from serum samples analyzed at the first thaw. The interassay CVs at 5.8 ng/dL (161 pmol/L) and 16.2 ng/dL (450 pmol/L) were 15.7% and 6.5%, respectively.

ENDPOINTS

The primary end point of the trial was the change in natriuretic peptide concentrations between baseline and week 8 (11). The focus of this prespecified analysis was the change in serum aldosterone concentration between baseline and the end of study. Of the 1101 patients enrolled in AVANT GARDE-TIMI 43, a baseline measurement of serum aldosterone was available in 1073. Of these, 8-week or a last available measurement taken between weeks 5 and 8 were available in 899 (208 aliskiren, 226 valsartan, 225 combination, and 240 placebo). Two patients with an extreme change in aldosterone, >36 ng/dL (1000 pmol/L), were excluded to minimize bias, as these values were outliers by several SDs from the cohort distribution of results. Secondary efficacy endpoints included a clinical composite end point of cardiovascular death, myocardial infarction, or heart failure hospitalization, which were adjudicated by an independent clinical events committee.

STATISTICAL ANALYSES

We performed comparisons between groups by the Cuzick and χ² tests for trend to detect differences in continuous and categorical baseline characteristics between quartiles of aldosterone. We also derived Spearman correlations between biomarker measurements at baseline and follow-up. Biomarkers of neurohormonal activation that had a skewed distribution were log-transformed for logistic regression analyses.
We performed efficacy analyses on an intention-to-treat basis, consisting of those with a baseline and at least 1 postbaseline aldosterone measurement. To evaluate the temporal change in serum aldosterone from baseline, we analyzed data using an analysis of covariance (ANCOVA) model with the $F$-test for linear trend across treatment groups and the $t$-test for pairwise comparisons between treatment groups and placebo or other therapies. The treatment differences between the least-square means, least-square mean differences, and 2-sided 95% CIs are reported. ANCOVA models included independent variable terms for baseline serum aldosterone concentrations, treatment group, and aldosterone × treatment interaction. Further stratification by whether baseline plasma NT-proBNP concentrations were higher or lower than the median was performed. We applied mixed models to determine whether a temporal change in plasma NT-proBNP was significantly modified by baseline aldosterone concentrations.

We ascertained the relationship between serum aldosterone and the clinical composite end point over 8 weeks with a logistic regression model that included independent variable terms for baseline serum aldosterone concentrations, treatment group, and aldosterone × treatment interaction. In the absence of a significant aldosterone × treatment interaction, analyses were presented in all patients. We derived odds ratio (OR), 95% CI, and $P$ value by comparing continuous log-transformed serum aldosterone per SD. All statistical analyses were performed with SAS, version 9.2 (SAS Institute). Data analysis was conducted independent of the trial sponsors by 3 authors (J.A. Udell, F. Ren, and E.B. Hoffman), who planned the data analysis and had access to the entire raw data set. The study was approved by the institutional review boards at each site according to local requirements, and written informed consent was obtained for all patients.

### Results

#### Baseline Characteristics

The median concentration of serum aldosterone at baseline was 9.26 ng/dL, interquartile range (IQR) (Table 1). The median concentration of serum aldosterone at baseline was 9.26 ng/dL, interquartile range (IQR) (Table 1).
7.12–12.76 (256.9 pmol/L, IQR 197.4–354.1). Baseline clinical characteristics stratified by treatment group in this analysis cohort were similar except for sex (see online Supplemental Table 1). No differences were observed in baseline neurohormonal biomarker concentrations, including aldosterone, between patients randomized to aliskiren, valsartan, combination therapy, or placebo (P > 0.1 for all).

The clinical characteristics of the patients stratified by quartile of aldosterone are summarized in Table 1. In general, patients presenting with higher quartiles of serum aldosterone were older and had more frequent prior use of ACE/ARB therapy and lower estimated glomerular filtration rate. Hyperlipidemia and smoking were inversely associated with aldosterone concentrations. Among other neurohormonal biomarkers, serum aldosterone was weakly correlated with higher plasma renin activity and NPs at baseline (ρ ≤ 0.10) (see online Supplemental Table 2).

### CHANGES IN SERUM ALDOSTERONE CONCENTRATIONS IN RESPONSE TO RAAS INHIBITOR THERAPY

In patients assigned to placebo, serum aldosterone increased by 19.7% [absolute change, 2.20 (0.36) ng/dL (60.9 [10.1] pmol/L); P < 0.01] from randomization to the end of study. In contrast, the rise in aldosterone was blunted in all active treatment arms. In patients assigned to aliskiren, serum aldosterone increased by 10.0% [absolute change, 1.36 (0.39) ng/dL (37.7 [10.8] pmol/L); P < 0.01]; valsartan 9.9% [absolute change, 1.02 (0.37) ng/dL (28.3 [10.4] pmol/L); P < 0.01]; and combination therapy 9.3% [absolute change, 0.85 (0.37) ng/dL (23.5 [10.4] pmol/L); P = 0.024]. When individual RAAS inhibition monotherapies were analyzed together, monotherapy resulted in a relative absolute aldosterone change compared to placebo of −1.01 (0.45) ng/dL [−28.0 (12.5) pmol/L; P = 0.026] (Table 2). Combination therapy significantly reduced the rise in serum aldosterone over time compared to placebo [relative absolute change compared to placebo, −1.35 (0.52) ng/dL (−37.4 [14.5] pmol/L; P = 0.01] (Table 2) with a trend toward a progressively lower temporal rise in aldosterone with more complete RAAS inhibition (P value for trend = 0.008) (Fig. 1). A similar trend was observed when any RAAS inhibition monotherapy (aliskiren or valsartan) was compared with placebo and combination therapy (P trend = 0.01) (Fig. 2). There was no significant difference in aldosterone concentrations achieved between dual vs single RAAS inhibition [relative absolute change compared to monotherapy, −0.34 (0.46) ng/dL (−9.4 [12.8] pmol/L; P = 0.47] (Fig. 2).

<p>| Table 2. Change in serum aldosterone by treatment group. |
|-------------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|</p>
<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Aliskiren</th>
<th>Valsartan</th>
<th>Monotherapy</th>
</tr>
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<tbody>
<tr>
<td>n</td>
<td>274</td>
<td>263</td>
<td>262</td>
<td>525</td>
</tr>
<tr>
<td>Mean serum aldosterone, ng/dL (SD)</td>
<td>10.88 (5.71)</td>
<td>11.54 (10.17)</td>
<td>10.58 (5.65)</td>
<td>11.06 (8.24)</td>
</tr>
<tr>
<td>Follow-upc</td>
<td>13.02 (6.65)</td>
<td>12.70 (10.50)</td>
<td>11.63 (6.59)</td>
<td>12.14 (8.69)</td>
</tr>
<tr>
<td>Absolute changed</td>
<td>2.20 (1.48-2.91)</td>
<td>1.36 (0.59-2.13)</td>
<td>1.02 (0.26-1.76)</td>
<td>1.18 (0.05-1.71)</td>
</tr>
<tr>
<td>Relative changee</td>
<td>1.01 (1.90 to 0.12)</td>
<td>1.18 (2.20 to 0.15)</td>
<td>1.01 (1.90 to 0.15)</td>
<td>1.18 (2.20 to 0.15)</td>
</tr>
<tr>
<td>P</td>
<td>0.026</td>
<td>0.025</td>
<td>0.026</td>
<td>0.026</td>
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</tbody>
</table>

a To convert aldosterone concentrations in pg/mL to pmol/L, multiply by 27.74.

b Individual aliskiren or valsartan therapy analyzed as a group.

c Mean (SD) at week 8, last observation carried forward.
d Least-squares mean (95% CI) change from baseline to follow-up by ANCOVA.
e Absolute difference between placebo and active treatment counterpart.

f Treatment relative change compared to placebo by t-test for continuous variables.

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We observed no significant correlation between concentrations of NPs and aldosterone at baseline (see online Supplemental Table 2); however, the temporal rise in aldosterone observed with RAAS inhibition may be modified by baseline plasma NT-proBNP concentrations (Table 3). The effect of RAAS inhibition on the relative rise in aldosterone tended to be greater in patients who presented with baseline NT-proBNP concentrations at or lower than the median, whereas among patients presenting with baseline NT-proBNP concentrations higher than the median, there was no significant difference in achieved aldosterone concentrations across treatment (treatment \times baseline NT-proBNP concentration interaction, \( P = 0.17 \)) (Table 3).

**Discussion**

To our knowledge, our report is the first to demonstrate a substantial and persistent rise in serum aldosterone in patients with increased natriuretic peptides after ACS but without heart failure or LVSD. We observed that more complete RAAS inhibition significantly mitigated the increase in aldosterone observed in these patients when initiated within 3–10 days after ACS hospitalization and titrated up over the subsequent 2 months, suggesting aldosterone is a modifiable target of therapy, thereby explaining 1 potential mechanism of benefit of RAAS inhibition therapy post-MI.

**Aldosterone in ACS**

Aldosterone, the major mineralocorticoid hormone secreted by the adrenal cortex, is a key modulator of neurohormonal hemodynamic regulation (13). In the setting of acute infarction, adverse remodeling, mediated in part by aldosterone, plays a deleterious role that worsens cardiac function and leads to left ventricular dysfunction.
dysfunction and heart failure (14). The clinical benefits of RAAS inhibition with ACE inhibitors, ARB therapy, or aldosterone blockade after ACS appear to be greatest in patients with large infarcts and depressed LV function, in whom RAAS inhibition improves survival through afterload reduction and improved myocardial remodeling (7, 8, 15–22). AVANT GARDE-TIMI 43 specifically excluded those types of patients and therefore focused on a different patient population with preserved left ventricular function, in whom the benefit of early RAAS inhibition remains unproven. Thus our results provide insight into a potential benefit of RAAS inhibition therapy to ameliorate cardiovascular risk after ACS with evidence of hemodynamic stress, by reducing a rise in aldosterone.

FINDINGS IN AVANT GARDE-TIMI 43
In patients with preserved left ventricular function but increased natriuretic peptides, serum concentrations of aldosterone measured 3–10 days after the index event were higher than those observed in other post-MI cohorts (1–3) or patients with stable coronary artery disease undergoing elective angiography (23). Baseline values among patients in AVANT GARDE-TIMI 43 were approximately 2-fold higher than those measured 1–3 days post-MI in a mix of patients with and without heart failure and LVSD in the OPERA registry (Observatoire sur la Prise en Charge Hospitaliére, l’Évolution à un An et les Caractéristiques de Patient Présentant un Infarctus du Myocarde avec ou sans Onde Q) (3). This difference may be a result of identifying a higher risk population than studied in OPERA on the basis of increased natriuretic peptides in our study or our slightly later sampling of aldosterone after ACS. Either scenario may identify patients who, after surviving their initial MI, had further time and better ability to achieve cardiovascular homeostasis with aldosterone elevation. An alternative hypothesis is that variation in aldosterone concentrations and associated cardiovascular risk across studies may be a result of differences in immunoassay analytical methods rather than clinical settings (24). For this reason, various standardization processes are ongoing for steroid hormones, including aldosterone, using reference materials, and other methods (25, 26). Regardless, in contrast to earlier studies that reported concentrations that peaked soon after an index MI and decreased substantially thereafter to a steady state (3, 9), we observed a persistent increase in serum aldosterone after ACS over the 8-week study period.

The mechanism leading to an approximate 20% increase in serum aldosterone in placebo patients is
unclear but is unlikely to be directly related to upregulation of mineralocorticoid activity to maintain cardiac output after ACS, since all patients had preserved systolic function at baseline (27, 28). Moreover, the observed aldosterone increases in these patients appeared to be relatively independent of presenting diagnosis (ST-elevated vs non-ST-elevated MI), degree of LV function, clinical risk factors, baseline or change in presenting diagnosis (8). Potential risk stratification post-MI with aldosterone may be of interest if this biomarker can further distinguish a relative clinical benefit of more complete RAAS blockade in these patients. Our trial results suggest that increases in serum aldosterone after ACS can be significantly lowered with more complete RAAS inhibition. Whether a reduction in this surrogate end point may translate into a clinically meaningful improvement in cardiovascular events in patients after ACS but without heart failure or LVSD remains unknown but warrants confirmation in large prospective clinical trials.

In this study, we observed that the reduction in the rise in aldosterone achieved with more complete RAAS inhibition appeared predominantly among patients with lower relative concentrations of NT-proBNP (400.0–873.1 ng/L). Beyond their physiologic role in enhancing natriuresis and blood pressure reduction in response to myocardial stress (29), natriuretic peptides directly antagonize the renin-angiotensin-aldosterone system and suppress aldosterone release (30–34). Conversely, a diminished response of endogenous natriuretic peptides seen in patients with increased concentrations of natriuretic peptides may be the result of a resistance to the biological effect of natriuretic hormones (35). Substantial amounts of the prohormone peptide of BNP (proBNP) can be detected in healthy subjects (36) and patients with heart failure (37), suggesting that the natriuretic peptide assayed in patients with cardiovascular disease may not in fact have similar biological activity (38). Thus, among patients with the highest concentrations of natriuretic peptides, a further reduction in
aldosterone concentration with more complete RAAS inhibition therapy may not be expected (33).

Several potential limitations of our study are worth noting. The AVANT GARDE-TIMI 43 clinical trial population was without heart failure, reduced LV function, and renal insufficiency and may not be representative of the general population of ACS patients. Aldosterone concentrations vary in a diurnal pattern, with positioning, and with salt intake by as much as 40%–50% among individuals (13), and exact positioning and timing of sampling were not standardized. Aldosterone was measured only at baseline and 8 weeks, limiting our ability to comment on aldosterone variability in intervening time points.

Conclusions

AVANT GARDE-TIMI 43 represents the largest randomized trial to date to demonstrate that serum aldosterone concentrations rise early after an uncomplicated acute coronary syndrome and are modifiable with more complete RAAS inhibition therapy. The suggested potential application of aldosterone to risk stratify patients post-MI and target those patients with more complete RAAS inhibition in this setting is intriguing. Two ongoing trials that are studying the efficacy of spironolactone (39) and eplerenone (40) in post-MI patients without heart failure or LVSD will provide additional insight into whether modifying aldosterone concentrations post-MI improves clinical outcomes.

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