High Plasma Aldosterone Levels on Admission Are Associated With Death in Patients Presenting With Acute ST-Elevation Myocardial Infarction

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Background—Aldosterone, the final mediator of the renin-angiotensin-aldosterone pathway, is at its highest plasma levels at presentation for ST-elevation myocardial infarction (STEMI). Whether aldosterone level at presentation for STEMI is associated with adverse outcome remains unknown.

Methods and Results—Plasma aldosterone levels were measured at presentation in consecutive patients referred for primary percutaneous coronary intervention for STEMI. We assessed the association between aldosterone levels and in-hospital events and mortality during a 6-month follow-up. Of 356 STEMI patients, 23 and 36 died during the hospital stay and 6-month follow-up period, respectively. Nine other patients survived in-hospital cardiac arrest. High aldosterone levels were associated with an almost stepwise increase in rates of in-hospital death ($P<0.01$), cardiovascular death ($P=0.03$), heart failure ($P=0.005$), ventricular fibrillation ($P=0.02$), and resuscitated cardiac arrest ($P=0.01$). After adjustment for age, Killip class, and reperfusion status, compared with patients in the first aldosterone quartile group, those in the highest quartile were at higher risk of death (hazard ratio 3.28, 95% CI 1.09 to 9.89, $P=0.035$) and death or resuscitated cardiac arrest (hazard ratio 3.74, 95% CI 1.40 to 9.98, $P=0.008$) during the follow-up.

Conclusions—Plasma aldosterone levels on admission among patients referred for primary percutaneous coronary intervention for STEMI are associated with early and late adverse clinical outcomes, including mortality. The association between high aldosterone levels and late mortality is independent of age, heart failure, and reperfusion status. Such results underline the pivotal role of aldosterone and justify a randomized trial to assess the early administration of aldosterone antagonists in the setting of STEMI. (Circulation. 2006;114:2604-2610.)

Key Words: myocardial infarction | reperfusion | angioptasy | hormones | morbidity | mortality

Blockade of the renin-angiotensin-aldosterone pathway by angiotensin-converting enzyme inhibitors is considered a pivotal treatment after myocardial infarction, whether associated with congestive heart failure or not.[1] Recently, decreased mortality was also reported with the use of the mineralocorticoid receptor blocker eplerenone, in addition to optimal therapy that included angiotensin-converting enzyme inhibitors, after acute myocardial infarction associated with congestive heart failure.[2]

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It has been shown that aldosterone, the final mediator of the renin-angiotensin-aldosterone pathway, exerts toxic effects on the myocardium,[3-5] and these effects are only partially and temporarily inhibited by angiotensin-converting enzyme inhibitors.[3-8] Although previous studies have reported high plasma aldosterone levels in myocardial infarction, these observations have most often been limited by their small sample size, heterogeneous study populations, late measurements of aldosterone (often days to months after the onset of myocardial infarction), and inconclusive results with regard to the association of aldosterone with further clinical events.[9-12]

The aim of the present study was to assess early plasma aldosterone release in patients presenting with ST-elevation myocardial infarction (STEMI) within 24 hours of symptom onset and to determine whether aldosterone levels are related to adverse outcomes in this setting. All patients were intended to be treated with immediate primary percutaneous coronary intervention (PCI) and were closely monitored for clinical complications for up to 6 months of follow-up.
Methods

Study Population
The study included consecutive patients referred to a single tertiary university hospital from January 1, 2004, to May 5, 2005, for primary PCI for acute STEMI within 24 hours of symptom onset and in whom the infarct-related artery was identified on the initial angiography. The diagnosis of STEMI justifying urgent catheterization was based on chest pain that lasted >30 minutes and ST-segment elevation of >0.2 mV in at least 2 contiguous ECG leads. Blood samples were drawn in all patients with such criteria. Biological measurements were performed only in patients with a discharge diagnosis of STEMI, who defined the final study population, with the exclusion of all patients undergoing urgent catheterization for non-STEMI, acute myocarditis, or noncardiac chest pain. All patients gave informed consent, and the study was approved by the ethics committee of our institution.

Coronary Angiography and PCI
Before the procedure, all patients received either heparin (100 IU/kg IV) or enoxaparin (0.5 mg/kg IV), aspirin (500 mg IV), and clopidogrel (300 mg orally). Absciximab (0.25-mg/kg IV bolus followed by a 12-hour infusion of 0.125 μg·kg⁻¹·min⁻¹, with a maximum of 10 μg/min) was administered to all patients before PCI on a routine basis unless judged contraindicated. Coronary angiography was performed by a transradial or femoral approach according to the Judkins technique. Antegrade coronary flow was visually graded according to Thrombolysis In Myocardial Infarction (TIMI) classification. Successful mechanical reperfusion was defined by a visually assessed diameter stenosis of <30% and TIMI grade 3 flow in the infarct-related artery. After PCI, patients received 75 mg of clopidogrel and 75 mg of aspirin daily, as well as β-blockers, statins, and angiotensin-converting enzyme inhibitors if believed appropriate.

Biological Measurements
Blood samples were drawn through the arterial sheath before cardiac catheterization with the patient in the supine position. Centrifugation was performed within 30 minutes, and 1-mL plasma aliquots were stored at -80°C. Plasma aldosterone levels were measured with a commercially available radioimmunoassay kit (ALDO-RIA CT, Schering AG, Berlin, Germany). The normal range is considered to be 42 to 201 pg/mL. Other blood samples were drawn for routine analysis, including troponin I and creatinine. Creatinine clearance was calculated with the Cockcroft-Gault formula. In-hospital Events and Follow-Up
In-hospital events, including death, resuscitated cardiac arrest, stroke, recurrent STEMI requiring urgent catheterization, urgent revascularization of the infarct-related artery, recurrent ischemia (defined as a new chest pain episode with dynamic ECG changes, including ST depression or T-wave inversion), new onset or worsening of heart failure (defined as an increase of ≥1 Killip class and/or the need for introduction or dose escalation of diuretics or dobutamine), ventricular tachycardia during coronary care unit stay (defined as ≥3 consecutive premature ventricular beats), ventricular fibrillation, major bleeding (defined as any bleeding leading to death, requiring surgery or blood transfusion, or with retroperitoneal, intraocular, or intracranial location), were prospectively recorded. Information regarding death was collected up to 6 months by contacting patients, their family, or their referring physician directly, by letter or telephone interviews.

Statistical Analysis
The primary and secondary end points of the study were defined by mortality and the composite of mortality or resuscitated cardiac death during the follow-up, respectively. Aldosterone levels were divided into quartiles that defined 4 patient groups. The association of aldosterone and both the primary and secondary end points was assessed with a multivariable Cox regression model that included age, Killip class, and reperfusion status as covariables. Indicator variables that coded aldosterone quartile membership were used. Thus, adjusted hazard ratios were calculated for patients in each of the 3 highest aldosterone quartiles relative to patients in the lowest aldosterone quartile (reference quartile).

Survival curves were derived from Kaplan-Meier estimates. The log-rank test was used to determine statistical differences in terms of survival. In-hospital events were analyzed with χ² or Fisher exact tests for global comparisons between groups defined by aldosterone level quartiles. A probability value <0.05 was considered significant. Analyses were performed with the SAS software package version 8.2 (SAS Institute, Cary, NC).

The authors had full access to the data and take full responsibility for their integrity. All authors have read and agree to the manuscript as written.

Results

Baseline Characteristics
A total of 356 consecutive patients presenting with STEMI within 24 hours of symptom onset underwent urgent cardiac catheterization and were enrolled in the study. PCI was attempted in 346 patients (97%), with placement of at least 1 bare-metal coronary stent in all. Intervention was considered successful in 310 patients (90%). Coronary intervention was not attempted in 4 patients with spontaneous full reperfusion, defined as a <30% diameter stenosis and a TIMI 3 flow grade on the initial angiogram, and in 6 patients with distal coronary occlusion who were considered inadequate candidates for mechanical revascularization. Overall, full reperfusion was observed in 314 patients (88%). Baseline clinical characteristics of the study population are presented in Table 1, which shows a moderate- to high-risk population of STEMI patients, with 21% of patients ≥75 years old, 20% with prior history of myocardial infarction, 14% with prior history of revascularization, 41% presenting with anterior myocardial infarction, and 5% presenting with cardiogenic shock. A total of 299 (84%) received abciximab, 257 (86%) during transfer or on admission but before sheath insertion and coronary angiography. Angiographic and biological characteristics, shown in Table 2, reflect a real-life population of primary PCI patients, with half having multivessel disease and a minority presenting with open arteries in the catheterization laboratory. The 32% TIMI 2 or 3 flow rate may reflect the precatheterization use of abciximab in a majority of patients of this series.

Aldosterone levels followed a skewed distribution in the study population, with a median value of 65.75 pg/mL and an interquartile range of 132.95 pg/mL in the global population. The global population was divided into 4 groups of 89 patients each, according to aldosterone-level quartiles. Such quartiles were respectively defined by aldosterone levels <31.05, 31.05 to 65.74, 65.75 to 163.99, and ≥164 pg/mL.

In-Hospital Events
During the hospital stay, 23 patients (6.5%) died. The cause of death was cardiac in 22 patients (refractory ventricular arrhythmia in 11, refractory heart failure in 10, and rupture of the left ventricular free wall in 1) and noncardiac in 1 (hemorrhagic shock). Successful resuscitation for cardiac arrest was performed in 21 patients. Among these patients, only 9 survived the hospital phase.
follow-up. Survival rates at 30-day follow-up were 96.6±1.9%, 93.3±2.7%, 93.1±2.7%, and 82.8±4.0% in quartile groups 1 to 4, respectively. Follow-up at 6 months was complete in 328 patients (92%). A total of 36 deaths were recorded at 6-month follow-up, including 13 that occurred between hospital discharge and end of follow-up. As shown on the Kaplan-Meier curves, high aldosterone plasma level was essentially a marker of early mortality (Figure 2).

On multivariable analysis (Figure 3), age, Killip class, unsuccessful reperfusion, and the highest aldosterone level quartile were independently correlated to mortality. All previous factors, with the exception of reperfusion status, were also independent correlates of the composite of death or resuscitated cardiac death. The hazard ratios associated with aldosterone quartiles 2 to 4 compared with the first quartile were 2.71 (95% CI 0.77 to 9.52), 2.15 (95% CI 0.64 to 7.20), and 3.28 (95% CI 1.09 to 9.89) for mortality and 2.04 (95% CI 1.09 to 9.89) for the composite of death or resuscitated cardiac death. The hazard ratios associated with aldosterone quartiles 2 to 4 compared with the first quartile were 2.71 (95% CI 0.77 to 9.52), 2.15 (95% CI 0.64 to 7.20), and 3.28 (95% CI 1.09 to 9.89) for mortality and 2.04 (95% CI 1.09 to 9.89) for the composite of death or resuscitated cardiac death. The hazard ratios associated with aldosterone quartiles 2 to 4 compared with the first quartile were 2.71 (95% CI 0.77 to 9.52), 2.15 (95% CI 0.64 to 7.20), and 3.28 (95% CI 1.09 to 9.89) for mortality and 2.04 (95% CI 1.09 to 9.89) for the composite of death or resuscitated cardiac death. The hazard ratios associated with aldosterone quartiles 2 to 4 compared with the first quartile were 2.71 (95% CI 0.77 to 9.52), 2.15 (95% CI 0.64 to 7.20), and 3.28 (95% CI 1.09 to 9.89) for mortality and 2.04 (95% CI 1.09 to 9.89) for the composite of death or resuscitated cardiac death. The hazard ratios associated with aldosterone quartiles 2 to 4 compared with the first quartile were 2.71 (95% CI 0.77 to 9.52), 2.15 (95% CI 0.64 to 7.20), and 3.28 (95% CI 1.09 to 9.89) for mortality and 2.04 (95% CI 1.09 to 9.89) for the composite of death or resuscitated cardiac death. The hazard ratios associated with aldosterone quartiles 2 to 4 compared with the first quartile were 2.71 (95% CI 0.77 to 9.52), 2.15 (95% CI 0.64 to 7.20), and 3.28 (95% CI 1.09 to 9.89) for mortality and 2.04 (95% CI 1.09 to 9.89) for the composite of death or resuscitated cardiac death. The hazard ratios associated with aldosterone quartiles 2 to 4 compared with the first quartile were 2.71 (95% CI 0.77 to 9.52), 2.15 (95% CI 0.64 to 7.20), and 3.28 (95% CI 1.09 to 9.89) for mortality and 2.04 (95% CI 1.09 to 9.89) for the composite of death or resuscitated cardiac death.

Discussion

The present study is the first to demonstrate that high aldosterone plasma levels among patients admitted for primary PCI for STEMI are strongly associated with mortality. This >2-fold increase in mortality is independent of other major prognostic factors, including heart failure. Aldosterone was also associated with the occurrence of major in-hospital events after acute myocardial infarction, such as death or resuscitated cardiac arrest, life-threatening ventricular arrhythmias, or heart failure.
Neurohormonal activation, including activation of the renin-angiotensin-aldosterone pathway, the sympathetic nervous system, and increased production of natriuretic peptides, occurs after acute myocardial infarction in response to hemodynamic changes. The prognostic implications of such activation have been studied over a wide spectrum of time after the onset of myocardial infarction (from 24 hours up to 3 months). Independent associations of natriuretic peptides, endothelin, norepinephrine, and renin or arginine-vasopressine with mortality or congestive heart failure have been reported after acute myocardial infarction. Aldosterone measured 3 to 16 days after myocardial infarc-

Figure 1. In-hospital event rates according to admission plasma aldosterone level quartiles. n=89 for each group; probability value is for global comparison between quartiles.

Figure 2. Cumulative survival in an analysis of death according to admission plasma aldosterone level quartiles. n=89 for each group on admission; probability value is for the log-rank test between the 4 groups.
tion in a subgroup of the Survival And Ventricular Enlargement (SAVE) study was not a predictor of 1-year mortality or congestive heart failure.\textsuperscript{11} When measured 3 months after myocardial infarction in the same population, high aldosterone levels were independently associated with the occurrence of severe heart failure but not mortality at 2 years’ follow-up.\textsuperscript{9} An obvious limitation of these 2 studies is the delay between the acute phase of myocardial infarction and the time of aldosterone measurement. Indeed, serial measurements of neurohormones performed in small groups of patients presenting with ongoing myocardial infarction have shown that plasma aldosterone is at its highest level on admission and decreases rapidly within hours of admission, with no evidence of a rapid action of angiotensin-converting enzyme inhibitors on its level.\textsuperscript{10,12} The present observation is unique in assessing the prognostic value of aldosterone at presentation of acute myocardial infarction in a large cohort of patients admitted for primary PCI.

Aldosterone is reported to promote a broad spectrum of deleterious cardiovascular effects, including acute endothelial dysfunction,\textsuperscript{19} inhibition of nitric oxide activity,\textsuperscript{20} increased endothelial oxidative stress,\textsuperscript{21} increased vascular tone,\textsuperscript{22} inhibition of tissue recapture of catecholamines,\textsuperscript{23} rapid occurrence of vascular smooth muscle cell and cardiac myocyte necrosis,\textsuperscript{3,5} collagen deposition in blood vessels, and myocardial hypertrophy and fibrosis.\textsuperscript{24–26} Moreover, the primary epithelial actions of aldosterone lead to Na\textsuperscript{+} retention and to potentially arrhythmogenic K\textsuperscript{+} and Mg\textsuperscript{2+} depletion. Aldosterone is believed to be effective through slow genomic mechanisms (within days to weeks), through activation of specific cytosolic mineralocorticoid receptors,\textsuperscript{27} and rapid nongenomic mechanisms (within minutes to hours), through activation of membrane receptors.\textsuperscript{4,28} Some rapid effects, such as angiotensin II– and \textsuperscript{N}G-nitro-L-arginine methyl ester–induced myocardial and vascular necrosis, may nevertheless involve, at least partially, the mineralocorticoid receptor, because their blockade by spironolactone prevents such phenomena in a mouse model.\textsuperscript{3}

The clinical consequences of mineralocorticoid receptor blockade have been assessed by a few trials. The Randomized Aldactone Evaluation Study (RALES) showed that the beneficial effect of the aldosterone antagonist spironolactone in addition to standard therapy was associated with a 30% reduction of the risk of mortality in the setting of severe heart failure,\textsuperscript{29} whether the cause of heart failure was ischemic or not. More recently, significant 15% and 21% reductions of the risks of all-cause mortality and sudden cardiac death were reported by the addition of the mineralocorticoid receptor blocker eplerenone to standard therapy that included angiotensin-converting enzyme inhibitors 3 to 14 days after myocardial infarction associated with left ventricular dysfunction and congestive heart failure in the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS).\textsuperscript{2} Moreover, at 30 days, eplerenone reduced the risk of all-cause mortality and sudden cardiac death by 31% and 37%, respectively.\textsuperscript{30} Interestingly, in both the RALES and EPHESUS trials, much of the benefit of aldosterone receptor blockade was due to a statistically significant reduction of sudden cardiac death early after randomization. The administration of spironolactone compared with placebo in patients with successful PCI for a first anterior wall STEMI has been reported to be associated with reduced left ventricular remodeling at 1-month follow-up.\textsuperscript{31} Nevertheless, the reduction of mortality in the RALES and EPHESUS trials appears very early after randomization and is unlikely to be exclusively related to the prevention...
of left ventricular remodeling by such drugs. These data suggest a deleterious action of aldosterone, which may rapidly be antagonized by mineralocorticoid receptor inhibitors. The benefit of aldosterone receptor blockade started within days or weeks after myocardial infarction, long after aldosterone levels have decreased (as in the EPHESUS trial), is important to acknowledge, but it is possible that an earlier administration during the first hours of acute myocardial infarction may be even more effective. However, such speculation requires testing in an adequately sized randomized study.

In the present study, the highest aldosterone level quartile was associated with an adverse clinical outcome, independently of age, heart failure, and success or failure of reperfusion. These findings support the need for a trial with mineralocorticoid receptor inhibitors in the general setting of STEMI. The limited sample size of the present study population is one of the study limitations that may impact the power of the present analysis.

In conclusion, the present data demonstrate a strong and independent association between plasma aldosterone levels at admission for acute STEMI and the risk of early and late death or resuscitated cardiac death, with a significant impact on mortality. Other major events such as cardiac arrest, life-threatening ventricular arrhythmias, and congestive heart failure are also linked to admission aldosterone levels. Thus, aldosterone appears to be a major marker of adverse clinical outcome, identifying high-risk patients among those presenting for mechanical reperfusion for STEMI. Whether early specific mineralocorticoid receptor blockade can improve outcome in such patients remains to be assessed.

Acknowledgments
The authors thank Dr Marie-Laure Tanguy from the Department of Biostatistics of the Pitié-Salpêtrière University Hospital for her expert advice on the statistical analyses; Delphine Brugier, Emmanuelle Dos Santos, and Vanessa Gallois for their contribution in collecting data and updating the database; and the Banque de Tissus pour la Recherche, Association Institut de Myologie for the conservation and management of the biological samples.

Disclosures
None.

References


**CLINICAL PERSPECTIVE**

Aldosterone has been reported to exert toxic effects on the myocardium. Serial measurements of aldosterone obtained from patients presenting with ST-elevation myocardial infarction (STEMI) have shown that plasma aldosterone is at its highest level on admission and decreases rapidly thereafter. We hypothesized that the level of aldosterone at presentation with STEMI may be associated with adverse outcomes. We therefore assessed the association between aldosterone levels at admission and in-hospital events and mortality during a 6-month follow-up in a consecutive series of 356 patients referred for primary percutaneous coronary intervention for STEMI. Our data demonstrated that elevated levels of aldosterone were significantly associated with an almost stepwise increase in the rates of in-hospital death, cardiovascular death, heart failure, ventricular fibrillation, and resuscitated cardiac arrest. During follow-up, patients with the highest aldosterone levels were at increased risk of death (hazard ratio 3.28, 95% CI 1.09 to 9.89, \(P = 0.035\)) and death or resuscitated cardiac arrest (hazard ratio 3.74, 95% CI 1.40 to 9.98, \(P = 0.008\)) compared with those with the lowest levels, independent of age, heart failure at admission, and reperfusion status. Although the benefit of aldosterone receptor blockade started within days or weeks after STEMI complicated by left ventricular dysfunction and heart failure has been demonstrated previously, our results suggest that earlier administration of aldosterone receptor antagonists during the first hours of STEMI may be even more effective and justify the need for a randomized clinical trial to assess this hypothesis.
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_Circulation_. 2006;114:2604-2610; originally published online November 20, 2006; doi: 10.1161/CIRCULATIONAHA.106.634626

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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