

# The Significance of Angiotensin Converting Enzyme Inhibitor or Angiotensin II Receptor Blocker Use in Sudden Cardiac Death

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## Abstract

**Objectives:** To investigate the relationship between the use of angiotensin converting enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB) and hyperkalemia in patients diagnosed with sudden cardiac death. **Methods:** We examined oral ACE inhibitor or ARB use among cardiopulmonary arrest patients brought by ambulance to our emergency room during a 5-year period from January 2012 to December 2016. The cause of death was determined to be sudden cardiac death, despite temporary return of spontaneous circulation after starting cardiopulmonary resuscitation. Subjects were dichotomized into 2 groups, those taking and those not taking an ACE inhibitor or ARB. Variables determined retrospectively included serum potassium, estimated glomerular filtration rate as an index of kidney function and time from cardiopulmonary arrest to return of spontaneous circulation. The Mann-Whitney U-test was used to compare continuous data, and the chi-square test to compare categorical data between groups. The results are expressed as the median plus range. Statistical significance was assumed at  $p < 0.05$ . **Results:** Thirty-five patients met the inclusion criteria. The mean age was 77.1 years (range, 35 - 93 years), and there were 26 males and 9 females. Eleven subjects were ACE inhibitor or ARB users, and 24 were non-users. The serum potassium level was significantly higher in users than non-users (median, 6.2 mEq/L (range, 4.5 - 10.0) vs. 5.2 mEq/L (range, 3.6 - 8.3);  $p = 0.001$ ). The estimated glomerular filtration rate was significantly lower in users than non-users (median, 25.1 mL/min/1.73 m<sup>2</sup> (range, 4.6 - 60.3) vs. 46.9 mL/min/1.73 m<sup>2</sup> (range, 19.8 - 97.1);  $p = 0.009$ ). There was no significant difference in time from cardiopulmonary arrest to return of spontaneous circulation between the 2 groups (median, 24 minutes (range, 3 - 111) vs. 29 minutes (range, 10 - 54);  $p = 0.355$ ). **Conclusion:** It is possible that hyperkalemia induced by ACE inhibitor

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or ARB use is a cause of sudden cardiac death, especially in patients with chronic kidney disease.

## Keywords

Angiotensin Converting Enzyme Inhibitors, Angiotensin II Receptor Blockers, Glomerular Filtration Rate, Hyperkalemia, Sudden Cardiac Death

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## 1. Introduction

Angiotensin converting enzyme (ACE) inhibitor and angiotensin II receptor blocker (ARB) are widely used for hypertension and heart disease. They act as inhibitors of the renin-angiotensin-aldosterone system and can sometimes evoke lethal hyperkalemia [1] [2] [3]. Sudden cardiac death is defined as unexpected death due to cardiac causes that occurs in a short time period (generally within 1 hour of symptom onset) in a person with known or unknown cardiac disease [4]. Hyperkalemia due to a drug side effect is considered one of the causes of sudden cardiac death. However, the relationship between the use of oral drugs and hyperkalemia in sudden cardiac death patients is unknown. The aim of this study was to investigate the relationship between ACE inhibitor or ARB use and hyperkalemia in patients diagnosed with sudden cardiac death.

## 2. Materials & Methods

Cardiopulmonary arrest patients (n = 455) were transported to our emergency room between January 2012 and December 2016. In all subjects enrolled in the study, the cause of death was determined to be sudden cardiac death despite temporary return of spontaneous circulation (ROSC) after starting cardiopulmonary resuscitation. Patients without temporary ROSC were excluded because of the possibility of hyperkalemia due to changes after death. Subjects were dichotomized into 2 groups: those taking an ACE inhibitor or ARB (users), and those not taking an ACE inhibitor or ARB (non-users). The users and non-users were compared according to age, sex, the results of general laboratory tests, estimated glomerular filtration rate (eGFR) as an index of kidney function [5] at the initial hospital, and the time from cardiopulmonary arrest to ROSC. The eGFR was calculated by the following formula:  $eGFR = 194 * \text{serum Cr}^{-1.094} * \text{age}^{-0.287} (*0.739 \text{ [if female]})$  [6].

The Mann-Whitney U-test was used to compare continuous data and the chi-square test to compare categorical data between groups. The results are expressed as the median plus range. The chi-square test for independence was used to test for differences in proportions. Statistical significance was assumed at  $p < 0.05$ . All statistical calculations were performed on a personal computer using SISS (Ver.2012 SISS for Windows, Tokyo).

Ethical aspects

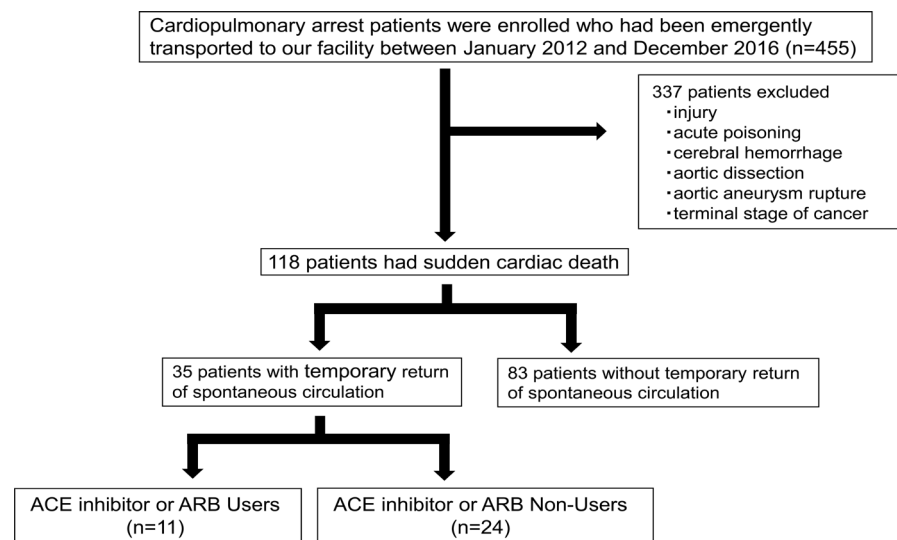
This study was approved by the ethics committee of the School of Medicine at Iwate Medical University (approval number: H28-171) prior to study enrollment and informed consents were obtained from the family of all patients.

### 3. Results

Thirty-five patients were the subject of this study (**Figure 1**). There were 26 males and 9 females, with a median age of 81 years (range: 35 - 93 years). They were divided into ACE inhibitor or ARB users (n = 11) and non-users (n = 24). Seven patients were taking loop diuretics or potassium-sparing diuretics (3 patients among users and 4 among non-users). The serum potassium level was significantly higher in users than non-users (6.2 mEq/L (range, 4.5-10.0) vs. 5.2 mEq/L (range, 3.6 - 8.3);  $p = 0.001$ ). The blood urea nitrogen concentration was significantly higher in users than non-users (40.3 mg/dL (range, 20.3 - 143.1) vs. 19.5 mg/dL (range, 11.3 - 64.7);  $p = 0.005$ ) and serum creatinine levels were significantly higher in users (2.0 mg/dL (range, 0.7 - 9.5) vs. 1.1 mg/dL (range, 0.5 - 2.3);  $p = 0.007$ ). The eGFR was 25.1 mL/min/1.73m<sup>2</sup> (range, 4.6 - 60.3) in users and 46.9 mL/min/1.73m<sup>2</sup> (range, 19.8 - 97.1) in non-users, and the difference was significant ( $p = 0.009$ ). There was no significant differences in the time from cardiopulmonary arrest to ROSC between the 2 groups (median, 24 minutes (range, 3 - 111) vs. 29 minutes (range, 10 - 54);  $p = 0.355$ ) (**Table 1**).

### 4. Discussion

In this study, we demonstrated that the serum potassium level was significantly higher in ACE inhibitor or ARB users than non-users. The frequency of hyperkalemia with chronic ACE inhibition or ARB treatment is approximately 3.3 percent, and the frequency with combination use is 5.6 percent [7]. However, ACE inhibitor or ARB therapy is infrequently associated with life-threatening hyperkalemia [8] [9] [10] [11]. There are no reports in the literature on the rela-



**Figure 1.** Flow diagram of the present study.

**Table 1.** Differences in clinical characteristics between users and non-users.

Characteristics	Normal range	Users (n = 11)	Non-users (n = 24)	p value
Age (years)		81 (65 - 89)	81 (35 - 93)	0.511
Sex (male/female)		9/2	17/7	0.403
WBC (/mm <sup>3</sup> )	3300 - 8600	12,020 (6900 - 17,730)	11,785 (7040 - 20,190)	0.776
Hb (g/dL)	13.7 - 16.8	10.7 (9.1 - 16.7)	12.5 (5.5 - 16.7)	0.102
Platelet ( $\times 10^4$ /mm <sup>3</sup> )	15.8 - 34.8	12.9 (4.8 - 33.9)	19.8 (3.6 - 37.4)	0.273
Na (mEq/L)	138 - 145	139 (135 - 158)	142 (127 - 164)	0.568
K (mEq/L)	3.6 - 4.8	6.2 (4.5 - 10.0)	5.2 (3.6 - 8.3)	0.001
Cl (mEq/L)	101 - 108	103 (99 - 106)	103 (87 - 117)	0.886
UN (mg/dL)	8.0 - 20.0	40.3 (20.3 - 143.1)	19.5 (11.3 - 64.7)	0.005
Creatinine (mg/dL)	0.7 - 1.1	2.0 (0.7 - 9.5)	1.1 (0.5 - 2.3)	0.007
T-Bil (mg/dL)	0.4 - 1.5	0.4 (0.2 - 1.0)	0.6 (0.2 - 2.1)	0.282
AST (IU/L)	13 - 30	152 (26 - 1665)	74 (22 - 1553)	0.365
ALT (IU/L)	10 - 42	111 (13 - 1295)	56 (14 - 446)	0.160
LDH (IU/L)	124 - 222	781 (262 - 2103)	492 (256 - 4928)	0.307
CK (IU/L)	59 - 248	180 (71 - 2197)	170 (51 - 5117)	0.749
CK-MB (IU/L)	0 - 12	28 (4 - 141)	33 (6 - 685)	0.804
CRP (mg/dL)	<0.1	0.6 (0.1 - 8.4)	0.4 (0.1 - 16.9)	0.744
PT-INR	0.92 - 1.04	1.23 (0.72 - 2.36)	0.98 (0.83 - 2.56)	0.221
pH	7.350 - 7.450	6.993 (6.751 - 7.263)	7.047 (6.685 - 7.335)	0.468
Base Ecess	-2.0 - 2.0	-15.0 (-27.5 - -6.8)	-10.7 (-22.3 - -3.0)	0.104
Time of CPA (minutes)		24 (3 - 111)	29 (10 - 54)	0.355
eGFR (mL/min/1.73 m <sup>2</sup> )		25.1 (4.6 - 60.3)	46.9 (19.8 - 97.1)	0.009

The results are expressed as median (range). WBC: white blood cell; Hb: hemoglobin; UN: urea nitrogen; T-Bil: total bilirubin; AST: aspartate transaminase; ALT: alanine transaminase; LDH: lactate dehydrogenase; CK: creatine kinase; CRP: C-reactive protein; PT-INR: prothrombin time-international normalized ratio; Time of CPA: time from cardiopulmonary arrest to return of spontaneous circulation; eGFR: estimated glomerular filtration rate.

tionship between hyperkalemia and ACE inhibitor or ARB use in sudden cardiac death patients. This study included only patients with ROSC, since these patients probably had a short cardiac arrest time. This was done to try to eliminate the effects of hyperkalemia as a result of the release of intracellular potassium stores after cardiac arrest [12] [13]. Since the serum potassium level was significantly higher in users than non-users, it is possible that one cause of hyperkalemia in acute cardiac death with ROSC is ACE inhibitor or ARB administration. Based on this, if patients with hypertension and heart disease are taking with ACE inhibitor or ARB, it is necessary for cardiologists to maintain careful monitoring of potassium levels.

The eGFR was significantly lower in users than non-users in the present study. The ONTARGET trial investigated the renal effects of an ACE inhibitor, an ARB

or their combination in patients with established atherosclerotic vascular disease or with diabetes and end-organ damage [14]. The trial showed that the need for dialysis or a doubling of serum creatinine from baseline values was more frequent with combination therapy than monotherapy, and the eGFR was significantly lower with ARB monotherapy or combination therapy than with ACE inhibitor monotherapy. Cittanova *et al.* [15] examined 249 patients who underwent aortic surgery and found a relationship between deterioration of postoperative renal function and chronic ACE inhibitor administration. Furthermore, Lim *et al.* [16] examined 26,287 patients who were admitted to the ICU and reported that patients on renin-angiotensin-aldosterone system blockers were more likely to develop acute kidney injury. Thus, ACE inhibitor or ARB administration may worsen renal function. On the other hand, ARB use was associated with significant renal benefits in patients with type 2 diabetes and nephropathy in the RENAAL study [17]. Furthermore, reduction in the risk of kidney failure was significantly greater with ARB use than with Ca antagonist use [18] [19]. Similarly, some studies reported that ACE inhibitor use was beneficial in patients with renal diseases of various origin [20] or type 2 diabetic nephropathy [21]. Therefore, we inferred that ACE inhibitors or ARBs were administered to patients with low eGFR in that study.

There are some reports that ACE inhibitor or ARB use in advancing stages of chronic kidney disease elevates the risk of hyperkalemia [22] [23] [24]. In patients with hypertensive chronic kidney disease treated with ACE inhibitors, hyperkalemia occurs frequently if the baseline and follow-up GFR is lower than 40 mL/min/1.73 m<sup>2</sup> [22]. Renal disease is identified as one of the predictors of hyperkalemia secondary to ACE inhibitor drug interaction [23]. In addition, Maddirala *et al.* [24] reported that the incidence of hyperkalemia increased with progression of the stage of chronic kidney disease in ACE inhibitor or ARB users. In the present study, the eGFR was significantly lower in users than non-users (25.1 mL/min/1.73m<sup>2</sup> vs. 46.9 mL/min/1.73m<sup>2</sup>;  $p = 0.009$ ). Therefore, if an ACE inhibitor or ARB is used in advanced chronic kidney disease patients, it is necessary to measure potassium levels frequently.

This study has several limitations. First, the sample size was small at 35 patients because the study involved only one institution. As a result, there was variability in data and the statistical power could have been insufficient. Another limitation was that the influence of other drugs was not considered. In particular, the diuretics taken by 7 patients might have affected the serum potassium levels. In addition, we examined only ROSC patients in this study. However, hyperkalemia as a result of the release of intracellular potassium stores after cardiac arrest may not be completely eliminated. Another limitation involved serum ACE inhibitor or ARB concentrations, which were not measured. As a result, it was not possible to determine the relationship between serum ACE inhibitor or ARB concentration and serum potassium levels. Future studies are needed to prospectively examine the relationship between serum potassium le-

vels and the use of an ACE inhibitor or ARB.

## 5. Conclusion

Hyperkalemia induced by the use of an ACE inhibitor or ARB raises the possibility that it may cause sudden cardiac death, especially in patients with chronic kidney disease.

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