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ORIGINAL RESEARCH

Effects of Renin-Angiotensin–Aldosterone System Inhibitors on Long-Term Major Adverse Cardiovascular Events in Sepsis Survivors

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BACKGROUND: Sepsis is known to increase morbidity and duration of hospital stay and is a common cause of mortality worldwide. Renin-angiotensin-aldosterone system inhibitors (RAASis) are commonly used to treat hypertension but are usually discontinued during hospitalization for sepsis because of concerns about renal hypoperfusion. The aim of our study was to investigate whether RAASis should be continued after discharge in sepsis survivors and to identify the effects on the clinical outcomes.

METHODS AND RESULTS: A total of 9188 sepsis survivors aged 20 years and older who were discharged from January 1, 2012 to December 31, 2019 were included in our analyses. We further divided sepsis survivors into RAASi users and nonusers. These groups were matched by propensity scores before the outcomes of interest, including all-cause mortality and major adverse cardiac events (MACE), were examined. After propensity score matching, 3106 RAASi users and 3106 RAASi nonusers were included in our analyses. Compared with RAASi nonusers, RAASi users had lower risks of all-cause mortality (hazard ratio [HR], 0.68; 95% CI, 0.62–0.75), MACEs (HR, 0.87; 95% CI, 0.81–0.94), ischemic stroke (HR, 0.85; 95% CI, 0.76–0.96), myocardial infarction (HR, 0.74; 95% CI, 0.61–0.90), and hospitalization for heart failure (HR, 0.84; 95% CI, 0.77–0.92). Subgroup analyses stratified by admission to the ICU and the use of inotropes showed similar results.

CONCLUSIONS: In our study, we found that RAASi users had reduced risks of all-cause mortality and MACEs. These findings suggested a beneficial effect of RAASi use by sepsis survivors after discharge.

Key Words: all-cause mortality ■ epidemiology ■ major adverse cardiac events ■ renin-angiotensin-aldosterone system inhibitors ■ sepsis

Sepsis is a life-threatening condition characterized by shock and multiple organ dysfunction, with an annual mortality rate >25% worldwide.[1,2] Despite advances in intensive care and medical treatments, sepsis continues to impose a major public health burden, with a consistently increasing incidence that ranges from 38 to 110 cases per 100 000 persons.[3] Sepsis leads to a complex immune response and evokes uncontrolled inflammatory responses that lead to a poor prognosis.[4,5] During sepsis, the renin-angiotensin–aldosterone system (RAAS) is activated. Angiotensin II, as the main RAAS agonist, then binds to angiotensin receptors to aggravate proinflammatory responses and cause vascular dysfunction, resulting in poor outcomes.[6,7] RAAS inhibitors (RAASis), such as angiotensin-converting enzyme inhibitors (ACEIs)

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CLINICAL PERSPECTIVE

What Is New?

- This cohort study including 9188 sepsis survivors demonstrated that use of renin-angiotensin-aldosterone system inhibitors (RAASis) after discharge from sepsis was associated with lower risks of all-cause mortality and major adverse cardiac events compared with no use of RAASis.

What Are the Clinical Implications?

- Because RAASis are often held during hospitalization for sepsis, this study may provide the insights that use of RAASi after discharge from hospitalization for sepsis confers benefits with regard to long-term survival and major adverse cardiac events in sepsis survivors.
- Physicians may consider prescribing RAASis in sepsis survivors after discharge if there are no contraindications.

Nonstandard Abbreviations and Acronyms

MACE	major adverse cardiovascular event
RAASi	renin-angiotensin–aldosterone system inhibitors

or angiotensin-II receptor blockers (ARBs), were thus thought to possibly improve outcomes by exerting anti-inflammatory effects, decreasing endotoxin-induced oxidative stress, and improving endothelial dysfunction.[8–10]

Previous animal models of sepsis have found that the blockade of RAAS decreases the levels of proinflammatory cytokines and improves survival after sepsis.[11,12] Most previous studies focused on RAASi use prior to hospitalization for sepsis, and the results were inconsistent.[13–15] Of note, RAASi use is frequently discontinued when a patient develops sepsis to avoid the possibility of renal hypoperfusion or hypotension episodes. However, whether RAASi use should be resumed by sepsis survivors after discharge is still unclear and warrants further investigation. In addition, an analysis of long-term follow-up datasets examining the possible impact of RAASi use on long-term clinical outcomes in sepsis survivors is lacking.

The present study aimed to address an important issue regarding the possible harms or benefits of RAASi use after discharge from hospitalization for sepsis. The study aims to examine the impact of RAASi use on long-term all-cause mortality and major adverse cardiovascular events (MACEs) in sepsis survivors.

METHODS

Study Population

The data that support the findings of this study may be available from the corresponding author upon reasonable request, subject to approval by the institution. Patients aged 20 years old with discharge diagnoses of sepsis identified using diagnostic codes from the *International Classification of Diseases*, *Ninth* and *Tenth* Revisions, Clinical Modification (038.x, 995.91, A40.x and A41.x), severe sepsis (995.92 and R65.20) or septic shock (785.52 and R65.21) between January 1, 2012 and December 31, 2019 were included in our study.[16] Patients who died before discharge were excluded from the present study. If a patient experienced multiple admissions for sepsis, we only included the first admission after 2012 to avoid survivor bias. This study was approved by the Institutional Review Board of Kaohsiung Veterans General Hospital (number 20-CT8-03(200618-3)) who waived the informed consent requirement because of de-identified data.

Cohort Definition

The subjects were classified into RAASi users and nonusers depending on ACEI or ARB use after discharge as follows: (1) RAASi users (sepsis survivors who received ACEI or ARB prescriptions after discharge from hospitalization for sepsis) and (2) RAASi nonusers (sepsis survivors who did not receive ACEI or ARB prescriptions after discharge from hospitalization for sepsis).

Study Variables

In our study, we extracted patient age, sex, comorbidities, concomitant medications, and laboratory data. The comorbidities included hypertension, coronary artery disease, diabetes, congestive heart failure, autoimmune disease, and malignancy. The history of intensive care unit (ICU) admission, the use of mechanical ventilation and the use of inotropes during hospitalization for sepsis were also collected. Concomitant medications were also identified, including antiplatelets, statins, nonsteroidal anti-inflammatory agents, oral hypoglycemic agents, and insulins. In addition, we also included laboratory test results for parameters that could be important risk factors for the outcomes, such as hemoglobin, serum low-density lipoprotein, glycated hemoglobin, and estimated glomerular filtration rate (eGFR). We estimated the GFR using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, which may provide more precise GFR estimations.[17–19] There were no missing data on age, sex, comorbidities, and concomitant medications.

However, there are missing values in the laboratory data (including hemoglobin, serum low-density lipoprotein, glycated hemoglobin, and eGFR). Due to the incompleteness of the laboratory data, we performed multivariate imputation by chained equations to address missing values.[20] The detailed information about missing values before and after imputation is shown in Table S1.

Outcomes of Interest

The long-term clinical outcomes were obtained using linkage to claims data from the hospital registry database. The outcomes of interest in our study were all-cause mortality and MACEs, including transient ischemic attack, ischemic stroke, myocardial infarction, and hospitalization for heart failure. All sepsis survivors were followed until death or the end of the study period.

Statistical Analysis

Continuous variables are described as the means with SDs for normally distributed variable and as the medians with interquartile ranges (IQRs) for nonnormally distributed variables and were compared using the t test or Mann-Whitney *U* test, respectively. Categorical variables are expressed as frequencies and percentages and were compared using Pearson χ^2 tests. In addition, we used propensity score matching to balance the baseline characteristics between RAASi users and nonusers. For each sepsis survivor, we calculated a propensity score for the likelihood of RAASi users using baseline covariates in a multivariate logistic regression model (Table S2). We matched one RAASi user with each RAASi nonuser according to propensity score based on nearest-neighbor matching without replacement.[21,22] The standardized difference was calculated to assess the balance between the two groups after propensity score matching. A Cox proportional hazards regression model was constructed to compute the corresponding hazard ratios (HRs).[23] The cumulative incidence estimates were calculated using the Kaplan-Meier method, and outcomes were assessed with log rank tests. Subgroup analyses were performed according to admission to the ICU and the use of inotropes to assess the consistency of the results across subgroups, and interactions were evaluated with likelihood ratio tests. All statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC) and R version 3.6.1 (R Project for Statistical Computing). Two-sided statistical significance was defined as $P<0.05$.

RESULTS

Study Population

A total of 9188 sepsis survivors who met the inclusion criteria were included in our study (Table 1). The median age was 76.8 (IQR 63.7–85.5) years, with relatively high proportions of patients with hypertension (74.5%), coronary artery disease (35.2%), diabetes (43.6%), and congestive heart failure (25.5%). Before propensity score matching, the RAASi users were older, were predominantly female, and had higher proportion of hypertension, coronary artery disease, diabetes, and congestive heart failure.

After propensity score matching, 3106 RAASi users were matched to similar RAASi nonusers, resulting in a final study cohort of 6212 sepsis survivors. The adequate balance across all included covariates was achieved between RAASi users and nonusers. The distributional balance of the propensity score between RAASi users and nonusers before and after propensity score matching is shown in Figure S1.

Outcomes

After propensity score matching, compared with RAASi nonusers, RAASi users had lower risks of all-cause mortality (HR, 0.68; 95% CI, 0.62–0.75, $P<0.001$), the composite MACE end point (HR, 0.87; 95% CI, 0.81–0.94, $P<0.001$), ischemic stroke (HR, 0.85; 95% CI, 0.76–0.96, $P=0.011$), myocardial infarction (HR, 0.74; 95% CI, 0.61–0.90, $P=0.003$) and hospitalization for heart failure (HR, 0.84; 95% CI, 0.77–0.92, $P<0.001$), but there was no difference in the risks of transient ischemic attack (HR, 0.96; 95% CI, 0.68–1.36, $P=0.826$) and peripheral artery occlusive disease (HR, 0.94; 95% CI, 0.69–1.27, $P=0.690$; Table 2). The results were similar after excluding patients with missing values (Table S3).

The results of the Kaplan–Meier survival analysis showed that RAASi users had lower risks of all-cause mortality (number needed to treat [NNT]=9; log-rank test, $P<0.001$), ischemic stroke (NNT=9; log-rank test, $P=0.011$), myocardial infarction (NNT=25; log-rank test, $P=0.003$), and hospitalization for heart failure (NNT=26; log-rank test, $P<0.001$; Figure).

Subgroup Analyses

In the subgroup analysis stratified by admission to the ICU, patients who had been admitted to the ICU had slightly lower HRs for the composite MACE end point (HR 0.84 versus 0.89, P for interaction<0.001), ischemic stroke (HR 0.79 versus 0.93, P for interaction=0.001), myocardial infarction (HR 0.70 versus 0.83, P for interaction<0.001), but a slightly higher HR

Table 1. Baseline Characteristics of the Study Population Before and After Propensity Score Matching

	Before propensity score matching				After propensity score matching*			
	All patients (n=9188)	RAASi nonusers (n=5984)	RAASi users (n=3204)	SMD	All patients (n=6212)	Matched RAASi nonusers (n=3106)	RAASi users (n=3106)	SMD
Age, y	76.8 [63.7, 85.5]	76.3 [62.6, 85.5]	77.8 [65.6, 85.4]	0.114	78.4 [65.9, 85.9]	78.9 [66.3, 86.3]	77.8 [65.6, 85.4]	0.055
Male sex, n (%)	3763 (41.0)	2420 (40.4)	1343 (41.9)	0.030	2549 (41.0)	1255 (40.4)	1294 (41.7)	0.026
Hgb, g/dL	10.5 [9.3, 12.0]	10.4 [9.2, 11.9]	10.8 [9.6, 12.1]	0.179	10.7 [9.5, 12.1]	10.7 [9.5, 12.2]	10.8 [9.6, 12.1]	0.002
LDL-C, mg/dL	93.0 [71.0, 115.0]	92.0 [71.0, 115.0]	94.0 [72.0, 116.0]	0.022	93.0 [72.0, 116.0]	93.0 [72.0, 116.0]	94.0 [72.0, 115.8]	0.003
HbA_{1c}, %	6.4 [5.8, 7.4]	6.3 [5.7, 7.3]	6.5 [5.8, 7.5]	0.109	6.4 [5.8, 7.5]	6.4 [5.8, 7.5]	6.5 [5.8, 7.5]	0.050
eGFR, mL/min per 1.73 m^2				0.144				0.035
≥90	2633 (28.7)	1817 (30.4)	816 (25.5)		1586 (25.5)	781 (25.1)	805 (25.9)	
60–89	2628 (28.6)	1644 (27.5)	984 (30.7)		1886 (30.4)	945 (30.4)	941 (30.3)	
30–59	2195 (23.9)	1373 (22.9)	822 (25.7)		1585 (25.5)	796 (25.6)	789 (25.4)	
15–29	794 (8.6)	558 (9.3)	236 (7.4)		454 (7.3)	220 (7.1)	234 (7.5)	
<15	938 (10.2)	592 (9.9)	346 (10.8)		701 (11.3)	364 (11.7)	337 (10.8)	
HTN, n (%)	6845 (74.5)	4073 (68.1)	2772 (86.5)	0.452	5381 (86.6)	2707 (87.2)	2674 (86.1)	0.031
CAD, n (%)	3238 (35.2)	1892 (31.6)	1346 (42.0)	0.217	2557 (41.2)	1268 (40.8)	1289 (41.5)	0.014
Diabetes, n (%)	4002 (43.6)	2330 (38.9)	1672 (52.2)	0.268	3163 (50.9)	1574 (50.7)	1589 (51.2)	0.010
CHF, n (%)	2340 (25.5)	1429 (23.9)	911 (28.4)	0.104	1751 (28.2)	863 (27.8)	888 (28.6)	0.018
Autoimmune disease, n (%)	427 (4.6)	276 (4.6)	151 (4.7)	0.005	278 (4.5)	129 (4.2)	149 (4.8)	0.031
Malignancy, n (%)	4427 (48.2)	3053 (51.0)	1374 (42.9)	0.164	2701 (43.5)	1343 (43.2)	1358 (43.7)	0.010
ICU admissions, n (%)	4802 (52.3)	3184 (53.2)	1618 (50.5)	0.054	3173 (51.1)	1590 (51.2)	1583 (51.0)	0.005
Use of ventilation, n (%)	2917 (31.7)	2028 (33.9)	889 (27.7)	0.133	1774 (28.6)	892 (28.7)	882 (28.4)	0.007
Use of inotropes, n (%)	3072 (33.4)	2201 (36.8)	871 (27.2)	0.207	1764 (28.4)	897 (28.9)	867 (27.9)	0.021
Antiplatelets, n (%)	3081 (33.5)	1701 (28.4)	1380 (43.1)	0.309	2587 (41.6)	1288 (41.5)	1299 (41.8)	0.007
Statins, n (%)	2081 (22.6)	1086 (18.1)	995 (31.1)	0.303	1784 (28.7)	875 (28.2)	909 (29.3)	0.024
NSAIDs, n (%)	4853 (52.8)	3172 (53.0)	1681 (52.5)	0.011	3257 (52.4)	1623 (52.3)	1634 (52.6)	0.007
OHAs, n (%)	2086 (22.7)	1195 (20.0)	891 (27.8)	0.185	1671 (26.9)	833 (26.8)	838 (27.0)	0.004
Insulins, n (%)	4452 (48.5)	2874 (48.0)	1578 (49.3)	0.024	3064 (49.3)	1533 (49.4)	1531 (49.3)	0.001

Data are presented as n (%) or medians and interquartile ranges. CAD indicates coronary artery disease; CHF, congestive heart failure; eGFR, estimated glomerular filtration rate; HbA_{1c}, hemoglobin A_{1c}; Hgb, hemoglobin; HTN, hypertension; ICU, intensive care unit; LDL-C, low-density lipoprotein cholesterol; NSAIDs, nonsteroidal anti-inflammatory drugs; OHA, oral hypoglycemic agents; RAASis, renin-angiotensin-aldosterone system inhibitors; and SMD, standardized mean difference.

*Covariates, such as age, sex, Hgb, LDL-C, HbA_{1c}, stages of chronic kidney disease, HTN, CAD, diabetes, CHF, autoimmune disease, malignancy, ICU admissions, use of ventilation, use of inotropes, use of antiplatelets, use of statins, use of NSAIDs, use of OHAs, and use of insulins, were included in the propensity score matching.

Table 2. Risks of All-Cause Mortality and Long-Term Clinical Outcomes in RAASi Users and Nonusers After Propensity Score Matching in Sepsis Survivors

Outcomes	Matched RAASi nonusers			RAASi users			HR (95% CI)	*P* value
	No. of events	Person-years	Incidence rate*	No. of events	Person-years	Incidence rate*		
All-cause mortality	942	4912	19.18	784	6256	12.53	0.68 (0.62–0.75)	<0.001
Major adverse cardiac events†	1324	3185	41.57	1346	4095	32.87	0.87 (0.81–0.94)	<0.001
Transient ischemic attack	59	4845	1.22	68	6138	1.11	0.96 (0.68–1.36)	0.826
Ischemic stroke	514	4145	12.40	526	5430	9.69	0.85 (0.76–0.96)	0.011
Myocardial infarction	213	4725	4.51	192	6047	3.18	0.74 (0.61–0.90)	0.003
HHF	942	3962	23.78	930	5014	18.55	0.84 (0.77–0.92)	<0.001
PAOD	77	4885	1.58	91	6201	1.47	0.94 (0.69–1.27)	0.690

HHF indicates hospitalization for heart failure; HR, hazard ratio; PAOD, peripheral artery occlusive disease; and RAASi, renin-angiotensin-aldosterone system inhibitors.

*Per 10^2 person-years.

†Major adverse cardiac events included transient ischemic attack, ischemic stroke, myocardial infarction, and hospitalization for heart failure.

for all-cause mortality (HR 0.72 versus 0.63, *P* for interaction<0.001) and hospitalization for heart failure (HR 0.86 versus 0.80, *P* for interaction<0.001) than those who had not been admitted to the ICU (Table 3).

After stratification by the use of inotropes, inotrope users had slightly lower HRs for the composite MACE end point (HR 0.78 versus 0.91, *P* for interaction<0.001), myocardial infarction (HR 0.69 versus 0.77,

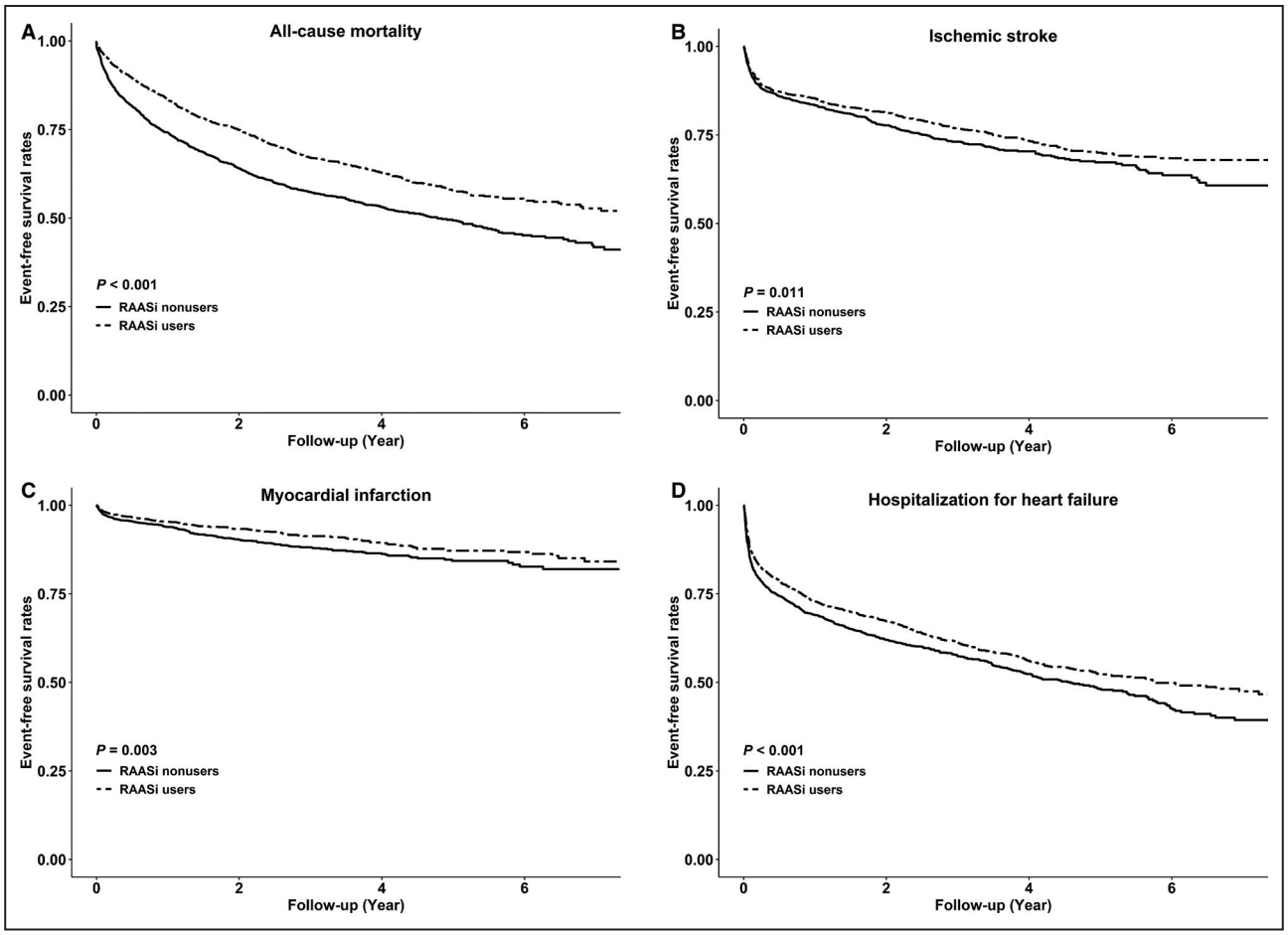

Figure 1. Kaplan–Meier curves for the risks of (A) all-cause mortality, (B) ischemic stroke, (C) myocardial infarction, (D) hospitalization for heart failure in renin-angiotensin-aldosterone system inhibitor (RAASi) users vs nonusers.
The event-free survival curves with the log-rank test showed that the risks of all outcomes were higher in RAASi nonusers. RAASi indicates renin-angiotensin-aldosterone system inhibitor.

Table 3. Risks of All-Cause Mortality and Long-Term Clinical Outcomes in RAASi Users and Nonusers Stratified by Admission to the ICU

Outcomes	Matched RAASi nonusers			RAASi users			HR (95% CI)	*P* value
	No. of events	Person-years	Incidence rate*	No. of events	Person-years	Incidence rate*		
All-cause mortality $P_{interaction}$<0.001								
Patients admitted to ICU	502	2214	22.67	454	2907	15.62	0.72 (0.64–0.82)	<0.001
Patients not admitted to ICU	440	2698	16.31	330	3349	9.85	0.63 (0.55–0.73)	<0.001
Major adverse cardiac events† $P_{interaction}$<0.001								
Patients admitted to ICU	805	1264	63.69	806	1645	49	0.84 (0.76–0.93)	0.001
Patients not admitted to ICU	519	1921	27.02	540	2449	22.05	0.89 (0.79–1.01)	0.071
Transient ischemic attack $P_{interaction}$=0.857								
Patients admitted to ICU	33	2185	1.51	32	2860	1.12	0.78 (0.48–1.28)	0.327
Patients not admitted to ICU	26	2660	0.98	36	3278	1.1	1.19 (0.72–1.96)	0.509
Ischemic stroke $P_{interaction}$=0.001								
Patients admitted to ICU	300	1831	16.38	290	2484	11.67	0.79 (0.67–0.93)	0.004
Patients not admitted to ICU	214	2314	9.25	236	2946	8.01	0.93 (0.78–1.12)	0.469
Myocardial infarction $P_{interaction}$<0.001								
Patients admitted to ICU	157	2075	7.57	135	2759	4.89	0.70 (0.56–0.88)	0.002
Patients not admitted to ICU	56	2650	2.11	57	3288	1.73	0.83 (0.57–1.19)	0.309
HHF $P_{interaction}$<0.001								
Patients admitted to ICU	581	1662	34.96	591	2111	28	0.86 (0.77–0.97)	0.011
Patients not admitted to ICU	361	2301	15.69	339	2904	11.67	0.80 (0.69–0.93)	0.003
PAOD $P_{interaction}$=0.013								
Patients admitted to ICU	54	2183	2.47	54	2867	1.88	0.76 (0.52–1.11)	0.156
Patients not admitted to ICU	23	2702	0.85	37	3334	1.11	1.32 (0.79–2.23)	0.294

HHF indicates hospitalization for heart failure; HR, hazard ratio; ICU, intensive care unit; PAOD, peripheral artery occlusive disease; and RAASi, renin-angiotensin-aldosterone system inhibitors.

*Per 10^2 person-years.

†Major adverse cardiac events included transient ischemic attack, ischemic stroke, myocardial infarction, and hospitalization for heart failure.

P for interaction<0.001), and hospitalization for heart failure (HR 0.73 versus 0.90, *P* for interaction<0.001), but a slightly higher HR for all-cause mortality (HR 0.72 versus 0.66, *P* for interaction<0.001) than those who did not use inotropes (Table 4).

DISCUSSION

In this cohort study of 9188 sepsis survivors, we found that RAASi users had lower risks of mortality and MACEs than RAASi nonusers. After propensity score matching, RAASi users had a 32% lower rate of mortality and a 13% lower rate of MACEs than RAASi nonusers. In addition, RAASi use was associated with a 26% reduction in the rate of myocardial infarction and a 16% reduction in the rate of hospitalization for heart failure. These findings are particularly important because RAASis are very frequently discontinued during hospitalization for sepsis. Our study suggests that RAASi use after discharge from hospitalization for sepsis may confer benefits with regard to survival and MACEs on sepsis survivors.

Angiotensin II is activated during sepsis and exerts proinflammatory effects, resulting in endothelial dysfunction and organ damage. Thus, the use of RAASis is thought to reduce the levels of inflammatory cytokines, microcirculatory dysfunction and sepsis-associated clinical adverse events, such as acute lung injury and cardiovascular dysfunction. Pretreatment with a blockade of the angiotensin II type 1 receptor with candesartan in animal models receiving *Escherichia coli* lipopolysaccharide endotoxin infusion resulted in higher survival rates because of preserved cardiac output, improved venous oxygen saturation, and increased intestinal blood flow.[11] RAASis were found to reduce superoxide levels and improve relaxation induced by acetylcholine in the aortas of mice treated with lipopolysaccharide,[24] which suggests that RAASis may decrease oxidative stress and improve endothelial dysfunction after sepsis. In another rat septic shock model, treatment with losartan was found to improve circulation dysfunction and decrease the levels of inflammatory cytokines, such as malondialdehyde, interleuin-1β and tumor necrosis factor-α.[25] This finding suggests that RASSis decrease the levels of inflammatory cytokines, suppress oxidative stress, and improve endothelial dysfunction after sepsis.

Table 4. Risks of All-Cause Mortality and Long-Term Clinical Outcomes in RAASi Users and Nonusers Stratified by Use of Inotropes During Hospitalization

Outcomes	Matched RAASi nonusers			RAASi users			HR (95% CI)	*P* value
	No. of events	Person-years	Incidence rate*	No. of events	Person-years	Incidence rate*		
All-cause mortality $P_{interaction}$<0.001								
Patients who received inotropes	292	1152	25.35	262	1533	17.09	0.72 (0.61–0.85)	<0.001
Patients who did not receive inotropes	650	3761	17.28	522	4722	11.05	0.66 (0.59–0.74)	<0.001
Major adverse cardiac events† $P_{interaction}$<0.001								
Patients who received inotropes	451	655	68.85	422	908	46.48	0.78 (0.68–0.89)	<0.001
Patients who did not receive inotropes	873	2529	34.52	924	3187	28.99	0.91 (0.83–1.00)	0.052
Transient ischemic attack $P_{interaction}$=0.040								
Patients who received inotropes	16	1135	1.41	10	1519	0.66	0.50 (0.23–1.11)	0.088
Patients who did not receive inotropes	43	3710	1.16	58	4619	1.26	1.14 (0.77–1.69)	0.518
Ischemic stroke $P_{interaction}$=0.280								
Patients who received inotropes	142	1002	14.17	149	1349	11.05	0.86 (0.68–1.08)	0.183
Patients who did not receive inotropes	372	3142	11.84	377	4081	9.24	0.85 (0.74–0.98)	0.030
Myocardial infarction $P_{interaction}$<0.001								
Patients who received inotropes	86	1081	7.96	72	1452	4.96	0.69 (0.51–0.95)	0.021
Patients who did not receive inotropes	127	3644	3.49	120	4595	2.61	0.77 (0.60–0.99)	0.045
HHF $P_{interaction}$<0.001								
Patients who received inotropes	348	823	42.28	308	1121	27.48	0.73 (0.63–0.86)	<0.001
Patients who did not receive inotropes	594	3139	18.92	622	3893	15.98	0.90 (0.80–1.01)	0.063
PAOD $P_{interaction}$=0.001								
Patients who received inotropes	29	1130	2.57	36	1514	2.38	0.93 (0.57–1.51)	0.757
Patients who did not receive inotropes	48	3755	1.28	55	4687	1.17	0.93 (0.63–1.37)	0.704

HHF indicates hospitalization for heart failure; HR, hazard ratio; ICU, intensive care unit; PAOD, peripheral artery occlusive disease; and RAASis, renin-angiotensin-aldosterone system inhibitors.

*Per 10^2 person-years.

†Major adverse cardiac events included transient ischemic attack, ischemic stroke, myocardial infarction, and hospitalization for heart failure.

Several observational studies have been conducted in humans, and most of them explored the effects of the use of RASSis prior to hospitalization for sepsis. ARB users were found to have lower levels of inflammatory cytokines and vascular microinflammation than nonusers.[26,27] A population-based study including 27 628 patients who were hospitalized for sepsis found that use of RAASis at least 30 days before admission was significantly associated with a lower risks of in-hospital mortality.[28] Another study including 33 213 sepsis patients also found that preadmission use of antihypertensive drugs with RAASi users were at lower risks of total hospital mortality in sepsis.[14] Other studies for 30-day mortality have yielded some conflicting results. A population-based study consisting of 52 982 patients hospitalization for sepsis found that prior RAASi users had lower 30-day mortality (HR, 0.84) and 90-day mortality (HR, 0.83) rates than nonusers.[29] In contrast, another study including 1965 patients hospitalized due to sepsis found that ACEI users seemed to be at increased risk of sepsis-related 30-day mortality.[13] The abovementioned studies were limited by the short duration of follow-up, and the effects of the use of RAASis after discharge from hospitalization for sepsis on long-term clinical outcomes are unknown.

If angiotensin II is suppressed by RAASis in patients with sepsis, renal hypoperfusion due to efferent arterial vasodilatation may contribute to the renal function fluctuation.[30–32] Therefore, RAASi therapy is often modified or discontinued during sepsis. The discontinuation of RAASi use during sepsis may induce the levels of angiotensin II to rebound, which may have adverse impact on the clinical outcomes in sepsis survivors. Our study attempted to clarify the effects of RAASi use in sepsis survivors, and we found that RAASi use was associated with lower risks of all-cause mortality and MACEs. Our findings support the continued use of RAASis after discharge from hospitalization for sepsis. In this study, we demonstrated that the continued use of RAASis was associated with the lowest risks of all-cause mortality and MACEs in a longer follow-up period. These results support findings from clinical studies regarding the physiological protective effects of the use of RAASis after discharge from hospitalization for sepsis, and RAASis may be a better choice of antihypertensive drugs in sepsis survivors.

Our study has some strengths and novel findings. Previous studies focused on the use of RAASis before hospitalization for sepsis. Sepsis survivors have elevated risks of mortality and cardiovascular events, which may be reduced by the use of RAASis. However, RAASi use is frequently discontinued during hospitalization for sepsis, and whether the continued use of RAASis after discharge from hospitalization for sepsis has never been explored before. Furthermore, the use of a large sample size of patients with sepsis allowed us to perform further analyses, including propensity score matching and subgroup analyses. Our results suggest that there is an important association between RASSi use and reduced risks of mortality and MACEs in sepsis survivors.

There are several limitations of the present study. First, as the study was retrospective, used administrative and laboratory data, and had an observational design, there was potential for indication or treatment bias.[33,34] The differences in patient characteristics between RAASi users and nonusers could have confounded the analysis. We used propensity score matching to balance the distribution of pretreatment covariates.[35] However, residual confounding factors still probably existed in the analysis. Second, some other potentially important covariates were not investigated in our study, such as nutritional status, smoking, alcohol consumption, exercise habits, and socioeconomic status. Third, missing data are unavoidable in pharmacoepidemiological research. In our study, we used multiple imputation for our analyses rather than using the traditional method of excluding patients with missing data from the analyses because excluding missing data may have introduced bias and resulted in a loss of statistical power.[36] Finally, by performing multiple subgroup analyses without correction, there may be increased risks of type 1 error in our study.

In conclusion, this study focused on whether continued RAASi use after discharge from hospitalization for sepsis in sepsis survivors and found that it was associated with lower risks of all-cause mortality and MACE, thereby adding to the body of knowledge on this topic.

ARTICLE INFORMATION

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Disclosures

None.

Supplementary Material

Tables S1–S3
Figure S1

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SUPPLEMENTAL MATERIAL

Table S1. Baseline characteristics of the study population before and after the imputation of missing values

	Before the imputation of missing values				After the imputation of missing values			
	All patients (*n* = 9,188)	**RAASi nonusers (*n* = 5,984)**	**RAASi users (*n* = 3,204)**	**SMD**	**All patients (*n* = 9,188)**	**RAASi nonusers (*n* = 5,984)**	**RAASi users (*n* = 3,204)**	**SMD**
Age, years	76.8 [63.7, 85.5]	76.3 [62.6, 85.5]	77.8 [65.6, 85.4]	0.114	76.8 [63.7, 85.5]	76.3 [62.6, 85.5]	77.8 [65.6, 85.4]	0.114
Male sex, *n*(%)	3,763 (41.0)	2,420 (40.4)	1,343 (41.9)	0.030	3,763 (41.0)	2,420 (40.4)	1,343 (41.9)	0.030
Hgb, g/dL	11.3 [9.7, 12.8]	11.2 [9.6, 12.7]	11.5 [10.0, 12.9]	0.130	10.5 [9.3, 12.0]	10.4 [9.2, 11.9]	10.8 [9.6, 12.1]	0.179
Available	9,075 (98.8%)	5,913 (98.8%)	3,162 (98.7%)		9,188 (100%)	5,984 (100%)	3,204 (100%)	
LDL-C, mg/dL	93.0 [72.0, 115.0]	92.0 [71.0, 115.0]	94.0 [73.0, 115.0]	0.025	93.0 [71.0, 115.0]	92.0 [71.0, 115.0]	94.0 [72.0, 116.0]	0.022
Available	5,827 (63.4%)	3,472 (58.0%)	2,355 (73.5%)		9,188 (100%)	5,984 (100%)	3,204 (100%)	
HbA_{1c}, %	6.4 [5.8, 7.4]	6.3 [5.7, 7.3]	6.5 [5.8, 7.6]	0.173	6.4 [5.8, 7.4]	6.3 [5.7, 7.3]	6.5 [5.8, 7.5]	0.109
Available	5,887 (64.1%)	3,601 (60.2%)	2,286 (71.3%)		9,188 (100%)	5,984 (100%)	3,204 (100%)	
eGFR, mL/min/1.73 m^2				0.190				0.144
Available	9,117 (99.2%)	5,936 (99.2%)	3,181 (99.3%)		9,188 (100%)	5,984 (100%)	3,204 (100%)	
≥ 90	1,796 (19.5)	1,308 (21.9)	488 (15.2)		2,633 (28.7)	1,817 (30.4)	816 (25.5)	
60–89	2,750 (29.9)	1,791 (29.9)	959 (29.9)		2,628 (28.6)	1,644 (27.5)	984 (30.7)	
30–59	2,626 (28.6)	1,592 (26.6)	1,034 (32.3)		2,195 (23.9)	1,373 (22.9)	822 (25.7)	
15-29	951 (10.4)	625 (10.4)	326 (10.2)		794 (8.6)	558 (9.3)	236 (7.4)	
<15	1,065 (11.6)	668 (11.2)	397 (12.4)		938 (10.2)	592 (9.9)	346 (10.8)	
HTN, *n* (%)	6,845 (74.5)	4,073 (68.1)	2,772 (86.5)	0.452	6,845 (74.5)	4,073 (68.1)	2,772 (86.5)	0.452
CAD, *n* (%)	3,238 (35.2)	1,892 (31.6)	1,346 (42.0)	0.217	3,238 (35.2)	1,892 (31.6)	1,346 (42.0)	0.217

Diabetes mellitus, *n* (%)	4,002 (43.6)	2,330 (38.9)	1,672 (52.2)	0.268	4,002 (43.6)	2,330 (38.9)	1,672 (52.2)	0.268
CHF, *n* (%)	2,340 (25.5)	1,429 (23.9)	911 (28.4)	0.104	2,340 (25.5)	1,429 (23.9)	911 (28.4)	0.104
Autoimmune disease, *n* (%)	427 (4.6)	276 (4.6)	151 (4.7)	0.005	427 (4.6)	276 (4.6)	151 (4.7)	0.005
Malignancy, *n* (%)	4,427 (48.2)	3,053 (51.0)	1,374 (42.9)	0.164	4,427 (48.2)	3,053 (51.0)	1,374 (42.9)	0.164
ICU admissions, *n* (%)	4,802 (52.3)	3,184 (53.2)	1,618 (50.5)	0.054	4,802 (52.3)	3,184 (53.2)	1,618 (50.5)	0.054
Use of ventilation, *n* (%)	2,917 (31.7)	2,028 (33.9)	889 (27.7)	0.133	2,917 (31.7)	2,028 (33.9)	889 (27.7)	0.133
Use of inotropes, *n* (%)	3,072 (33.4)	2,201 (36.8)	871 (27.2)	0.207	3,072 (33.4)	2,201 (36.8)	871 (27.2)	0.207
Antiplatelets, *n* (%)	3,081 (33.5)	1,701 (28.4)	1,380 (43.1)	0.309	3,081 (33.5)	1,701 (28.4)	1,380 (43.1)	0.309
Statins, *n* (%)	2,081 (22.6)	1,086 (18.1)	995 (31.1)	0.303	2,081 (22.6)	1,086 (18.1)	995 (31.1)	0.303
NSAIDs, *n* (%)	4,853 (52.8)	3,172 (53.0)	1,681 (52.5)	0.011	4,853 (52.8)	3,172 (53.0)	1,681 (52.5)	0.011
OHAs, *n* (%)	2,086 (22.7)	1,195 (20.0)	891 (27.8)	0.185	2,086 (22.7)	1,195 (20.0)	891 (27.8)	0.185
Insulin, *n* (%)	4,452 (48.5)	2,874 (48.0)	1,578 (49.3)	0.024	4,452 (48.5)	2,874 (48.0)	1,578 (49.3)	0.024

[*]Data are presented as n (%) or medians and interquartile ranges.

RAASis, renin-angiotensin-aldosterone system inhibitors; SMD, standardized mean difference; Hgb, hemoglobin; LDL-C, low-density lipoprotein cholesterol; HbA_{1c}, hemoglobin A_{1c}; eGFR, estimated glomerular filtration rate; HTN, hypertension; CAD, coronary artery disease; CHF, congestive heart failure; ICU, intensive care unit; NSAIDs, nonsteroidal anti-inflammatory drugs; OHA, oral hypoglycemic agents.

Table S2. Propensity score model results of probability of use of renin-angiotensin-aldosterone system inhibitors among sepsis survivors

			95% CI		
Parameter	**Estimate**	**Odds**	**Lower**	**Upper**	**P value**
Age, years	-0.0028	0.9972	0.9938	1.0007	0.1187
Male	0.0884	1.0924	0.9940	1.2005	0.0665
Hemoglobin, g/dL	0.0639	1.0659	1.0382	1.0945	<0.0001
LDL-C, mg/dL	0.0001	1.0000	0.9987	1.0013	0.9969
HbA1c, %	0.0289	1.0294	0.9987	1.0610	0.0606
eGFR, mL/min/1.73 m^2					
≥ 90		1			
60–89	0.0963	1.1011	0.9754	1.2430	0.1193
30–59	0.0454	1.0465	0.9189	1.1919	0.4935
15-29	-0.2537	0.7760	0.6425	0.9372	0.0084
<15	0.0110	1.0111	0.8470	1.2069	0.9029
HTN	0.8784	2.4070	2.1212	2.7313	<0.0001
CAD	0.1103	1.1166	1.0048	1.2410	0.0406
Diabetes mellitus	0.3168	1.3727	1.2182	1.5468	<0.0001
CHF	0.0983	1.1032	0.9882	1.2317	0.0803
Autoimmune disease	0.0890	1.0930	0.8790	1.3592	0.4238
Malignancy	-0.2303	0.7943	0.7246	0.8708	<0.0001
ICU admissions	0.0043	1.0044	0.8923	1.1305	0.9426
Use of ventilation	-0.0479	0.9532	0.8397	1.0820	0.4587
Use of inotropes	-0.3771	0.6858	0.6123	0.7681	<0.0001
Antiplatelets	0.3481	1.4163	1.2762	1.5718	<0.0001
Statins	0.4043	1.4983	1.3421	1.6727	<0.0001
NSAIDs	-0.0309	0.9695	0.8843	1.0631	0.5103
OHAs	0.1312	1.1402	1.0028	1.2965	0.0453
Insulin	-0.1846	0.8314	0.7405	0.9335	0.0018

CI, confidence interval; LDL-C, low-density lipoprotein cholesterol; HbA1c, hemoglobin A1c; eGFR, estimated glomerular filtration rate; HTN, hypertension; CAD, coronary artery disease; CHF, congestive heart failure; ICU, intensive care unit; NSAIDs, nonsteroidal anti-inflammatory drugs; OHA, oral hypoglycemic agents.

Table S3. Risks of all-cause mortality and long-term clinical outcomes in RAASi users and nonusers in sepsis survivors after excluding missing data

Outcomes	RAASi nonusers			RAASi users			HR (95% CI)	*P* value
	No. of Events	Person-years	Incidence Rate†	No. of Events	Person-years	Incidence Rate†		
All-cause mortality	482	2,785	17.31	439	3,799	11.56	0.69 (0.61-0.79)	<0.001
Major adverse cardiac events‡	836	1,689	49.5	854	2,389	35.75	0.79 (0.72-0.87)	<0.001
Transient ischemic attack	38	2,742	1.39	53	3,702	1.43	1.09 (0.72-1.65)	0.692
Ischemic stroke	346	2,263	15.29	360	3,186	11.3	0.81 (0.70-0.94)	0.006
Myocardial infarction	136	2,674	5.09	126	3,659	3.44	0.71 (0.56-0.90)	0.006
HHF	588	2,187	26.89	583	3,017	19.32	0.78 (0.69-0.87)	<0.001
PAOD	53	2,771	1.91	66	3,751	1.76	0.93 (0.65-1.33)	0.686

†per 10^2 person-years.

‡Major adverse cardiac events included transient ischemic attack, ischemic stroke, myocardial infarction and hospitalization for heart failure. RAASi, renin-angiotensin-aldosterone system inhibitors; No., number; HR, hazard ratio; CI, confidence interval; HHF, hospitalization for heart failure; PAOD, peripheral artery occlusive disease.

Figure S1. Distributional balance for propensity score before and after propensity-score matching