Impact of Previous Statin and Angiotensin II Receptor Blocker Use on Mortality in Patients Hospitalized with Sepsis

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Study Objective. To examine the effect of previous outpatient use of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) and/or angiotensin II receptor blockers (ARBs) on 30-day mortality in patients hospitalized with sepsis.

Design. Retrospective national cohort study.

Data Source. Department of Veterans Affairs (VA) national patient care and pharmacy databases.

Patients. A total of 3018 patients who were hospitalized with sepsis in fiscal year 2000, had at least 1 year of previous VA outpatient care, and had at least one active and filled VA prescription within 90 days of admission.

Measurements and Main Results. The primary outcome was 30-day mortality. The primary analysis was a multilevel model with hospital as a random effect and control variables that included comorbid conditions, demographics, and other drugs. Among the 3018 patients hospitalized with sepsis, mean age was 74.4 years, 2975 (98.6%) were male, and 811 (26.9%) died within 30 days of admission. Regarding prescription drug use, 480 patients (15.9%) were taking statins and 107 (3.5%) were taking ARBs. After adjusting for potential confounders, statin use (odds ratio [OR] 0.48, 95% confidence interval [CI] 0.36–0.64) and ARB use (OR 0.42, 95% CI 0.24–0.76) were significantly associated with decreased 30-day mortality.

Conclusions. Use of statins and/or ARBs before admission was associated with decreased mortality in patients hospitalized with sepsis. Further research is needed to determine if these drugs might be started on admission for those with sepsis.

Key Words: sepsis, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor, statin, angiotensin II receptor blocker, mortality.

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Sepsis is the 10th leading cause of death in the United States[1] and has a mortality rate of up to 70%.[2, 3] Inpatients with sepsis have a 26-fold increased risk for death compared with patients without sepsis who are in the intensive care unit.[3] New drugs are urgently needed to prevent or treat sepsis since only a few new classes of antibiotics have been added to the available drugs in the past 10 years, and only one new class of drug specifically targeting sepsis (drotrecogin alfa) has been added.[4]

Recently, several classes of drugs including 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) and angiotensin II receptor blockers (ARBs) have been found to attenuate the systemic inflammatory response.[5–13] Statins have been demonstrated to have protective endothelial effects and have also been proposed to influence the balance between endothelial nitric oxide and inducible nitric oxide to promote hemodynamic stability.[14] Several epidemiologic studies have demonstrated that patients receiving statins who

were hospitalized with bacteremia and community-acquired pneumonia had improved clinical outcomes or decreased frequency of sepsis[15–20]; however, we found no studies that examined the effect of ARB use on infectious disease–related outcomes. Further research is needed to clarify the roles and importance of these drugs in the treatment of patients with sepsis.

Thus, the objective of this study was to assess the effect of outpatient use of statins and ARBs on 30-day mortality in patients hospitalized with sepsis, after adjusting for other potential confounders.

Methods

This study was conducted with Department of Veterans Affairs (VA) administrative and outpatient pharmacy data from 19 of 22 VA health care networks that were collected as part of a larger study of inappropriate prescribing practices in the elderly.[21] The institutional review board of the University of Texas Health Science Center at San Antonio classified this as an exempt study.

Inclusion and Exclusion Criteria

Patients who were aged 65 years or older on October 1, 1999, had at least one outpatient clinic visit during fiscal year 1999 (October 1, 1998–September 30, 1999), were hospitalized during fiscal year 2000 with a primary or secondary discharge diagnosis of sepsis (*International Classification of Diseases, Ninth Edition,* code 038.xx),[22] and received at least one active and filled prescription within 90 days of admission, were included in this study. Analyses included only the first admission for patients with multiple sepsis-related hospitalizations.

Patients with a history of human immunodeficiency virus infection were excluded.

Data Source

This study used data from the VA's National Patient Care Database, the VA Pharmacy Benefit Management Group, and the Beneficiary Identification Records Locator Subsystem death file. Encrypted patient identifiers were used to link the information from each database for each patient.

Demographic information (age, sex, race-ethnicity, marital status) was obtained from inpatient and outpatient data (fiscal year 1998 through fiscal year 2000). Missing race-ethnicity data were supplemented by using self-reported race-ethnicity from the 1999 Large Health Survey of Veterans, a nationally representative survey of VA enrollees (July 1, 1999–January 1, 2000).[23] Race-ethnicity categories included Caucasian, African-American, Hispanic, and other or unknown.

Comorbid conditions were obtained from inpatient and outpatient administrative data. The Charlson Comorbidity Index score was used to control for preexisting comorbid conditions.[24, 25] The Charlson score is based on 19 comorbid conditions, each of which has an associated prognostic weight ranging from 1–6. The following comorbid conditions compose the Charlson score: myocardial infarction, angina, cardiac arrhythmia, hypertension, heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, ulcer disease, mild liver disease, diabetes mellitus, hemiplegia, moderate renal disease, any malignancy, moderate liver disease, metastatic solid tumor, and acquired immunodeficiency syndrome (an exclusion criterion in our study). Age was not included in the Charlson score.

Pharmacy data were obtained from the VA Pharmacy Benefits Management database. Data collected included the drug and dosage prescribed, date prescription was filled, and number of days supply. Use of a single drug at different dosages was considered one unique drug. Patients were considered a current user of a given drug if they

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had an adequate supply to last until the date of hospitalization, assuming an 80% compliance rate.[26] Drugs classified as statins were atorvastatin, cerivastatin, fluvastatin, lovastatin, pravastatin, and simvastatin. Drugs classified as ARBs were candesartan, cilexetil, irbesartan, losartan, telmisartan, and valsartan. To adjust for other potential confounding drugs, we used a count of individual drugs by class, which were refilled or filled within 90 days of admission. These classes included cardiac drugs (VA formulary classes CV050–CV900 excluding statins and ARBs), angiotensin-converting enzyme (ACE) inhibitors, antidiabetic drugs (VA formulary classes HS501 and HS502), and corticosteroids (VA formulary class IM600). Previous research has demonstrated that using the count of these drugs is superior to adjusting for the individual drugs or using a drug-based risk adjustment system such as the chronic disease score.[27]

In addition, we created categories for nonstatin lipid-lowering agents (e.g., niacin, bile acid sequestrants, and fibric acid derivatives) and respiratory agents (VA formulary classes RE101–RE900) filled within 90 days of hospital admission so as to examine confounding in our models.

Primary Outcome

We used 30-day mortality as the primary outcome for this study. Mortality was assessed by using the Beneficiary Identification Records Locator Subsystem death file and inpatient portion of the National Patient Care Database. Previous studies have demonstrated that after 1972, this methodology had a sensitivity of approximately 96% for veterans' deaths.[28]

Sample Size

Our sample size calculations were based on the use of statins since only a very small number of our patients were using ARBs. For our sample size calculations, we assumed the following: a 15% overall utilization of statins; that patients not taking statins had a 3-fold increased odds of 30-day mortality; sample size was further boosted to account for random effects of facility by a factor of 1.2; the squared multiple correlation among the covariates in the models was no more than 0.40; and type I error and power were set at 0.05 and 0.90, respectively. Therefore, we calculated that 2400 patients were needed to detect a significant mortality difference at 30 days.

Statistical Analyses

Bivariate statistics were used to test the association of sociodemographic characteristics, clinical characteristics, and drugs prescribed with all-cause 30-day mortality. Categoric variables were analyzed by using the χ^2 test, and continuous variables were analyzed with the Student *t* test. Angiotensin-converting enzyme inhibitor use was not significantly associated with 30-day mortality ($p=0.87$) in the bivariate analyses, so it was included only as a potential confounding drug in the rest of the analyses.

We included variables in the multilevel model if previous research demonstrated a relationship between a variable and sepsis-related mortality[2] or if the variable was significantly associated ($p\leq0.05$) with 30-day mortality or prescription for statins and/or ARBs in the bivariate analyses.

We analyzed time to death for patients for the two classes of drugs, statins and ARBs, both of which had a statistically significant association ($p<0.05$) with 30-day mortality in the bivariate analysis. We used separate Cox proportional hazard models to estimate, and graph, the baseline survivor functions after adjusting for the Charlson Comorbidity Index score, age, sex, marital status, race-ethnicity, and counts of potentially confounding drugs.

Our primary analysis used generalized linear mixed-effect models with patient's hospital as a random effect by using the Stata GLLAMM program[29] to estimate the impact of previous use of statins and ARBs on 30-day mortality. Use of ARBs and statins were the independent variables of interest. Potential confounders included in the models were Charlson Comorbidity Index score, age, sex, marital status, race-ethnicity, and counts of drugs from each class of potentially confounding drugs (cardiac drugs excluding ARBs and statins, antidiabetic drugs, ACE inhibitors, and corticosteroids). Interactions were assessed by using cross-product terms. No interaction terms, except between drug classes (cardiovascular and antidiabetic drugs), were statistically significant ($p<0.10$), so this was the only interaction term included in the final model.

We then examined the association of nonstatin lipid-lowering drugs or respiratory drugs with 30-day mortality after adjusting for potential confounders (including statin and ARB use) by using the same methodology as above. We hypothesized that these drugs would not be associated with mortality since they have not been demonstrated to have immunomodulatory

Table 1. Characteristics of the 3018 Patients with Sepsis by Use of Statins and/or Angiotensin II Receptor Blockers versus Nonuse of Either Drug

Characteristic	Statin and/or ARB Users (n=547)	Nonusers (n=2471)	p Value
Age (yrs), mean ± SD	73.1 ± 5.5	74.7 ± 6.2	<0.001
	No. (%) of Patients		
Male	535 (98)	2440 (99)	0.1
Race, ethnicity			
Caucasian	410 (75)	1667 (67)	
African-American	93 (17)	584 (24)	
Hispanic	30 (5)	160 (6)	
Other or unknown	14 (3)	60 (2)	0.004
Married	353 (65)	1306 (53)	<0.001
Charlson Comorbidity Index comorbid conditions			
Myocardial infarction	214 (39)	533 (22)	<0.001
Heart failure	292 (53)	1048 (42)	<0.001
Peripheral vascular disease	212 (39)	701 (28)	<0.001
Stroke	244 (45)	949 (38)	0.007
Chronic lung disease	248 (45)	1173 (47)	0.4
Peptic ulcer	68 (12)	372 (15)	0.1
Rheumatologic disease	18 (3)	135 (5)	0.04
Diabetes without complications	307 (56)	1130 (46)	<0.001
Diabetes with complications	181 (33)	533 (22)	<0.001
Dementia	39 (7)	360 (15)	<0.001
Mild liver disease	8 (2)	83 (3)	0.02
Moderate liver disease	5 (1)	62 (3)	0.02
Hemiplegia	62 (11)	231 (9)	0.2
Renal disease	124 (23)	593 (24)	0.5
Any malignancy	227 (42)	1042 (42)	0.8
Metastatic solid tumor	0 (0)	17 (1)	0.05

ARB = angiotensin II receptor blocker.

effects or have significant effects on mortality.

All analyses were performed with the Stata 8 software (StataCorp, College Station, TX).

Results

Of 142,169 patients who had an inpatient stay in 2000, 3018 patients (2.1%) met our inclusion and exclusion criteria. Mean ± SD age was 74.4 ± 6.1 years, 55% of patients were married, and 98.6% where male. In this cohort, 69% were Caucasian, 22% were African-American, 6% were Hispanic, and 3% unknown or other. In our cohort, 811 patients (27%) died within 30 days of presentation, and 1140 (38%) died within 90 days of presentation.

Table 1 shows patient characteristics stratified by users of statins and/or ARBs and by nonusers of either drug. Sociodemographic variables associated with statin and/or ARB use included younger age, Caucasian, and being married. Significant differences between groups were noted in several comorbid conditions: statin and/or ARB users were more likely to have a history of myocardial infarction, heart failure, peripheral vascular disease, stroke, diabetes without complications, and diabetes with complications; nonusers were more likely to have rheumatologic disease, dementia, mild or moderate liver disease, and metastatic cancer.

Table 2 shows patient characteristics and their relationship with 30-day mortality. Variables significantly associated with increased 30-day mortality in the bivariate analysis included increasing age, history of myocardial infarction, heart failure, stroke, peripheral vascular disease, chronic lung disease, dementia, and moderate liver disease. Diabetes without complications was associated with decreased 30-day mortality.

In our cohort, 480 patients (16%) were statin users, and 107 (4%) were ARB users. Both statin use and ARB use were significantly associated with lower 30-day mortality (Table 2).

Regarding other potentially confounding drugs, the mean ± SD number of cardiac drugs/patient in the 90 days before admission was 3.0 ± 3.1, antidiabetic drugs 0.6 ± 1.3, and

Table 2. Characteristics of the 3018 Patients with Sepsis by Vital Status at 30 Days After Admission

Characteristic	Alive at 30 Days (n=2207)	Died Within 30 Days (n=811)	p Value
Age (yrs), mean ± SD	74.1 ± 6.0	75.1 ± 6.1	<0.001
	No. (%) of Patients		
Male	2179 (99)	796 (98)	0.24
Race, ethnicity			
Caucasian	1518 (69)	559 (69)	
African-American	493 (22)	184 (23)	
Hispanic	139 (6)	51 (6)	
Other or Unknown	57 (3)	17 (2)	0.35
Married	1212 (55)	447 (55)	0.95
Charlson Comorbidity Index comorbid conditions			
Myocardial infarction	521 (24)	226 (28)	0.02
Heart failure	948 (43)	392 (48)	<0.001
Peripheral vascular disease	646 (29)	267 (33)	0.05
Stroke	848 (38)	345 (43)	0.04
Chronic lung disease	1015 (46)	406 (50)	0.05
Peptic ulcer	328 (15)	112 (14)	0.47
Rheumatologic disease	106 (5)	47 (6)	0.27
Diabetes without complications	1087 (49)	350 (43)	0.03
Diabetes with complications	541 (25)	173 (21)	0.07
Dementia	262 (12)	137 (17)	<0.001
Mild liver disease	64 (3)	27 (3)	0.54
Moderate liver disease	35 (2)	32 (4)	<0.001
Hemiplegia	213 (10)	80 (10)	0.86
Renal disease	530 (24)	188 (23)	0.63
Any malignancy	925 (42)	343 (42)	0.85
Metastatic solid tumor	10 (1)	7 (1)	0.18
Previous use			
Statins	401 (18)	79 (10)	<0.001
Angiotensin II receptor blockers	90 (4)	17 (2)	<0.001

corticosteroids 0.27 ± 0.7. In our population, 2264 patients (75%) received at least one other cardiovascular drug (excluding statins, ACE inhibitors, or ARBs), 483 (16%) received corticosteroids, and 845 (28%) received one or more antidiabetic drugs.

Figures 1 and 2 were created by using Cox proportional hazard models to estimate and graph the baseline survivor functions for statin use (Figure 1) and ARB use (Figure 2) over the first 30 days after admission. Both statin use and ARB use were significantly associated with decreased 30-day mortality (p<0.0001) after adjusting for potential confounders.

In the generalized linear mixed-effects model (Table 3), after adjusting for potential confounders and admitting hospital, use of a statin (odds ratio [OR] 0.48, 95% confidence interval [CI] 0.36–0.64) and use of an ARB (OR 0.42, 95% CI 0.24–0.76) were significantly associated with decreased 30-day mortality.

In our cohort, 918 patients (30%) received at least one respiratory drug and 85 (3%) received a nonstatin lipid-lowering drug. In the generalized linear mixed-effects model that examined nonstatin lipid-lowering drug use, there was no

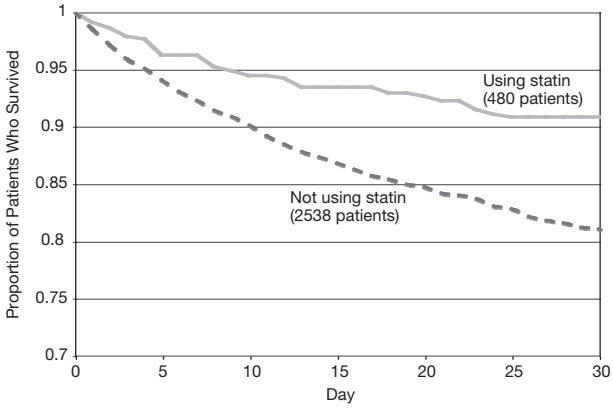

Figure 1. Proportion of surviving patients hospitalized with sepsis by use of a statin versus nonuse (p<0.0001).

Table 3. Results of the Generalized Linear Mixed-Effects Model with 30-Day Mortality as the Dependent Variable

Variable	Odds Ratio	95% Confidence Interval
Statin use	0.48	0.36–0.64
ARB use	0.42	0.24–0.76
Age (per yr)	1.02	1.01–1.13
Male	0.70	0.33–1.44
Married	1.09	0.90–1.30
Race, ethnicity		
African-American	0.97	0.76–1.23
Hispanic	0.79	0.50–1.16
Charlson Comorbidity Index score (per point)	1.07	1.04–1.10
Cardiovascular drugs	1.20	1.05–1.36
Antidiabetic drugs	1.04	0.77–1.41
Interaction term[a]	0.82	0.69–0.98

[a]Between antidiabetic and cardiovascular drugs.

significant association with mortality (OR 0.90, 95% CI 0.52–1.53). In the model that examined respiratory drugs, there was also no significant association with mortality (OR 1.05, 95% CI 0.84–1.31).

Discussion

We found that the use of statins and/or ARBs was associated with decreased 30-day mortality for patients hospitalized with sepsis. Our results support the findings of recent studies that patients hospitalized with bacteremia, sepsis, and/or pneumonia who were taking statins on admission had a significant reduction in mortality [15–18] or decreased rates of sepsis.[20] Several excellent review articles discuss potential mechanisms of statins on sepsis.[30, 31] In one study,[15] after adjustment for confounding factors, including comorbid conditions, age, concurrent drugs, site of infection, vital signs, and laboratory data, not taking a statin was significantly associated with mortality (OR 7.6, 95% CI 1.01–57.5). Our previous retrospective cohort study of patients hospitalized at two hospitals demonstrated that previous outpatient use of statins was associated with decreased pneumonia-related mortality (OR 0.36, 95% CI 0.14–0.92).[17] This previous research, combined with our current results, supports the need for randomized controlled trials to examine the impact of statins in the treatment of infectious diseases.

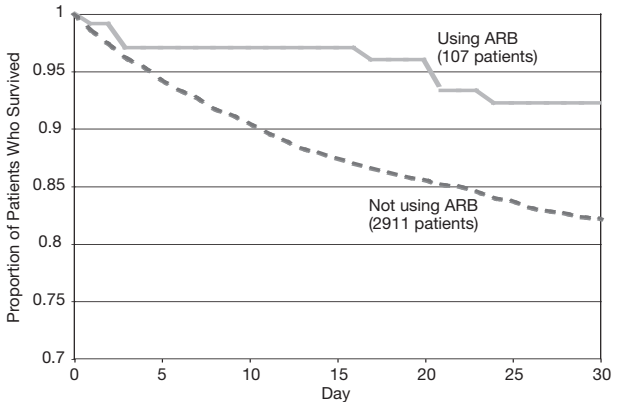

Figure 2. Proportion of surviving patients hospitalized with sepsis by use of an angiotensin II receptor blocker (ARB) versus nonuse ($p<0.0001$).

In addition, our study demonstrated a benefit from ARBs on sepsis-related mortality. Although there are several studies that demonstrate reduced levels of systemic inflammation for patients taking ARBs,[12, 13] we found no previous studies that have examined whether these drugs are associated with improved outcomes for patients with infectious diseases. Additional research should examine whether ARBs may have a role in the treatment of patients with serious infectious diseases such as sepsis.

The ACE inhibitors were also one of the initial drug classes examined. Previous data indicate that this class of drugs also has immunomodulatory effects,[32–36] and studies have demonstrated that ACE inhibitor use is protective for patients with pneumonia.[16, 37, 38] Therefore, we wanted to examine whether this protective association was related to sepsis (which is frequently the cause of death for patients with pneumonia) or the underlying pulmonary infection. From these results, which demonstrated no significant association between ACE inhibitor use and mortality, we believe that the previously demonstrated association between ACE inhibitor use and decreased mortality is not due to the effect on sepsis.

In our bivariate analyses, several variables including younger age, being Caucasian versus African-American or Hispanic, being married, and not having dementia were associated with use of statins or ARBs. These associations suggest the existence of a "healthy user" effect.[39] A strength of our study is that our cohort has the same access to medical care and to low- to no-cost prescriptions because of the structure of the VA health care system.[40] In addition, in models that examined respiratory and nonstatin lipid-lowering drugs, which we hypothesized would have no biologic plausible effect on sepsis, no significant association with mortality was noted. Finally, users of these drugs were also more likely

to have numerous comorbid conditions, including history of myocardial infarction, heart failure, and history of stroke, all of which are associated with increased mortality, which supports our hypothesis that these drugs are protective for those with sepsis. Future observational studies will need to adjust for these and other potential characteristics that may affect the prescription and use of these drugs.

Although our study was a large database analysis and subject to the recognized limitations of such studies, we carefully assembled our cohort from complete patient discharge data to avoid ascertainment bias. Our sample was predominantly men due to our use of VA administrative data, and it is possible, but unlikely, that women may have differential responsiveness to these drugs compared with men. Also, we were unable to assess factors such as inpatient continuation of these drugs or the effect of dosage because of the lack of availability of these data. Further research is needed to examine these factors. In addition, due to unavailability of the data, we were not able to adjust for whether or not patients received pneumococcal or influenza vaccinations. However, previous studies of vaccination in the elderly demonstrated only a mild effect on mortality,[41, 42] so we are unsure if this would have a significant effect on our results. Finally, as in any nonexperimental study, we are unable to state conclusively that the previous outpatient use of statins or ARBs is the cause of decreased mortality in this cohort.

Conclusion

Our study found that previous outpatient use of statins and ARBs reduces mortality in patients hospitalized with sepsis. These results add an additional potential benefit of statin and ARB use to their demonstrated benefits for patients with vascular and renal disease. Randomized clinical trials are needed to elucidate whether statins and/or ARBs may have a role in the treatment of patients hospitalized with sepsis.

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