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Chronic Statin Use and Long-Term Rates of Sepsis: A Population-Based Cohort Study

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Abstract

PURPOSE—“Statins” have immunomodulatory and anti-inflammatory effects and may attenuate the risk of infections. We sought to determine the association between chronic statin use and long-term rates of sepsis events.

MATERIALS AND METHODS—We used data from 30,183 adult (≥ 45 years old) community-dwelling participants in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) cohort. The primary exposure was statin use. The primary outcome was

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AUTHORSHIP

HEW, GH and MMS conceived the study. HEW and MMS organized and oversaw data collection. HEW, NIS, MMS and GH obtained funding for the study. HEW and RG conducted the analysis, and all authors contributed to review of results. HEW drafted the manuscript, and all authors contributed to its editorial review and revision. HEW assumes responsibility for the work as a whole.

CONFLICTS OF INTEREST

Dr. Safford reports the following potential conflicts of interest: Amgen - salary support to study patterns of statin use in Medicare and other large databases; diaDexus - salary support for a research grant on lipids and CHD outcomes; diaDexus - consulting to help with FDA application; NIH, AHRQ - salary support for research grants Drs. Wang, Griffin, Shapiro and Howard do not report any related conflicts of interest.

hospitalization or Emergency Department treatment for sepsis. Using Cox proportional hazards models, we determined associations between statin use and first sepsis events, adjusting for subject demographics, health behaviors, chronic medical conditions, degree of medication adherence, baseline high sensitivity C-reactive protein (hsCRP) and propensity for statin use.

RESULTS—Approximately one-third of participants reported statin use (n=9,475, 31.4%). During the ten-year follow-up period 2003–2012, there were 1,500 incident sepsis events. Statin use was not associated with rates of sepsis after multivariable adjustment for demographics, health behaviors, chronic medical conditions, medication adherence, abnormal hsCRP, and propensity for statin use; HR 0.93 (95% CI: 0.81–1.06). Statin use was similarly not associated with rates of sepsis when stratified by propensity for statin use or medication adherence.

CONCLUSIONS—In the REGARDS cohort, statin use at baseline was not associated with rates of future sepsis events.

Keywords

sepsis; infections; statins; epidemiology

INTRODUCTION

Sepsis, the syndrome of microbial infection complicated by systemic inflammation, is a major public health problem associated with significant morbidity and mortality.¹ The substantial national burden of severe sepsis care in the US encompasses 750,000 hospital admissions, 570,000 Emergency Department visits, 200,000 deaths and \$16.7 billion in medical expenditures annually.^{2–4}

Originally developed to reduce cholesterol levels, HMG-CoA reductase inhibitors (“statins”) also appear to modulate immune response and attenuate the pathophysiologic responses of sepsis.^{5–10} These findings have led to the hypothesis that statins may exert a protective effect in patients with infections or sepsis. For example, statin users admitted to the hospital for acute infections exhibit reduced morbidity and mortality compared with non-statin users.^{5,11–21} However, these prior studies have focused exclusively on acutely ill individuals and the use of statins as a form of *secondary prevention* or *acute therapy*, to mitigate the progression of sepsis. There have been few examinations of the influence of chronic statin use on long-term community-acquired sepsis susceptibility in healthy individuals. Such an association would suggest a potential role for chronic statin use in the *primary prevention* of sepsis.

The Reasons for Geographic and Racial Differences in Stroke (REGARDS) study is one of the largest population-based cohorts of community-dwelling individuals in the United States.²⁸ In this study we sought to determine the association between chronic statin use and long-term rates of sepsis events in the REGARDS cohort.

METHODS

Study Design

We utilized data from the longitudinal population-based REGARDS cohort. The study received approval by the Institutional Review Board of the University of Alabama at Birmingham.

Selection of Participants

REGARDS is one of the largest ongoing national cohorts of community-dwelling individuals in the US, encompassing 30,239 individuals ≥45 years old.²⁸ Designed to evaluate reasons for geographic and racial variations in stroke mortality, REGARDS includes individuals from all regions of the continental US. Participant representation included over-sampling from the Southeastern US, with 21% of the cohort originating from the coastal plains of North Carolina, South Carolina and Georgia (the “buckle” of the stroke belt), and 35% originating from the remainder of North Carolina, South Carolina and Georgia plus Tennessee, Mississippi, Alabama, Louisiana and Arkansas (the “stroke belt”). The cohort is 45% male and 42% African American and does not include Hispanics. Approximately 69% of individuals were ≥60 years old at enrollment.

REGARDS enrolled participants during 2003–7, obtaining baseline data for each participant using both computer-assisted telephone interview and in-person evaluations. Participant baseline characteristics included medical history, functional status, health behaviors, physical characteristics (height, weight), physiologic measures (blood pressure, pulse, electrocardiogram), and an inventory of medications. Each participant provided blood and urine specimens. Self-administered questionnaires evaluated diet, family history of diseases, psychosocial factors and prior residences. On a semi-annual basis, study personnel contact each participant to determine the date, location and attributed reason for all hospitalizations during the follow-up interval. The study team also reviews death certificates and related medical records and interviews proxies to ascertain the circumstances of the participant deaths.

Identification of Sepsis Events

Using published taxonomies, we identified all hospitalizations and Emergency Department visits attributed by participants to a serious infection.^{2,3} Two abstractors independently reviewed all relevant medical records to confirm the presence of a serious infection on initial hospital presentation. The abstractors also confirmed that the serious infection was a major reason for hospitalization. Discordances were resolved by abstractor consensus, with additional physician-level review as needed.

We defined sepsis as presentation to the hospital with an infection plus two or more systemic inflammatory response syndrome (SIRS) criteria, including 1) heart rate >90 beats/minute, 2) fever (temperature >38.3°C or <36°C), 3) tachypnea (>20 breaths/min) or PCO₂<32 mmHg, and 4) leukocytosis (white blood cells [WBC] >12,000 or <4,000 cells/mm³ or >10% band forms). We examined vital signs and laboratory test results for the initial 28-hours of hospitalization to encompass Emergency Department care and up to one full day of

inpatient treatment. Because of our focus on “community acquired” sepsis, we did not examine vital signs or laboratory findings from later time points, or sepsis developing at later phases of hospitalization. Initial review of 1,349 hospital records indicated excellent inter-rater agreement for presence of a serious infection ($\kappa=0.92$) and the presence of sepsis ($\kappa=0.90$) upon hospital presentation.

We did not include organ dysfunction in the primary definition of sepsis. However, in the sensitivity analysis, we did examine the secondary outcomes severe sepsis, defined as sepsis + organ dysfunction. We also studied sepsis hospital death, defined as death after sepsis hospitalization.

Covariates - Definition of Statin Use

At the initial interview, REGARDS obtained an inventory of all medications used by participants. Specific statins reported by subjects included atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, and simvastatin. The study did not account for changes in medication patterns over time.

Other covariates examined in the study included sociodemographic characteristics, health behaviors, chronic medical conditions, baseline high sensitivity C-reactive protein (hsCRP), and the Morisky Medication Adherence Scale. Sociodemographic characteristics included age, sex, race, geographic region, self-reported annual household income and self-reported education (years of school). Geographic region included participant residence in the stroke “buckle,” stroke “belt,” and elsewhere, as defined for the REGARDS recruitment sampling strategy.²⁸ Health behaviors included tobacco and alcohol use. Smoking status included current, past and never. Based upon National Institute on Alcohol Abuse and Alcoholism classifications, alcohol use included none, moderate (1 drink per day for women or 2 drinks per day for men) and heavy (>1 drink per day for women and >2 drinks per day for men).²⁹

Evaluated chronic medical conditions included history of obesity, diabetes, dyslipidemia, hypertension, stroke, myocardial infarction, coronary artery disease, atrial fibrillation, deep vein thrombosis, peripheral artery disease, chronic kidney disease and chronic lung disease. We defined obesity as participants with large waist circumference or obese body mass index (BMI). Weight, height and waist circumference were measured during initial subject examination at the beginning of the REGARDS study. Calculated as weight/height^2 (kg/m^2), we categorized BMI as underweight ($<18.5 \text{ kg/m}^2$), normal ($18.5\text{--}25.0 \text{ kg/m}^2$), overweight ($25.0\text{--}29.9 \text{ kg/m}^2$), obese ($30\text{--}39.9 \text{ kg/m}^2$), and morbidly obese ($\geq 40 \text{ kg/m}^2$).³⁰ Determined with the subject standing, waist circumference (WC) was measured midway between the lowest rib and the iliac crest, with normal WC defined as $\leq 102 \text{ cm}$ for males and $\leq 88 \text{ cm}$ for females and large WC as $>102 \text{ cm}$ for males and $>88 \text{ cm}$ for females.³¹

Diabetes included a fasting glucose $\geq 126 \text{ mg/L}$ (or a glucose $\geq 200 \text{ mg/L}$ for those not fasting) or the use of insulin or oral hypoglycemic agents. Dyslipidemia included individuals with self-reported high cholesterol or the use of lipid lowering medications. Hypertension consisted of systolic blood pressure $\geq 140 \text{ mm Hg}$, diastolic blood pressure $\geq 90 \text{ mm Hg}$, or the self-reported use of antihypertensive agents. Stroke consisted of the self-reported history of stroke. Myocardial infarction included individuals with a self-reported history of

myocardial infarction or baseline electrocardiographic evidence of myocardial infarction. Coronary artery disease consisted of individuals with a self-reported history of myocardial infarction, coronary intervention or baseline electrocardiographic evidence of myocardial infarction.

Chronic kidney disease consisted of an estimated glomerular filtration rate <60 ml/min/1.73m^{2.32} Because REGARDS did not collect information on pulmonary conditions such as asthma and chronic obstructive pulmonary disease, we considered participant use of pulmonary medications as a surrogate for chronic lung disease. Obtained from each participant's medication inventory, pulmonary medications included beta agonists, leukotriene inhibitors, inhaled corticosteroids, combination inhalers, and other pulmonary medications such as ipratropium, cromolyn, aminophylline and theophylline.

hsCRP was determined by particle-enhanced immunonephelometry. In contrast with conventional CRP assays, the hsCRP technique is able to detect levels as low as 0.04 mg/L. Consistent with prior cardiovascular studies, we defined elevated baseline hsCRP as >3.0 mg/L.³³ We previously identified an association between baseline hsCRP and rates of sepsis.³⁴

For sepsis hospitalizations, we identified organ dysfunctions using the Sequential Organ Failure Assessment (SOFA) using the worst laboratory and physiologic findings during the first 28-hours of hospitalization for respiratory, renal, hepatic, cardiovascular, hematologic, and neurologic systems.³⁵

During initial interview for the REGARDS study, participants reported medication adherence using the four-question version of the Morisky Medication Adherence Scale, which provides a measure of individual compliance with medication use.³⁶ (Appendix 1) We defined medication adherence as 0=good, 1=fair, and 2–4=poor.

Data Analysis

We compared differences in participant baseline characteristics between baseline statin users and non-users using the chi-square test.

Although individual statin use is influenced by cardiovascular risk, past reports suggest that statin users in general are healthier than non-users.^{37,38} Observational studies may therefore find apparent protective effects of statins that may reflect the healthier nature of statin users relative to non-users ("healthy user effect"), and not true statin effects *per se*.³⁹ Because of this likely influence in the present study, we defined a propensity score to reflect the propensity for baseline statin use for each study subject.^{40,41} We calculated the propensity score using the "pscore" module of Stata, specifying a logit model. Initial efforts using an unparsimonious model with all defined clinical covariates failed to satisfy the balancing property.⁴⁰ However, a propensity score based upon obesity, dyslipidemia, diabetes, myocardial infarction and elevated hsCRP satisfied the balancing property.

We conceptualized that the association between baseline statin use and rates of sepsis may be influenced by the participant's propensity for statin use, demographics, health behaviors, chronic medical conditions, degree of medication adherence, and baseline hsCRP. We

therefore fit a sequence of multivariable Cox proportional hazards models examining the association of baseline statin use with risk of first sepsis event, sequentially adjusting for each of the relevant covariates. Because they were used for propensity score estimation, we excluded obesity, diabetes, hypercholesterolemia, history of myocardial infarction, and abnormal hsCRP from the multivariable models. We censored participants who died before their first sepsis event or who were lost to follow-up. We excluded individuals with missing outcome, exposure or confounder values.

To verify the robustness of the findings, we repeated the analysis stratifying by propensity score tertiles (corresponding to low, medium, high propensity for statin use).^{40,42–44} We also repeated the analysis stratified by categories of Morisky medication adherence (0, 1 and 2–4, corresponding to good, fair and poor medication adherence). We verified the proportional hazard assumption by examining log-log and observed vs. predicted survival plots, testing Schoenfeld residuals, and fitting a model with statin use as a time-varying covariate. We verified the absence of collinearities by examining Variance Inflation Factors.

Many studies have evaluated the association between statin use and the severity of or mortality after sepsis.^{16,17,19,20,45–48} In a sensitivity analysis of sepsis hospitalizations only, we examined the association between statin use and 1) severe sepsis, and 2) hospital death after sepsis. We conducted the sensitivity analysis using multivariable logistic regression, adjusting for participant's propensity for statin use, demographics, health behaviors, chronic medical conditions, degree of medication adherence, baseline hsCRP, and Mortality of Emergency Department Sepsis (MEDS) score.⁴⁹

We performed the analysis using Stata v.12.1 (Stata, Inc., College Station, Texas).

RESULTS

From February 5, 2003 through December 31, 2012, among the 30,183 REGARDS participants included in the analysis, a total of 1,500 individuals experienced a sepsis event; of these first-sepsis events, 1,089 (72.6%) met severe sepsis criteria and 138 (9.2%) resulted in hospital death. (Figure 1) Median follow-up time was 6.6 years (IQR 5.1–8.1 years). Among the first sepsis events, the most common infection types were pneumonia, kidney and urinary tract infections, and abdominal infections. (Table 1)

Approximately, one-third of REGARDS participants were baseline statin users (n=9,475, 31.4%). Statin users were more likely to be older, female and white. (Table 2) Although statin users were more likely to have chronic medical conditions, they were less likely to have elevated hsCRP (>3.0 mg/dL). Statin users reported higher Morisky medication adherence.

Overall the cohort accounted for 186,420 person-years and 1,498 first sepsis events (sepsis incidence = 8.0 per 1,000 person-years, 95% CI: 7.6–8.5). (Figure 2) Statin users accounted for 58,412 person-years and 552 first sepsis events (incidence 9.5 per 1,000 person-years, 95% CI: 8.7–10.3), and non-statin users accounted for 128,008 person-years and 946 first sepsis events (incidence 7.4 per 1,000 person-years, 95% CI: 6.9–7.9).

On bivariate analysis, baseline statin use was associated with increased risk of first sepsis events. (Table 3) However, statin use was no longer associated with rates of sepsis after multivariable adjustment for propensity score, demographics, health behaviors, chronic medical conditions, abnormal hsCRP and medication adherence (adjusted HR 0.93; 95% CI: 0.81–1.06).

Multiplicative [statin $\times$ propensity score] and [statin $\times$ Morisky Scale] interactions were not statistically significant. When stratified by propensity score tertile, statin use was not associated with rates of sepsis after adjustment for confounders. While not associated with rates of sepsis for individuals with fair or poor medication adherence, statin use showed a tendency towards a protective effect in the subgroup with good medication adherence.

Among first sepsis hospitalizations, the presence of severe sepsis was not associated with statin use after adjustment for confounders and MEDS score (OR 1.34; 95% CI: 0.95–1.90). Hospital death after sepsis was not associated with statin use, after adjustment for confounders and MEDS score (OR 0.72; 95% CI: 0.42–1.23).

DISCUSSION

Based upon data from a large population-based cohort of community dwelling adults in the United States, we found that baseline statin use was not associated with the long-term rates of future sepsis events. This observation persisted after adjustment for a host of clinical confounders, including propensity for statin use as well as medication adherence. Furthermore, among first sepsis events, statin use was not associated with the presence of severe sepsis or sepsis hospital death.

To understand the importance and novelty of these findings, one must understand the three potential roles for statins in sepsis treatment: 1) primary prevention (preventing an individual from acquiring sepsis), 2) secondary prevention (continuation of statin use in acutely ill individuals to limit progression to severe sepsis or death), and 3) acute treatment (initiation of statin use to reduce sepsis-induced morbidity and mortality).²⁷ Our study clearly falls into the primary prevention category. However in contrast to other studies of primary sepsis prevention, our unique study was able to characterize the association of *baseline chronic statin use* with *long-term rates of community-acquired sepsis in healthy community-dwelling adults*.

Mermis and Simpson provide a comprehensive review of the role of statins in sepsis treatment and prevention.²⁷ Most studies characterized as primary prevention efforts 1) have been retrospective, 2) included only intensive care unit or hospitalized inpatients, and 3) focused on sepsis progression or mortality as endpoints.^{16–20,26,45–48} Furthermore, these studies characterized statin use retrospectively, hence addressing “current” statin use versus “chronic” statin use evaluated in our study. For example, Yende, et al. and Murugan, et al. studied 1,895 patients hospitalized for community acquired pneumonia, finding no association between prior statin use (reported by the patient) and 90-day survival or rates of acute kidney injury.^{18,45} In a study of 121,254 pneumonia inpatients, Rothberg, et al. found that statin use was associated with reduced mortality, but statin use was defined as drug

administration on day 1 or 2 of hospitalization.¹⁶ While our primary analysis focused on susceptibility to community acquired sepsis, in secondary analyses limited to first sepsis hospitalizations, we found no association between chronic statin use and severe sepsis or hospital death.

Select studies do have closer resemblance to our analysis. Gupta, et al. prospective studied a cohort of 1,041 dialysis patients in the United States Renal Data System; over a mean follow-up period of 3.4 years, statin users were less likely to be hospitalized for sepsis (HR 0.38; 95% CI: 0.21–0.67).²³ Using claims data from Ontario, Canada, Hackam, et al. studied 69,168 individuals hospitalized for acute coronary syndrome, ischemic stroke or revascularization; over a mean follow-up period of almost 4 years, rates of sepsis were lower for statin users than non-users (HR 0.81; 95% CI: 0.72–0.90).²⁴ The JUPITER trial randomized 18,802 individuals to statins or placebo; in a two-year follow-up of trial participants, Novack, et al. found that the risk of pneumonia was lower among those randomized to rosuvastatin (HR 0.81; 95% CI 0.67–0.97); however, infections were identified from adverse event reports, not active surveillance.^{26,50}

Our analysis has important contrasts with these prior studies. REGARDS is a large population-based cohort of community-dwelling adults. Our study was not limited to individuals admitted to the hospital or to cohorts with significant comorbidities such as end-stage renal disease. We were able to follow subjects for over 10 years, exceeding the observation period of the prior studies.

Unlike the Novack, et al. study, we examined a range of sepsis events – not just pneumonia.²⁶ We also identified sepsis events through prospective review of medical records; we did not rely upon hospital discharge diagnoses to identify sepsis events. Observational studies of medication usage and outcomes may be influenced by confounding by indication or “healthy user” effects.⁴¹ Unlike the prior studies, we were better able to account for propensity for statin use as well as medication adherence.

Could statin use still play a role in reducing rates of sepsis? In our prior efforts we have found that rates of sepsis are associated with a host of cardiovascular medical conditions, including diabetes, coronary artery disease, dyslipidemia and atrial fibrillation.^{51,52} It is possible that statins may indirectly reduce rates of sepsis by mediating the adverse influences of these related factors. We observed that statin use did show a slight tendency towards reduced rates of sepsis in the subgroup reporting good medication adherence. If additional studies were to confirm the protective effect of statins against sepsis, we would expect this association to be more prominent among those demonstrating good medication compliance. Additional studies must clarify this relationship.

LIMITATIONS

Our analysis assumed that REGARDS participants continued statin use throughout the entire 10 year follow-up period. However, statin use may have varied over time, with select individuals ceasing - or initiating - the medication. These potential misclassifications may have led to over- or under-estimates of the protective effects of statin use. Because of the

design of the study, we could not ascertain changes in statin use over time. However, REGARDS is one of the few cohorts with the design necessary to evaluate the long-term risk of sepsis associated with chronic statin use, and thus our study reflects the best data currently available. Other studies have retrospectively identified statin use on hospital admission, but this approach does not allow evaluation of the long-term effects of long-term statin use. We tried to mitigate the effects of statin misclassification by controlling for medication adherence. REGARDS is in the process of re-interviewing all participants, and thus in the future it may be possible to ascertain changes in statin use in the cohort.

While we applied numerous analytic strategies to compensate for confounding by indication, there may be unmeasured or immeasurable confounders related to statin use.^{41,53} While the multivariable models indicate a range of characteristics associated with sepsis susceptibility, in this analysis these covariates were intended for risk adjustment only. Identification of subject characteristics independently associated with sepsis is beyond the scope of this analysis.

By design, the REGARDS cohort includes only African Americans and whites, and thus these results may not generalize to other ethnic groups. We did not examine the association between statin use and sepsis in racial or geographic subgroups. Also, our study was able to detect the presence of chronic medical conditions but not their level of severity. The data did not have information on history of immunocompromise. We focused on community acquired sepsis – our study did not evaluate sepsis developing at later points of hospitalization. While a small portion of patients received Emergency Department treatment only (without hospital admission), we verified through review of medical records that all of these individuals fulfilled sepsis criteria. While some variables had missing values, the frequency of missingness was relatively limited. Because REGARDS is not a surveillance study, we may not have detected all sepsis events.

CONCLUSION

In this large national cohort of community dwelling adults, baseline statin use was not associated with long-term rates of sepsis.

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APPENDIX 1

Elements of the 4-item Morisky Medication Adherence Scale.³⁶

1. Do you ever forget to take your medicine?
2. Are you careless at times about taking your medicine?
3. When you feel better, do you sometimes stop taking your medicine?
4. Sometimes if you feel worse when you take the medicine, do you stop taking it?

APPENDIX 2

Full multivariable Cox regression model evaluating association between statin use and sepsis hospitalization.

Variable	Hazard Ratio (95% CI)
Statin Use	0.93 (0.81–1.06)

Variable	Hazard Ratio (95% CI)
Demographics	
Age (mean $\pm$ SD)	1.02 (1.02–1.03)
Sex	
Male	1.30 (1.15–1.48)
Female	Referent
Race	
White	Referent
Black	0.70 (0.61–0.80)
Geographic Region	
Non-Belt	Referent
Belt	1.26 (1.11–1.44)
Buckle	1.22 (1.05–1.43)
Income	
<\$20,000	Referent
\$20,000–34,000	0.85 (0.72–1.00)
\$35,000–74,000	0.71 (0.59–0.84)
\$75,000	0.61 (0.47–0.77)
Unknown	0.67 (0.54–0.83)
Education	
Less than high school	Referent
High school graduate	0.95 (0.79–1.14)
Some college	0.98 (0.81–1.18)
College or higher	0.81 (0.67–1.00)
Health Behaviors	
Tobacco Use	
Never	Referent
Past	1.26 (1.11–1.44)
Current	1.73 (1.46–2.06)
Alcohol Use	
None	Referent
Moderate	0.82 (0.72–0.94)
Heavy	0.85 (0.62–1.17)
Chronic Medical Conditions	
Atrial Fibrillation	1.40 (1.18–1.66)
Chronic Kidney Disease	1.75 (1.52–2.03)
Chronic Lung Disease	2.06 (1.78–2.39)
Coronary Artery Disease	1.27 (1.10–1.46)
Deep Vein Thrombosis	1.24 (1.01–1.54)
Hypertension	1.24 (1.09–1.41)
Peripheral Artery Disease	1.35 (1.00–1.83)
Stroke	1.27 (1.04–1.54)
Morisky Medication Adherence Scale	

Variable	Hazard Ratio (95% CI)
0 (Good)	Referent
1 (Fair)	1.01 (0.88–1.16)
2–4 (Poor)	1.27 (1.04–1.55)
Missing	
Propensity Score	
Tertile 1	Referent
Tertile 2	1.37 (1.16–1.61)
Tertile 3	1.07 (0.91–1.26)

APPENDIX 3

Full multivariable Cox regression model evaluating association between statin use and sepsis hospitalization, stratified by propensity for statin use. Statin use propensity defined by propensity score tertiles: high = propensity score 0.43; medium = propensity score 0.09–0.43; low = propensity score <0.09.

Variable	High Propensity Hazard Ratio (95% CI)	Medium Propensity Hazard Ratio (95% CI)	Low Propensity Hazard Ratio (95% CI)
Statin Use	0.93 (0.79–1.11)	0.90 (0.71–1.14)	0.82 (0.47–1.42)
Demographics			
Age (mean $\pm$ SD)	1.01 (1.00–1.02)	1.04 (1.02–1.05)	1.03 (1.02–1.05)
Sex			
Male	1.27 (1.05–1.53)	1.37 (1.08–1.72)	1.26 (0.97–1.62)
Female	Referent	Referent	Referent
Race			
White	Referent	Referent	Referent
Black	0.76 (0.62–0.92)	0.56 (0.44–0.71)	0.78 (0.60–1.02)
Geographic Region			
Non-Belt	Referent	Referent	Referent
Belt	1.11 (0.92–1.34)	1.31 (1.03–1.68)	1.54 (1.19–1.99)
Buckle	1.29 (1.04–1.60)	1.28 (0.95–1.71)	0.96 (0.68–1.37)
Income			
<\$20,000	Referent	Referent	Referent
\$20,000–34,000	0.93 (0.73–1.18)	0.90 (0.67–1.21)	0.69 (0.49–0.97)
\$35,000–74,000	0.74 (0.56–0.96)	0.63 (0.45–0.89)	0.77 (0.54–1.10)
\$75,000	0.77 (0.55–1.08)	0.42 (0.25–0.71)	0.52 (0.31–0.87)
Unknown	0.59 (0.42–0.83)	0.79 (0.54–1.15)	0.69 (0.45–1.05)
Education			
Less than high school	Referent	Referent	Referent
High school graduate	0.96 (0.73–1.26)	0.98 (0.71–1.35)	0.85 (0.57–1.27)
Some college	1.06 (0.80–1.40)	0.87 (0.62–1.21)	0.94 (0.63–1.40)

Variable	High Propensity Hazard Ratio (95% CI)	Medium Propensity Hazard Ratio (95% CI)	Low Propensity Hazard Ratio (95% CI)
College or higher	0.93 (0.70–1.25)	0.78 (0.54–1.12)	0.65 (0.43–1.01)
Health Behaviors			
Tobacco Use			
Never	Referent	Referent	Referent
Past	1.22 (1.02–1.48)	1.21 (0.94–1.55)	1.38 (1.05–1.82)
Current	1.44 (1.10–1.88)	1.44 (1.04–2.00)	2.83 (2.03–2.95)
Alcohol Use			
None	Referent	Referent	Referent
Moderate	0.72 (0.59–0.87)	0.99 (0.77–1.26)	0.83 (0.63–1.09)
Heavy	0.70 (0.42–1.19)	1.04 (0.59–1.85)	0.93 (0.54–1.60)
Chronic Medical Conditions			
Atrial Fibrillation	1.40 (1.11–1.77)	1.46 (1.07–2.00)	1.31 (0.89–1.94)
Chronic Kidney Disease	1.87 (1.53–2.28)	1.59 (1.21–2.08)	1.68 (1.18–2.40)
Chronic Lung Disease	1.97 (1.58–2.46)	2.14 (1.64–2.79)	2.12 (1.57–2.87)
Coronary Artery Disease	1.36 (1.13–1.63)	1.12 (0.87–1.44)	1.56 (0.87–2.80)
Deep Vein Thrombosis	1.34 (0.999–1.79)	1.38 (0.95–2.00)	0.83 (0.47–1.47)
Hypertension	1.28 (1.06–1.56)	1.21(0.95–1.55)	1.17 (0.91–1.50)
Peripheral Artery Disease	1.30 (0.88–1.92)	1.47 (0.80–2.69)	1.53 (0.71–3.28)
Stroke	1.38 (1.07–1.78)	1.001 (0.95–1.55)	1.32 (0.83–2.11)
Morisky Medication Adherence Scale			
0 (Good)	Referent	Referent	Referent
1 (Fair)	1.03 (0.85–1.25)	1.03 (0.79–1.33)	0.91 (0.67–1.23)
2–4 (Poor)	1.18 (0.87–1.61)	1.48 (1.04–2.09)	1.18 (0.78–1.79)

APPENDIX 4

Full multivariable Cox regression model evaluating association between statin use and sepsis hospitalization, stratified by Morisky Medication Adherence (0 = Good, 1 = Fair, 2–4= Poor).

Variable	Good Medication Adherence Hazard Ratio (95% CI)	Fair Medication Adherence Hazard Ratio (95% CI)	Poor Medication Adherence Hazard Ratio (95% CI)
Statin Use	0.83 (0.71–0.98)	1.15 (0.88–1.51)	1.21 (0.78–1.87)
Demographics			
Age (mean ± SD)	1.03 (1.02–1.04)	1.02 (1.00–1.04)	1.02 (0.999–1.04)
Sex			
Male	1.37 (1.18–1.60)	1.18 (0.90–1.54)	1.02 (0.66–1.57)
Female	Referent	Referent	Referent
Race			
White	Referent	Referent	Referent

Variable	Good Medication Adherence Hazard Ratio (95% CI)	Fair Medication Adherence Hazard Ratio (95% CI)	Poor Medication Adherence Hazard Ratio (95% CI)
Black	0.67 (0.57–0.79)	0.81 (0.61–1.06)	0.70 (0.47–1.06)
Geographic Region			
Non-Belt	Referent	Referent	Referent
Belt	1.25 (1.07–1.47)	1.17 (0.89–1.53)	1.54 (1.01–2.35)
Buckle	1.32 (1.10–1.59)	0.92 (0.65–1.31)	1.19 (0.67–2.11)
Income			
<\$20,000	Referent	Referent	Referent
\$20,000–34,000	0.87 (0.72–1.06)	0.80 (0.57–1.14)	0.82 (0.49–1.36)
\$35,000–74,000	0.71 (0.57–0.89)	0.72 (0.49–1.06)	0.57 (0.31–1.04)
\$75,000	0.61 (0.45–0.82)	0.67 (0.41–1.11)	0.33 (0.12–0.92)
Unknown	0.60 (0.46–0.79)	0.72 (0.46–1.12)	0.98 (0.54–1.78)
Education			
Less than high school	Referent	Referent	Referent
High school graduate	0.89 (0.71–1.12)	0.89 (0.61–1.29)	1.68 (0.92–3.09)
Some college	1.02 (0.81–1.28)	0.75 (0.51–1.12)	1.47 (0.77–2.84)
College or higher	0.82 (0.64–1.05)	0.64 (0.42–0.97)	1.37 (0.68–2.73)
Health Behaviors			
Tobacco Use			
Never	Referent	Referent	Referent
Past	1.24 (1.06–1.45)	1.33 (1.01–1.76)	1.31 (0.82–2.07)
Current	1.80 (1.46–2.23)	1.32 (0.88–1.97)	2.34 (1.40–3.94)
Alcohol Use			
None	Referent	Referent	Referent
Moderate	0.78 (0.66–0.91)	1.03 (0.78–1.36)	0.72 (0.45–1.16)
Heavy	0.75 (0.50–1.12)	1.24 (0.69–2.21)	1.02 (0.36–2.87)
Chronic Medical Conditions			
Atrial Fibrillation	1.38 (1.13–1.70)	1.48 (1.04–2.10)	1.39 (0.81–2.39)
Chronic Kidney Disease	1.84 (1.55–2.19)	1.73 (1.26–2.37)	1.28 (0.75–2.21)
Chronic Lung Disease	2.06 (1.71–2.47)	2.16 (1.61–2.92)	1.98 (1.26–3.12)
Coronary Artery Disease	1.34 (1.13–1.58)	1.06 (0.79–1.43)	1.38 (0.85–2.24)
Deep Vein Thrombosis	1.10 (0.83–1.45)	1.70 (1.14–2.55)	1.10 (0.59–2.07)
Hypertension	1.30 (1.11–1.52)	1.08 (0.83–1.42)	1.21 (0.79–1.87)
Peripheral Artery Disease	1.32 (0.89–1.97)	1.13 (0.63–2.03)	2.57 (1.14–5.80)
Stroke	1.20 (0.95–1.53)	1.58 (1.08–2.33)	1.001 (0.50–2.02)
Propensity Score			
Tertile 1	Referent	Referent	
Tertile 2	1.31 (1.08–1.60)	1.48 (1.03–2.12)	1.41 (0.82–2.43)
Tertile 3	1.06 (0.87–1.29)	1.14 (0.80–1.64)	0.93 (0.51–1.68)

FIGURE 1.
Overview of study population, statin use, sepsis events and sepsis outcomes.

FIGURE 2. Kaplan-Meier survival curves depicting proportion of REGARDS cohort sepsis-free over 10 years of follow-up, stratified by statin use.

TABLE 1

Infection types associated with first hospitalizations for sepsis. Includes both uncomplicated and severe sepsis. Total of 1,500 first sepsis events.

Infection Type	Number of First Sepsis Hospitalizations N (%)
Pneumonia	592 (39.5)
Kidney and Urinary Tract Infections	251 (16.7)
Abdominal	230 (15.3)
Bronchitis, Influenza and other Lung Infections	137 (9.1)
Skin and Soft Tissue	121 (8.1)
Sepsis	98 (6.5)
Fever of Unknown Origin	50 (3.3)
Surgical Wound	10 (0.7)
Catheter (IV/Central/Dialysis)	6 (0.4)
Meningitis	5 (0.3)

TABLE 2

Baseline characteristics of REGARDS participants, stratified by statin use.

Participant Characteristic	Statin Non-User (n=20,708) N (col %)	Statin User (n=9,475) N (col %)	P-value
Demographics			
Age (mean $\pm$ SD)	64 (10)	67 (9)	<0.001
Sex			
Male	8,756 (42)	4,795 (51)	<0.001
Female	11,952 (58)	4,680 (49)	
Race			
White	11,817 (57)	5,852 (62)	<0.001
Black	8,891 (43)	3,623 (38)	
Geographic Region			
Non-Belt	9,171 (44)	4,258 (45)	<0.001
Belt	7,333 (35)	3,114 (33)	
Buckle	4,204 (20)	2,103 (22)	
Income			
<\$20,000	3,783 (18)	1,695 (18)	0.009
\$20,000–34,000	4,952 (24)	2,355 (25)	
\$35,000–74,000	6,061 (29)	2,853 (30)	
\$75,000	3,358 (16)	1,396 (15)	
Unknown	2,554 (12)	1,176 (12)	
Education			
Less than high school	2,503 (12)	1,289 (14)	<0.001
High school graduate	5,244 (25)	2,560 (27)	
Some college	5,646 (27)	2,444 (26)	
College or higher	7,300 (35)	3,172 (33)	
Missing	15 (0.1)	10 (0.1)	
Health Behaviors			
Tobacco Use			
Never	9,714 (47)	3,890 (41)	<0.001
Past	7,697 (37)	4,370 (46)	
Current	3,215 (16)	1,181 (12)	
Missing	82 (0.4)	34 (0.4)	
Alcohol Use			
None	12,679 (61)	5,868 (62)	0.05
Moderate	6,765 (33)	3,091 (33)	
Heavy	857 (4)	330 (3)	
Missing	407 (2)	186 (2)	
Chronic Medical Conditions			
Atrial Fibrillation	1,581 (8)	1,012 (11)	<0.001
Chronic Kidney Disease	1,820 (9)	1,471 (16)	<0.001
Chronic Lung Disease	1,710 (8)	1,055 (11)	<0.001

Participant Characteristic	Statin Non-User (n=20,708) N (col %)	Statin User (n=9,475) N (col %)	P-value
Coronary Artery Disease	2,244 (11)	3,070 (32)	<0.001
Deep Vein Thrombosis	993 (5)	589 (6)	<0.001
Diabetes	3,557 (17)	3,257 (34)	<0.001
Dyslipidemia	8,706 (42)	8,522 (90)	<0.001
Hypertension	11,062 (53)	6,785 (72)	<0.001
Myocardial Infarction	1,741 (8)	2,032 (21)	<0.001
Obesity (abnormal BMI or WC)	10,584 (51)	5,559 (59)	<0.001
Peripheral Artery Disease	336 (2)	336 (4)	<0.001
Stroke	998 (5)	932 (10)	<0.001
High Sensitivity C-Reactive Protein			
3.0 mg/dL	11,224 (54)	5,534 (58)	<0.001
>3.0 mg/dL	8,154 (39)	3,317 (35)	
Missing	1,330 (6)	624 (7)	
Morisky Medication Adherence Scale			
0 (Good)	12,963 (63)	6,286 (66)	<0.001
1 (Fair)	3,757 (18)	2,310 (24)	
2–4 (Poor)	1,427 (7)	660 (7)	
Missing	2,561 (12)	219 (2)	

TABLE 3

Multivariable hazard ratios for associations between statin use and rates of first-sepsis events. Total of 1,500 first-sepsis events. Propensity score for statin use based upon history of obesity, hyperlipidemia, diabetes, myocardial infarction, and high sensitivity C-reactive protein ≥ 3.0 mg/dL; these variables were not included in the main multivariable models. Full multivariable models presented in Appendices 2–4.

Model	Crude Hazard Ratio for Sepsis (95% CI)	Adjusted Hazard Ratio for Sepsis (95% CI)
Full Cohort (n=27,312)	1.28 (1.15–1.42)	0.93 (0.81–1.06) [*]
Stratified by Propensity for Statin Use		
High Propensity for Statin Use (0.43 propensity score; n=12,132)	1.20 (1.02–1.41)	0.93 (0.79–1.11) [†]
Medium Propensity for Statin Use (0.09 propensity score <0.43; n=6,159)	1.08 (0.87–1.34)	0.90 (0.71–1.14) [†]
Low Propensity for Statin Use (propensity score <0.09; n=9,021)	1.17 (0.71–1.94)	0.82 (0.47–1.42) [†]
Stratified by Morisky Medication Adherence		
Good Medication Adherence (Morisky Scale=0; n=19,249)	1.10 (0.97–1.26)	0.83 (0.71–0.98) [‡]
Fair Medication Adherence (Morisky Scale=1; n=6,067)	1.46 (1.17–1.82)	1.15 (0.88–1.51) [‡]
Poor Medication Adherence (Morisky Scale= 2–4; n=2,087)	1.39 (0.97–1.98)	1.21 (0.78–1.87) [‡]

^{*} Adjusted for subject demographics, health behaviors, chronic medical conditions, Morisky medication adherence and propensity for statin use.

[†] Adjusted for subject demographics, health behaviors, chronic medical conditions and Morisky medication adherence.

[‡] Adjusted for subject demographics, health behaviors, chronic medical conditions and propensity for statin use.