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Impact of statins and ACE inhibitors on mortality for subjects hospitalized with pneumonia

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ABSTRACT

Recent studies suggest that statins and ACE inhibitors may have beneficial effects for some types of infections. The purpose of our study was to examine the association of outpatient use of these medications on 30-day mortality for subjects > 65 years of age hospitalized with community-acquired pneumonia.

We conducted a retrospective national cohort study conducted using Department of Veterans Affairs administrative data including subjects ≥65 years of age hospitalized with community-acquired pneumonia, and having at least one year of prior Veterans Affairs outpatient care.

We identified 8652 subjects with a mean age of 75 years, 98.6% were male, and 9.9% of subjects died within 30-days of presentation. In this cohort, 18.1% of subjects were using statins and 33.9% were using ACE inhibitors. After adjusting for potential confounders, current statin use (odds ratio 0.54, 95% confidence interval 0.42-0.70) and ACE inhibitor use (0.80, 0.68-0.89) were significantly associated with decreased 30-day mortality.

Use of statins and ACE inhibitors prior to admission is associated with decreased mortality in subjects hospitalized with community-acquired pneumonia. Randomized controlled trials are needed to examine whether the use of these medications in patients hospitalized with community-acquired pneumonia may be beneficial.

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INTRODUCTION

Pneumonia and influenza together are the seventh leading cause of death and the leading causes of infectious death in the United States [1]. For those > 65 years of age the rate of hospitalizations and deaths due to pneumonia are increasing even though for all other age groups they are decreasing [2]. Although mortality due to community-acquired pneumonia decreased significantly with the introduction of antibiotics in the 1950s, since that time mortality has been stable and hospitalizations are increasing [2]. Despite this, only a few new classes of antibiotics have been added to the armamentarium for treating community-acquired pneumonia in the last 20 years and only one new class of medications (drotrecogin alfa) has been added [3].

Cytokines play an important role in host defense mechanisms for subjects with community-acquired pneumonia but under certain conditions may lead to septic shock or acute respiratory distress syndrome [4-6]. Recent studies have demonstrated that HMG-CoA reductase inhibitors ("statins") and angiotensin converting enzyme (ACE) inhibitors have significant immunomodulatory effects and reduce systemic cytokine levels [7-11]. In addition, several studies have demonstrated that for subjects hospitalized with bacteremia, diabetic lower extremity infections, or community-acquired pneumonia, those subjects who were taking statins or ACE inhibitors at presentation had a significantly decreased odds of death [12-15], or decreased rates of severe sepsis [16, 17]. However, other studies have shown either no association with mortality or increased mortality with the use of these medications in subjects with infectious diseases. [12, 18, 19].

The study aims were to assess the association of the use of statins and ACE inhibitors on 30-day mortality for subjects > 65 years of age hospitalized with community-acquired pneumonia after adjusting for other potential confounders using the administrative databases of the Department of Veterans Affairs (VA), and to examine the impact of the prior statin and ACE inhibitor use on mortality for subjects hospitalized with pneumonia during the influenza season.

METHODS

This study was conducted with VA inpatient and outpatient administrative data that was collected as part of a larger study of inappropriate prescribing practices in the elderly [20]. 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

Subjects who were a) aged 65 and older on October 1 1999, b) had at least one outpatient clinic visit during fiscal year (FY) 1999 (October 1 1998—September 30 1999), c) were hospitalized during FY 2000 with a primary discharge diagnosis of pneumonia or influenza (ICD-9 codes 480.0-483.99 or 485-487) and d) received at least one active and filled medication within 90-days of admission were included in this study. Previous research has validated the use of these ICD-9 codes for identifying cases of CAP [21-23]. We excluded subjects with a history of human immunodeficiency virus (HIV) or who received chemotherapeutic agents within 90-days of presentation. If a subject was

admitted more than once during the study period due to pneumonia, only the first hospitalization was included.

Data

This study used data from the National Patient Care Database at the Austin Automation Center, pharmacy data from the VA Pharmacy Benefit Management group, and vital status data from the Beneficiary Identification Records Locator Subsystem death file and inpatient portion of the National Patient Care Database.

Demographic information (age, sex, race) was obtained from inpatient and outpatient data. Missing race data were supplemented using self-reported race from the 1999 Large Health Survey of Veterans, a nationally representative survey of VA enrollees (July 1, 1999—January 1, 2000 [24]. Race categories included white, black, Hispanic, and other/unknown. In addition, we utilized information on the VA means test as a surrogate for income, and use of geriatric clinics in preceding year as a potential indicator of patient frailty.

Comorbid conditions were obtained from inpatient and outpatient administrative data. Charlson's comorbidity score was used to assign a comorbidity score for preexisting comorbid conditions [25, 26]. Charlson's comorbidity score is based on 19 comorbid conditions each of which has an associated prognostic weight, which ranges from 1 to 6. Age was not included in the Charlson score.

Pharmacy data were obtained from the Pharmacy Benefits Management group databases. Subjects were considered a current user of a given medication if they had enough pills to last until the date of hospitalization assuming an 80% compliance rate. Medications classified as statins were atorvastatin, cerivastatin, fluvastatin, lovastatin, pravastatin, and simvastatin. Medications classified as ACE inhibitors were benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, quinapril, and ramipril. To further control for potential confounding by medications, a count of unique drugs in each of the following classes per patient was calculated for drugs refilled/filled within 90-days of presentation: cardiac medications (excluding statins, ACE inhibitors, and non-statin lipid lowering agents), and diabetic medications. A dichotomized variable for was created for corticosteroid use. Previous research has demonstrated that using the count of these medication classes is preferable to adjusting for the individual medications [27].

In addition, we created a category of non-statin lipid lowering agents (e.g., niacin, bile acid sequestrants, and fibric acid derivatives) filled within 90-days of hospital presentation so as to examine confounding in our models.

Outcome

We used 30-day mortality as the primary outcome for this study. Previous research has demonstrated that 30-day mortality is primarily due to the community-acquired pneumonia rather than other co-existing co-morbid conditions [28]. Mortality was assessed using the Beneficiary Identification Records Locator Subsystem and the

National Patient Care Database. Previous studies have demonstrated that after 1972 this methodology had a sensitivity of ~96% for veterans' deaths [29].

Sample Size

For our sample size calculations we assumed: (i) a 15% overall utilization of statins and ACE inhibitors; (ii) that subjects not on statins had a 2.8 x increased odds, and for ACE inhibitors 2.3 x increased odds, of 30-day mortality based on our previous studies [14, 15]; (iii) sample sizes were further boosted to account for the random effects by a factor of 1.2 or less; (iv) the squared multiple correlation among the covariates in the models is no more than 0.40; and (v) type I error and power are set at 0.05 and 0.90, respectively. Therefore we calculated that overall 4,256 subjects were needed in the statin cohort, and 3,620 in the ACE inhibitor cohort, to have 90% probability to detect a significant mortality difference at 30-days.

Statistical Analyses

Bivariate statistics were used to test the association of sociodemographic and clinical characteristics with all-cause 30-day mortality. Categorical variables were analyzed using the Chi-square test and continuous variables were analyzed using Student's t-test.

A propensity score technique was used to balance covariates associated with medication use between groups [30-32]. We created separate propensity scores for statins, ACE inhibitors, and to examine potential confounding, non-statin lipid lowering medications. The propensity score was derived from a logistic regression model. We included

variables in the propensity score if previous research demonstrated a relationship between a variable and pneumonia-related mortality [33, 34], if we hypothesized that it may be related to prescription of the medications, or if the variable was significantly associated ($p \leq 0.05$) with 30-day mortality or prescription of ACE inhibitors and/or statins in the bivariate analyses. The covariates included in the propensity score models were age, gender, race, being married, VA means test, classes of medications and the Charlson composite score (without age). Classes of medications included cardiac medications (excluding ACE inhibitors, statin, and non-statin lipid lowering medications), diabetic medications, and corticosteroids. We then created an ordered categorical variable based on a quintile stratification of the propensity score to include in the Cox and regression models.

To analyze time-to-death (starting at the time of hospital admission) for subjects by medication use (statin or ACE inhibitor) we used Cox proportional hazard models to estimate, and graph, the baseline survivor functions after adjusting for the respective propensity score.

Our primary analysis employed generalized linear mixed-effect models with patient's hospital as a random effect using STATA's GLLAMM program [35]. We created separate models with either ACE inhibitors or statin use as the independent variables of interest, and adjusting for the appropriate propensity score. In addition, to examine the impact of the medications of interest on pneumonia secondary to influenza, we split the population by whether the patient was hospitalized during a period that influenza was

endemic. Those who were admitted between October 1 1999 and March 31 2000, which according to the Centers for Disease Control and Prevention was the period with almost all of the influenza cases during our study period [36], were considered to be during the influenza season while those hospitalized during other periods were considered to be not related to influenza. We repeated both of the generalized linear mixed-effect models to examine whether statins or ACE inhibitors were associated with decreased mortality for those hospitalized during the influenza season.

We used a similar methodology to examine the association of non-statin lipid lowering drugs with 30-day mortality after adjusting for potential confounders using the appropriate propensity scores. We hypothesized that non-statin lipid lowering medications would not be associated with mortality since they have not been demonstrated to have immunomodulatory effects.

All analyses were performed using STATA 8 (College Station, Texas).

RESULTS

Of the patients who had an inpatient stay in 2000 (n=142,169), 8652 subjects (6.1%) met our inclusion criteria. The mean age was 75.2 years with a standard deviation (SD) of 6.1 years, 54.5% of subjects were married, and 98.6% were male. In this cohort 13.5% were black, 78.7% were white, 5.3% were Hispanic, and 2.5% were other/unknown. In our cohort 9.9% of the subjects died within 30-days of presentation, and 17.2% died within

90-days of presentation. Table 1 shows the variables examined by use of statins and/or ACE inhibitors versus non-users of either.

In our cohort 18.1% (n=1567) were on statins and 33.9% (n=2930) were on ACE inhibitors. There were 2161 subject who were only receiving ACE inhibitors, 769 on both ACE inhibitors and statins, and 798 who were receiving only statins. In the bivariate analyses, both statin (10.9% vs. 5.0%, $p<0.001$) and ACE inhibitor use (11% vs. 7.8%, $p<0.0001$) were both significantly associated with decreased 30-day mortality. There was a significant difference in both statin and ACE inhibitor use by age group with younger subjects more likely to have received the medication(s) of interest. For statins 22.5% of subjects 65-74 years, 15.5% of those 75-84, and 6.2% for those >85 years of age received statins. While 35.6% of subjects 65-74, 33.2% for those 75-84, and 27.0% of those >85 years of age received ACE inhibitors. When we stratified by age group comparing use of the medications of interest and 30-day mortality there was a survival benefit for those taking the medications of interest for each group (Table 2).

Figures 1 and 2 were created using Cox proportional hazard models to estimate, and graph, the baseline survivor functions for statin use (Figure 1) and ACE inhibitor use (Figure 2) over the first 30-days after admission. Both statin and ACE inhibitor use were significantly associated with improved 30-day survival ($p<0.0001$).

In the generalized linear mixed-effect models, after adjusting for the appropriate propensity score and admitting hospital, prior use of a statin (odds ratio (OR) 0.54, 95%

confidence interval (CI) 0.42-0.70) or ACE inhibitor use (0.80, 95% CI 0.68-0.89) were significantly associated with decreased 30-day mortality. **When we included the variables used in the propensity score separately in the respective regression models the odds ratios (and confidence intervals) for statin or ACE inhibitors were very similar to the prior results (statins OR 0.57, 95% CI 0.45-0.73 and ACE inhibitor use OR 0.84, 95% CI 0.72-0.98).**

In addition, to examine whether there were interactions between statins and ACE inhibitors, we re-ran our model with 3 medication variables (statin use only, ACE inhibitor use only, both statins and ACE inhibitors) and the individual potential confounders, rather than the propensity score. We found that all 3 groups were associated with decreased mortality: ACE inhibitors alone (OR 0.84, 95% CI 0.70-1.00), statins alone (0.58, 0.42-0.80), and those using both (0.45, 0.31- 0.66).

Among subjects who were hospitalized during the influenza season (n=5379) we reran both of the generalized linear mixed-effect models and found that statin use was still significantly associated with decreased 30-day mortality (OR 0.52, 95% CI 0.38-0.73), but ACE inhibitor (OR 0.92, 95% CI 0.75-1.15) use was not significantly associated with mortality.

In the generalized linear mixed-effect model that examined non-statin lipid lowering medication use there was no significant association with mortality (OR 0.97, 95% CI 0.51-1.83)

DISCUSSION

We found that prior outpatient use of statins and ACE inhibitors was associated with decreased 30-day mortality for subjects > 65 years of age hospitalized with community-acquired pneumonia. This group is uniquely subject to increasing incidence of pneumonia and pneumonia-related mortality. In addition, we found that, when we restricted our analyses to those subjects hospitalized with pneumonia during the influenza season, there continued to be decreased mortality for those who used a statin. Further studies, including randomized controlled trials, are needed to examine the impact of statins and ACE inhibitors, both pre-hospitalization and acute, on subjects hospitalized with community-acquired pneumonia and influenza.

Our study supports the findings of the recent studies which demonstrated that subjects hospitalized with bacteremia and pneumonia who were on statins at admission had a significant reduction in in-hospital or 30-day mortality [12-16]. In the study by Liappis et al.[12], after adjustment for confounding factors (including comorbid conditions, age, concurrent medications, site of infection, vital signs, and laboratory data), not being on a statin (odds ratio 7.6, 95% confidence interval 1.01-57.5) was significantly associated with mortality. Our previous retrospective cohort study of subjects hospitalized with community-acquired pneumonia demonstrated that prior outpatient use of statins was associated with decreased pneumonia-related mortality (odds ratio 0.36, 95% confidence interval 0.14-0.92) [14].

Our results do not support the recent study by Majumdar, et al. [19], which showed that statins were not associated with improved outcomes for patients with pneumonia. Although this study had a prospectively derived cohort with rich clinical data, there were several problems with this study including a failure to assess interactions and multicollinearity in the face of counter-intuitive results. For example, their findings that age > 65 years, ischemic heart disease, and using levofloxacin are protective against in-hospital mortality and ICU admission , or that pneumonia severity index [33] class III has an OR 2.45, have not been previously reported.

Regarding the use of ACE inhibitors, our results suggest that although they may be protective for some subjects with pneumonia there does not appear to be a benefit for those who have pneumonia secondary to influenza. The protective effect seen in this study and others [15] may be due to ACE inhibitors increasing serum levels of substance P, which is hypothesized to lead to a better gag reflex and increased clearance of secretions [37], rather than immunomodulatory effects [9-11]. In addition, ACE inhibitors have also been demonstrated to have pulmonary protective effects [38] and two recent studies demonstrated that a genetic polymorphism associated with increased activity of the renin-angiotensin system is also associated with increased incidence of acute respiratory distress syndrome [39] or higher mortality from ARDS [40]. Although it appears that statins have a stronger effect upon pneumonia-related mortality, future research should still examine the impact of both classes of medications on infectious disease-related outcomes.

We found that in the bivariate analyses several variables including lower age, being married, and not having dementia or history of malignancy were associated with use of statins or ACE inhibitors. These associations suggest the possible existence of a "healthy user" effect [41]. A strength of our study is that our cohort has the same access to medical care, and low to no-cost prescriptions due to the structure of the VA health care system [42]. In addition, we adjusted for these sociodemographic characteristics and comorbid conditions in our models. Future observational studies need to adjust for these, and other potential characteristics, that may impact the prescription and use of these medications.

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 statins as compared to men. Also we are unable to assess factors such as inpatient continuation of the statins or the dose effect due to the lack of availability of these data. Further research is needed to examine these factors. Also we are unable to specifically examine the impact of statin use on subjects with influenza due to the infrequent testing for this condition and the fact that it is an infrequently coded discharge diagnosis [43]. However, since we found a protective association when we examined those who were hospitalized with pneumonia during the influenza season, it is possible that statins may be beneficial for those at high-risk of death due to influenza. Finally, as in any non-experimental study, we are unable to state conclusively that the

prior outpatient use of statins is the cause of decreased mortality in this cohort. However, since subjects on statins have numerous medical conditions that are significantly associated with increased short-term mortality, and our analyses were adjusted for several factors that are associate with patient frailty or "healthy user bias", we feel that we have good evidence that these medications may have beneficial effects for subjects hospitalized with community-acquired pneumonia.

In conclusion, our study finds that prior outpatient use of statins, and to a lesser extent ACE inhibitors, are associated with lower mortality for subjects hospitalized with community-acquired pneumonia. These results suggest that there may be an additional benefit of statin and ACE inhibitor use to the already compelling data for their use in subjects with vascular disease and diabetes. Randomized trials are needed to confirm the magnitude of the impact of statin and ACE inhibitor use, either pre-hospitalization or acute, on subjects hospitalized with community-acquired pneumonia and to elucidate the mechanism(s) by which they may work.

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Table 1: Characteristics of subjects (N=8,652) with pneumonia by use of statin and/or ACE inhibitors versus non-use of either medication*

Variables	Users of statins or ACE inhibitors (N= 3728)	Non-users (N=4924)	P-value
Age	74.6 ± 5.9	75.7 ± 6.3	< 0.001
Men	3669 (98)	4858 (99)	0.4
Race			
White	2941 (79)	3869 (79)	
Black	491 (13)	680 (14)	
Hispanic	206 (6)	256 (5)	
Other/Unknown	90 (2)	119 (2)	0.8
Married	2181 (59)	2523 (51)	< 0.001
Charlson Comorbid Conditions			
Myocardial infarction	1115 (30)	687 (14)	< 0.001
Congestive heart failure	2184 (59)	1552 (32)	< 0.001
Peripheral vascular disease	1138 (31)	1013 (21)	< 0.001
Stroke	1322 (35)	1356 (28)	< 0.001
Chronic lung disease	2689 (72)	3457 (70)	0.05
Peptic ulcer	547 (15)	678 (14)	0.2

Rheumatologic disease	202 (5)	273 (6)	0.8
Mild liver disease	60 (2)	101 (2)	0.1
Diabetes	1767 (47)	1268 (26)	< 0.001
Dementia	351 (9)	663 (14)	< 0.001
Diabetes with complications	797 (21)	417 (8)	< 0.001
Moderate Liver disease	18 (0.5)	34 (1)	0.2
Hemiplegia	171 (5)	227 (5)	0.9
Renal disease	485 (13)	429 (9)	< 0.001
Any malignancy	1436 (39)	2088 (42)	< 0.001
Metastatic solid tumor	283 (8)	542 (11)	< 0.001

*Data are presented as number (%) or mean $\pm$ standard deviation

Table 2- 30-day mortality by statin or ACE inhibitor use stratified by age group

Age group	Statin use		ACE inhibitor use	
	Yes	No	Yes	No
65-74	4.3%	9.2%	6.0%	9.2%
75-84	6.1%	11.2%	8.8%	11.2%
>85	5.4%	20.0%	15.4%	20.5%

Figure 1- Proportion of surviving patients hospitalized with CAP by use of statin versus non-use (p<0.0001)

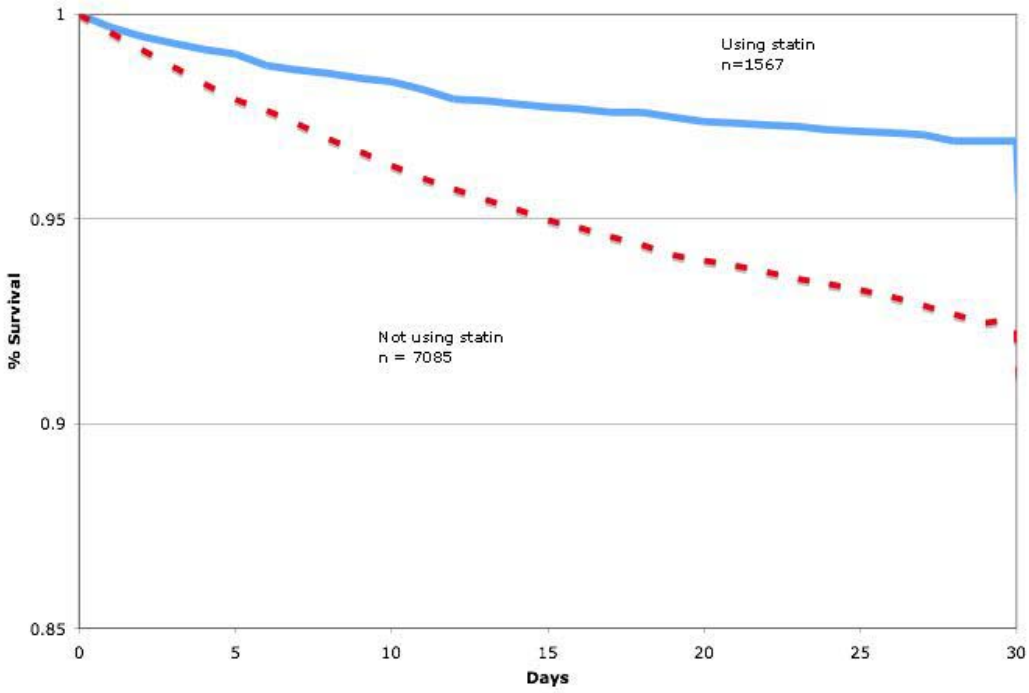

Figure 2- Proportion of surviving patients hospitalized with CAP by use of ACE inhibitor versus non-use (p<0.0001)