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Statin use and medically attended acute respiratory illness among influenza vaccine recipients

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ABSTRACT

Background: Previous studies have suggested that statins decrease influenza vaccine effectiveness and increase risk of medically attended acute respiratory illness (MAARI).
Objectives: To examine the association of incident statin use and MAARI in a cohort of influenza vaccine recipients.
Methods: This retrospective cohort study evaluated influenza vaccine recipients within the Tricare population. The primary outcome compared MAARI incidence during the follow-up period in a propensity score-matched cohort of incident statin users and statin non-users. Secondary analysis included propensity score-adjusted comparisons between incident statin users and statin non-users in the entire cohort and prespecified sub-cohorts with and without comorbidities. The propensity score was derived from 72 variables encompassing demographics, medical history, comorbidities, medication use, and healthcare utilization.
Results: MAARI incidence in statin users was similar to non-users in the propensity score-matched cohort (odds ratio [OR] 0.92; 95% confidence interval [CI] 0.84–1.01). In contrast, statin users with lower comorbidity had lower OR for MAARI compared to non-users (Charlson Score zero cohort: 0.85 [CI 0.74–0.98]; No Diabetes cohort: 0.88 [CI 0.80–0.96]).
Conclusion: Incident statin use was not associated with increased MAARI incidence and may be associated with lower incidence of MAARI in those with less comorbidity. This study thus offers reassurance regarding the effectiveness of the influenza vaccine in statin users.

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1. Introduction

Despite efforts to expand vaccination against influenza virus and improvements in its medical management, morbidity and mortality from influenza continues to be high, particularly among older populations [1]. Statins are among the most commonly prescribed medications for primary and secondary prevention of cardiovascular diseases. Possibly mediated by immuno-modulatory effects through induction of regulatory T lymphocytes [2–4], statins have recently been reported to decrease influenza vaccine efficacy as measured by various parameters including higher rates of confirmed H3N2 influenza cases [5], a higher incidence of medically attended acute respiratory illness (MAARI) [6], and reduced serum antibody responses to the influenza vaccine [7,8].

In contrast, several earlier studies had reported decreased mortality from influenza and pneumonia among statin users [9–11], although some analyses proposed that these beneficial effects could largely be explained by a healthy user bias [12]. Additionally, a recent analysis of the US Vaccine Effectiveness Network study over 6 influenza seasons found no difference in influenza vaccine

Abbreviations: ACE/ARB, angiotensin-receptor blockers & angiotensin converting enzyme inhibitors; AHRQ-CCS, Agency for Health Research and Quality-Clinical Classifications Software; FY, Fiscal year; MAARI, Medically attended acute respiratory illness; MDR, Military Health System Data Repository; MHS, Military Health System; NSAID, non-steroidal anti-inflammatory drugs; PASBA, Patient Administration Systems & Biostatistics Activity; PDTS, Pharmacy Data Transaction Service; TMA, Tricare Management Activity office.

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effectiveness against laboratory-confirmed influenza in statin users older than 45 years old [13]. Based on these conflicting results in the literature, some experts have debated whether to withhold statins prior to influenza vaccine administration or to consider different augmented vaccination strategies [14]. Such questions bear particular relevance for statin users who are only receiving statins for primary prevention of cardiovascular diseases and who are at the lower spectrum of cardiovascular risk.

This study examined the association of incident statin use with MAARI incidence in a large cohort of influenza vaccine recipients within an integrated healthcare system with similar access and availability of healthcare to minimize socioeconomic confounders [15,16].

2. Methods

After obtaining permission from the Tricare Management Activity office (TMA), we extracted national Tricare archival data from fiscal year (FY) 2002 to FY 2005 (10/1/2001 to 9/30/2005) from the Military Health System (MHS) Data Repository (MDR). Tricare is the health care program for the United States (US) Department of Defense, which covers service members and enrolled veterans and their families. The MDR contains patients' demographic information, all outpatient and inpatient medical encounters (including those at non-military health facilities), and the Pharmacy Data Transaction Service (PDTS), which tracks all drug utilization regardless of pharmacy location. MDR data are managed according to a published and approved protocol to ensure raw data integrity and quality [17,18]. To comply with Tricare Data Sharing Agreement, all data were de-identified, including rounding dates of medical encounters to the nearest quarter of the year.

The Patient Administration Systems & Biostatistics Activity (PASBA) at Fort Sam Houston, TX extracted data of patients registered in Tricare and actively receiving care throughout the study registration period and who had a medical encounter during FY 2005. Two treatment groups were identified: Incident statin users and non-users. We defined incident statin users as patients who newly filled a statin prescription during FY 2005 and continuously filled a statin prescription during FY 2005 for a cumulative duration of at least 360 days to ensure actual medication intake throughout the vaccination period and influenza season since our TMA agreement required that all dates be rounded to the nearest quarter of the year. We excluded all patients who had already received statins in FY 2002–2004; such an incident user design minimizes the impact of healthy user bias [19]. We also required that incident statin users to have received statins only in FY 2005 (based on search of PDTS through FY 2011) to allow better comparability in comorbid conditions between incident statin users and non-users, since studies have shown that short-term statin users frequently lack the comorbidities that accompany longer term statin use [20,21]. Statin non-users were defined as those patients who never received a statin throughout the study registration period. Since the number of these patients was very large, we limited non-users to those who had medical encounters in the first 6 months of FY 2005.

Patients who received influenza vaccination during the first half of FY 2005 (October 1, 2004 to March 31, 2005) were identified. We identified receipt of influenza vaccination using Current Procedural Terminology (CPT), International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) procedural codes, and Healthcare Common Procedure Coding System (HCPCS) administrative codes (Appendix). We further limited the study to patients aged between 35 and 85 years of age.

Baseline data were derived from the beginning of FY 2002 (October 1, 2001) to the quarter of FY2005 in which the patient had received influenza vaccination (index quarter). The period during which outcomes were captured lasted from the index quarter until the end of the third quarter of FY 2005 (June 30, 2005). We selected this end date to ensure capture of all relevant outcomes because Centers for Disease Control and Prevention (CDC) data indicated continuing activity in the month of April 2005 for that influenza season [22].

Our outcome was occurrence of MAARI based on inpatient or outpatient ICD-9-CM during the follow-up period (Appendix). MAARI is a commonly used indicator of the population impact of influenza and has been validated and widely used in studies of real-world influenza vaccine effectiveness [6,14,23–25].

2.1 Statistical analyses

Patients' comorbidities at baseline were identified using ICD-9-CM codes as defined by the Agency for Health Research and Quality-Clinical Classifications Software (AHRQ-CCS) [26]. Patients' Charlson comorbidity total score was calculated using Deyo's method [27]. Baseline characteristics also included several measures of healthcare utilization such as number of inpatient and outpatient medical encounters, and cumulative number of hospital bed days during the baseline period. We also captured the occurrence of MAARI during baseline period and receipt of influenza vaccination in prior years.

We used a propensity score approach to match incident statin users to similar statin non-users based on 72 variables including: demographics, personal history, comorbidities [26], healthcare utilization, use of different medication classes [28], receipt of influenza vaccination in prior years, and MAARI occurrence in the baseline period (Table 1). We then used logistic regression to create a propensity score and performed nearest number matching with a caliper of 0.01, as described previously [29–33]. After matching, we compared differences in baseline characteristics between groups using chi-square for categorical variables and Student's *t* test for continuous variables.

For our primary analysis, we used conditional logistic regression to calculate odds ratio (OR) and 95% confidence intervals (95% CI) of MAARI incidence in the propensity score-matched cohort. One of the limitation of propensity score matching is that it decreases the sample size. Therefore, we performed secondary analysis that encompassed all individuals that fulfilled inclusion and exclusion criteria. For secondary analyses, we examined the MAARI incidence (OR) using propensity score-adjusted logistic regression with statin use and the propensity score as covariates in the model, in several prespecified cohorts:

1. Overall cohort: This cohort included all patients who met the study inclusion and exclusion criteria before propensity score matching.
2. No comorbidity cohort (Charlson score zero): In this subcohort, we excluded patients who had Charlson comorbidity score greater than zero.
3. No-MAARI at baseline cohort: In this subcohort, we excluded patients who had previous MAARI event during the baseline period.
4. MAARI at baseline cohort: In this subcohort, we only included patients who had previous MAARI event during the baseline period.
5. No-diabetes at baseline cohort: In this subcohort, we excluded patients who had diabetes at baseline period.
6. Diabetes at baseline cohort: In this subcohort, we only included patients who had diabetes at baseline period.

We also performed the following post-hoc analyses to further explore the association of statin use and MAARI:

Table 1
Baseline characteristics of propensity score-matched incident statin users and non-users.

	Non-users (N = 6264)	Statin users (N = 6264)	p-value
Age in years: mean (SD)	64.2 (10.5)	64.0 (10.5)	0.44
Female sex: n (%)	3538 (56.5)	3542 (56.5)	0.94
Health care use: n (%) unless otherwise noted			
Number of inpatient admissions during baseline period: mean (SD)	0.6 (1.3)	0.6 (1.4)	0.73
Number of inpatient days during baseline period: mean (SD)	2.6 (9.8)	2.6 (9.5)	0.80
Number of outpatient medical encounters during baseline period: mean (SD)	76.5 (64.1)	76.6 (59.2)	0.91
Rehabilitation care, fitting of prostheses, and adjustment of devices	1415 (22.6)	1436 (22.9)	0.66
Prior influenza vaccination during baseline period	912 (14.6)	902 (14.4)	0.80
Pneumococcal vaccination during baseline period	1047 (16.7)	1065 (17.0)	0.69
MAARI Outcome during baseline period: n (%)	2368 (37.8)	2383 (38.0)	0.80
Social & family history: n (%)			
Smoking[1]	802 (12.8)	809 (12.9)	0.87
Family history of cardiovascular diseases[2]	113 (1.8)	119 (1.9)	0.74
Illicit drug use	51 (0.8)	48 (0.8)	0.84
Alcohol abuse/dependence	80 (1.3)	76 (1.2)	0.81
Comorbid conditions/diseases[3]: n (%) unless otherwise noted			
Charlson comorbidity score: mean (SD)[4]	1.4 (1.8)	1.5 (1.8)	0.56
Charlson comorbidity score ≥ 2	2351 (37.5)	2357 (37.6)	0.99
Obese-overweight	1058 (16.9)	1035 (16.5)	0.60
Diabetes mellitus without complications	1662 (26.5)	1700 (27.1)	0.46
Diabetes mellitus with complications	1009 (16.1)	1041 (16.6)	0.44
Valvular heart disease	761 (12.1)	757 (12.1)	0.91
Pericarditis, endocarditis, myocarditis	167 (2.7)	171 (2.7)	0.87
Hypertension	4799 (76.6)	4743 (75.7)	0.24
Hypertension with complication or secondary hypertension	464 (7.4)	475 (7.6)	0.73
Myocardial infarction	67 (1.1)	77 (1.2)	0.40
Coronary artery disease	970 (15.5)	964 (15.4)	0.90
Non-specific chest pain	1805 (28.8)	1808 (28.9)	0.97
Cor-pulmonale	147 (2.3)	144 (2.3)	0.91
Other/ill-defined heart disease	357 (5.7)	385 (6.1)	0.31
Conduction disorders	187 (3.0)	197 (3.1)	0.61
Cardiac dysrhythmias	1138 (18.2)	1135 (18.1)	0.96
Arrest ventricular fibrillation	19 (0.3)	22 (0.4)	0.64
Congestive heart failure	297 (4.7)	298 (4.8)	1.00
Acute cerebrovascular disease	196 (3.1)	216 (3.4)	0.32
Cerebrovascular disease	397 (6.3)	426 (6.8)	0.30
Peripheral vascular disease	411 (6.6)	413 (6.6)	0.94
Aortic, peripheral, and visceral artery aneurysms	99 (1.6)	113 (1.8)	0.37
Embolism or thrombosis	32 (0.5)	39 (0.6)	0.48
Chronic obstructive pulmonary disease and bronchiectasis	1158 (18.5)	1184 (18.9)	0.55
Asthma	736 (11.7)	737 (11.8)	0.98
Respiratory failure	91 (1.5)	84 (1.3)	0.65
Nephritis and nephrosis	101 (1.6)	97 (1.5)	0.78
Acute and unspecified renal failure	124 (2.0)	132 (2.1)	0.66
Chronic kidney disease	149 (2.4)	147 (2.3)	0.95
Rheumatoid arthritis and systemic lupus	282 (4.5)	275 (4.4)	0.80
Pathologic fracture	58 (0.9)	51 (0.8)	0.50
Schizophrenia and psychosis	50 (0.8)	46 (0.7)	0.76
Suicide	0 (0)	1 (0)	1.00
Dementia[4]	35 (0.6)	30 (0.5)	0.62
Mild liver disease[4]	51 (0.8)	49 (0.8)	0.84
Severe liver disease[4]	16 (0.3)	15 (0.2)	0.86
Malignancy[4]	840 (13.4)	801 (12.8)	0.31
AIDS/HIV[4]	32 (0.5)	31 (0.5)	1.00
Medications during baseline period: n (%)			
Smoking cessation medication	140 (2.2)	126 (2.0)	0.42
Beta-blocker	1610 (25.7)	1627 (26.0)	0.73
Diuretic	2000 (31.9)	1987 (31.7)	0.80
ACE/ARB	3065 (48.9)	3015 (48.1)	0.38
Calcium channel blocker	1257 (20.1)	1245 (19.9)	0.81
Other antihypertensive medication	179 (2.9)	168 (2.7)	0.59
Oral hypoglycemic	854 (13.6)	890 (14.2)	0.35
Aspirin	1977 (31.6)	1997 (31.9)	0.72
NSAID	2697 (43.1)	2693 (43.0)	0.96
Bisphosphonate	1108 (17.7)	1070 (17.1)	0.38
Calcium	58 (0.9)	52 (0.8)	0.63
Sedative	972 (15.5)	1015 (16.2)	0.30
SSRI	865 (13.8)	855 (13.6)	0.80
Antipsychotic	61 (1.0)	55 (0.9)	0.64
Tricyclic anti-depressant	19 (0.3)	18 (0.3)	0.87

(*continued on next page*)

Table 1 (*continued*)

	Non-users (N = 6264)	Statin users (N = 6264)	p-value
Systemic corticosteroid	548 (8.7)	548 (8.7)	1.00
Hormone replacement therapy	887 (14.2)	875 (14.0)	0.95
Testosterone	52 (0.8)	52 (0.8)	1.00
Non-statin lipid lowering drug	608 (9.7)	647 (10.3)	0.25
Cytochrome p450	381 (6.1)	381 (6.1)	1.00

Abbreviations: AIDS: Acquired immunodeficiency syndrome; ACE/ARB: angiotensin-receptor blockers & angiotensin converting enzyme inhibitors; Cytochrome p450: medications that inhibit the Cytochrome p450 system as identified in a recent FDA warning [28]; FY: fiscal year; HIV: Human Immunodeficiency Virus; MAARI: medically attended acute respiratory illness; NSAID: non-steroidal anti-inflammatory drugs; SD: standard deviation; SSRI: selective serotonin reuptake inhibitors.

[1] Smoking as defined using ICD-9-CM codes: 3051 and V1582.

[2] Family history of cardiovascular disease as defined using ICD-9-CM codes: V171, V1749, V174, V1741, and V173.

[3] Diagnoses as defined by the Agency for Health Research and Quality (AHRQ) Clinical Classifications Software disease categories [26].

[4] Using Deyo et al. method in calculating Charlson comorbidity score using administrative data. We also matched the cohort on the 17 components of the Charlson comorbidity score (not all of which are listed in this table) [27].

1. Risk of MAARI stratified by age: (<65-year old and ≥65-year old).
2. Risk of MAARI stratified by statin type: (atorvastatin users vs, nonusers; and simvastatin users vs nonusers); in this analysis, we only included those who exclusively used either atorvastatin or simvastatin throughout FY 2005 and excluded from analysis those who used other statins or changed statin type during FY 2005.
3. Risk of MAARI stratified by quarter of the year in which the influenza vaccine was given.

This study was approved by the Institutional Review Board at Brooke Army Medical Center and the VA North Texas Health System.

3. Results

Out of 128,740 individuals who met the inclusion criteria, a total of 40,148 fulfilled both the inclusion and exclusion criteria of the study (10,071 incident statin users and 30,077 statin non-users; Fig. 1). Among incident statin users, 77% of prescriptions were for simvastatin, 17% for atorvastatin, 4% for pravastatin, and 2% for other statins.

We matched 6264 incident statin users and 6264 statin non-users by propensity score for the primary analysis, achieving well-balanced groups for all baseline characteristics (Table 1).

For the primary outcome analysis in the propensity score-matched cohort, the OR of MAARI incidence was not significantly

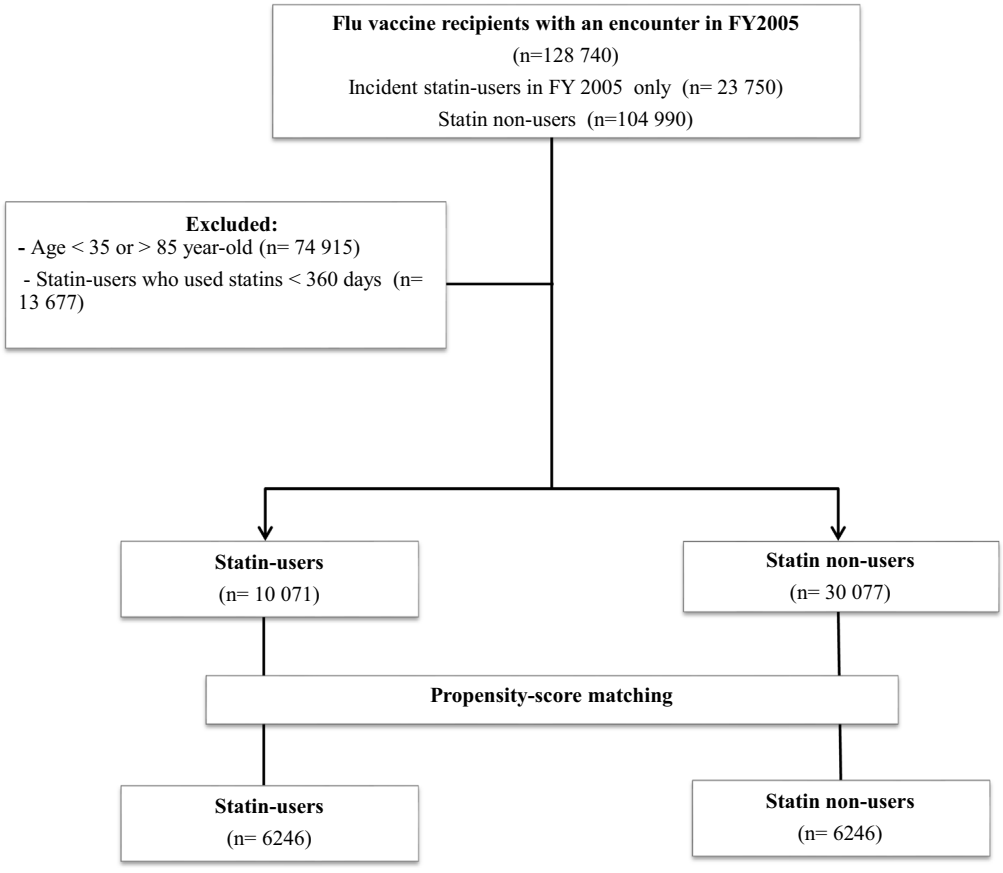

Fig. 1. Study cohort flow chart.

Table 2
Risk of MAARI in influenza vaccine recipients in incident statin users and non-users.

Variable	Statin users	Non-users	Odds ratio (95% CI)	P value
Primary Analysis				
Propensity score matched cohort (6264 Statin users & 6264 non-users)				
MAARI during follow-up period	1124 (17.9%)	1200 (19.2%)	0.92 (0.84–1.01)	0.08
Secondary Analyses*				
Overall cohort (10071 Statin users & 30,077 non-users)				
MAARI during follow-up period	1892 (18.8%)	5322 (17.7%)	0.90 (0.83–0.97)*	0.006
No-Charlson comorbidity cohort (2760 Statin users & 19,611 non-users)				
MAARI during follow-up period	325 (11.8%)	2566 (13.1%)	0.85 (0.74–0.98)*	0.03
No-MAARI at baseline cohort (6091 Statin users & 19,425 non-users)				
MAARI during follow-up period	800 (13.1)	2503 (12.9%)	0.89 (0.80–0.995)*	0.04
MAARI at baseline cohort (3980 Statin users & 10,652 non-users)				
MAARI during follow-up period	1092 (27.4%)	2819 (26.5%)	0.90 (0.81–1.00)*	0.06
No-diabetes at baseline cohort (5680 Statin users & 27,726 non-users)				
MAARI during follow-up period	970 (17.1%)	4767 (17.2%)	0.88 (0.80–0.96)*	0.005
Diabetes at baseline cohort (4391 Statin users & 2351 non-users)				
MAARI during follow-up period	922 (21.0%)	555 (23.6%)	0.93 (0.81–1.07)*	0.31
Post-hoc Analyses*				
Analysis stratified by age				
Age < 65-year old (4560 Statin users & 24,025 non-users)				
MAARI during follow-up period	1012 (22.2%)	4410 (18.4%)	0.89 (0.81–0.99)*	0.04
Age ≥ 65-year old (5511 Statin users & 6052 non-users)				
MAARI during follow-up period	880 (16.0%)	912 (15.1%)	0.90 (0.80–1.01)*	0.08
Analysis stratified by statin type (1432 atorvastatin users; 7732 simvastatin users; 30,077 non-users)				
MAARI in atorvastatin users vs non-users	266 (18.6%)	5322 (17.7%)	0.88 (0.75–1.02)*	0.09
MAARI in simvastatin users vs non-users	1417 (18.3%)	5322 (17.7%)	0.89 (0.82–0.96)*	0.004
Analysis stratified by quarter of the year in which vaccine was administered				
Vaccine administered during the first quarter of FY 2005 (8367 statin users & 18,971 non-users)				
MAARI during follow-up period	1627 (19.4)	3637 (19.2)	0.91 (0.83–0.99)*	0.02
Vaccine administered during the second quarter of FY 2005 (1704 statin users & 11,106 non-users)				
MAARI during follow-up period	265 (15.6)	1685 (15.2)	0.85 (0.71–1.02)*	0.08

* Adjusted odds ratios with propensity score and statin use as covariates.

different between incident statin users and non-users (OR 0.92, 95% CI: 0.84–1.01; p = 0.08) (Table 2).

In several of our secondary analyses, incident statin users had lower propensity score-adjusted ORs for MAARI incidence compared to statin non-users (Table 2). For example, the overall cohort, the no comorbidity cohort, no-MAARI at baseline cohort, and the no-diabetes at baseline cohort had lower propensity-score adjusted OR of MAARI incidence in incident statin users compared to non-users. Moreover, the lower ORs in these sub-cohorts were of similar magnitude, ranging from 0.89 to 0.85. Other secondary analyses showed a trend toward similar lower ORs, but did not reach statistical significance.

We also performed several post-hoc analyses to explore if there is difference in MAARI in relation to patients' age, type of statin used, and quarter of the year in which the vaccine was administered. Overall, OR of MAARI were generally similar across all explored subgroups (Table 2).

4. Discussion

In this propensity score-matched cohort study of influenza vaccine recipients, incident statin users had a similar odds ratio for the incidence of MAARI compared to statin non-users. However, in secondary analyses of several subcohorts with lower comorbidity, incident statin use was associated with lower odds of MAARI compared to non-users.

It is difficult to ascertain if the decreased odds ratios for MAARI in our secondary analyses are due to less robust adjustment for confounders compared to the propensity score matching in our primary analysis or due to an actual protective statin effect that was not captured in our primary analysis due to smaller sample size. However, these findings offer reassurance that statins are not detrimental, at least, to overall incidence of MAARI among influenza vaccine recipients. However, our findings are similar to other recent studies that noted that statin use around the time of vaccination does not substantially affect the risk of influenza-related medical encounters among older adults [34] and that current statin use does not appear to affect vaccine effectiveness against laboratory-confirmed influenza illness [13].

These reassuring results are important because cardiovascular diseases are a major contributor to excess mortality during influenza outbreaks [35]. Hence, based on this and other data, continuing statins throughout the influenza season seems prudent. In one study of 3043 patients hospitalized with laboratory-confirmed influenza, the OR of 30-day mortality in patients on statins either prior to or during hospitalization was 0.59 (95%CI: 0.38–0.92), after adjusting for other variables, such as age, underlying medical conditions, and influenza vaccination [9]. An analysis of documented 2009/H1N1 pandemic influenza cases from the United Kingdom also noted a trend toward reduced mortality related to statin use although these results did not reach statistical significance [36].

However, a definitive answer on the impact of statins on influenza clinical outcomes has been elusive. A recent propensity score-matched cohort study from the United Kingdom comparing 5181 statin users and 5181 non-users concluded that the apparent beneficial effect of statins on clinical outcomes from influenza may be due to healthy-user bias [12]. In that study, the 30-day incidence of hospitalization or death from influenza was lower among statin users; however, there was significant attenuation of the effect of statins with the new-user design, and additional sub-group analyses evaluating the effect of statins on non-influenza-related outcomes (such as risk of burns) suggested that the beneficial effect of statins on influenza-related adverse outcomes were explained by a healthy user bias [12].

Our primary findings of a trend toward lower odds of MAARI among statin users who received influenza vaccine without apparent decrement in vaccine effectiveness have not been uniformly found across the prior literature. In a post-hoc analysis of a randomized controlled trial in persons aged >65 years [7], statin users

in comparison to non-users had significantly reduced serum hemagglutinin-inhibition antibody responses, suggesting reduced vaccine immunogenicity related to statin use. However, statin users in this study had more comorbidities and a sizable proportion of their population were from non-US countries. In another retrospective study using data from a managed care organization, statin users had significantly lower vaccine effectiveness (as measured by MAARI) than non-users [6]. However, there were significant differences in characteristics of statin users and non-users, and data on influenza vaccine use in the prior years were not included in this analysis.

Our study has several notable strengths. We included patients who received care in the same healthcare system for a prolonged period of time to ensure stable and comparable healthcare access and to minimize disparities between treatment groups. Tricare enrollees have similar access and standards of healthcare to a large extent. Additionally, we successfully propensity score-matched statin users and non-users across a large number of variables including patient demographics, a wide array of comorbidities and healthcare utilization measures (to mitigate ascertainment bias among statin users who may have more healthcare contact), prior influenza and pneumococcal vaccine history (both of which may affect MAARI and be surrogate markers for healthy user bias), and occurrence of MAARI during baseline period. We also matched for medications that may contribute to increased risk of MAARI such as corticosteroids. We have also adopted several measures, such as a new user design as detailed in the methods section, to minimize common biases that affect observational studies. Overall, our findings were generally consistent throughout analyses, which increase confidence in our results.

The limitations of our study include its retrospective nature, which may result in unrecognized confounders. Also, our study only included one influenza season (during FY 2005) during which there was reported heterogeneity in influenza vaccine effectiveness [37]. It has been shown that statins' effect on vaccine effectiveness may vary by influenza strain [5]. Due to data use agreement constraints, we only had access to vaccination dates rounded to the nearest quarter of the year so we could not ascertain the temporal relationship between statin use and receiving influenza vaccine. We mitigated this problem by only analyzing patients with continuous statin use (>360 days) during FY 2005 to ensure that influenza vaccine was received while the patient was taking a statin among incident statin users. We also could not ascertain the exact temporal relation between the date of MAARI and date of influenza vaccine if both events occurred in the same quarter of the year. For example, some patients may have received the influenza vaccine followed by a MAARI outcome while others may have had a MAARI outcome followed by influenza vaccine. In both of these scenarios where MAARI and influenza vaccination occurred in the same quarter, the MAARI outcome will be counted as a baseline characteristic not an outcome according to our method (prior MAARI at baseline). However, such a misclassification is expected to affect both incident statin users and non-users equally (non-differential misclassification).

Another limitation to the study is using MAARI as an outcome. Although MAARI has been widely used and validated in studies of real-world influenza vaccine effectiveness [6,13,22–24], it is an imperfect surrogate for influenza. We cannot completely exclude the possibility that statins affect incident MAARI due to other causes besides influenza. Also, since non-users did not use statins at any time during the study period, the study may be exposed to the potential for bias due to "prevalent non-users". To minimize this bias, we propensity score-matched treatment groups on 72 variables including demographics, personal history, comorbidities, healthcare utilization, use of different medication classes, receipt of influenza vaccination in prior years, and MAARI occurrence in the baseline period. We also limited statin users to those who used statins in FY 2005 only, as we detailed earlier. However, the decision to limit our analysis to "incident users" may reduce the generalizability of these results to those on chronic long-term statin use if this has a differential effect on vaccine effectiveness.

In conclusion, incident statin use among recipients of influenza vaccine was not associated with increased risk of MAARI and may even have been associated with a lower risk in those with lower comorbidity. These results offer reassurance for clinicians and patients to continue statins during influenza season. Further prospective studies including large registries of statin users are needed to thoroughly examine these important questions of the interactions between one of the most commonly prescribed medication classes and one of the most commonly administered vaccines.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2019.09.024.

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