Use of Oseltamivir After Influenza Infection Is Associated With Reduced Incidence of Recurrent Adverse Cardiovascular Outcomes Among Military Health System Beneficiaries With Prior Cardiovascular Diseases

S. Ward Casscells, MD; Elder Granger, MD, FACP, FACPE; Amii M. Kress, MPH; Andrea Linton, MS; Mohammad Madjid, MD, MSc; Linda Cottrell, BS

Background—Influenza infection has been associated with increased risk of adverse cardiac and cerebral vascular outcomes. Oseltamivir, a treatment for influenza, has been shown to decrease the severity of an influenza episode, but few data exist regarding its potentially protective effect against recurrent vascular outcomes among influenza patients with a history of vascular disease.

Methods and Results—Electronic healthcare service and pharmacy records for 37 482 TRICARE beneficiaries, aged 18 and older, with a coded history of cardiovascular (CV) disease and a subsequent diagnosis of influenza from October 1, 2003, through September 30, 2007, were examined. Subjects were grouped according to whether they had filled a prescription for oseltamivir within 2 days of their influenza diagnosis. The incidence of recurrent CV events within 30 days after the influenza diagnosis among oseltamivir-treated and untreated subjects was 8.5% and 21.2%, respectively (P<0.005). Subject age was a persistent and significant contributor to the likelihood of recurrent CV outcomes. After controlling for the differences in demographics among treated and untreated cohorts using a propensity-scored logistic regression model, a statistically significant protective effect was associated with oseltamivir treatment (odds ratio, 0.417; 95% CI, 0.349 to 0.498).

Conclusions—Our findings suggests that oseltamivir treatment for influenza is associated with significant decrease in the risk of recurrent CV events in subjects with a history of CV disease. These findings merit confirmation in further prospective and controlled studies. Meanwhile, in patients with CV disease, strict adherence with current practice guidelines for prevention and treatment of influenza is recommended.

Key Words: complications epidemiology follow-up studies prevention

Substantial evidence exists that influenza infection is associated with an elevated risk of adverse cardiac and cerebral vascular outcomes.\(^1\)\(^-\)\(^3\) Increased hospitalizations and mortality attributed to cardiovascular (CV) disease and stroke have been consistently observed during periods of influenza epidemic;\(^7\)\(^-\)\(^6\) and influenza vaccination has been widely accepted as appropriate clinical practice among subgroups at risk for influenza-related complications.\(^7\)\(^-\)\(^8\) Studies examining the relationship between influenza vaccination and incident or recurrent CV and other outcomes have generally confirmed the safety and efficacy of this vaccination practice.\(^9\)\(^-\)\(^12\) but the literature is more limited regarding adverse CV outcomes among already infected patients receiving influenza treatment.

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Oseltamivir (Tamiflu, Roche Laboratories, Inc), an oral neuraminidase inhibitor, was approved by the US Food and Drug Administration in 1999 for the treatment of influenza in adults and children 1 year of age or older. Oseltamivir has been considered both a well-tolerated and effective treatment for seasonal influenza even among the elderly and patients with prior CV disease.\(^13\)\(^-\)\(^14\) Initial oseltamivir studies focused on duration of influenza symptoms, respiratory-related complications, hospitalization, or antibiotic use as primary outcomes of interest among otherwise healthy populations.\(^15\)\(^-\)\(^16\) Recently, however, oseltamivir use has received scrutiny regarding potential adverse CV, neuropsychiatric, and other outcomes.\(^17\)\(^-\)\(^20\) Retrospective studies performed to date have consistently reinforced the use of oseltamivir as a safe and effective influenza treatment, but the number of study subjects with prior CV or cerebrovascular risk has generally been small.\(^21\)

With \(~9.2\) million beneficiaries, the US Department of Defense’s TRICARE Program represents one of the largest integrated healthcare delivery organizations in the United States. The Military Health System encompasses both a healthcare delivery system, which staffs and operates military hospitals, clinics, and pharmacies, and TRICARE, a health plan that provides comprehensive and integrated health and prescription-drug insurance coverage for beneficiaries who receive care from civilian providers. Military Health System beneficiaries include active duty service members and their dependents and retirees.
SUMMARY

- Influenza infection has been associated with increased risk of adverse cardiac and cerebral vascular outcomes. Oseltamivir, a treatment for influenza, has been shown to decrease the severity of an influenza episode, but few data exist regarding its potentially protective effect against recurrent vascular outcomes among influenza patients with a history of vascular disease.

- In our retrospective study of 37,482 cardiovascular patients aged 18 and older who were diagnosed with influenza, the rate of recurrent vascular outcomes (myocardial infarction, angina pectoris, stroke, heart failure, and sudden cardiac death) within 30 days after influenza diagnosis was significantly lower among the oseltamivir-treated group (8.6%) relative to the untreated group (21.1%) overall and for each outcomes examined (P<0.005).

- The mean days to recurrence of cardiovascular outcome after influenza diagnosis was significantly longer among oseltamivir-treated subjects (12.7 ± 8.6 days) relative to untreated subjects (8.1 ± 8.4 days) (P<0.005). The relatively short (6 to 10 hours) half-life of the drug’s active metabolite suggests that the drug does not persist in the body much beyond the recommended 5-day treatment regimen, so these findings suggest that oseltamivir protects the cardiovascular patient by simply reducing the severity and duration of influenza infection, as the drug is intended to do.

- Significantly higher recurrence rates were observed among men relative to women (10.5% and 6.9% for treated subjects, and 24.5% and 18.7% for untreated subjects, respectively; P<0.005) and among the higher socioeconomic (SES) group relative to the lower one (11.2% and 7.5% for treated subjects, and 25.7% and 19.5% for untreated subjects, respectively; P<0.005). The mean ages of men and women who suffered recurrent cardiovascular events were similar, but the mean age among the higher SES group was statistically higher relative to that among the lower SES group (78.6 ± 9.8 and 72.6 ± 10.8 years for treated subjects, and 81.8 ± 8.3 and 75.4 ± 10.0 years for untreated subjects, respectively; P<0.005), suggesting a potential age-confounding effect on the incidence rate among the higher SES subgroup.

- A propensity-weighted logistic regression model yielded a protective effect associated with oseltamivir (odds ratio, 0.417; 95% CI, 0.349 to 0.498) and increased likelihood of recurrent cardiovascular outcome for increasing age (odds ratio, 1.074; 95% CI, 1.071 to 1.077) and diuretic use (odds ratio, 1.914; 95% CI, 1.801 to 2.033). No significant effect was observed among gender or SES subgroups or among users of angiotensin-converting enzyme inhibitors, angalgesics, antilipidemics, antidiabetics, β-blockers, or calcium-channel blockers.

- Our findings suggest that strict adherence with current practice guidelines for prevention and treatment of influenza is recommended among patients with cardiovascular disease.

and their dependents. This study focuses on oseltamivir use and recurrent CV or cerebrovascular outcomes among beneficiaries diagnosed with influenza who had prior diagnoses of CV disease.

Methods

The source of data for this study was an enterprise-wide data repository that captures patient’s demographic and healthcare information each time a beneficiary uses their TRICARE benefit to obtain healthcare services or fill a prescription. This centralized data repository enables the generation of a common patient profile regardless of where healthcare services are rendered, or a military pharmacy, a commercial pharmacy, or the TRICARE Mail Order Pharmacy is used to fill prescriptions. Establishing one central patient’s medication profile allows providers to review a patient’s medication history to reduce exposure to unnecessary safety risks, and supports tracking of provider prescribing patterns throughout the Military Health System. Pharmacy filled healthcare service records for inpatient stays and ambulatory encounters are forwarded to this data repository and coded with an automatically generated, pseudopatient identifier that enables researchers to link different records for the same person without the inclusion of any protected health information in the study data sets.

The sample-selection methodology is summarized in the Figure. A census of records for all enrolled TRICARE beneficiaries, aged 18 years and older, diagnosed with any CV disease before a diagnosis of influenza, during the study period from October 1, 2003 through September 30, 2007, was examined. The TRICARE pharmacy benefit is available to all Department of Defense beneficiaries, many of whom are not required to use TRICARE to obtain healthcare services. Thus, the study population was limited to those beneficiaries who were continuously enrolled in TRICARE for a minimum of 24 consecutive months during the study time frame to ensure sufficient data were available to assess CV history. The beneficiary’s CV history was assessed using the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) diagnosis and procedure codes and Current Procedural Terminology procedure codes found in the electronic healthcare service records. Beneficiaries were included in this study if the healthcare service records contained evidence of preexisting CV disease including myocardial infarction (MI), angina pectoris, heart failure, or stroke, or history of cardiac intervention including angioplasty or coronary bypass before a diagnosis of influenza (ICD codes 487.1, 487.1, 487.8). If an individual received multiple diagnoses of influenza during the period, only the first diagnosis was examined. A total of 21 individuals with missing demographic data; 13 individuals who received treatment with zanamivir (Relenza, GlaxoSmithKlein), another neuraminidase inhibitor; and 749 individuals who filled their prescription for oseltamivir outside the recommended 2-day window after the influenza diagnosis, were then eliminated from the study population. Because the efficacy of oseltamivir treatment has only been established if taken within 2 days after the onset of symptoms, it is not clear whether taking the medication after the recommended 2-day window would yield sufficient therapeutic effect for the subject to have been considered “treated.” It is also likely that subjects who filled prescriptions significantly later than the time they were written may have inteded the medication for someone else’s use. The final study cohort consisted of 37,482 individuals.

Study subjects who filled a prescription for oseltamivir (identified using the National Drug Code) within 2 calendar days of their diagnosis of influenza were placed in the “treated” group. The remaining subjects were placed in the “untreated” group. Healthcare service records for the 30-day period after the influenza diagnosis were then screened. Subjects were flagged as having a recurrent CV outcome if any of the following CV diagnoses were rendered within that period: MI (ICD 410), angina pectoris (ICD 413), heart failure (ICD 428 to 429), stroke (ICD 430 to 438), or sudden cardiac death (SCD) (cardiac arrest or ventricular fibrillation, ICD 427). Among subjects in the treatment group, the oseltamivir fill date had to precede the date of the recurrent CV event.
Cross-tabulations were performed to compare the frequency of oseltamivir treatment and 30-day recurrent CV outcomes (MI, angina pectoris, stroke, heart failure, and SCD) by gender (male, female), age group (<45 years, 45 to 64 years, ≥65 years), and socioeconomic status (enlisted, officer) between treatment groups. Because income and educational level data were not available, the pay grade of the service member was used as a proxy for socioeconomic status. In general, military officers are college educated and draw a larger salary than their enlisted counterparts. The values for pay grade were dichotomized into officer (includes active duty, retired, and warrant officers and their family members) and enlisted (includes active duty and retired enlisted personnel and their family members). Statistical significance was assessed using χ² test (P<0.05) for categorical data and using t tests (P<0.05) for continuous data.

Multivariate logistic regression models were developed to predict the probability of a recurrent CV outcome by oseltamivir treatment, controlling for patient gender, age (continuous), and rank. Because the influenza infection may alter the effectiveness of or adherence to a subject’s use of prescription medications to manage their CV conditions, CV medication classes being used at the time of influenza diagnosis were included as covariates in the regression analysis. Pharmacy fill records for the 90-day period preceding the influenza diagnosis date were screened to identify maintenance medications used by study subjects in the following classes: angiotensin-converting enzyme inhibitors, analgesics and antipyretics, antidiabetics, antilipidemics, antihypertensives, β-adrenergic blocking agents (ie, β-blockers), calcium-channel blockers, diuretics. Beneficiaries were coded as using the class if one or more prescriptions for a medication within that class were filled during the 90-day period.

Multicollinearity between age and gender and age and rank were observed in preliminary analyses of the data, so interaction terms were included in the regression models in an effort to separate the main effects of gender, age, and rank from the variable effect of age on each gender and rank subgroup. The age variable was centered before building the interaction terms by subtracting the mean age from each case’s value for age. In each regression model, female gender and enlisted rank were the reference values for the main effects and female*age and enlisted*age were the reference values for the interaction effects.

To address potential bias introduced by differences in the probability of a subject receiving oseltamivir treatment, a propensity score-weighted regression model was then developed.22 Propensity scores were calculated using logistic regression with the dependent variable being the likelihood of receiving oseltamivir treatment, and the independent variables being gender, age, rank, and use of each class of CV medications in the 90 days before the influenza diagnosis. Propensity score weights were calculated as the inverse of the propensity score and adjusted to reflect the differing size of the 2 treatment groups. Regression models were then run using propensity-weighted values for independent variables, which continued to be significantly different between the treatment groups. The c statistic was used to evaluate model discrimination. SAS version 9.2 (SAS Institute, Inc, Cary, NC) was used for analysis of the study data. The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results
The number and percentage of study subjects in each treatment group by gender, age, rank, and concomitant medication utilization are presented in Table 1. Of the 37 482 CV patients diagnosed with influenza, 18.1% of study subjects filled a prescription for oseltamivir within 2 days after their influenza diagnosis. A greater percentage of the study population were female (56.1%) and enlisted (72.3%). No statistically significant difference in gender (P=0.060) but a significant difference in socioeconomic status (P=0.009) was observed between treatment groups. The mean age among the treated group was significantly younger relative to that of the untreated group, 64.2±15.8 years and 68.2±16.2 years, respectively (P<0.005). Among the medication classes examined, the treated group used significantly more antilipidemics relative to the untreated group (34.3% and 28.8%, respectively; P<0.005) and significantly fewer diuretics (18.0% and 21.4%, respectively; P<0.005).

The incidence of a recurrent CV diagnosis within 30 days of an influenza diagnosis among each treatment group is presented in Table 2. The 30-day incidence of recurrent CV outcome was 18.9% for the study population. Heart failure (10.1%) and SCD (9.6%) occurred most frequently, followed by stroke (4.6%), MI (1.2%), and angina pectoris (1.1%). The
The incidence of recurrent CV outcomes was significantly higher among the untreated group (21.1%) relative to the treated group (8.6%) overall, and for all CV outcomes examined ($P<0.005$). The mean days to recurrence was significantly longer among treated subjects ($12.7\pm8.6$ days) relative to untreated subjects ($8.1\pm8.4$ days) ($P<0.005$).

Table 1. TRICARE Beneficiaries With a Preexisting Cardiovascular Disease Who Were Diagnosed With Influenza, by Beneficiary Characteristics and Oseltamivir Treatment, October 1, 2003 to September 30, 2007

<table>
<thead>
<tr>
<th>Total</th>
<th>Oseltamivir Treatment</th>
<th>No Oseltamivir Treatment</th>
<th>$P^\dagger$</th>
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</thead>
<tbody>
<tr>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Total</td>
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<td>6771</td>
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<td>Male</td>
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<td></td>
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<tr>
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<td>25 814</td>
<td>4111</td>
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</tr>
<tr>
<td>Mean ± SD</td>
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<td>64.2±15.8</td>
</tr>
<tr>
<td>Rank</td>
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<td></td>
<td></td>
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<tr>
<td>Enlisted</td>
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<td>73.7</td>
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<tr>
<td>Officer</td>
<td>10 354</td>
<td>1783</td>
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<td>Maintenance medications*</td>
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<td></td>
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<td>6712</td>
<td>1236</td>
<td>18.3</td>
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<td>34.3</td>
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<td>15.9</td>
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<tr>
<td>Diuretics</td>
<td>7772</td>
<td>1216</td>
<td>18.0</td>
</tr>
</tbody>
</table>

ACE indicates angiotensin-converting enzyme.

*Subgroups are not mutually exclusive because subjects may use medications in multiple classes in the 90-day period before the influenza diagnosis.

†$x^2$ or ANOVA test used to test for statistically significant differences between treatment groups ($P<0.05$).

The incidence of a recurrent CV diagnosis by patient characteristics within the 30 days of an influenza diagnosis among each treatment group is presented in Table 3. Significantly, higher recurrence rates were observed for the untreated group for all gender, age, and rank subgroups examined ($P<0.05$). The incidence rate was significantly higher
among men relative to women (10.5% and 6.9% for treated subjects, and 24.5% and 18.7% for untreated subjects, respectively; \( P < 0.005 \)); significantly higher among officers relative to enlisted personnel (11.2% and 7.5% for treated subjects, and 25.7% and 19.5% for untreated subjects, respectively; \( P < 0.005 \)); and increased with patient’s age with a mean age of 74.7±10.9 years and 77.6±9.9 years for treated and untreated subjects, respectively (\( P < 0.005 \)). Because the raw incidence rates observed between gender and rank subgroups differed from the relative distribution of the original study population presented in Table 1, the mean age for each gender and rank subgroups was included in Table 3. The mean ages of men and women who suffered recurrent CV events were similar, but the mean age among officers was statistically higher relative to that among enlisted personnel (78.6±9.8 years and 72.6±10.8 years for treated subjects, and 81.8±8.3 years and 75.4±10.0 years for untreated subjects, respectively; \( P < 0.005 \)), suggesting a potential age-confounding effect on the incidence rate among the officer subgroup.

The results of multivariate logistical regression analyses for predicting the likelihood of a recurrent CV diagnosis are presented in Table 4. The initial unweighted model yielded significant protective effects associated with oseltamivir treatment (odds ratio [OR], 0.412; 95% CI, 0.375 to 0.453), officer status (OR, 0.845; 95% CI, 0.769 to 0.929), and use of antilipidemics (OR, 0.878; 95% CI, 0.824 to 0.935). Males (OR, 1.278; 95% CI, 1.188 to 1.375), older age (OR, 1.069; 95% CI, 1.066 to 1.073), and users of antidiabetics (OR, 1.318; 95% CI, 1.220 to 1.424), \( \beta \)-blockers (OR, 1.955; 95% CI, 1.835 to 2.083), calcium-channel blockers (OR, 1.13118; 95% CI, 1.054 to 1.214), and diuretics (OR, 1.667; 95% CI, 1.562 to 1.778) were significantly more likely to experience a recurrent CV diagnosis. The age/gender interaction yielded a small but significant contribution to the model. After applying the propensity score weights, ANOVA and \( \chi^2 \) tests indicated that oseltamivir treatment, age, antilipidemic use, and diuretic use continued to differ significantly between treatment groups. The weighted values for each of these variables were introduced into a second model. The weighted model yielded a protective effect associated with oseltamivir (OR, 0.417; 95% CI, 0.349 to 0.498), and increased likelihood of recurrent CV outcome for increasing age (OR, 1.074; 95% CI, 1.071 to 1.077) and diuretic use (OR, 1.914; 95% CI, 1.801 to 2.033). Both the age\*gender and age\*rank interaction terms yielded small but significant effects in the final model, suggesting that per-unit increases in patient’s age placed males at higher risk of a recurrent CV outcome relative to females (OR, 1.020; 95% CI, 1.016 to 1.025), and officer personnel at lower risk relative to enlisted personnel (OR, 0.994; 95% CI, 0.990 to 0.998).

The value of the c statistic indicates that the model accurately predicted a recurrent CV outcome 75.8% of the time among pairs of subjects, where one has a recurrent CV outcome and one does not.

**Discussion**

Therapeutic use of oseltamivir has been consistently observed to decrease the severity of an influenza episode and the
Oseltamivir may potentially diminish these blood viscosity. Oseltamivir may potentially diminish these increasing prothrombotic factors, hemodynamic stress, and exacerbating inflammation at the systemic and arterial levels suggested that influenza can trigger acute cardiac events by the systemic and arterial levels suggested that influenza can trigger acute cardiac events by patient remains to be elucidated. Previous studies have pectoris, stroke, and heart failure episodes. With a decreased incidence of recurrent MI, SCD, angina receiving oseltamivir therapy, oseltamivir use was associated with a decreased incidence of recurrent MI, SCD, angina protection mechanisms are unclear, logic dictates that oseltamivir treatment may protect patients against recurrent CV outcomes simply by reducing the severity and duration of influenza infection, as the drug is intended to do.

Other mechanisms may be also involved. CV patients typically rely on multiple medications to manage their CV and other chronic conditions. Common flu symptoms such as nausea, fever, or loss of appetite can disrupt a patient’s compliance with their daily medication regimen or alter the effectiveness of the regimen. The use of over-the-counter medications or home remedies to treat flu symptoms may further compromise the effectiveness of or compliance with medications used to manage the patient’s chronic condition. A prolonged infection often leaves the patient more susceptible to pneumonia and other respiratory complications, which in turn prolongs the period of vascular risk and, per se, increases the risk for cardiac events. These analyses indicate a longer time-to-event among oseltamivir-treated patients relative to those who were not treated, suggesting a slower overall rate of recurrent CV incidence. More detailed study of disease progression among these patients would be warranted to explain this finding.

Few reports are available with which this study can be directly compared. Most studies relating oseltamivir use with CV outcomes focus on oseltamivir as a prophylactic rather than a treatment for influenza. Although several studies have shown a clear benefit from the use of influenza vaccine to prevent CV events, this study’s findings suggest a more pronounced protective effect associated with the therapeutic use of oseltamivir among patients with a prior CV history. Enger et al reported a small protective effect among CV patients who received oseltamivir therapeutically relative to those that did not, but the effect was not specific to oseltamivir. Similar effects were observed for CV patients who were treated with other influenza drugs (amantadine, rimantadine, or zanamivir). Enger et al also observed consistent findings when comparing CV outcomes for a 14-day observation with those of a 30-day observation period.

Not surprisingly, subject’s age was a persistent contributor to the likelihood of recurrent CV outcomes. In the unweighted model, there was a significantly higher likelihood of recurrent CV outcomes among men relative to women, and among enlisted personnel and their dependents relative to officers and their dependents. Significant differences across gender and rank subgroups were not apparent once treatment selection bias was considered in the model. Although other differences likely persist among the enlisted and officer subgroups, Department of Defense healthcare policy promotes benefit uniformity to ensure equal access to healthcare services, regardless of the beneficiary’s location, ability to pay, or previous medical condition. The absence of a significant oseltamivir treatment-rate difference between officer and enlisted populations supports the Department’s belief that socioeconomic status has diminished influence on beneficiaries’ access to and utilization of healthcare services. Similar healthcare utilization patterns across these 2 socioeconomic status subgroups, Department of Defense healthcare policy promotes benefit uniformity to ensure equal access to healthcare services, regardless of the beneficiary’s location, ability to pay, or previous medical condition. The absence of a significant oseltamivir treatment-rate difference between officer and enlisted populations supports the Department’s belief that socioeconomic status has diminished influence on beneficiaries’ access to and utilization of healthcare services. Similar healthcare utilization patterns across these 2 socioeconomic.
subgroups in the Department of Defense have been reported elsewhere.  

Although there are many strengths to this study, several limitations should be considered. The use of administrative data introduces a potential source of error. Undercoding, which may occur when diagnoses are documented in the patient’s medical record, but fail to be recorded in the electronic record, may have resulted in missed influenza or CV diagnoses. A missed influenza diagnosis would result in the exclusion of an individual who should otherwise be included in the study. Although missed CV diagnoses would clearly impact our subject-selection process and calculated outcome rates, the nature and severity of these outcomes suggest a high likelihood of their inclusion in administrative data. There is no compelling reason, however, to assume that either coding bias would impact the oseltamivir-treated and untreated groups differently.

Though our analyses were adjusted for differences in likelihood of a patient receiving oseltamivir treatment, factors beyond those available from our administrative data set were not considered. The degree to which propensity scoring may adjust for treatment bias is dependent on the variables used to calculate the propensity weight. Omission of potentially important variables associated with the receipt of treatment, such as the severity and prior duration of the patient’s symptoms at the time of the influenza diagnosis, presence of specific comorbidities that may be further aggravated by an influenza infection, or prior prophylactic treatment with oseltamivir may have limited our attempts to effectively balance the treatment groups. Circumstances concurrent with the 30-day observation period after the influenza diagnosis such as subject compliance with critical medications, or death of a subject due to causes unrelated to the influenza infection may also have confounded our findings. Finally, we had no visibility of patients who may have suffered a recurrent event or death outside a healthcare setting, if the event was not documented on a medical claim.

This existing study could be further strengthened by more rigorous screening of subjects’ medical history to enable the treated group to be case matched and compared with untreated patients of a similar medical and prescription medication history. Preexisting or prior respiratory illnesses, such as asthma, chronic obstructive pulmonary disease, and bronchitis, were not examined in this study, but can significantly impact the extent to which a patient’s health status is compromised by an influenza infection. A patient’s use of other influenza treatments, antibiotics, and over-the-counter medications, as well as compliance with their maintenance medications during the influenza infection, should also be considered when matching cases and controls. The ideal study would not rely on administrative data alone, but would use chart reviews and prospective medical surveillance of influenza patients. The health status of the patient before the influenza diagnosis, relative severity of the influenza infection at the time of diagnosis, the timing and compliance with oseltamivir treatment as well as other medications being used by the patient, and the timing and severity of recurrent CV outcomes should be evaluated and documented using standard protocols. A randomized, controlled study will offer a more definitive answer.

Although more rigorous study is required to confirm oseltamivir’s function in protecting influenza patients from recurrent vascular events, this study found evidence to suggest that oseltamivir treatment for influenza is associated with a statistically significant reduction in the odds of recurrent CV events. Given the significant role that oseltamivir is expected to play in the event of a pandemic influenza infection, further studies of oseltamivir use among chronically ill and older patients are warranted. A sharp rise in CV events is expected during the next influenza pandemic, and use of oseltamivir may be associated with a significant reduction in such events.

**Note Added in Proof**

These data were collected when resistance to oseltamivir was low but rising. Resistance would cause underestimation of the potential benefit of antiviral treatment on incidence of cardiovascular outcomes. Importantly, the current 99% resistance of this season’s dominant strain (H1N1) means that cardiovascular patients with influenza should receive amantadine or zanamivir rather than oseltamivir.

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**References**


Few data are available regarding therapeutic use of oseltamivir and the recurrence of adverse vascular events after influenza infection among patients with vascular risk. In a retrospective study of 37,482 cardiovascular patients aged 18 and older who were diagnosed with influenza, the rate of recurrent vascular outcomes (myocardial infarction, angina pectoris, stroke, and other atherosclerotic vascular disease) within 30 days after the influenza diagnosis was 2.6 times lower among those treated with oseltamivir relative to those who were not (odds ratio, 0.417; 95% CI, 0.349 to 0.498). The mean time to recurrent outcome was 12.7 days for treated subjects and 8.1 days for untreated subjects. The exact mechanisms by which oseltamivir protects the cardiovascular patient is not clear, but influenza is believed to trigger acute cardiac events by exacerbating inflammation at the systemic and arterial levels and by increasing prothrombotic factors, hemodynamic stress, and blood viscosity. The relatively short (6 to 10 hour) half-life of the drug's active metabolite suggests that the drug does not persist in the body much beyond the recommended 5-day treatment regimen, so it is likely that oseltamivir protects the cardiovascular patient by simply reducing the severity and duration of influenza infection, as the drug is intended to do.
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Supplementary Material

Appendix. Propensity Scoring and Weighting the Treatment Groups

In this study, subjects were categorized into treatment groups, based on whether or not an oseltamivir prescription was filled within 2 days of their influenza diagnosis. The beneficiary characteristics and medications obtained prior to the influenza diagnosis are presented previously in Table 1.

To mitigate the limitation associated with nonrandomized assignment to each treatment group, a propensity score, i.e., the predicted probability of receiving treatment, was calculated for each subject. The propensity score was calculated using a logistic regression model with the dependent variable being the likelihood of receiving oseltamivir treatment, and the independent variables being gender, age, rank, and use of each class of CV medications in the 90 days prior to the influenza diagnosis. Histograms of the resulting propensity scores for each treatment indicates sizeable overlap between treatment groups, suggesting that the treatment groups are reasonably comparable.
Estimated probability of oseltamivir treatment

Cases weighted by WEIGHT
Estimated probability of oseltamivir treatment

Cases weighted by WEIGHT

Propensity score weights were calculated as the inverse of the propensity score and normalized to reflect the differing size of the two treatment groups. The propensity score-weighted measures for the treatment groups are present below. Statistically significant differences between groups persisted for the age, antilipidemic, and diuretic variables (p <0.05).

<table>
<thead>
<tr>
<th>Propensity Score Weighted Measures by Beneficiary Characteristics and Oseltamivir Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristics</td>
</tr>
<tr>
<td>Gender</td>
</tr>
<tr>
<td>Female (%)</td>
</tr>
<tr>
<td>Male (%)</td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>&lt;45 (%)</td>
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</tbody>
</table>
Regression models were then run including the propensity-weighted values for the age (as a continuous variable), antilipidemic and diuretic variables, and interaction terms associated with the age variable.