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Acute Cardiovascular Events Associated With Influenza in Hospitalized Adults:

A Cross-sectional Study

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Abstract

Background: Influenza may contribute to the burden of acute cardiovascular events during annual influenza epidemics.

Objective: To examine acute cardiovascular events and determine risk factors for acute heart failure (aHF) and acute ischemic heart disease (aIHD) in adults with a hospitalization associated with laboratory-confirmed influenza.

Design: Cross-sectional study.

Setting: U.S. Influenza Hospitalization Surveillance Network during the 2010-to-2011 through 2017-to-2018 influenza seasons.

Participants: Adults hospitalized with laboratory-confirmed influenza and identified through influenza testing ordered by a practitioner.

Measurements: Acute cardiovascular events were ascertained using discharge codes from the International Classification of Diseases (ICD), Ninth Revision, Clinical Modification, and ICD, 10th Revision. Age, sex, race/ethnicity, tobacco use, chronic conditions, influenza vaccination, influenza antiviral medication, and influenza type or subtype were included as exposures in logistic regression models, and marginal adjusted risk ratios and 95% CIs were estimated to describe factors associated with aHF or aIHD.

Results: Among 89 999 adults with laboratory-confirmed influenza, 80 261 had complete medical record abstractions and available ICD codes (median age, 69 years [interquartile range, 54 to 81 years]) and 11.7% had an acute cardiovascular event. The most common such events (non-mutually exclusive) were aHF (6.2%) and aIHD (5.7%). Older age, tobacco use, underlying cardiovascular disease, diabetes, and renal disease were significantly associated with higher risk for aHF and aIHD in adults hospitalized with laboratory-confirmed influenza.

Limitation: Underdetection of cases was likely because influenza testing was based on practitioner orders. Acute cardiovascular events were identified by ICD discharge codes and may be subject to misclassification bias.

Conclusion: In this population-based study of adults hospitalized with influenza, almost 12% of patients had an acute cardiovascular event. Clinicians should ensure high rates of influenza vaccination, especially in those with underlying chronic conditions, to protect against acute cardiovascular events associated with influenza.

Primary Funding Source: Centers for Disease Control and Prevention.

Cardiovascular disease is the leading cause of death and health care expenditure in the United States (1). Acute infections (2, 3), specifically influenza virus infections (4-8), have been a clinically underrecognized contributor to the burden of cardiovascular disease. Annual influenza epidemics in the United States result in 140 000 to 810 000 hospitalizations and 12 000 to 61 000 deaths each year (9). Although respiratory disease is a hallmark of influenza virus infection, cardiovascular events are also important complications of influenza (8, 10).

A relationship between influenza virus infection and cardiovascular disease has been demonstrated through strong temporal associations between syndromic influenza activity and cardiovascular mortality (8, 11-15). In a recent study using laboratory-confirmed influenza, rates of acute myocardial infarction were higher in the 7 days after a positive result on an influenza test than in control time intervals (4). In addition, influenza may exacerbate other types of chronic cardiovascular conditions, such as heart failure, or contribute to acute cardiovascular events, including acute myocarditis (5, 16, 17), acute pericarditis (18, 19), and cardiac tamponade (20, 21). However, few population-based studies have estimated the frequency of acute cardiovascular events associated with influenza.

In this study, we describe the spectrum of acute cardiovascular events among adults hospitalized with laboratory-confirmed influenza between 2010 and 2018 using data from the U.S. Influenza Hospitalization Surveillance Network (FluSurv-NET). We also assess factors associated with risk for acute heart failure (aHF) and acute ischemic heart disease (aIHD).

Methods

Study Design, Setting, and Participants

Our study is a cross-sectional analysis of data from FluSurv-NET, a large, multicenter, U.S. network that is sponsored by the Centers for Disease Control and Prevention (CDC) and conducts population-based surveillance for hospitalizations associated with laboratory-confirmed influenza (22). The network was established in 2003 through a partnership among the CDC, state and local health departments, and academic institutions. Data from FluSurv-NET are used to generate age-stratified hospitalization rates (23) and national estimates of influenza disease burden (24, 25). This analysis includes adult patients aged 18 years or older who were hospitalized in the FluSurv-NET catchment area between 1 October and 30 April during the 2010-to-2011 through 2017-to-2018 influenza seasons. During this time, the FluSurv-NET catchment area (covering 9% of the U.S. population) included selected counties in California, Colorado, Connecticut, Georgia, Maryland, Michigan, Minnesota, New Mexico, New York, Ohio, Oregon, Tennessee, and Utah. Additional counties in Idaho (2010 to 2011), Iowa (2012 to 2013), Oklahoma (2010 to 2011), and Rhode Island (2010 to 2013) also contributed to the network.

The CDC determined that this surveillance project was not human subjects research; therefore, approval by the CDC's institutional review board was not required. Data were deidentified before delivery to the CDC. Each participating site submitted the FluSurv-NET protocol to their state and local institutional review boards for review as appropriate. In the preparation of this manuscript, we adhered to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) reporting guidelines.

Variables, Data Sources, and Measurements

We defined laboratory-confirmed influenza as a positive test result within 14 days before or 3 days after hospital admission by rapid antigen assay, reverse transcriptase polymerase

chain reaction, direct or indirect fluorescent staining, or viral culture. From medical records, trained surveillance officers abstracted patient demographic characteristics; underlying medical conditions; antiviral use; influenza vaccination status for the current season (vaccinated at least 2 weeks before hospital admission); discharge diagnoses and outcomes, including length of hospital stay; intensive care unit admission; mechanical ventilatory support; extracorporeal membrane oxygenation; and in-hospital death. We described the timing of earliest antiviral treatment with relation to hospital admission date. We defined early treatment as beginning antiviral therapy 2 days before through up to 1 day after hospital admission and late treatment as beginning antiviral therapy after 1 day of hospitalization. Data were not available to determine timing of treatment relative to the acute cardiovascular event.

We identified and classified acute cardiovascular events using primary and secondary discharge diagnostic codes from the International Classification of Diseases (ICD), Ninth Revision, Clinical Modification, and ICD, 10th Revision (up to 9 codes were abstracted for each FluSurv-NET patient) (Appendix Table 1, available at Annals.org). We restricted ICD codes to those that used the terms *acute*, *acute-on-chronic*, or *exacerbation* to better capture acute events. We also included diagnoses that are not known to be chronic conditions, including cardiac tamponade, cardiogenic shock, and hypertensive crisis. We excluded diagnoses for which we could not distinguish between acute and chronic conditions by ICD discharge codes alone, such as atrial fibrillation and other cardiac arrhythmias. We classified the acute cardiovascular events into the following 7 groups: acute myocarditis, acute pericarditis, aHF, aIHD, cardiac tamponade, cardiogenic shock, and hypertensive crisis. Consistent with proposed changes to ICD, 11th Revision, we classified cerebrovascular accidents and hemorrhages as neurologic diagnoses rather than acute cardiovascular events (26, 27).

Between the 2010-to-2011 and 2016-to-2017 influenza seasons, surveillance officers abstracted complete medical record data for all patients with laboratory-confirmed influenza identified in the FluSurv-NET catchment area. During the 2017-to-2018 influenza season, surveillance officers collected a minimum set of variables for all patients but implemented a sampling scheme for complete medical record abstraction for patients aged 50 years or older. Random numbers were autogenerated and assigned to each case as soon as a case identification number was entered into the database; random samples of cases, stratified by age group and surveillance site, were drawn using these random numbers. Individual surveillance sites were given the option to abstract complete medical record information from 25%, 50%, or 100% random samples of patients aged 65 years or older and 50% or 100% random samples of patients aged 50 to 64 years. Of the 14 surveillance sites in 2017 to 2018, 7 opted to review medical records on all identified cases and 7 implemented a sampling strategy. Complete medical record abstractions were done for all patients younger than 50 years and all patients of any age who died during their hospitalization (28). Among surveillance sites that chose to sample case report forms during the 2017-to-2018 season, the distribution of sampled versus nonsampled cases was even across facilities, showing that sampled cases were representative of the FluSurv-NET catchment area (data not shown).

Statistical Analysis

We used survey procedures in SAS, version 9.4 (SAS Institute), to appropriately weight data to reflect the probability of sampling for complete medical record abstraction for patients aged 50 years or older. Sample sizes are listed as unweighted numbers, whereas percentages, medians, and interquartile ranges are reported as weighted values. We described the frequency of demographic and clinical characteristics for patients with and without any acute cardiovascular event.

Influenza A subtype was not reported for 52% of patients with influenza A virus infection. We used multiple imputation (70 imputations) to estimate missing values of influenza A subtype using patient age, surveillance site, and admission month in the imputation model. Patients were excluded from the imputation analysis if influenza type could not be distinguished between influenza A and B or if they were co-infected with A(H1N1)pdm09 and A(H3N2). We analyzed each of the 70 imputed data sets using logistic regression models for aHF and aIHD and pooled the estimates using the built-in option in SAS-Callable SUDAAN for analyzing multiply imputed data in regression procedures.

We used bivariate and multivariable logistic regression models to estimate the adjusted prevalence, or marginal predicted probabilities, of aHF and aIHD as 2 separate outcomes and to identify risk factors for these outcomes using marginal standardization (29). Our final models included season, surveillance site, age, sex, race/ethnicity, body mass index (BMI), tobacco use history, chronic medical conditions (including atrial fibrillation, chronic heart failure or cardiomyopathy, coronary artery disease, diabetes, and chronic renal disease), influenza vaccination status for the current season, antiviral therapy, and influenza type or subtype. For our final analysis, we excluded patients who began influenza antiviral therapy more than 2 days before hospital admission, those who were missing information for BMI or vaccination status, and those for whom influenza subtype imputation was not done. We included antiviral therapy to adjust for possible confounding but could not assess effectiveness because the timing of therapy relative to the cardiovascular outcomes was unknown. We identified collinearity between chronic respiratory condition and tobacco use history; we chose to include tobacco use history in place of chronic respiratory condition in the final model. For each model, our comparison group consisted of patients who had no acute cardiovascular events.

For all of our data analyses, we used SAS software or SAS-Callable SUDAAN software, version 9.4, to account for the complex survey design and to conduct marginal standardization.

Role of the Funding Source

The CDC designed and conducted the study; received, managed, analyzed, and interpreted the data; prepared, reviewed, and approved the manuscript; and had a role in the decision to submit the manuscript for publication.

Results

During influenza seasons from 2010 through 2018, FluSurv-NET received reports of 89 999 adults hospitalized with laboratory-confirmed influenza (Figure 1). We excluded 1854 patients with no ICD discharge codes. Among 80 261 adults sampled for medical record review and included in our analysis (median age, 69 years [interquartile range, 54 to 81 years]), 11.7% had an ICD discharge code for an acute cardiovascular event, most commonly aHF (6.2%) or aIHD (5.7%) and less commonly hypertensive crisis (1.0%), cardiogenic shock (0.3%), acute myocarditis (0.1%), acute pericarditis (0.05%), or cardiac tamponade (0.02%).

The unadjusted weighted prevalence of acute cardiovascular events was higher in patients who had underlying medical conditions–particularly chronic cardiovascular conditions, chronic metabolic conditions, chronic renal disease, and chronic hematologic conditions- than in those without acute cardiovascular events (data not shown). In this study, 20.6% of those with chronic cardiovascular disease, 19.3% of those with chronic renal disease, and 14.8% of those with diabetes had an acute cardiovascular event (Appendix Table 2, available at Annals.org). Overall, 47.2% of patients received an influenza vaccine in the current season, 39.2% did not receive it, and 13.6% had unknown vaccination status (data not shown).

Among patients with an acute cardiovascular event, 53.5% had aHF, 49.3% aIHD, 8.3% hypertensive crisis, 2.7% cardiogenic shock, 0.8% acute myocarditis, 0.5% acute pericarditis, and 0.2% cardiac tamponade. Most patients with acute myocarditis, acute pericarditis, or cardiogenic shock were aged 18 to 64 years, whereas most with aHF or aIHD were aged 65 years or older (Figure 2).

Overall, patients with acute cardiovascular events had a median length of hospital stay of 5 days, 31.2% were admitted to the intensive care unit, 14.0% required mechanical ventilatory support, and 7.3% died in the hospital (Table 1). Patients with cardiogenic shock had the longest median length of stay (9 days), and 38.9% died during the hospitalization. When we excluded cardiogenic shock from the analysis, 6.4% of patients with another acute cardiovascular event died in the hospital. Among the 2683 patients who died in the hospital, 23.7% had an associated acute cardiovascular event, excluding the diagnosis of cardiogenic shock (data not shown). In-hospital outcomes did not differ substantively between male and female patients with acute cardiovascular events (data not shown).

After excluding patients who received antiviral treatment 2 days or more before hospital admission; those with missing data on antiviral treatment, vaccination status for the current season, and BMI; and those for whom influenza subtype was not imputed, we included 61 856 patients (Figure 1) in the multivariable logistic regression models to examine factors associated with aHF and aIHD.

Compared with patients aged 18 to 49 years, older patients had increased risk for aHF (50 to 64 years: adjusted risk ratio [aRR], 1.40 [95% CI, 1.22 to 1.61]; 65 to 74 years: aRR, 1.58 [CI, 1.36 to 1.84]; 75 to 84 years: aRR, 1.88 [CI, 1.62 to 2.18]; and ≥85 years: aRR, 2.32 [CI, 2.00 to 2.70]) (Table 2). Other factors associated with increased risk for aHF included

extreme obesity (aRR, 1.19 [CI, 1.06 to 1.33]), current tobacco use (aRR, 1.17 [CI, 1.07 to 1.28]), atrial fibrillation (aRR, 1.40 [CI, 1.30 to 1.52]), chronic heart failure or cardiomyopathy (aRR, 8.33 [CI, 7.60 to 9.12]), coronary artery disease (aRR, 1.18 [CI, 1.10 to 1.27]), diabetes mellitus (aRR, 1.09 [CI, 1.01 to 1.17]), and chronic renal disease (aRR, 1.22 [CI, 1.14 to 1.32]). Risk for aHF was significantly lower for patients vaccinated against influenza at least 2 weeks before hospitalization than for unvaccinated patients (aRR, 0.86 [CI, 0.80 to 0.92]).

Older age was also significantly associated with higher risk for aIHD compared with age 18 to 49 years (50 to 64 years: aRR, 2.04 [CI, 1.72 to 2.43]; 65 to 74 years: aRR, 2.93 [CI, 2.44 to 3.51]; 75 to 84 years: aRR, 3.43 [CI, 2.85 to 4.12]; and ≥85 years: aRR, 4.37 [CI, 3.64 to 5.25]) (Table 2). Other factors associated with higher risk for aIHD included current tobacco use (aRR, 1.33 [CI, 1.20 to 1.48]), chronic heart failure or cardiomyopathy (aRR, 2.11 [CI, 1.93 to 2.31]), coronary artery disease (aRR, 1.75 [CI, 1.61 to 1.91]), diabetes mellitus (aRR, 1.15 [CI, 1.06 to 1.24]), and chronic renal disease (aRR, 1.25 [CI, 1.15 to 1.36]). Women (aRR, 0.87 [CI, 0.80 to 0.93]) and obese patients (aRR, 0.84 [CI, 0.77 to 0.93]) had lower risk for aIHD, as did patients who were vaccinated against influenza at least 2 weeks before hospitalization compared with those who were not vaccinated (aRR, 0.80 [CI, 0.74 to 0.87]).

Patients who received late antiviral treatment had higher risk for aHF and aIHD than those who received early antiviral treatment; however, information on the timing of antiviral treatment in relation to that of acute cardiovascular events was not available.

Discussion

In this study of more than 80 000 adults hospitalized with laboratory-confirmed influenza in the United States, approximately 12% of patients had acute cardiovascular events, most commonly aHF and aIHD. Although respiratory tract diagnoses are most commonly associated with influenza (28), acute cardiovascular events are important contributors to influenza-related morbidity and mortality. Almost one third of patients with an acute cardiovascular event were admitted to the intensive care unit, and 7% (6% excluding those with cardiogenic shock) ultimately died during hospitalization, underscoring the severity of cardiovascular complications with concomitant influenza virus infection. Underlying cardiovascular disease was strongly associated with both aHF and aIHD among patients hospitalized with influenza. Our findings highlight the importance of preventing influenza virus infection, especially in those with underlying chronic conditions.

Influenza may be an important but underrecognized contributor to the health care burden of hospitalized cardiovascular disease. In 1 prospective study in which all patients admitted to a coronary care unit were systematically tested for influenza, 8% were found to have influenza virus infection (30). Another study estimated the proportion of myocardial infarction–associated hospitalizations that are related to influenza to be 3% to 5% in England and Wales and 8% in Hong Kong at the peak of influenza circulation (31). Costs associated with cardiovascular disease may increase in the next 20 years, with lost productivity from illness and premature death (32). Public health interventions should include focused attention on

preventable causes of this health care burden, including prevention of influenza virus infection.

Although this analysis was not designed to assess the effectiveness of influenza vaccination or antiviral medications, evidence suggests that these interventions may have benefits in attenuating disease severity. Several studies have found that vaccination (33, 34) and influenza antiviral medication (35, 36) help decrease severity of disease and symptom duration. Yet despite these benefits, influenza vaccination rates are suboptimal: Only 33.9% to 56.3% of U.S. adults (varying by state) received the influenza vaccine in the 2018-to-2019 season (37). Especially among patients with risk factors for acute cardiovascular events, practitioners may play an essential role in mitigating the burden of cardiovascular disease by maintaining high rates of annual influenza vaccination (38-41) and providing early antiviral treatment to patients with suspected or confirmed influenza (42-44).

The most common acute cardiovascular events among adults hospitalized with influenza were aHF and aIHD. Although causality cannot be determined from our study alone, the pathophysiologic mechanisms that lead to cardiovascular events after influenza virus infection have been described. For example, systemic inflammatory response in the setting of influenza virus infection promotes oxidative stress, leading to hemodynamic consequences and activation of prothrombotic pathways (13, 15, 45-47) as evidenced by increased levels of serum troponin (48) and myosin light chains (49) in some patients hospitalized with influenza. Patients with preexisting conditions may be at greater risk for cardiovascular decompensation because decreased circulatory reserve at baseline leads to increased risk for in-hospital morbidity and mortality in the setting of influenza infection (50, 51). In patients with aIHD, various factors—including direct results of plaque disruption (3), vasoconstrictive effects of systemic inflammation (46), increased metabolic demand from systemic inflammation (15), and ambient temperature (52, 53)—may be the basis for these acute cardiovascular events in the setting of influenza infection. Although direct associations between heart failure exacerbation and influenza have not been well characterized (54), aHF-associated hospitalizations correlate with influenza activity (55, 56). During the influenza season, practitioners should consider an influenza diagnosis when a patient is hospitalized with an exacerbation of or new-onset cardiovascular event (57). Early identification of influenza, especially in those at greater risk for complications like acute cardiovascular events, could lead to earlier treatment with antiviral medication, reduce unnecessary antibiotic use, and lessen the morbidity and mortality of disease (57).

We found that older patients may have a higher risk for aHF and aIHD when hospitalized with influenza, a finding supported by previous studies (4, 31, 58, 59). We showed that patients with preexisting cardiovascular conditions, namely chronic heart failure or cardiomyopathy, and known cardiovascular risk factors, such as tobacco use, diabetes, and renal disease, had the highest risk for aHF or aIHD with influenza. In fact, 1 in 5 patients with a chronic cardiovascular condition who were hospitalized with influenza also had an acute cardiovascular event during the hospitalization. Of note, extreme obesity was found to be associated with higher risk for aHF, but obesity was associated with lower risk for aIHD in patients hospitalized with influenza virus infection. In observational studies, this finding may be related to the previously described obesity paradox, whereby certain subgroups of

patients who are obese have better cardiovascular outcomes than those with lower BMI (60). Other explanations that contribute to these findings may include nonpurposeful weight loss associated with chronic disease (61), changes in inflammatory response due to obesity (62), increased muscle mass interpreted as obesity (61), or a practitioner's threshold for admission of patients who are obese or have a history of chronic comorbid conditions. Ultimately, the reasons for the reduced association between obesity and aIHD in patients with influenza are not clear, and additional studies are required to better understand these associations.

Our study adds to the growing body of literature on the effect of acute cardiovascular events on the morbidity and mortality associated with influenza. These include long hospital stays and severe in-hospital outcomes, including death. Previous studies have shown that patients with influenza virus infection and cardiovascular complications, such as heart failure (50) and acute myocardial infarction (63), had higher mortality than those without influenza. They demonstrate that cardiovascular complications related to influenza may be significant outcomes of infection and that estimations of influenza burden relying solely on respiratory diagnoses are likely to underestimate the true burden of influenza-related complications.

Our study has limitations to consider. First, patients were identified from practitioner-initiated influenza testing. Practitioners are more likely to test for influenza in patients presenting with symptoms of respiratory infection and other influenza-like illness (64); thus, we may have underestimated the true prevalence of influenza-associated cardiovascular events (65). Second, because our study included only hospitalized patients with laboratory-confirmed influenza, uncontrolled collider bias is possible if influenza testing is a common effect of the exposures we considered (66). Third, we used ICD discharge codes to classify acute cardiovascular event groups, and diagnoses were not based on laboratory confirmation of a cardiovascular event. Although ICD codes are a common method to identify cardiovascular complications (4, 15, 31, 55), administrative codes may be subject to misclassification bias if they are carried over from recent hospitalizations or if ICD coding is affected by billing practices, the experience of medical coders, or incomplete capture of medical information documented by the clinician (67). Using ICD discharge codes also limits our ability to distinguish between acute and chronic conditions and may bias the observed association between acute and underlying cardiovascular diseases. We attempted to lessen this risk for misclassification by selecting ICD discharge codes of diagnoses that were most likely limited to the current hospital stay. In addition, FluSurv-NET captures only the first 9 ICD codes listed in the medical record, and diagnoses listed thereafter are not included in the analysis. Fourth, we could not assess the timing of antiviral therapy relative to the onset of aHF or aIHD; thus, our finding of higher odds of aHF and aIHD among those who received late antiviral treatment should be interpreted with caution. Antiviral therapy was included in the model to control for confounding, and the aRRs should not be interpreted as a measure of antiviral effectiveness against aHF or aIHD. Last, we may not have captured all confounders within our regression models for aHF and aIHD. For example, hypertension and hyperlipidemia are known risk factors for heart failure and ischemic heart disease but were not collected as underlying conditions in FluSurv-NET.

In this study, acute cardiovascular events were common diagnoses among adults hospitalized with influenza, particularly among older patients and those with underlying chronic disease.

A high percentage of patients with acute cardiovascular events experienced in-hospital morbidity and mortality. Increasing rates of influenza vaccination, especially among those with cardiovascular risk factors, is essential in preventing infection and potentially attenuating influenza-related cardiovascular complications and adverse outcomes.

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Appendix

Appendix Table 1.

ICD Discharge Diagnostic Codes (ICD-9 and ICD-10), by Acute Cardiovascular Event

Disease Condition	ICD-9 Code	ICD-10 Code
Acute myocarditis		
Acute myocarditis	422	I40
Influenza due to other identified influenza virus with myocarditis	—	J10.82
Influenza due to unidentified influenza virus with myocarditis	—	J11.82
Acute pericarditis	420	I30
Cardiac tamponade	423.3	I31.4
Cardiogenic shock	785.51	R57.0
Acute heart failure		
Acute systolic heart failure	428.21	I50.21
Acute-on-chronic systolic heart failure	428.23	I50.23
Acute diastolic heart failure	428.31	I50.31
Acute-on-chronic diastolic heart failure	428.33	I50.33
Acute combined systolic and diastolic heart failure	428.41	I50.41
Acute-on-chronic combined systolic and diastolic heart failure	428.43	I50.43
Acute right heart failure	428.9	I50.811
Acute-on-chronic right heart failure	428.9	I50.813
Hypertensive crisis	—	I16

Disease Condition	ICD-9 Code	ICD-10 Code
Malignant essential hypertension	401.0	—
Malignant hypertensive heart disease	402.0	—
Malignant hypertensive heart disease without heart failure	402.00	—
Malignant hypertensive heart disease with heart failure	402.01	—
Malignant hypertensive renal disease	403.0	—
Malignant hypertensive heart and renal disease	404.0	—
Malignant secondary hypertension	405.0	—
Malignant renovascular hypertension	405.01	—
Other malignant secondary hypertension	405.09	—
Hypertensive urgency	—	I16.0
Hypertensive emergency	—	I16.1
Hypertensive crisis, unspecified	—	I16.9
Acute ischemic heart disease		
Unstable angina	411.1	I20.0
Acute myocardial infarction	410	I21
Acute myocardial infarction of anterolateral wall	410.0	—
Acute myocardial infarction of other anterior wall	410.1	—
Acute myocardial infarction of inferolateral wall	410.2	—
Acute myocardial infarction of inferoposterior wall	410.3	—
Acute myocardial infarction of other inferior wall	410.4	—
Acute myocardial infarction of other lateral wall	410.5	—
True posterior wall infarction	410.6	—
Subendocardial infarction	410.7	—
Acute myocardial infarction of other specified sites	410.8	—
Acute myocardial infarction of unspecified site	410.9	—
ST-segment elevation myocardial infarction of anterior wall	—	I21.0
ST-segment elevation myocardial infarction of inferior wall	—	I21.1
ST-segment elevation myocardial infarction of other sites	—	I21.2
ST-segment elevation myocardial infarction of unspecified site	—	I21.3
Non-ST-segment elevation myocardial infarction	410.71	I21.4
Acute myocardial infarction, unspecified	—	I21.9
Subsequent ST-segment elevation and non–ST-segment elevation myocardial infarction	410.01–410.11	I22
Subsequent ST-segment elevation myocardial infarction of anterior wall	410.21, 410.31, 410.41	I22.0
Subsequent ST-segment elevation myocardial infarction of inferior wall	410.21, 410.31, 410.41	I22.1
Subsequent non-ST-segment elevation myocardial infarction	410.71	I22.2
Subsequent ST-segment elevation myocardial infarction of other sites	410.51, 410.61, 410.81	I22.8
Subsequent ST-segment elevation myocardial infarction of unspecified site	410.91	I22.9
Other acute and subacute forms of ischemic heart disease	411	I24

ICD = International Classification of Diseases; ICD-9 = ICD, Ninth Revision; ICD-10 = ICD, 10th Revision.

Appendix Table 2.

Unadjusted Weighted Prevalence of Acute Cardiovascular Events, by Patient Characteristic*

Characteristic	Total (*n* = 80 261), *n*	Patients With Acute Cardiovascular Events (*n* = 9046), *n (%)*	Patients Without Acute Cardiovascular Events (*n* = 71 215), *n (%)*
Influenza season			
2010–2011	4520	360 (8.0)	4160 (92.0)
2011–2012	1842	113 (6.1)	1729 (93.9)
2012–2013	10 085	1087 (10.8)	8998 (89.2)
2013–2014	7978	717 (9.0)	7261 (91.0)
2014–2015	14 902	1820 (12.2)	13 082 (87.8)
2015–2016	7263	711 (9.8)	6552 (90.2)
2016–2017	15 275	1887 (12.4)	13 388 (87.6)
2017–2018	18 396	2351 (13.2)	16 045 (86.8)
Age			
18–49 y	16 142	656 (4.1)	15 486 (95.9)
50–64 y	19 020	1652 (8.9)	17 368 (91.1)
65–74 y	14 456	1726 (12.0)	12 730 (88.0)
75–84 y	14 057	2049 (14.7)	12 008 (85.3)
≥85 y	16 586	2963 (17.7)	13 623 (82.3)
Sex			
Male	35 571	4361 (12.5)	31 210 (87.5)
Female	44 690	4685 (10.8)	40 005 (89.2)
Race/ethnicity			
White, non-Hispanic	49 308	5887 (12.2)	43 421 (87.8)
Black, non-Hispanic	14 674	1534 (10.5)	13 140 (89.5)
Hispanic	5657	458 (8.7)	5199 (91.3)
Other	10 622	1167 (11.4)	9455 (88.6)
BMI			
Underweight (<18.5 kg/m^2)	3068	335 (10.8)	2733 (89.2)
Normal (18.5–24.9 kg/m^2)	20 921	2480 (12.0)	18 441 (88.0)
Overweight (25.0–29.9 kg/m^2)	20 516	2368 (11.9)	18 148 (88.1)
Obesity(30.0–39.9 kg/m^2)	19 979	2223 (11.5)	17 756 (88.5)
Extreme obesity (≥40.0 kg/m^2)	7376	889 (12.3)	6487 (87.7)
Influenza vaccination status in corresponding year			
Yes	34 732	4511 (10.0)	32 921 (90.0)
No	32 218	3157 (12.3)	29 061 (87.7)
Missing status	10 611	1378 (13.5)	9233 (86.5)
Tobacco use history			
Current†	15 427	1526 (10.2)	13 901 (89.8)
Previoust‡	22 384	3178 (14.5)	19 206 (85.5)
Never used or unknown†	36 416	3882 (10.9)	32 534 (89.1)

Characteristic	Total (n = 80 261), n	Patients With Acute Cardiovascular Events (n = 9046), n (%)	Patients Without Acute Cardiovascular Events (n = 71 215), n (%)
Medical history[§]			
No known medical history	6064	312 (5.3)	5752 (94.7)
Chronic disease			
Neurologic	19 829	2254 (11.3)	17 575 (88.7)
Respiratory tract	33 481	3770 (11.5)	29 711 (88.5)
Cardiovascular	31 919	6519 (20.6)	25 400 (79.4)
Atrial fibrillation	10 467	2370 (22.8)	8097 (77.2)
Coronary artery disease	15 956	3400 (21.5)	12 556 (78.5)
Chronic heart failure or cardiomyopathy	14 866	4589 (31.0)	10 277 (69.0)
Metabolic	33 578	4697 (14.1)	28 881 (85.9)
Diabetes mellitus	24 637	3637 (14.8)	21 000 (85.2)
Renal	15 655	3037 (19.3)	12 618 (80.7)
Hepatic disease[†]	3065	319 (10.9)	2746 (89.1)
Hematologic[†]	3677	493 (13.6)	3184 (86.4)
Immunosuppressive[†]	13 669	1247 (9.3)	12 422 (90.7)
Pregnant	2188	5 (0.2)	2183 (99.8)
Antiviral therapy[‖]			
No treatment	10 579	1115 (10.8)	9464 (89.2)
Early treatment	62 772	6903 (11.3)	55 869 (88.7)
Late treatment[¶]	6312	973 (15.8)	5339 (84.2)
Influenza type or subtype, imputed[**]			
A(H1N1) pdm09	15 443	1333 (8.8)	14 110 (91.2)
A(H3N2)	49 597	6030 (12.4)	43 567 (87.6)
B	15 024	1671 (11.4)	13 353 (88.6)

BMI = body mass index.

[*] Numbers are unweighted values, and percentages are weighted values. Percentages are row percentages.

[†] From 2011–2018.

[‡] From 2012–2018.

[§] Diagnoses are not mutually exclusive.

[‖] 598 patients received influenza antiviral therapy >2 d before hospital admission and were excluded from this frequency. Treatment timing was relative to the patient's hospital admission date and not relative to the acute cardiovascular event or initial symptom onset.

[¶] 90 patients received antiviral treatment >6 d after hospital admission.

[**] Patients were excluded from influenza subtype imputation if influenza type could not be distinguished between influenza A and B or if they had A(H1N1)pdm09 and A(H3N2) co-infection (n = 197); frequencies are averaged from 70 imputed data sets.

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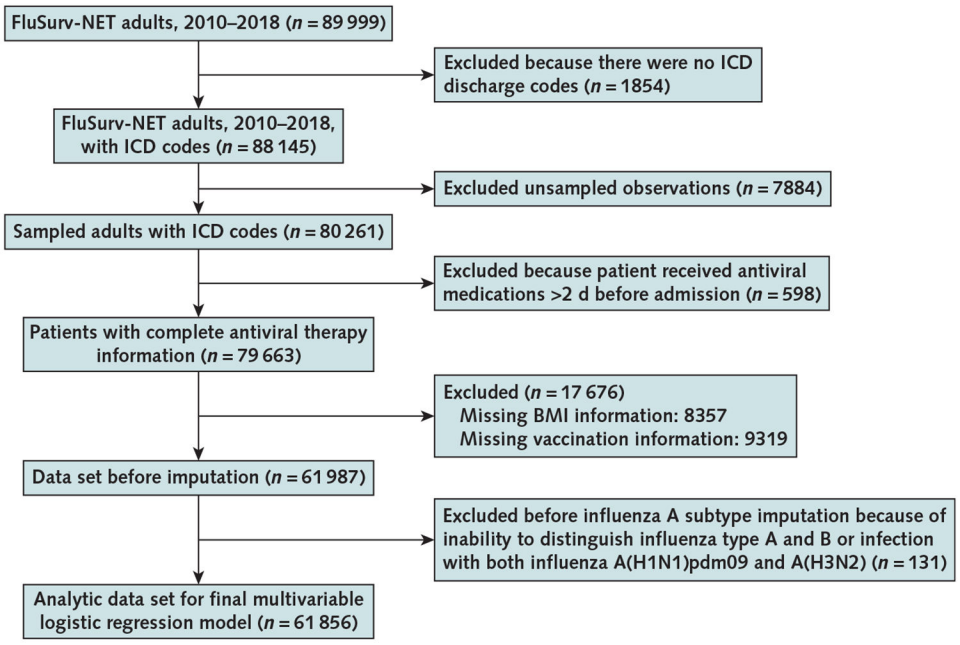

Figure 1.

Flow chart of study population.

BMI = body mass index; FluSurv-NET = U.S. Influenza Hospitalization Surveillance Network; ICD = International Classification of Diseases.

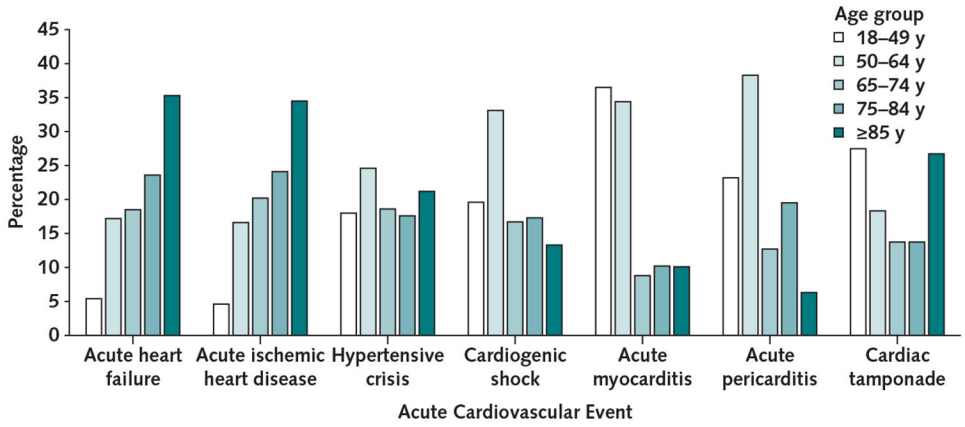

Figure 2.
Distribution of acute cardiovascular events, by age group (n = 9046).

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Table 1.

Hospital Outcomes of Adults With Laboratory-Confirmed Influenza Virus Infection, by Acute Cardiovascular Event*

Acute Diagnosis	Total†	Median Length of Stay (IQR), *d*	Intensive Care Unit Admission	Mechanical Ventilatory Support	Extracorporeal Membrane Oxygenation	In-Hospital Death
All acute cardiovascular events‡	9046 (11.5)	5 (3–8)	2901 (31.2)	1319 (14.0)	40 (0.4)	740 (7.3)
Acute heart failure	4828 (6.2)	5 (3–9)	1443 (29.2)	595 (11.9)	15 (0.3)	352 (6.5)
Acute ischemic heart disease	4412 (5.7)	5 (3–8)	1645 (35.9)	777 (16.8)	13 (0.3)	423 (8.5)
Hypertensive crisis	788 (1.0)	4 (2–6)	182 (23.4)	60 (7.6)	1 (0.1)	10 (1.2)
Cardiogenic shock	261 (0.3)	9 (4–17)	239 (92.2)	174 (65.8)	15 (5.6)	105 (38.9)
Acute myocarditis	74 (0.1)	4 (2–8)	33 (46.9)	21 (30.4)	6 (7.6)	9 (11.3)
Acute pericarditis	42 (0.1)	3 (2–7)	12 (32.0)	2 (10.9)	2 (4.2)	1 (2.1)
Cardiac tamponade	19 (0.03)	7 (5–12)	9 (54.2)	3 (13.8)	2 (9.2)	1 (4.6)
Noncardiovascular event	71 215 (88.5)	3 (2–5)	9897 (13.5)	3907 (5.3)	191 (0.3)	1943 (2.5)

FluSurv-NET = U.S. Influenza Hospitalization Surveillance Network; IQR = interquartile range.

*Numbers are unweighted values, and percentages are weighted values. Values are numbers (percentages) unless otherwise specified.

†Percentage listed out of all FluSurv-NET patients with and without acute cardiovascular events (n = 80 261).

‡Acute cardiovascular events are non–mutually exclusive diagnoses.

Table 2.

Factors Associated With Acute Ischemic Heart Disease and Acute Heart Failure in Adults Hospitalized With Influenza (n = 61 856)*

Factor	Acute Heart Failure			Acute Ischemic Heart Disease		
	Unadjusted Risk Ratio (95% CI)	Adjusted Prevalence (95% CI)	Adjusted Risk Ratio (95% CI)	Unadjusted Risk Ratio (95% CI)	Adjusted Prevalence (95% CI)	Adjusted Risk Ratio (95% CI)
Age group						
18–49 y	Reference	3.90 (3.39–4.39)	Reference	Reference	2.07 (1.74–2.39)	Reference
50–64 y	2.6 (2.28–2.97)	5.46 (5.04–5.88)	1.40 (1.22–1.61)	2.94(2.54–3.41)	4.12 (3.83–4.59)	2.04 (1.72–2.43)
65–74 y	3.51 (3.06–4.01)	6.17 (5.68–6.66)	1.58 (1.36–1.84)	4.45 (3.84–5.16)	6.04 (5.52–6.56)	2.93 (2.44–3.51)
75–84 y	4.63 (4.07–5.28)	7.31 (6.79–7.82)	1.88 (1.62–2.18)	5.55 (4.80–6.41)	7.07 (6.52–7.63)	3.43 (2.85–4.12)
≥85 y	5.95 (5.25–6.73)	9.04 (8.47–9.62)	2.32 (2.00–2.70)	6.84 (5.95–7.86)	9.02 (8.36–9.68)	4.37 (3.64–5.25)
Sex						
Male	Reference	6.81 (6.48–7.14)	Reference	Reference	6.43 (6.09–6.76)	Reference
Female	0.89 (0.84–0.95)	6.74 (6.43–7.05)	0.99 (0.93–1.06)	0.77 (0.73–0.82)	5.56 (5.27–5.86)	0.87 (0.80–0.93)
Race/ethnicity						
White, non-Hispanic	Reference	6.84 (6.56–7.12)	Reference	Reference	5.83 (5.56–6.09)	Reference
Black, non-Hispanic	0.76 (0.70–0.83)	6.41 (5.87–6.95)	0.94 (0.85–1.03)	0.77 (0.70–0.84)	6.02 (5.4–6.60)	1.03 (0.93–1.15)
Hispanic	0.65 (0.57–0.76)	7.15 (6.10–8.20)	1.05 (0.90–1.22)	0.75 (0.65–0.87)	6.53 (5.42–7.64)	1.12 (0.94–1.34)
Other	0.82 (0.74–0.90)	6.74 (6.03–7.45)	0.99 (0.88–1.10)	1.06 (0.96–1.16)	6.46 (5.77–7.15)	1.11 (0.99–1.25)
BMI						
Underweight(<18.5 kg/m^2)	0.77 (0.64–0.93)	5.64 (4.61–6.66)	0.84 (0.70–1.02)	0.97 (0.82–1.13)	6.80 (5.71–7.90)	1.05 (0.89–1.25)
Normal (18.5–24.9 kg/m^2)	Reference	6.68 (6.26–7.10)	Reference	Reference	6.47 (6.05–6.88)	Reference
Overweight (25.0–29.9 kg/m^2)	1.01 (0.92–1.09)	6.27 (5.87–6.67)	0.94 (0.86–1.02)	0.94 (0.86–1.02)	5.88 (5.47–6.28)	0.91 (0.83–1.00)
Obesity (30.0–39.9 kg/m^2)	1.08 (1.00–1.18)	7.07 (6.65–7.50)	1.06 (0.97–1.15)	0.78 (0.71–0.85)	5.46 (5.06–5.86)	0.84 (0.77–0.93)
Extreme obesity (≥40.0 kg/m^2)	1.3 (1.18–1.45)	7.94 (7.19–8.68)	1.19 (1.06–1.33)	0.68 (0.60–0.78)	5.74 (4.95–6.52)	0.89 (0.76–1.03)
Tobacco use						
None	Reference	6.57 (6.24–6.90)	Reference	Reference	5.62 (5.31–5.94)	Reference
Current	0.86 (0.79–0.94)	7.70 (7.11–8.30)	1.17 (1.07–1.28)	0.98 (0.90–1.08)	7.47 (6.81–8.13)	1.33 (1.20–1.48)
Previous	1.41 (1.31–1.51)	6.66 (6.30–7.03)	1.01 (0.94–1.09)	1.37 (1.28–1.48)	5.82 (5.46–6.18)	1.03 (0.95–1.13)
Medical history†						
Atrial fibrillation	3.49 (3.28–3.71)	8.56 (8.02–9.10)	1.40 (1.30–1.52)	1.95 (1.80–2.11)	6.32 (5.76–6.88)	1.08 (0.97–1.19)

Factor	Acute Heart Failure			Acute Ischemic Heart Disease		
	Unadjusted Risk Ratio (95% CI)	Adjusted Prevalence (95% CI)	Adjusted Risk Ratio (95% CI)	Unadjusted Risk Ratio (95% CI)	Adjusted Prevalence (95% CI)	Adjusted Risk Ratio (95% CI)
Chronic heart failure or cardiomyopathy	11.27 (10.55–12.04)	20.33 (19.39–21.26)	8.33 (7.60–9.12)	3.05 (2.86–3.25)	10.05 (9.36–10.74)	2.11 (1.93–2.31)
Coronary artery disease	2.78 (2.62–2.95)	7.53 (7.11–7.96)	1.18 (1.10–1.27)	2.81 (2.64–3.00)	8.63 (8.08–9.18)	1.75 (1.61–1.91)
Diabetes mellitus	1.67 (1.58–1.78)	7.11 (6.73–7.49)	1.09 (1.01–1.17)	1.42 (1.33–1.52)	6.51 (6.11–6.90)	1.15 (1.06–1.24)
Chronic renal disease	2.53 (2.38–2.69)	7.73 (7.30–8.16)	1.22 (1.14–1.32)	1.93 (1.80–2.07)	7.00 (6.51–7.49)	1.25 (1.15–1.36)
Influenza vaccination status						
Vaccinated	0.74 (0.69–0.79)	6.39 (6.11–6.67)	0.86 (0.80–0.92)	0.81 (0.75–0.87)	5.48 (5.21–5.75)	0.80 (0.74–0.87)
Not vaccinated	Reference	7.44 (7.05–7.83)	Reference	Reference	6.82 (6.43–7.21)	Reference
Antiviral therapy‡						
No treatment	1.02 (0.93–1.11)	7.11 (6.50–7.72)	1.10 (1.00–1.20)	0.86 (0.78–0.96)	5.79 (5.14–6.43)	0.99 (0.88–1.11)
Early treatment	Reference	6.47 (6.22–6.72)	Reference	Reference	5.86 (5.62–6.10)	Reference
Late treatment	1.64 (1.49–1.79)	9.25 (8.39–10.10)	1.43 (1.29–1.58)	1.3 (1.18–1.44)	7.56 (6.61–8.32)	1.27 (1.13–1.44)
Influenza type or subtype						
B	Reference	6.67 (6.15–7.18)	Reference	Reference	5.59 (5.09–6.10)	Reference
A(H1N1)pdm09	0.77 (0.69–0.86)	7.22 (6.27–8.17)	1.08 (0.93–1.26)	0.73 (0.65–0.83)	6.38 (5.34–7.42)	1.14 (0.95–1.37)
A(H3N2)	1.09 (1.00–1.18)	6.71 (6.39–7.03)	1.01 (0.92–1.10)	1.16 (1.06–1.27)	6.00 (5.69–6.32)	1.07 (0.96–1.20)

BMI = body mass index.

*Patients were excluded if they were missing BMI, were missing influenza vaccination information, had been treated with influenza antiviral medication >2 d before hospital admission, had an infection that could not be distinguished between influenza type A and B, or were co-infected with A(H1N1)pdm09 and A(H3N2). To adjust for possible confounding by site, we included site as a variable in the model for both acute heart failure and acute ischemic heart disease. The final models for both of these conditions were adjusted for season, surveillance site, age group, sex, race/ethnicity, BMI, tobacco use history, medical history of atrial fibrillation, chronic congestive heart failure or cardiomyopathy, coronary artery disease, diabetes mellitus, chronic renal disease, influenza vaccination status, antiviral therapy, and influenza type or subtype. Regression models were run on each of the 70 imputed data sets and combined using SAS Callable-SUDAAN.

†For each medical condition, no history of the condition was used as the reference group.

‡Antiviral treatment timing was determined relative to the patient's admission date and not the acute cardiovascular event or initial symptom onset.