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Influenza Vaccine in Heart Failure

Cumulative Number of Vaccinations, Frequency, Timing, and Survival: A Danish Nationwide Cohort Study

Editorial, see p XXX

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BACKGROUND: Influenza infection is a serious event for patients with heart failure (HF). Little knowledge exists about the association between influenza vaccination and outcome in patients with HF. This study sought to determine whether influenza vaccination is associated with improved long-term survival in patients with newly diagnosed HF.

METHODS: We performed a nationwide cohort study including all patients who were >18 years of age and diagnosed with HF in Denmark in the period of January 1, 2003, to June 1, 2015 (n=134 048). We collected linked data using nationwide registries. Vaccination status, number, and frequency during follow-up were treated as time-varying covariates in time-dependent Cox regression.

RESULTS: Follow-up was 99.8% with a median follow-up time of 3.7 years (interquartile range, 1.7–6.8 years). The vaccination coverage of the study cohort ranged from 16% to 54% during the study period. In unadjusted analysis, receiving ≥1 vaccinations during follow-up was associated with a higher risk of death. After adjustment for inclusion date, comorbidities, medications, household income, and education level, receiving ≥1 vaccinations was associated with an 18% reduced risk of death (all-cause: hazard ratio, 0.82; 95% CI, 0.81–0.84; $P<0.001$; cardiovascular causes: hazard ratio, 0.82; 95% CI, 0.81–0.84; $P<0.001$). Annual vaccination, vaccination early in the year (September to October), and greater cumulative number of vaccinations were associated with larger reductions in the risk of death compared with intermittent vaccination.

CONCLUSIONS: In patients with HF, influenza vaccination was associated with a reduced risk of both all-cause and cardiovascular death after extensive adjustment for confounders. Frequent vaccination and vaccination earlier in the year were associated with larger reductions in the risk of death compared with intermittent and late vaccination.

Key Words: communicable diseases ■ heart failure ■ influenza, human ■ prognosis ■ survival ■ therapeutics ■ vaccination

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Clinical Perspective

What Is New?

- Currently, little is known about the effect of influenza vaccination on survival in heart failure.
- This study assessed the association between influenza vaccination and survival in a large, nationwide cohort of unselected patients with heart failure.
- The present study is the largest cohort study examining outcomes after influenza vaccination in patients with heart failure.

What Are the Clinical Implications?

- Our study suggests that influenza vaccination may improve outcome in patients with heart failure, but because this was an observational study, our results must be replicated in randomized clinical trials before finite conclusions can be drawn.

Heart failure is responsible for significant morbidity and mortality.[1] Heart failure affects >6.5 million individuals in the United States alone, and this number is expected to increase significantly by 2030.[1–3] Hence, a clear need for continued efforts to improve management and treatment of patients with heart failure remains.

An influenza infection is a serious event for patients with heart failure.[4] Patients with heart failure have decreased circulatory reserve and often exhibit signs of frailty,[5] and >80% of patients are >65 years of age.[1] Hence, patients with heart failure may fail to meet the increased metabolic demand of infection, and this may possibly result in decompensation or exacerbation of heart failure symptoms.

Several studies have suggested that influenza vaccination may be beneficial in high-risk cardiovascular conditions.[6] Thus, the European Society of Cardiology and the American College of Cardiology/American Heart Association encourage annual influenza vaccination in patients with heart failure.[7–9] However, in the heart failure guidelines, no class of recommendation or level of evidence is given for influenza vaccination of patients with heart failure because of a lack of sufficient evidence.[7–9] Although a few observational studies have indicated that influenza vaccination may improve outcome in heart failure,[10,11] there have been no randomized controlled trials to establish benefits among patients with heart failure receiving an influenza vaccine or placebo.

Given these preliminary results, it may be hypothesized that influenza vaccination may improve prognosis in patients with heart failure. A randomized controlled trial to test the effects of a high-dose trivalent influenza vaccine versus a standard-dose quadrivalent vaccine on outcome in heart failure and other high-risk cardiovascular patients is currently enrolling (INVESTED [Influenza Vaccine to Effectively Stop Cardio Thoracic Events and Decompensated Heart Failure], ClinicalTrials.gov identifier NCT02787044). However, it will be some years before the results of this trial are available, and in daily clinical practice, the question of any influenza vaccine versus no vaccine remains up for debate. Although a few studies have indicated beneficial effects with influenza vaccination in patients with heart failure, several questions remain about the effect of the cumulative number of vaccinations, the importance of vaccination frequency, vaccination timing, and whether a dose-response relationship applies. If influenza vaccination significantly improves survival in heart failure, perhaps it should be given more emphasis in heart failure guidelines. Hence, our aim was to investigate whether influenza vaccination after heart failure diagnosis was associated with reduced all-cause and cardiovascular mortality in a Danish nationwide cohort including all patients with a first diagnosis of heart failure who survived for >30 days after diagnosis.

METHODS

The data, analytical methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure. Because this study used data from human subjects, the data and everything pertaining to the data are governed by the Danish Data Protection Agency and cannot be made available to other researchers.

Data Sources

In Denmark, a unique personal identification number is assigned to all individuals at the time of birth or immigration. This unique identifier is used throughout the comprehensive Danish Civil Registration System,[12] which allows linkage of health and administrative data at the individual level[13] and ensures near-complete follow-up. All Danish citizens in Denmark have equal access to free government-paid health care regardless of socioeconomic status, including both primary and hospital care. For this study, anonymized data were retrieved from 5 different registries made available by Statistics Denmark, a central government authority, after central encryption of the unique identifiers.[12] More detail, including an overview of registries used in this study, is available in the online-only Data Supplement ("Data sources" section and Table I in the online-only Data Supplement). In Denmark, ethics committee approval and informed consent are not warranted for registry-based studies using anonymized data provided by Statistics Denmark.

Study Subjects

We identified all patients in Denmark diagnosed with new heart failure in the period of January 1, 2003, to June 1, 2015 (*International Classification of Diseases, Tenth Revision* [*ICD-10*] codes I50, I110, I130, and I132; n=151 328), using the Danish National Patient Registry,[14,15] which contains records of all inpatient and outpatient diagnoses from all hospitals

in Denmark coded with *ICD-10* since 1994. Patients who died within 30 days from their heart failure diagnosis were excluded (n=16 711). Five hundred sixty-nine patients were excluded because they were <18 years of age. This resulted in a final study population of 134 048 patients.

Influenza Vaccination Status

In Denmark, influenza vaccination is recommended by the Danish Health Authority and is offered free of charge to individuals with cardiovascular disease (including heart failure). A record of administered vaccines for an individual patient can be retrieved with the use of the unique personal identification within the Danish National General Practitioners Reimbursement Registry. General practitioner consultations are free for all Danish citizens, and general practitioners are paid on a fee-for-service basis by the Danish government. With the purpose of assessing exposure to influenza vaccination, we defined the following variables: (1) vaccination exposure (yes/no), defined as whether a patient received at least 1 influenza vaccination within the follow-up period and thus after their heart failure diagnosis; (2) the cumulative number of vaccinations during the follow-up period; (3) the vaccination frequency during the follow-up period; and (4) the time of year for each administrated vaccine. Multiple vaccinations recorded as being received on the same day were treated as 1 vaccination. Vaccination frequency (annual vaccination versus less frequent than annual) was defined using the time span between successive vaccinations, which was updated for each patient throughout the follow-up period.

Baseline Characteristics

Information on baseline characteristics was collected from the National Patient Registry, the National Prescription Registry, and the National Population Registry. Further details are provided in the online-only Data Supplement ("Baseline characteristics" section and Tables II and III).

End Points

The primary end points of this study were all-cause death and cardiovascular death. This information was retrieved from the Danish National Cause of Death Registry. Cardiovascular death was defined as cause of death coded as *ICD-10* code I00-I99. Patients were followed up from the time of their heart failure diagnosis until death, emigration, or the end of the follow-up period. We had access to follow-up data on mortality status until January 1, 2017. However, data on the cause of death were available only until January 1, 2016. Therefore, the patients were followed up for all-cause death until January 1, 2017, and for cardiovascular death until January 1, 2016. Secondary end points of this study were incident atrial fibrillation or flutter (AF/AFL; *ICD-10* code I48) and a composite outcome consisting of ventricular tachycardia or ventricular fibrillation (*ICD-10* codes I470, I472, and I490) and cardiac arrest (*ICD-10* code I46). This information was obtained from the Danish National Patient Registry.[14] The positive predictive values for these diagnoses in the Danish registries are 80% (95% CI, 71–87) for ventricular tachycardia/ventricular fibrillation, 94% (95% CI, 88–97) for cardiac arrest, and 95% (95% CI, 89–98) for AF/AFL.[16] We also assessed the incidence of a composite end point consisting of hospitalization for influenza or pneumonia. This information was obtained from the Danish National Patient Registry.[14] Information on the incidence of the secondary end points was available up to January 1, 2016.

Statistical Analysis

Differences in continuous variables between groups were compared with the Student *t* test or the Wilcoxon rank-sum test as appropriate. Categorical variables were compared with the χ^2 test. Patients who emigrated from Denmark before the end of the study were censored from the analysis at the time of emigration (n=667). Our study examined a classifying exposure (influenza vaccination) administered during the follow-up period. Hence, our study is prone to survival bias.[17,18] Survival bias may be managed by the use of time-dependent Cox regression.[17–19] Therefore, vaccination exposure during follow-up (≥1), cumulative number of vaccinations, vaccination frequency based on the time span between successive vaccinations, and vaccination time of year were all treated as time-dependent covariates in the Cox regression models as appropriate. We constructed multivariable time-dependent Cox regression models with adjustment for all variables in Table 1 with the addition of inclusion year. The online-only Data Supplement provides further details ("Statistical Analysis" section). In influenza seasons 2007 to 2008 and 2015 to 2016, the vaccine was partially mismatched to the circulating influenza strains (see the online-only Data Supplement, "Landmark analysis and influenza vaccine match during the study period" section, for further details). To determine whether the association between vaccination and outcome differed in these 2 seasons compared with the other season, we also analyzed the association between influenza vaccination and outcome in each influenza season included in the study period. In these analyses, follow-up was counted from September 1 to April 1 the next year, encompassing the influenza season in Denmark. The "Landmark analysis and influenza vaccine match during the study period" section in the online-only Data Supplement provides further details on these analyses.

RESULTS

Follow-Up and Vaccination Status

The median follow-up for all-cause death was 3.7 years (interquartile range, 1.7–6.8 years). The median follow-up for cardiovascular death was 3.3 years (interquartile range, 1.3–6.3 years). Follow-up was 99.8%. Vaccines administered in September to December accounted for 98% of all vaccinations. The vaccination coverage of the study cohort varied by year and ranged from 16% in 2003 to 52% in 2015 with a peak of 54% in 2009 (Figure 1). During follow-up, 77 956 (58%) patients died of all causes and 47 966 (36%) died of cardiovascular causes.

Baseline Characteristics by Vaccination Status

Baseline characteristics for the overall cohort and stratified by vaccination status are presented in Table 1. Patients who received ≥1 vaccinations during follow-up

Table 1. Baseline Characteristics Stratified by Vaccination Status After Heart Failure Diagnosis

Demographics	All Patients	No Vaccine	1 or >1 Vaccine	*P* Value
n (%)	134048	55669 (42)	78379 (58)	
Age, y (SD)	73.3 (13.1)	72.8 (14.6)	73.7 (11.8)	<0.001
Male, n (%)	74940 (55.9)	30720 (55.2)	44220 (56.4)	<0.001
Household income quartile, n (%)*				<0.001
1	NA	13875 (25.1)	14350 (18.4)	
2	NA	13938 (25.3)	19594 (25.1)	
3	NA	12889 (23.4)	21893 (28.0)	
4	NA	14481 (26.2)	22342 (28.6)	
Highest education level, n (%)				<0.001
Basic school <10 y	57657 (43.0)	23240 (41.2)	34417 (43.9)	
High school, +3 y	2053 (1.5)	951 (1.7)	1102 (1.4)	
Vocational education	38474 (28.7)	14956 (26.9)	23518 (30.0)	
Short/medium higher, +2–4 y	11743 (8.8)	4407 (7.9)	7336 (9.4)	
Long higher, +5 y or more	4073 (3.0)	1543 (2.8)	2530 (3.2)	
Unknown	20048 (15.0)	10572 (19.0)	9476 (12.1)	
Prior vaccine, n (%)	60272 (45.0)	14648 (26.3)	45624 (58.12)	<0.001
Implantable cardioverter-defibrillator, n (%)	3495 (2.0)	1208 (1.4)	2287 (2.6)	<0.001
Comorbidities, n (%)				
Hypertension	52020 (38.8)	20400 (36.7)	31620 (40.3)	<0.001
Acute myocardial infarction	27167 (20.3)	11168 (20.1)	15999 (20.4)	0.11
Ischemic heart disease	52357 (39.1)	19636 (35.3)	32721 (41.2)	<0.001
Valvular disease	17102 (12.8)	6846 (12.3)	10256 (13.1)	<0.001
Cerebrovascular disease	16192 (12.1)	7276 (13.1)	8916 (11.4)	<0.001
Bleeding	15150 (11.3)	6563 (11.8)	8587 (11.0)	<0.001
Systemic embolus	4234 (3.2)	1875 (3.4)	2359 (3.0)	<0.001
Cancer	14631 (10.9)	6905 (12.4)	7726 (9.9)	<0.001
Cardiac arrhythmia	51623 (38.5)	20560 (36.9)	31063 (39.6)	<0.001
AF/AFL	44681 (33.3)	17963 (32.2)	26718 (34.1)	<0.001
Chronic renal failure	6791 (5.1)	3369 (6.1)	3422 (4.4)	<0.001
Acute renal failure	4669 (3.5)	2419 (4.4)	2250 (2.9)	<0.001
Anemia	12767 (9.5)	6074 (10.9)	6693 (8.5)	<0.001
Diabetes mellitus	21379 (16.0)	8318 (14.9)	13061 (16.7)	<0.001
Diabetes mellitus with complications	13864 (10.3)	5721 (10.3)	8143 (10.4)	0.51
Chronic obstructive pulmonary disease	23706 (17.7)	9093 (16.3)	14613 (18.6)	<0.001
Peripheral vascular disease	8474 (6.3)	3890 (7.0)	4584 (5.9)	<0.001
Liver disease	2096 (1.6)	1055 (1.9)	1041 (1.3)	<0.001
Hemiplegia or paraplegia	356 (0.3)	153 (0.3)	203 (0.3)	0.58
Rheumatic disease	4375 (3.3)	1753 (3.2)	2622 (3.4)	0.05
Peptic ulcer	9527 (7.1)	4055 (7.3)	5472 (7.0)	0.03
Medications, n (%)				
Statin	57214 (42.7)	19946 (35.8)	37268 (47.6)	<0.001
Renin-angiotensin system inhibitor	85189 (63.6)	32825 (56.0)	52364 (66.8)	<0.001
Antithrombotic	98938 (73.8)	38387 (67.0)	60551 (77.2)	<0.001
β-Blocker	75909 (56.6)	29457 (52,9)	46452 (59,3)	<0.001
Diuretic	103204 (77.0)	42104 (75.6)	61100 (78.0)	<0.001

(*Continued*)

Table 1. Continued

Demographics	All Patients	No Vaccine	1 or >1 Vaccine	*P* Value
Spironolactone	26507 (19.8)	11058 (19.9)	15449 (19.7)	0.49
Heart failure triple therapy†	14300 (10.7)	5432 (9.8)	8868 (11.3)	<0.001
Digoxin	27534 (20.5)	11415 (20.5)	16119 (20.6)	0.79
Calcium antagonist	36239 (27.0)	13484 (24.2)	22755 (29.0)	<0.001
Aspirin	74599 (55.7)	28892 (51.9)	45707 (58.2)	<0.001
Plavix	18556 (13.8)	6874 (12.4)	11682 (14.9)	<0.001
Opioid	32576 (24.3)	13964 (25.1)	18612 (23.4)	<0.001
Antipsychotic	6760 (5.0)	3185 (5.7)	3575 (4.6)	<0.001
Antidepressant	25190 (18.8)	10330 (18.6)	14860 (18.9)	0.06
Antiepileptic	6932 (5.2)	2853 (5.1)	4079 (5.2)	<0.001
Systemic glucocorticoid	16919 (12.6)	6695 (12.0)	10224 (13.0)	<0.001
Proton-pump inhibitor	38469 (28.7)	15599 (28.0)	22870 (29.2)	<0.001

Percentages may not sum up to 100% because of rounding. AF/AFL indicates atrial fibrillation/flutter; NA, not available; and SD, standard deviation.
*Average 5-year income before heart failure diagnosis stratified into quartiles.
†Triple therapy is defined as combination therapy with a renin-angiotensin inhibitor, a β-blocker, and an aldosterone antagonist.

were slightly older, more frequently male, and more likely to have received an influenza vaccination before the heart failure diagnosis (all *P*<0.001). They had slightly higher average income and similar education levels compared with patients who did not receive a vaccination during the follow-up period. They displayed a higher prevalence of most comorbidities and a markedly higher use of most medications (Table 1).

Survival After Heart Failure Diagnosis

In unadjusted analysis, receiving ≥1 influenza vaccinations during the study period was associated with a higher risk of death (all-cause death: hazard ratio [HR], 1.28; 95% CI, 1.26–1.30; *P*<0.001; cardiovascular death: HR, 1.26; 95% CI, 1.23–1.28; *P*<0.001; Table IV in the online-only Data Supplement). The cumulative number of vaccinations received during the study period and the vaccination frequency were also significantly associated with a higher risk of death in unadjusted analysis (Table IV in the online-only Data Supplement). However, after adjustment for all confounders included in Table 1, receiving ≥1 influenza vaccinations during follow-up was associated with an 18% reduction in the risk of both all-cause and cardiovascular death (all-cause death: 0.82; 95% CI, 0.81–0.84; *P*<0.001; cardiovascular death: 0.82; 95% CI, 0.81–0.84; *P*<0.001; Figure 2 and Table IV in the online-only Data Supplement). We found that the cumulative number of vaccines was significantly associated with a reduced risk of all-cause and cardiovascular death (*P* for trend <0.001; Figure 2 and Table IV in the online-only Data Supplement). Annual vaccination after heart failure diagnosis was significantly associated with a 19% reduction in the risk of both all-cause and cardiovascular death compared with no vaccination (both *P*<0.001; Figure 2 and Table IV in the online-only Data Supplement). A vaccination frequency of less than once per year but >0 was associated with a 13% reduced risk of all-cause death and an 8% reduced risk of cardiovascular death (Figure 2 and Table IV in the online-only Data Supplement).

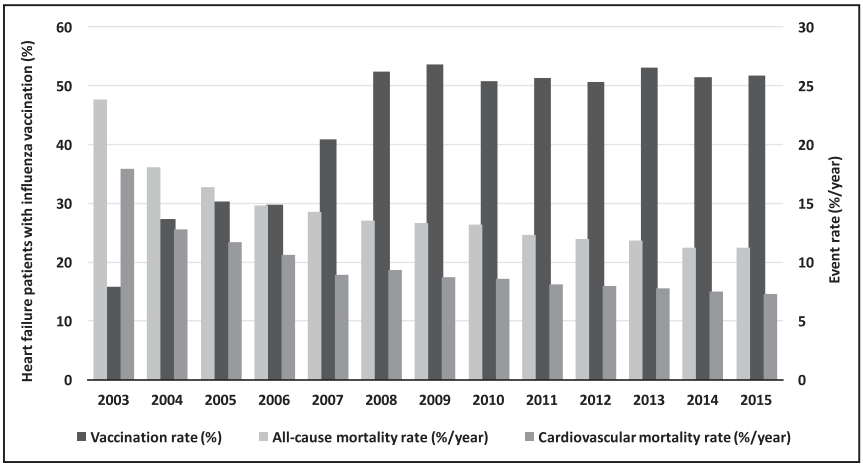

Figure 1. Vaccination rate and mortality by year.
Vaccination coverage, all-cause mortality rate, and cardiovascular mortality rate of the study cohort by year.

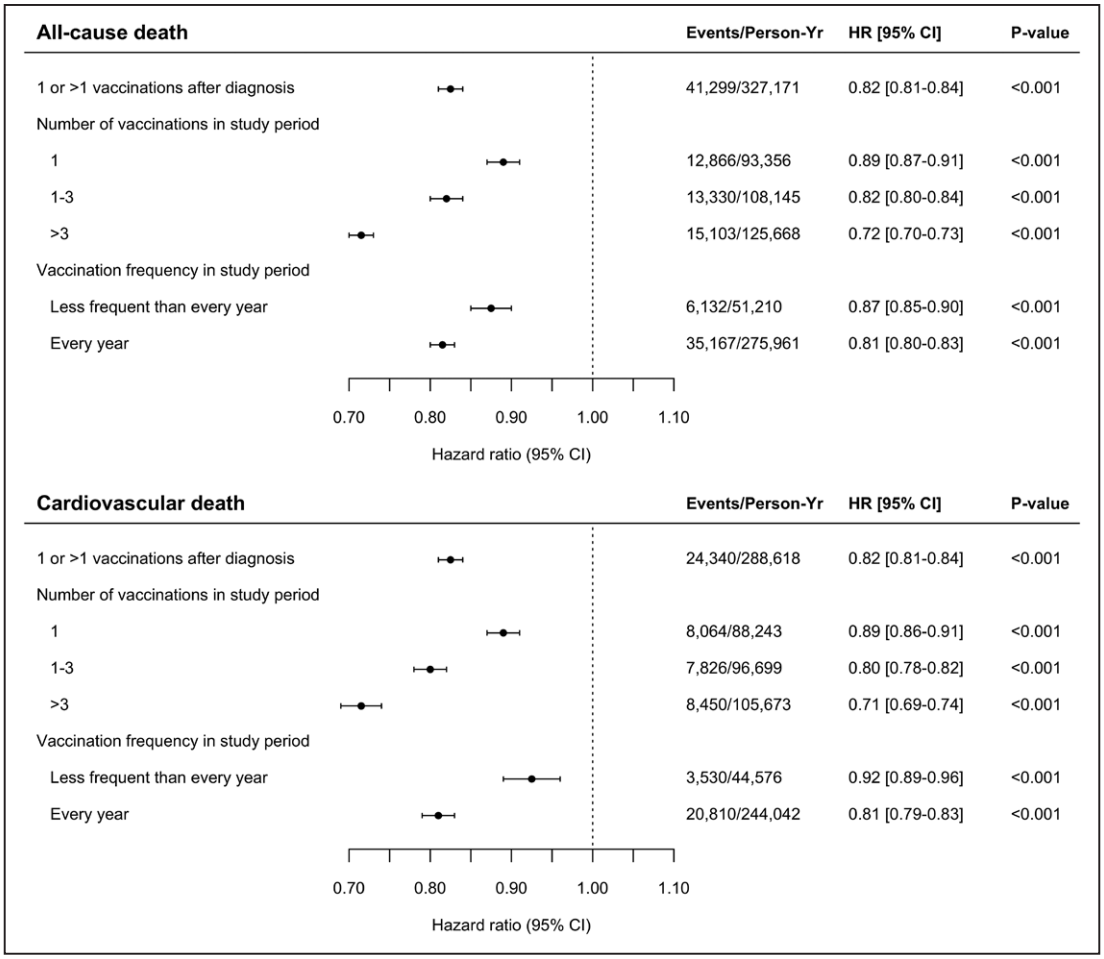

Figure 2. Vaccination and outcome.
Forest plots of the association between vaccination after heart failure diagnosis (≥1), the cumulative number of vaccinations received after diagnosis, and the vaccination frequency after diagnosis and the risk of death. Error bars represent 95% CIs. Vaccination parameters and age were entered as time-varying covariates in a time-dependent Cox regressions model adjusted for all variables displayed in Table 1 with the addition of inclusion year. HR indicates hazard ratio.

We also assessed whether the time of year of the vaccination was associated with the risk of death (Figure 3). After adjustment for all confounders in Table 1 with the addition of inclusion year, receiving the vaccination in September and October was associated with larger reductions in the risk of both cardiovascular and all-cause death compared with receiving the vaccination in November and December (Figure 3). Hence, early vaccination was associated with a larger reduction in the risk of death compared with late vaccination (*P* for trend <0.001; Figure 3).

Vaccination and Survival by Influenza Season

In landmark analyses, we estimated the effect of influenza vaccination on survival by season. In general, influenza vaccination was consistently associated with a reduced risk of both all-cause and cardiovascular death in most influenza seasons during the study period (Table 2). In Denmark, a high proportion of the circulating influenza strains in the 2007 to 2008 and 2015 to 2016 seasons were type B, and in these seasons, a mismatch between the influenza vaccine type B strain and the circulating seasonal type B strain occurred. We found that in the 2007 to 2008 season, vaccination was not associated with a reduced risk of cardiovascular death (Table 2). In contrast, vaccination was associated with a reduced risk of cardiovascular death in the adjacent seasons (2008–2009 and 2006–2007). Although vaccination was associated with a reduced risk of all-cause death in the 2007 to 2008 season, this association was weaker (HR was closer to 1) compared with the adjacent seasons (Table 2). In the 2015 to 2016 season, vaccination was not associated with a reduced risk of all-cause death (Table 2). In contrast, vaccination was associated with a reduced risk of death in the adjacent season (Table 2). Similarly, vaccination was not associated a reduced risk of cardiovascular death in the 2015 to 2016 season (Table 2).

Influenza Vaccination and Arrhythmia

In unadjusted analysis, receiving ≥1 influenza vaccinations during the study period was associated with a higher risk

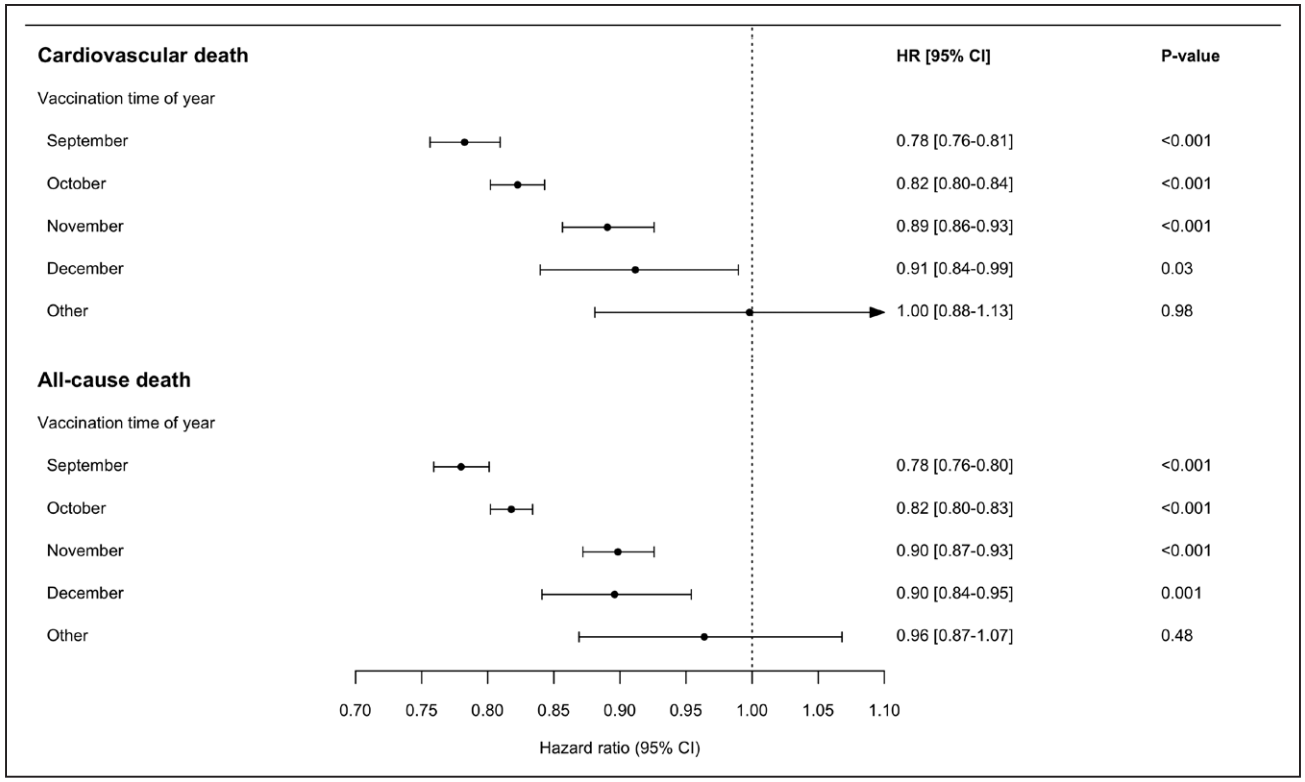

Figure 3. Vaccination time of year and outcome.
Association between the vaccination time of year and the risk of death. The reference was no vaccination. Error bars represent 95% CIs. Vaccination time of year was entered as a time-varying covariate in a time-dependent Cox regression model adjusted for all variables in Table 1 with the addition of inclusion year. HR indicates hazard ratio.

of AF/AFL (HR, 1.40; 95% CI, 1.35–1.46; *P*<0.001; Table V in the online-only Data Supplement). However, after adjustment for all confounders in Table 1 with the addition of inclusion year, receiving ≥1 influenza vaccinations during the study period was associated with a reduced risk of incident AF/AFL (HR, 0.94; 95% CI, 0.90–0.99; *P*=0.009; Table V in the online-only Data Supplement). The cumulative number of vaccinations and vaccination frequency were also associated with a reduced risk of incident AF/AFL (Table V in the online-only Data Supplement). In a subgroup analysis considering only patients with implantable cardioverter-defibrillators, receiving ≥1 influenza vaccinations was not associated with a composite outcome consisting of ventricular tachycardia or ventricular fibrillation and/or cardiac arrest (Table VI in the online-only Data Supplement). This was the case in both unadjusted and fully adjusted analyses (Table VI in the online-only Data Supplement). Results were similar when the cumulative number of vaccinations or the vaccination frequency was considered (Table V in the online-only Data Supplement).

Vaccination and Hospitalization for Influenza or Pneumonia

In unadjusted analysis, receiving ≥1 influenza vaccinations during the study period was associated with a higher risk of hospitalization for influenza or pneumonia (HR, 1.38; 95% CI, 1.35–1.41; *P*<0.001; Table VII in the online-only Data Supplement). However, in fully adjusted analysis, adjusting for all variables in Table 1 with the addition of inclusion year, receiving ≥1 influenza vaccinations during follow-up was associated with a reduced risk of hospitalization for influenza or pneumonia (HR, 0.96; 95% CI, 0.93–0.98; *P*=0.002; Table VII in the online-only Data Supplement). Again, results were similar when the cumulative number of vaccinations received and the vaccination frequency were considered (Table VII in the online-only Data Supplement).

DISCUSSION

In the present study, we show that influenza vaccination is associated with a reduced risk of all-cause and cardiovascular death in a Danish nationwide cohort of 134 048 patients with heart failure. We also show that annual vaccination of patients with heart failure is associated with a reduced risk of death compared with less frequent vaccination and that vaccination earlier in the year may be more protective than vaccination later in the year. The present study is the largest cohort study examining outcomes after influenza vaccination in a cohort of patients with heart failure. Our study provides strong indications for a beneficial effect of annual

Table 2. Landmark Analyses Assessing the Association Between Influenza Vaccination and All-Cause and Cardiovascular Mortality in Each Influenza Season Included in the Study Period

All-Cause Death					Cardiovascular Death				
Season	Patients, n	Events, n	HR (95% CI)	*P* Value	Season	Patients, n	Events, n	HR (95% CI)	*P* Value
2003–2004	7765	851	0.69 (0.56–0.85)	<0.001	2003–2004	7765	620	0.65 (0.51–0.84)	0.001
2004–2005	17726	1663	0.76 (0.66–0.87)	<0.001	2004–2005	17726	1177	0.76 (0.65–0.89)	0.001
2005–2006	25565	2092	0.83 (0.73–0.95)	0.007	2005–2006	25565	1467	0.87 (0.75–1.02)	0.09
2006–2007	32337	2577	0.81 (0.70–0.93)	0.003	2006–2007	32337	1663	0.76 (0.64–0.91)	0.003
2007–2008*	37867	2826	0.88 (0.78–0.99)	0.03	2007–2008*	37867	1760	0.88 (0.76–1.02)	0.09
2008–2009	42598	3187	0.84 (0.75–0.95)	0.004	2008–2009	42598	2121	0.83 (0.72–0.96)	0.01
2009–2010	47044	3339	0.80 (0.71–0.90)	<0.001	2009–2010	47044	2180	0.78 (0.67–0.91)	0.001
2010–2011	51159	3525	0.79 (0.69–0.90)	<0.001	2010–2011	51159	2307	0.80 (0.68–0.94)	0.007
2011–2012	54917	3657	0.75 (0.66–0.85)	<0.001	2011–2012	54917	2455	0.80 (0.68–0.93)	0.003
2012–2013	58252	3926	0.80 (0.71–0.91)	<0.001	2012–2013	58252	2604	0.73 (0.63–0.85)	<0.001
2013–2014	61275	3762	0.71 (0.62–0.81)	<0.001	2013–2014	61275	2508	0.76 (0.65–0.89)	0.001
2014–2015	64336	4087	0.87 (0.77–0.98)	0.02	2014–2015	64336	2713	0.87 (0.75–1.01)	0.07
2015–2016*	64556	3907	0.88 (0.76–1.01)	0.07	2015–2016*	64556	1399	0.91 (0.72–1.18)	0.52

For each season, follow-up was counted from September 1 to April 1 the next year, encompassing the influenza season in Denmark. Influenza vaccination was implemented as a time-varying covariate in time-dependent Cox regression, and patients were switched to the vaccinated group at the time of vaccination if they were vaccinated during the season. The Cox regression models were adjusted for all variables displayed in Table 1 with the addition of inclusion year and time since heart failure diagnosis. HR indicates hazard ratio.

*In these seasons, known mismatches between vaccine influenza strains and circulating strains occurred.

influenza vaccination in patients with heart failure to increase survival.

Influenza Vaccination in Heart Failure

Little is known about the impact of influenza vaccination in patients with heart failure. Influenza vaccination of patients with heart failure is recommended by most cardiac societies and health authorities.[7–9] Currently, no data are available from randomized clinical trials in support of these recommendations. Small-scale randomized clinical trials assessing the benefit of influenza vaccination in high-risk cardiovascular conditions with respect to adverse outcome have focused on patients with acute coronary syndrome or coronary artery disease. These trials have shown positive and promising results.[20–22] In 1 such study, investigators randomized 200 patients with myocardial infarction and 101 patients planned for angioplasty to either influenza vaccination or placebo. They found that vaccination significantly reduced the risk of adverse cardiovascular events during 1 year of follow-up by almost 50%.[20] In a meta-analysis of 5 randomized clinical trials randomizing high-risk cardiovascular patients to either influenza vaccination or placebo, vaccination significantly reduced the risk of adverse cardiovascular outcomes, with the largest effect seen in patients with recent acute coronary syndrome.[6] However, none of the trials included in this meta-analysis focused on patients with heart failure.

Evidence for the effects of influenza vaccination in patients with heart failure is currently limited to observational studies.[10,11,23] In a study from the United Kingdom that used a self-controlled case series design based on health record data, influenza vaccination was associated with a reduced risk of cardiovascular hospitalization in a population of 59202 patients with heart failure.[11] Although those investigators used a case series design and had no access to data on mortality, their results are interesting and in accordance with the results of the present study, demonstrating influenza vaccination to be associated with improved survival after extensive adjustment for confounders. In an observational study from Israel, Kopel and colleagues[23] considered a cohort of patients hospitalized for acute heart failure (incident acute heart failure or exacerbation of chronic heart failure) and assessed the association between a history of influenza vaccination in the 12 months before hospitalization and all-cause mortality during follow-up. They found that a history of vaccination was associated with improved 1- and 4-year mortality but not with in-hospital mortality. The authors themselves hypothesize that the association may in fact be a marker of improved quality and access to health care because it is unlikely that a vaccination in the 12 months leading up to hospitalization for heart failure would improve 4-year survival after hospital discharge. To support this, they found that in the Israel General Population Health Survey, a sample population representative of the source population for the patients with heart failure, influenza vaccination was associated with a higher likelihood of having supplementary health coverage beyond basic coverage offered by the Israeli government. The findings of the study are interesting, but important differences between their study and ours

make direct comparisons difficult. First, they considered only patients hospitalized for acute heart failure. Therefore, only vaccinated and unvaccinated patients who needed hospitalization for heart failure were included. Patients with heart failure who were vaccinated and who did not require hospitalization for heart failure during the inclusion period, possibly because the vaccination prevented influenza infection and thus reduced the risk of exacerbation of heart failure, would not have been included. This is different from our study, which included all patients diagnosed with heart failure during our inclusion period and subsequently assessed their exposure to influenza vaccination and the association with survival, thus avoiding the introduction of selection bias. In addition, in the Israeli general population, vaccination was a marker of supplementary healthcare coverage, suggesting that the Israeli healthcare system is not entirely homogeneous. In Denmark, health care is universal, with free influenza vaccination for patients with heart failure, and supplementary or private insurance is uncommon because the government covers all expenses related to health care. In another observational study, a substudy of the PARADIGM heart failure trial (Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure), Vardeny and colleagues[10] examined predictors of influenza vaccination in 8099 patients with heart failure, as well as outcomes during 27 months of follow-up. They found that influenza vaccination was associated with lower risks of death resulting from all causes, but not cardiovascular causes, in unadjusted analysis and after controlling for confounding through propensity adjustment, which differs from our results. However, the study population from the PARADIGM heart failure trial,[24] a multicenter trial that enrolled subjects on a global scale, differs from our study sample in important ways. In the PARADIGM population, vaccination rates varied widely by country, with many Asian, Eastern European, and South American countries displaying very low rates of only 0% to 15%.[10] This suggests that access to health care was not uniform within their population, but unfortunately, no data on healthcare access or socioeconomic status were available to the investigators. In our study sample, healthcare access was homogeneous, and vaccination rates were higher and more consistent. These differences make direct comparisons challenging. In our study, we found vaccination to be associated with an increased risk of both all-cause and cardiovascular death in unadjusted analysis and with a decreased risk of mortality after adjustment for confounders. This large change in the association between influenza vaccination and outcome with statistical adjustment is indicative of effective adjustment for confounding, signifying the robustness of our results.[25] Furthermore, that the association changed from a hazardous effect to a protective effect with this adjustment suggests that our unadjusted estimates were confounded by selection bias, perhaps because sicker, older patients with more comorbidity are more likely to be vaccinated.[25] The probable reason is that patients who received a vaccination were older, had higher medication use, and had more comorbidities.

Vaccination Time of Year and the Cumulative Number of Vaccinations

An interesting finding of our study was the greater reduction in mortality associated with vaccination early in the season and with a greater cumulative number of vaccinations. Vaccination early in the season may be more efficient for preventing influenza infection because the patient is allowed less time during the season to contract influenza before vaccination. Thus, it may be beneficial to administer the vaccine as early in the season as possible. An influenza infection may exacerbate heart failure symptoms and possibly advance the progression of the disease. Thus, if multiple episodes of infection are prevented by multiple vaccinations, it is possible that the patient is spared unnecessary disease progression caused by multiple influenza infections, and this may explain in part why a greater cumulative number of vaccinations was associated with greater reductions in mortality. In addition, evidence suggests that influenza vaccines against particular strains may confer partial protection against other strains (referred to as cross-protection).[26] This may also be part of the explanation for why more vaccinations were associated with greater reductions in mortality.

Influenza Vaccination and Standard Treatment in Heart Failure

Influenza vaccination is regarded as a safe, low-cost, highly effective strategy for reducing influenza-related morbidity.[27] In our study, we show that influenza vaccination is likely to improve survival in patients with heart failure. Influenza vaccination was associated with an ≈18% reduced risk of death. We also show that annual vaccination and vaccination early in the year may be particularly beneficial. Annual vaccination frequency was associated with an almost 20% reduced risk of both cardiovascular and all-cause death, whereas a vaccination frequency of <1 per year yet still >0 was associated with a 13% reduced risk of all-cause death and an 8% reduced risk of cardiovascular death. These are substantial reductions in mortality given the safety, feasibility, and cost efficiency of influenza vaccination. For example, β-blockers and angiotensin-converting enzyme inhibitors are first-line therapeutics for heart failure according to contemporary guidelines.[28] Both have been demonstrated to improve survival in patients with heart failure in randomized clinical trials

with reductions in mortality of ≈20% to 25%, respectively.[29,30] In addition, in support of a potential causal association, several biological mechanisms seem plausible. First, influenza infection may result in increased metabolic demand, hypoxia, and adrenergic surges,[31] which may lead to acute decompensation or exacerbation of heart failure symptoms because of an already compromised cardiac reserve. Second, infection may induce a hypercoagulable state and has been suggested to be a trigger of acute coronary syndromes[31] leading to further deterioration of left ventricular function. Third, influenza has been associated with direct myocardial depression,[32] and histological evidence of myocarditis and myocardial necrosis has been reported from the autopsy of patients who died of influenza-related causes.[33] Given these considerations and the results of the present study, influenza vaccination may be a valuable treatment strategy to improve survival in heart failure. Although vaccine coverage improved from 16% of patients in the beginning of the study period to a consistent 50% to 55% coverage rate in the later study years, these numbers remain low. Influenza vaccination uptake in patients with heart failure is even lower on a global scale.[10] Currently, because of a lack of evidence, the major cardiac societies encourage influenza vaccination in patients with heart failure but provide no class of recommendation or evidence level as a result of a lack of sufficient evidence.[7–9] This might contribute to low vaccination rates. Influenza vaccination should be considered as a potential treatment strategy comparable to other medical treatments such as β-blockers and angiotensin-converting enzyme inhibitors to improve survival in heart failure. Emphasizing this in future heart failure guidelines would encourage vaccination of patients with heart failure and likely improve patient survival.

Limitations

In this study, we had information only on vaccines administered by general practitioners. Hence, if some patients received vaccines from a different provider—for instance, a work-related healthcare program—this would go undetected. However, if this were the case, these patients would have been classified as unvaccinated, and this would likely only serve to weaken any potential association between influenza vaccination and outcome. Furthermore, we lacked data on important clinical variables such as left ventricular ejection and brain natriuretic peptide levels. In addition, the Danish National General Practitioners Reimbursement Registry used to assess the exposure to influenza vaccination in this study has not been previously validated. However, because the single-payer healthcare system in Denmark is fully tax-funded and paid for by the government, all general practitioner consultations and services are free and unrestricted for all Danish citizens. Hence, the general practitioners rely on the validity of the Danish National General Practitioners Reimbursement Registry to receive payment for services rendered to patients. Furthermore, although the association between vaccination and mortality remained relatively consistent throughout the study period as determined in the landmark analyses, we were not able to identify why the vaccination rates increased significantly in 2006 to 2008 during the study period.

CONCLUSIONS

In patients with heart failure, influenza vaccination was associated with a reduced risk of both all-cause and cardiovascular death after extensive adjustment for confounders. Annual vaccination, a greater cumulative number of vaccinations, and vaccination early in the year were associated with larger reductions in the risk of both cardiovascular and all-cause death compared with less frequent vaccination and vaccination later in the year. Annual influenza vaccination may be an effective treatment strategy to improve survival in heart failure.

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