

ORIGINAL RESEARCH

Flu Vaccine and Mortality in Hypertension: A Nationwide Cohort Study

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BACKGROUND: Influenza infection may increase the risk of stroke and acute myocardial infarction (AMI). Whether influenza vaccination may reduce mortality in patients with hypertension is currently unknown.

METHODS AND RESULTS: We performed a nationwide cohort study including all patients with hypertension in Denmark during 9 consecutive influenza seasons in the period 2007 to 2016 who were prescribed at least 2 different classes of antihypertensive medication (renin-angiotensin system inhibitors, diuretics, calcium antagonists, or beta-blockers). We excluded patients who were aged <18 years, >100 years, had ischemic heart disease, heart failure, chronic obstructive lung disease, cancer, or cerebrovascular disease. The exposure to influenza vaccination was assessed before each influenza season. The end points were defined as death from all-causes, from cardiovascular causes, or from stroke or AMI. For each influenza season, patients were followed from December 1 until April 1 the next year. We included a total of 608 452 patients. The median follow-up was 5 seasons (interquartile range, 2–8 seasons) resulting in a total follow-up time of 975 902 person-years. Vaccine coverage ranged from 26% to 36% during the study seasons. During follow-up 21 571 patients died of all-causes (3.5%), 12 270 patients died of cardiovascular causes (2.0%), and 3846 patients died of AMI/stroke (0.6%). After adjusting for confounders, vaccination was significantly associated with reduced risks of all-cause death (HR, 0.82; $P<0.001$), cardiovascular death (HR, 0.84; $P<0.001$), and death from AMI/stroke (HR, 0.90; $P=0.017$).

CONCLUSIONS: Influenza vaccination was significantly associated with reduced risks of death from all-causes, cardiovascular causes, and AMI/stroke in patients with hypertension. Influenza vaccination might improve outcome in hypertension.

Key Words: acute myocardial infarction ■ all-cause death ■ hypertension ■ influenza ■ influenza vaccination ■ stroke ■ vaccination

Influenza infection has been suggested as a major trigger of acute myocardial infarction (AMI)^{1–3} and stroke.² Yet, little is known about the effect of influenza vaccination on mortality in individuals with hypertension. It is known that the risk of AMI and stroke is elevated during the acute phase of influenza infection.^{2,4} Accordingly, influenza vaccination has been shown to reduce the risk of AMI and cardiovascular death in small-scale randomized clinical trials of patients with previous AMI or stable coronary artery disease.^{5,6} In a meta-analysis

of several smaller randomized clinical trials of patients with high-risk cardiovascular disease, influenza vaccination was shown to significantly reduce the risk of major adverse cardiovascular outcome.⁷ Consequently, influenza vaccination is recommended by the American Heart Association in patients with coronary artery disease as a secondary preventative measure (Class of recommendation: I, level of evidence B).⁸ However, no studies have investigated the effect of influenza vaccination on mortality in individuals with hypertension

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CLINICAL PERSPECTIVE

What Is New?

- Our study shows that influenza vaccination may reduce the risk of all-cause death, cardiovascular death, and death from acute myocardial infarction or stroke in patients with hypertension.

What Are the Clinical Implications?

- Our results emphasize the benefit of influenza vaccination in patients with hypertension and our findings suggest that the benefit of vaccination may stretch beyond reducing the likelihood of influenza and respiratory infections to include a reduced risk of cardiovascular death.

Nonstandard Abbreviations and Acronyms

PIN personal identification number

without prevalent significant cardiovascular disease. Since individuals with hypertension are at a greatly increased risk of dying from cardiovascular causes, particularly from stroke or AMI,⁹ it is possible that annual influenza vaccination may reduce mortality and improve outcome in hypertension. If this is the case, the cost-effectiveness, safety, and feasibility of annual influenza vaccination make it an ideal preventive measure for improving outcome in hypertension. Therefore, this study sought to investigate the effect of influenza vaccination on mortality and outcome in a large nationwide cohort free of serious cardiovascular disease.

METHODS

Data Availability Statement

For this study, the authors were granted full access to raw data in nationwide administrative registers following central encryption of personal identification numbers (PIN) by Statistics Denmark (Central Authority on Danish Statistics). According to Danish law, informed consent and approval by a local ethics committee is not required for register-based studies. The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure. Since this study uses data from human subjects, the data and everything pertaining to it are governed by the Danish Data Protection Agency and can only be made available to any additional researchers if a formal request is filed with the Danish Authorities.

Data Sources

All Danish citizens are assigned a unique PIN at birth.¹⁰ This PIN is used all throughout the Danish public sector for data registration and general administrative purposes including the healthcare system. With this PIN, health and administrative data at the individual level may be linked throughout registers ensuring complete follow-up.¹¹ The single-payer healthcare system in Denmark provides equally available health care to all Danish citizens free of charge irrespective of social status and financial means. In this study data we collected data from several nationwide registers. More detail and an overview of the registers used in this study are available in Table S1.

Study Design and Definition of Hypertension

We used a modified cohort design for this study. This design uses a season-specific approach to assess the association between influenza vaccination and outcome. It is reasonable to assume that a causal association between vaccination and reduced mortality, if present, would result from either a reduced probability of influenza infection or a reduced severity of infection. In Denmark, epidemiological studies have found that the majority all influenza activity occurs in months December, January, February, and March.¹² Consequently, a potential association between influenza vaccination and a reduced risk of death is assumed to be strongest during these months. Therefore, we chose to confine our study to consider these 4 months. For the remainder of this report, the period December 1 to April 1 the following year (a time period spanning the 4 months of high influenza activity) will be referred to as an influenza “season”. For the present study, we considered all influenza seasons in the period 2007 to 2016, resulting in a total of 9 seasons and 9 distinct periods of observation. In each of these seasons, all patients living with hypertension in Denmark on December 1 were identified using nationwide registers and followed until April 1 the following year (Figure 1). In Denmark, hypertension is mainly diagnosed and managed by primary care physicians. Thus, the in-hospital *International Classification of Diseases, Tenth Revision (ICD-10)* diagnosis code for essential hypertension (*ICD-10: I10*) does not accurately reflect the burden of hypertension in the population. Therefore, we defined patients with hypertension as patients treated with at least 2 antihypertensive drugs in the 6 months leading up to each season (ie, in the 6 months leading up to December 1), including beta-blockers, diuretics, calcium antagonists, and renin-angiotensin system inhibitors, as previously described.^{13,14} Defining hypertension through use of

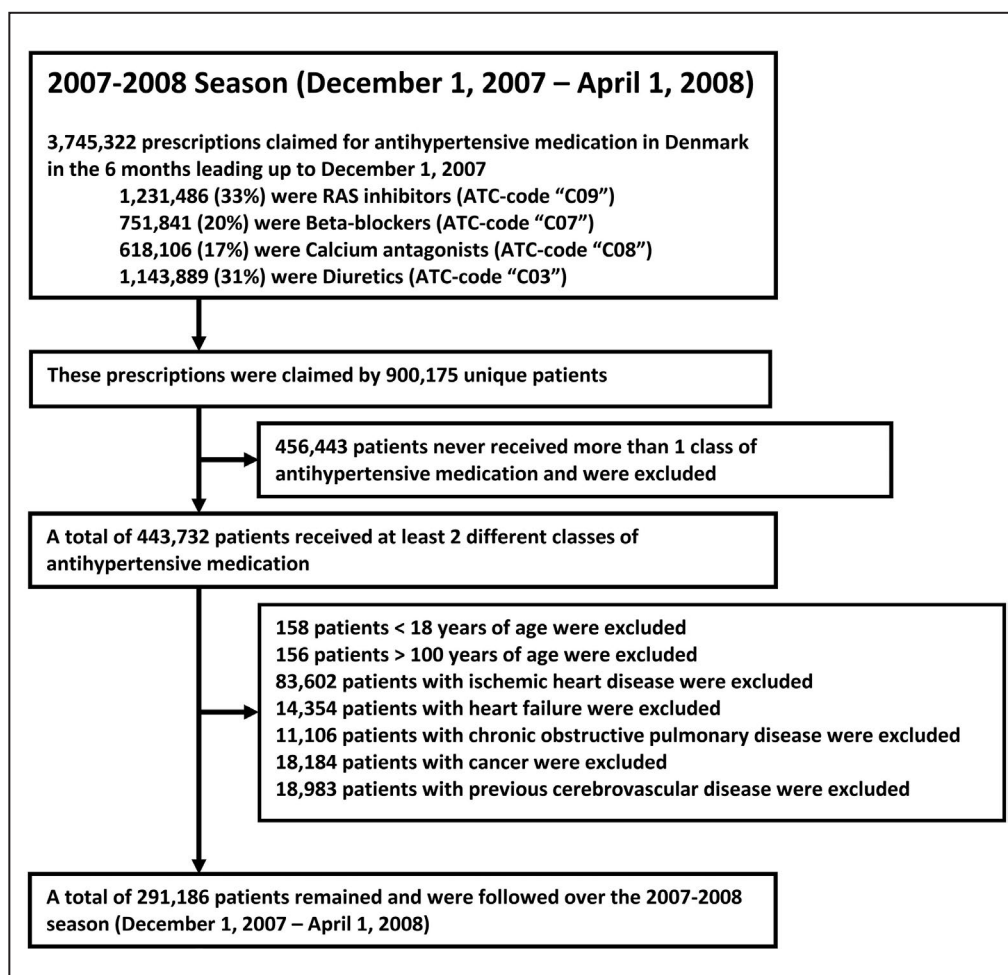


Figure 1. Flowchart depicting the inclusion procedure.

In this example, the inclusion process for the 2007 to 2008 season is shown. An identical process was used for including patients in the remaining 8 seasons from 2008 to 2016. ATC indicates Anatomical Therapeutic Chemical Classification System; and RAS, renin-angiotensin system.

2 antihypertensive drugs has a high positive predictive value of 80% and a specificity of 94%.¹³ Since 1995, all prescriptions filled in Danish pharmacies have been recorded in the National Prescription register. The register is used for drug cost reimbursement purposes and has been shown to be accurate.¹⁵ Thus, using the National Prescription register, we identified all prescriptions filled in Denmark in the 6 months before the start of each season (December 1) for the 4 common classes of antihypertensive medications using Anatomical Therapeutic Chemical Classification System codes (renin-angiotensin system inhibitors-inhibitors [C09], calcium antagonists [C08], beta-blockers [C07], and diuretics [C03]) (Figure 1). A patient was classified as hypertensive if the patient had filled ≥ 1 prescriptions for at least 2 of these 4 classes of medications (Figure 1). To ensure that antihypertensive drugs were prescribed for hypertension, and to include primarily individuals

with hypertension without significant comorbidity, we excluded patients with known ischemic heart disease, heart failure, chronic obstructive pulmonary disease, cancer, and prior or prevalent cerebrovascular disease (Figure 1). Furthermore, we only considered patients aged >18 years and <100 years of age. Figure 1 displays the inclusion process for the 2007 to 2008 season. For the remaining 8 seasons, an inclusion procedure identical to the process displayed in Figure 1 was used.

Patient Characteristics

We assessed patient characteristics at the beginning of each season (December 1). Information on comorbidities, medications, household income, and education level were obtained from nationwide administrative registers. Please refer to Data S1 and tables S2 and S3 for further details.

Influenza Vaccination Status

Influenza vaccine administration in general practice and the PIN of the patient receiving the vaccine is recorded in the General Practitioners Reimbursement register. In Denmark, general practitioners receive compensation from the government for services provided to Danish patients through a fee-for-service payment model. The general practitioners use the General Practitioners Reimbursement register to document services provided to patients and thus rely on the accuracy of this register for reimbursement purposes. We used this register to assess the exposure of patients to influenza vaccination. We assessed whether patients had been vaccinated in the 4 months before the start of each season (before December 1). This period was chosen because almost all influenza vaccines administered in Denmark are dispensed in months September, October, and November. If a patient had received a vaccination in the 4 months before the beginning of a given season, we considered the patient vaccinated for that season.

Outcomes

The main end points of this study were all-cause death, cardiovascular death, and death from AMI or stroke. Both AMI and stroke were included in the cardiovascular death end point. AMI was defined as *ICD-10* codes I21-I22. Stroke was defined as *ICD-10* codes I61-I64. In each season, we followed patients from December 1 until their death or until April 1 the following year, whichever occurred first. For the purposes of sensitivity analysis, we also examined the incidence of cancer during follow-up (*ICD-10* codes: C00-C97).

Statistical Analysis

The statistical analysis was performed with Stata 16 (StataCorp, College Station, TX). Because of the season-specific cohort approach, patients were allowed to contribute with follow-up in multiple seasons when considering all seasons included in the study. For example, a patient diagnosed with hypertension fulfilling inclusion criteria and treated with at least 2 antihypertensive drugs before December 1, 2007 would be included in the 2007 to 2008 season. Then, should the patient not die in the 2007 to 2008 season, and if the patient did not develop any of the exclusion criteria conditions (ischemic heart disease, heart failure, chronic obstructive pulmonary disease, cancer, or cerebrovascular disease) and continued to receive at least 2-drug antihypertensive therapy in the 6 months before the index of the next season (December 1, 2008), the patient would also be included in the 2008 to 2009 season. Thus, in the Table, patients were classified per whether they received at least 1 influenza vaccination in at least 1 season during the study

period. Furthermore, the characteristics listed in the Table correspond to patient characteristics at the time of their first inclusion into the study. A figure illustrating the modified cohort design of the study may be found in Figure S3. We used survival analysis implemented through Stata *stcox* command to assess the association between vaccination and outcome. When considering all seasons, we used multivariable Cox regression with multiple follow-up intervals per patient. The multivariable model (referred to as “fully adjusted results” for the remainder of this report) was adjusted for all variables in the Table. The follow-up interval for each season began on December 1 and ended at the time of death or April 1 of the following year, whichever occurred first. This allowed for a contribution of up to 120 days per patient per season. To account for multiple observation periods per patient, the analyses were stratified by year and a clustered variance estimator treating observation periods from the same patient as clusters was used. Patient characteristics were reassessed and updated on the index date of each season to account for any changes between seasons. For sensitivity purposes, the association between vaccination and mortality was assessed in the “off-season” months (April 1–December 1 the following year). In this analysis, we extended follow-up from the 4 months “in-season” period (December 1–April 1 the following year) to 1 full year (December 1–December 1 the following year). To address the robustness of our results, we performed multiple sensitivity analyses which are described in Data S1 and S2. We used survival probabilities and hazard ratio estimates from the fully adjusted Cox regression estimates to derive adjusted numbers needed to treat to prevent 1 death over 1 season associated with vaccination when considering all seasons included in the study.¹⁶ To investigate whether vaccination may be more beneficial for patients with hypertension than patients with normotension, we matched patients with hypertension 1:1 on birth year and sex with patients with normotension sourced from the Danish general background population in each season (defined as no prescriptions for any antihypertensive medications in the 6 months leading up to each season and otherwise identical inclusion criteria) and assessed the fully adjusted association between vaccination and outcome in both groups. Finally, we assessed the association between vaccination and death in each separate season included in the study. In influenza seasons 2007 to 2008 and 2015 to 2016 known partial mismatches between vaccine influenza strain and circulating influenza strains occurred. In these 2 seasons a moderate amount of influenza B activity was recorded in Denmark (2007–2008: 36% influenza B, 64% influenza A)(2015–2016: 44% influenza B, 56% influenza A), and epidemiological surveillance data from Statens Serum Institut indicate that

Table. Patient Characteristics Assessed at the Time of Inclusion Stratified by Vaccination Status

Demographics	All patients	No vaccine	Ever vaccinated in study	P Value
n	608 452	321 623 (52.9%)	286 829 (47.1%)	
Age, y	65.2 (13.1)	60.1 (12.8)	70.8 (11.0)	<0.001
Men	266 683 (43.8%)	146 803 (45.6%)	119 880 (41.8%)	<0.001
Household income quartile				<0.001
1st quartile	NA	58 785 (8.4%)	92 407 (32.3%)	
2nd quartile	NA	65 189 (20.5%)	86 003 (30.1%)	
3rd quartile	NA	85 513 (26.8%)	65 679 (23.0%)	
4th quartile	NA	109 256 (34.3%)	41 936 (14.7%)	
Highest education level				<0.001
Basic school <10 y	237 382 (39.0%)	110 439 (34.3%)	126 943 (44.3%)	
High school, +3 y	13 879 (2.3%)	9457 (2.9%)	4422 (1.5%)	
Vocational education	215 765 (35.5%)	123 505 (38.4%)	92 260 (32.2%)	
Short/medium higher education, +2–4 y	84 933 (14.0%)	50 201 (15.6%)	34 732 (12.1%)	
Long higher education, +5 y or more	22 180 (3.7%)	13 145 (4.1%)	9035 (3.2%)	
Unknown	34 313 (5.6%)	14 876 (4.6%)	19 437 (6.8%)	
Vaccination in previous season	131 602 (21.6%)	7172 (2.2%)	124 430 (43.4%)	<0.001
No. of seasons included	5 (2–8)	4 (2–7)	6 (3–9)	<0.001
Comorbidities				
Valvular disease	10 132 (1.7%)	3844 (1.2%)	6288 (2.2%)	<0.001
Systemic embolus	3160 (0.5%)	1358 (0.4%)	1802 (0.6%)	<0.001
Atrial fibrillation or flutter	33 291 (5.5%)	12 784 (4.0%)	20 507 (7.2%)	<0.001
Chronic renal failure	8080 (1.3%)	4129 (1.3%)	3951 (1.4%)	0.001
Anemia	10 477 (1.7%)	4370 (1.4%)	6107 (2.1%)	<0.001
Diabetes	79 822 (13.1%)	31 816 (10.0%)	48 006 (16.7%)	<0.001
Peripheral vascular disease	9199 (1.5%)	3531 (1.1%)	5668 (2.0%)	<0.001
Liver disease	5703 (0.9%)	3271 (1.0%)	2432 (0.9%)	<0.001
Rheumatic disease	9739 (1.6%)	3822 (1.2%)	5917 (2.1%)	<0.001
Peptic ulcer	13 619 (2.2%)	5865 (1.8%)	7763 (2.7%)	<0.001
Medications				
No. of antihypertensive drugs				<0.001
2 drugs	482 440 (79.3%)	265 250 (82.4%)	217 190 (75.2%)	
3 drugs	108 986 (17.9%)	49 339 (15.3%)	59 647 (20.8%)	
4 drugs	17 026 (2.8%)	7034 (2.2%)	9992 (3.5%)	
Renin-angiotensin system inhibitor	458 579 (75.4%)	247 094 (76.8%)	211 485 (73.3%)	<0.001
Beta blocker	222 531 (36.6%)	110 623 (34.4%)	111 908 (39.0%)	<0.001
Diuretic	357 311 (58.7%)	176 397 (54.9%)	180 914 (63.0%)	<0.001
Calcium antagonist	321 521 (52.8%)	172 539 (53.7%)	148 982 (51.9%)	<0.001
Statin	192 417 (31.6%)	84 642 (26.3%)	107 775 (37.6%)	<0.001
Lipid-lowering	194 548 (32.0%)	132 535 (29.7%)	62 013 (38.4%)	<0.001
Glucose-lowering	79 822 (13.1%)	31 816 (10.0%)	48 006 (16.7%)	<0.001
Antithrombotic	180 473 (29.7%)	65 989 (20.5%)	114 484 (39.9%)	<0.001
Spironolactone	16 964 (2.8%)	7565 (2.4%)	9399 (3.3%)	<0.001
Digoxin	17 284 (2.8%)	5298 (1.7%)	11 986 (4.2%)	<0.001
Aspirin	146 065 (24.0%)	53 349 (16.7%)	92 716 (32.2%)	<0.001
Opioid	70 265 (11.6%)	29 953 (9.3%)	40 312 (14.1%)	<0.001

(Continued)

Table. Continued

Demographics	All patients	No vaccine	Ever vaccinated in study	P Value
Antipsychotic	17 203 (2.8%)	7824 (2.4%)	9379 (3.3%)	<0.001
Antidepressant	72 719 (12.0%)	33 442 (10.4%)	39 277 (13.7%)	<0.001
Antiepileptic	18 158 (3.0%)	8450 (2.6%)	9708 (3.4%)	<0.001
Systemic glucocorticoid	23 606 (3.9%)	9340 (2.9%)	14 266 (5.0%)	<0.001
Proton-pump inhibitor	85 310 (14.0%)	37 799 (11.8%)	47 511 (16.6%)	<0.00116

A patient was considered “ever vaccinated” if the patient was vaccinated at least once in at least 1 season. Percentages may not sum to 100% because of rounding.

the influenza B vaccine component in these 2 seasons did not match the circulating influenza B strains. These analyses are described in Data S1, S2 and Figure S2.

RESULTS

Study Population

We included 608 452 unique patients with hypertension over 9 consecutive influenza seasons during the time period 2007 to 2016 (Figure 1). The majority of patients were included before the first season (2007–2008). The median follow-up was 5 seasons (interquartile range, 2–8). The vaccination coverage varied by season and ranged from 26% in the 2007 to 2008 season to 35% in the 2015 to 2016 season with a peak of 36% in the 2013 to 2014 season (Figure S1). During the study period, 24.9% of vaccines were administered during November, 68.2% were administered in October, and 5.5% in September. A total of 16637 patients (3.7%) received a vaccine during the follow-up period in at least 1 season and were thus categorized as not vaccinated in those seasons. The Table displays the characteristics of patients who were vaccinated at least once during the study period and patients who were never vaccinated during the study at the time of their first inclusion into the study. Generally, vaccinated patients were older, less likely to be men, had lower household income, lower education level, displayed a higher prevalence of almost all comorbidities and used more medications (Table).

Follow-Up

Patients were followed for a total of 975 902 person-years. During this follow-up, 21 571 patients died of all-causes (3.5%), 12 270 patients died of cardiovascular causes (2.0%) and 3846 patients died of AMI or stroke (0.6%). In unadjusted analysis considering all seasons, influenza vaccination was significantly associated with a higher risk of all-cause death, cardiovascular death and death from AMI or stroke (all-cause death: hazard ratio [HR], 1.84; 95% CI, 1.79–1.89; $P<0.001$; cardiovascular death: HR, 1.89; 95% CI,

1.82–1.96; $P<0.001$; death from stroke or AMI: HR, 2.06; 95% CI, 1.93–2.20; $P<0.001$). Following adjustment for age, vaccination was significantly associated with a reduced risk of all-cause death, cardiovascular death and death from AMI or stroke (all-cause death: HR, 0.84; 95% CI, 0.81–0.86; $P<0.001$; cardiovascular death: HR, 0.85; 95% CI, 0.82–0.88; $P<0.001$; death from stroke or AMI: HR, 0.93; 95% CI, 0.88–0.99; $P=0.042$). In fully adjusted analysis, vaccination remained significantly associated with a reduced risk of all-cause death, cardiovascular death, and death from AMI or stroke (all-cause death: HR, 0.82; 95% CI, 0.79–0.85; $P<0.001$; cardiovascular death: HR, 0.84; 95% CI, 0.80–0.89; $P<0.001$; death from stroke or AMI: HR, 0.90; 95% CI, 0.82–0.98; $P=0.017$) (Figure 2). The adjusted number needed to treat (NNT) to prevent 1 death over 1 season associated with vaccination was 977 (95% CI, 837–1172). When we extended follow-up to 1 full year, we found that the fully adjusted association between vaccination and reduced mortality appeared strongest in months December to January and February to March (Figure 3), although the association between vaccination and a reduced risk of death in the “off-season” months April to November remained statistically significant (Figure 3). When patients with hypertension were matched 1:1 to patients with normotension in each season, in fully adjusted analysis, vaccination was associated with a reduced risk of all-cause death in both the hypertensive and normotensive group (hypertensive: HR, 0.82; 95% CI, 0.79–0.85; $P<0.001$; normotensive: HR, 0.81; 95% CI, 0.77–0.86; $P<0.001$). However, the NNT to prevent 1 death over a single season associated with vaccination was statistically significantly lower in the hypertensive group (NNT: 977; 95% CI, 837–1172) as compared with the normotensive group (NNT: 2026; 95% CI, 1674–2750; P value for difference: $P<0.001$). The association between vaccination and all-cause death and between vaccination and cardiovascular death was significantly modified by age (P for interaction: $P<0.001$ and $P=0.004$, respectively). However, when considering the outcome death from AMI or stroke no interaction between vaccination and age was present ($P=0.21$). In fully adjusted analysis

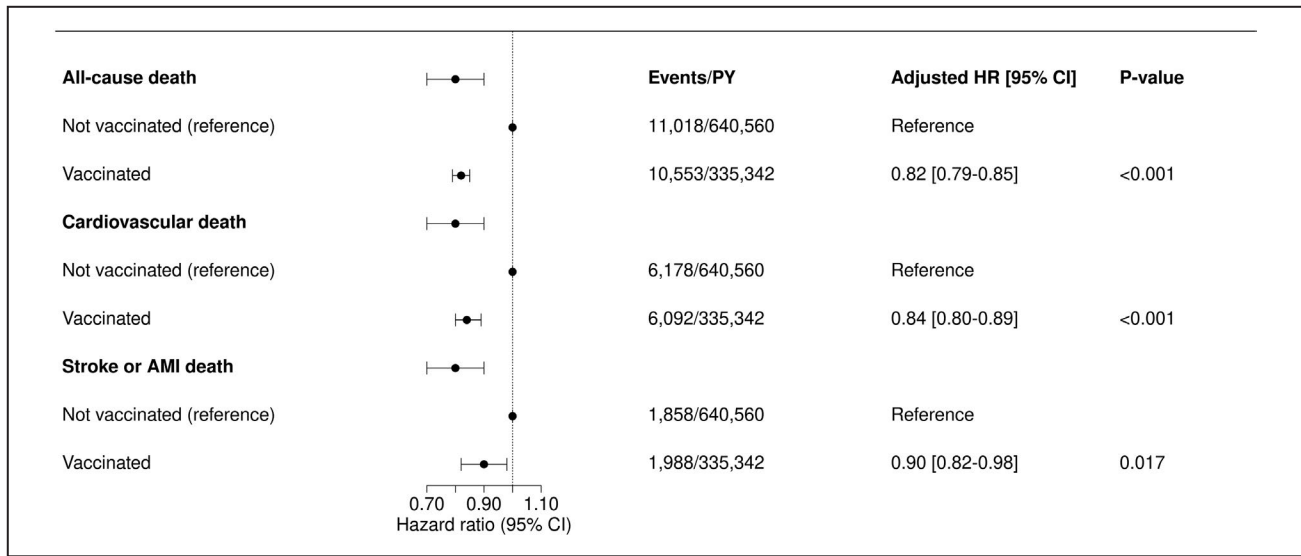


Figure 2. Association between influenza vaccination and the risk of death when considering all seasons included in the study with 95% CIs depicted as error bars.

Hazard ratios were produced with multivariable Cox regression models stratified on season year with patient-level cluster variances. The models were adjusted for all variables from the Table. AMI indicates acute myocardial infarction; HR, hazard ratio; and PY, person-years.

considering only patients aged <65 years, no statistically significant association between vaccination and all-cause death (HR, 0.95; 95% CI, 0.82–1.09; $P=0.47$) or cardiovascular death (HR, 0.92; 95% CI, 0.75–1.12; $P=0.41$) was present. In fully adjusted analysis considering only patients aged ≥ 65 years, vaccination was significantly associated with a reduced risk of both all-cause (HR, 0.81; 95% CI, 0.78–0.85; $P<0.001$) and cardiovascular death (HR, 0.84; 95% CI, 0.80–0.89; $P<0.001$).

Sensitivity Analyses

We found that vaccination was significantly associated with an increased risk of incident cancer (HR, 1.59; 95% CI, 1.55–1.63; $P<0.001$) in unadjusted analysis considering all seasons. In fully adjusted analysis, vaccination remained significantly associated with an increased risk of incident cancer although the strength of association was markedly reduced (HR, 1.06; 95% CI, 1.02–1.11; $P=0.002$). In fully adjusted analysis, vaccination in the second season was associated with

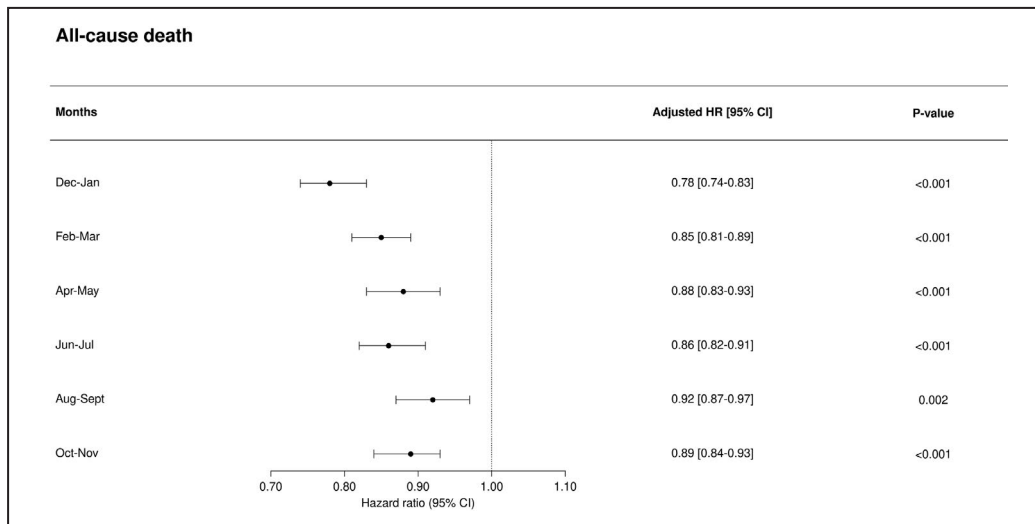


Figure 3. Association between vaccination and all-cause mortality was assessed for each 2-month period of follow-up as landmark analyses.

This analysis considers all seasons with follow-up extended from the 4 months “in-season” period (December 1–April 1 the following year) to a full year (December 1–December 1 the following year). The reference is no vaccination in the given season and the Cox regression models were adjusted for all variables displayed in the Table.

a reduced risk of all-cause death (HR, 0.79; 95% CI, 0.73–0.87; $P<0.001$) and cardiovascular death (HR, 0.82; 95% CI, 0.73–0.92; $P=0.001$) during the second season, while vaccination in the previous season was not associated with either a reduced or increased risk of death in the second season (all-cause death: HR, 0.97; 95% CI, 0.89–1.06; $P=0.54$; cardiovascular death: HR, 0.94; 95% CI, 0.84–1.006; $P=0.31$). In fully adjusted analysis, when excluding patients receiving loop diuretics ($n=75\,388$), vaccination was significantly associated with a reduced risk of all-cause death and cardiovascular death (all-cause death: HR, 0.83; 95% CI 0.79–0.87; $P<0.001$; cardiovascular death: HR, 0.86; 95% CI, 0.81–0.92; $P<0.001$).

DISCUSSION

In a Danish nationwide study considering 9 consecutive influenza seasons from 2007 to 2016, including >600 000 unique patients with hypertension, we found that influenza vaccination was significantly associated with a reduced risk death from all-causes, cardiovascular causes, and from AMI or stroke. Finally, we found statistically significant interactions between vaccination and age with respect to outcomes all-cause death and cardiovascular death, with results suggesting that vaccination may be more beneficial for elderly patients (over 65 years of age) with hypertension. To our knowledge, this study is the first to specifically assess the association between influenza vaccination and outcome in patients with hypertension without significant cardiovascular comorbidity.

Hypertension and Influenza Vaccination

No prior studies have assessed the effect of influenza vaccination in patients with hypertension without significant cardiovascular disease. Influenza vaccination is not mentioned in the 2017 hypertension guidelines from the American Heart Association¹⁷ or the 2013 guidelines from the European Society of Cardiology.¹⁸ Yet, influenza infection has been identified as a trigger of AMI,¹ and it has been shown in several small-scale randomized clinical trials that influenza vaccination reduces the risk of AMI in patients with coronary artery disease.^{5,7,19} Thus, it is becoming increasingly apparent that infections may increase the risk of acute ischemic events.³ Accordingly, influenza vaccination is now recommended in the guidelines on secondary prevention and risk reduction in patients with coronary artery disease and other atherosclerotic vascular disease by the American Heart Association, as a secondary preventative measure in patients with coronary artery disease.⁸ However, no recommendation on the role of influenza vaccination for the primary prevention of adverse cardiovascular outcomes in patients with hypertension

exists,^{17,18} and a systematic Cochrane review of randomized trials recently concluded that more evidence is needed before such recommendation can be made.²⁰ Hypertension is a major risk factor for stroke and coronary artery disease, and together these conditions are responsible for a large part of the deaths caused by hypertension.⁹ Furthermore, influenza-like illness has been shown to increase the risk of stroke,⁴ and this risk is attenuated by influenza vaccination.^{19,21} Therefore, it is likely that influenza vaccination may also reduce the risk of AMI and stroke in patients with hypertension without prevalent coronary artery disease or previous stroke and lead to improved outcome and reduced mortality. This notion is supported by our results, since we found that influenza vaccination was associated with significant reductions in the risk of all-cause, cardiovascular, and AMI or stroke death. Also, since the NNT to prevent 1 death over 1 season associated with vaccination was significantly lower in patients with hypertension (NNT 977) as compared to patients without hypertension (NNT 2026), our results support the notion that vaccination may be particularly beneficial for improving outcome in patients with hypertension.

Causality, Confounding, and Limitations

In this study, we used a sensitive method based on drug use to identify a widely representative cohort of patients with hypertension free from significant cardiovascular or chronic disease. Even though we excluded significant cardiovascular disease, we cannot guarantee that the antihypertensive medications we used to identify patients were prescribed solely for hypertension, as the indication for treatment was not available in the registers. However, this method has been proven effective for identifying patients with hypertension in the general population using the same Danish registers as used in this study.^{13,14} Because of this limitation, our results should be replicated in a population of patients with an adjudicated diagnosis of hypertension. Furthermore, since our study was observational, we cannot prove causation. However, several aspects of our findings provide support for a potential causal association between vaccination and improved outcome in hypertension: (1) In unadjusted analysis, influenza vaccination was associated with a markedly higher risk of death. Patients who underwent vaccination were older, had lower household income, lower education attainment, more comorbidity, and higher medication use. After adjustment for these confounders, vaccination was significantly associated with a substantially reduced risk of death. This change in association with adjustment suggests that our analysis effectively controlled for confounding by indication and speaks to the validity of our results.²² Also, that the association changed from hazardous to protective with adjustment

suggests that our data were confounded by selection bias, possibly because patients who were vaccinated were older and sicker.²² This is supported by our results, since we found that vaccination was significantly associated with an increased risk of incident cancer in both unadjusted and fully adjusted analysis. It is highly unlikely that vaccination would increase cancer rates, and thus an increased risk of cancer with vaccination suggests sicker patients with more comorbidities were more likely to receive vaccination. (2) When follow-up was extended from the 4 months “in-season” period (December 1–April 1 the following year) to 1 full year (December 1–December 1 the following year), we found that the association between vaccination and reduced mortality was strongest in months December 1 to April 1 and declined throughout months April 1 to December 1. Thus, the association appeared strongest in months with high influenza activity but was not absent in the “off-season” months following the influenza season. This pattern is consistent with recent findings suggesting the risk of ischemic events associated with acute infection is highest shortly following infection and declines but remains elevated for months after the infection before returning to baseline.^{3,23} However, it is also possible that the association between vaccination and outcome found in the “off-season” months is the result of residual confounding perhaps because of increased propensity for health-seeking behavior among vaccinated patients. (3) When considering only the outcome of patients during their second season in the study, in fully adjusted analysis, vaccination in the second season was associated with a reduced risk of death, while vaccination in the prior season was not significantly related to survival during the second season. If vaccination was a marker of a healthier patient, we would expect vaccination in the prior season to be associated with improved outcome in the second season. (4) We found that in the 2007 to 2008 season (1 of the 2 seasons where known mismatches between vaccine strains and circulating strains occurred) no association between vaccination and a reduced risk of cardiovascular death was present. This adds further support for a potential causal relationship between vaccination and a reduced risk of death. However, another known partial mismatch occurred in the 2015 to 2016 season, and in this season vaccination was associated with a reduced risk of both all-cause and cardiovascular death, which we did not expect. Since the known mismatch occurred only between the influenza B vaccine component and the circulating B strain, it is possible that the 2 different influenza A strains contained in the vaccine offered adequate protection from influenza infection in that season. As only 44% of recorded influenza activity in the 2015 to 2016 season were of type B, and the remaining 56% were of type A, this might explain why an association between

vaccination and a reduced risk of death was present in this season. Ideally, more information on the degree of match between influenza vaccine strains and circulating viruses would have allowed for more detailed comparisons. However, although unlikely, it must be acknowledged that our study was observational, and therefore another potential explanation is also that our findings may be explained by residual confounding not addressed by our analyses. Therefore, our results must be replicated in future randomized controlled trials. Finally, we only had information on vaccines administered by general practitioners. Hence, if some patients received vaccines from a different provider, for instance from a job-related healthcare program, this would not be detected. However, these patients would have been classified as unvaccinated, and this would only serve to weaken any potential association between influenza vaccination and outcome. Also, since this was a register-based study, we did not have access to important hypertension-related parameters such as the presence of obesity or the level of blood pressure control achieved by each individual patient.

CONCLUSIONS

In this nationwide study which included 9 consecutive influenza seasons and >600 000 patients with hypertension free from significant cardiovascular disease identified through medication use, we found that influenza vaccination was significantly associated with a reduced risk of death from all-causes, cardiovascular causes, and AMI or stroke. The association between vaccination and improved outcome was strongest for elderly patients aged >65 years. Influenza vaccination might improve patient outcome in hypertension, and the potential effect on outcome may be strongest in elderly patients >65 years.

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Supplemental Material

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Supplemental Material

Data S1

Supplemental Methods

Patient characteristics

Patient comorbidities at the beginning of each season (December 1) were retrieved from the Danish National Patient Registry[24] and defined using ICD-10 codes (Supplemental Table S2). All diagnoses from the Danish National Patient Register included in the Charlson comorbidity index have been validated with positive predictive values of 96% to 100%[25]. Patient medications at the beginning of each season were retrieved from the Danish National Prescription Registry[26] and defined as at least 1 filled prescription up to 6 months prior to baseline. Information regarding household income at the beginning of each season and patient educational level was collected from the Danish National Population Registry[10]. Patient age, vaccination status in previous season, comorbidities, medications and household income and were reassessed at each the beginning of each season to account for changes between seasons.

Influenza vaccine match

Statens Serum Institut (SSI) is the principal governmental agency responsible for the monitoring and management of infectious diseases, including influenza, at the population level in Denmark (Similar to the Centers for Disease Control and Prevention (CDC) in the United States). SSI collects patient samples obtained from suspected influenza patients from hospitals and general practitioners all throughout the influenza season. These samples are used to determine the types and sub-types of influenza virus circulating in each season. Briefly, they examine the received samples to determine the following influenza types and subtypes: influenza type A subtype H3N2, A/H1N1, A/H1N1pdm09 (this subtype emerged in 2009 and caused a pandemic) (this virus outcompeted the older seasonal H1N1 subtype), influenza type B lineage Yamagata or B/Victoria. The influenza vaccine used in Denmark is trivalent with two influenza type A strains and a single type B influenza strain. During the study period (2007-2016), the vaccine contained one influenza A H3N2 strain, one influenza A H1N1 strain and one influenza B (Yamagata or Victoria) strain. However, due to the frequent antigenic drift of influenza, it is difficult to assess vaccine match and adequacy based only on the subtype level (A/H3N2, A/H1N1, A/H1N1pdm09, B/Yamagata and B/Victoria) and information on strains included in the vaccine[27]. To rigorously determine whether any given vaccine was well matched with the influenza strains circulating in that particular season, dedicated vaccine effectiveness studies must be conducted[28]. Therefore, it is not possible to assess vaccine match for every season included in the study period. However, it is possible to derive some information from the subtyping information: In general, it is mainly influenza type A viruses that cause influenza illness in Denmark, but during some seasons, a moderate proportion of influenza cases were caused by influenza type B viruses. In some of these years, the type B virus lineage included in the vaccine was not a match for the type B virus lineage circulating in the population during that year, and therefore it is possible that the vaccine did not provide effective protection against the influenza type B virus during that season. Specifically, in the season 2007-2008, 36% of influenza samples received by Statens Serum Institut were of the B/Yamagata lineage, while 0% were of the B/Victoria lineage. However, in the 2007-2008 season, the vaccine contained influenza B/Victoria and not B/Yamagata, indicating that the vaccine effect may have been reduced in this season. Similarly, in the season 2015-2016, 34% of influenza samples received by Statens Serum Institut were of the B/Victoria lineage, while only 9% were of B/Yamagata. In the 2015-2016 season, the vaccine contained B/Yamagata and not B/Victoria, again suggesting a reduced effect of the vaccine in this season. Therefore, to determine whether the association between vaccination and mortality in these two seasons of interest (2007-2008 and 2015-2016) differed from the remaining seasons included in the study period, we assessed the association between vaccination and mortality by season using multivariable Cox regression.

Sensitivity analyses

We conducted several sensitivity analyses to ascertain the robustness of our results. Firstly, we assessed the fully adjusted association between vaccination and incident cancer. It is highly unlikely that vaccination would increase cancer rates. Thus, an increased risk of cancer with vaccination suggests sicker patients with more comorbidities are more likely to receive vaccination. Secondly, we attempted to specifically address whether our vaccination estimates were confounded by an association to a healthier patient phenotype (healthy user bias) not addressed by our extensive statistical adjustment. In this analysis, we only considered the outcome of patients during their 2nd season in the study while assessing the fully adjusted association between vaccination in the previous season and outcome in the 2nd season. If vaccination in the prior season is associated with a reduced risk of death in the 2nd season, this could potentially be due to confounding by healthy user bias. Thirdly, we have previously shown using Danish Nationwide Registry data that influenza vaccination was significantly associated with reduced mortality in patients with heart failure[29]. In the present study, we sought to study the association between influenza vaccination and outcome in patients with hypertension. Therefore, in this study, we excluded patients with prevalent heart failure to ensure that any potential association between vaccination and outcome applies to patients with hypertension, and may not simply be explained by the inclusion of heart failure patients in the study sample. However, although the specificity and positive predictive value associated with a heart failure diagnosis in the Danish registers are high, the sensitivity is low[30]. A more sensitive method for identifying patients with heart failure in the Danish registers involves considering the use of loop diuretics as a proxy for heart failure, as done in previous Danish register based studies[14,31–32]. Thus, to ensure that our results may not be explained by the potential inclusion of patient with heart failure in the study sample, we assessed the fully adjusted association between vaccination and outcome when excluding all patients receiving loop diuretics.

Data S2

Supplemental Results

Influenza vaccine match

Overall, when considering each influenza season separately in fully adjusted analysis, vaccination was significantly associated with a reduced risk of death in most seasons (Supplemental Figure S2). However, in seasons 2007-2008, 2009-2010, 2012-2013 and 2014-2015, vaccination was not significantly associated with a reduced risk of cardiovascular death (Supplemental Figure S2).

SUPPLEMENTAL TABLES

Table S1. Nationwide registries used in the present study

	National Patient Registry	National Prescription Registry	National Population Registry	National Cause of Death Registry	National General Practitioners Reimbursement Registry
Created and established	1977	1995	1976	1970	1990
Examples of data in the registries	Hospital diagnoses, hospital contacts, procedure codes	Filled prescriptions for all Danish citizens	Date of birth, sex, emigration status, household income and education level	Time and cause of death	Type and time of administration of all services in the general practice sector
Coding	ICD-10	ATC-codes	N/A	ICD-10	Unique governmental reimbursement codes
Data used in the present study	Patient comorbidities at the beginning of each season	Patient medication use at the beginning of each season	Age, sex, income and education level at the beginning of each season	Outcome (all-cause death, cardiovascular death, AMI and stroke death, incident cancer) and follow-up time	Vaccination exposure prior to each season
Data-linkage	Personal identification number	Personal identification number	Personal identification number	Personal identification number	Personal identification number

ATC; anatomical therapeutic chemical classification system. ICD-10; International Classification of Diseases 10th revision. AMI, acute myocardial infarction.

Table S2. Anatomical Therapeutic Chemical (ATC) Classification codes used for the definition of medication use.

Medication	ATC-code
Statin	C10AA
Lipid-lowering	C10
Glucose-lowering	A10
Renin-angiotensin system inhibitor	C09
Anti-thrombotic	B01
Beta blocker	C07
Diuretic	C03
Spironolactone	C03D
Digoxin	C01AA05
Calcium Antagonist	C08
Aspirin	B01AC06
Opioid	N02A
Antipsychotic	N05A
Antidepressant	N06A
Antiepileptic	N03A
Systemic glucocorticoid	H02AB
Proton-pump inhibitor	A02BC

Table S3. International Classification of Disease 10th revision (ICD-10) used for the definition of comorbidities.

Comorbidity	ICD-10 Codes
Acute myocardial infarction	I21-I22
Ischemic heart disease	I20-I25
Valvular disease	I34-I37
Cerebrovascular disease	I60-I69
Systemic embolus	I26, I74
Cancer	C00-C97
Atrial Fibrillation	I48
Chronic renal failure	N18, I12-I13
Anemia	D50, D62, D64
<i>Diabetes*</i>	<i>ATC-code: A10*</i>
Chronic obstructive pulmonary disease	J42, J44
Peripheral vascular disease	I70, I74
Liver disease	K70-K77, B150, B160, B190
Rheumatic disease	M05-M06, M32-M34, M353
Peptic ulcer	K25-K27, K29

*Diabetes was defined as at least 1 prescription filled for glucose-lowering medication up to a maximum of 6 months before the index date of a given season.

FIGURE S1

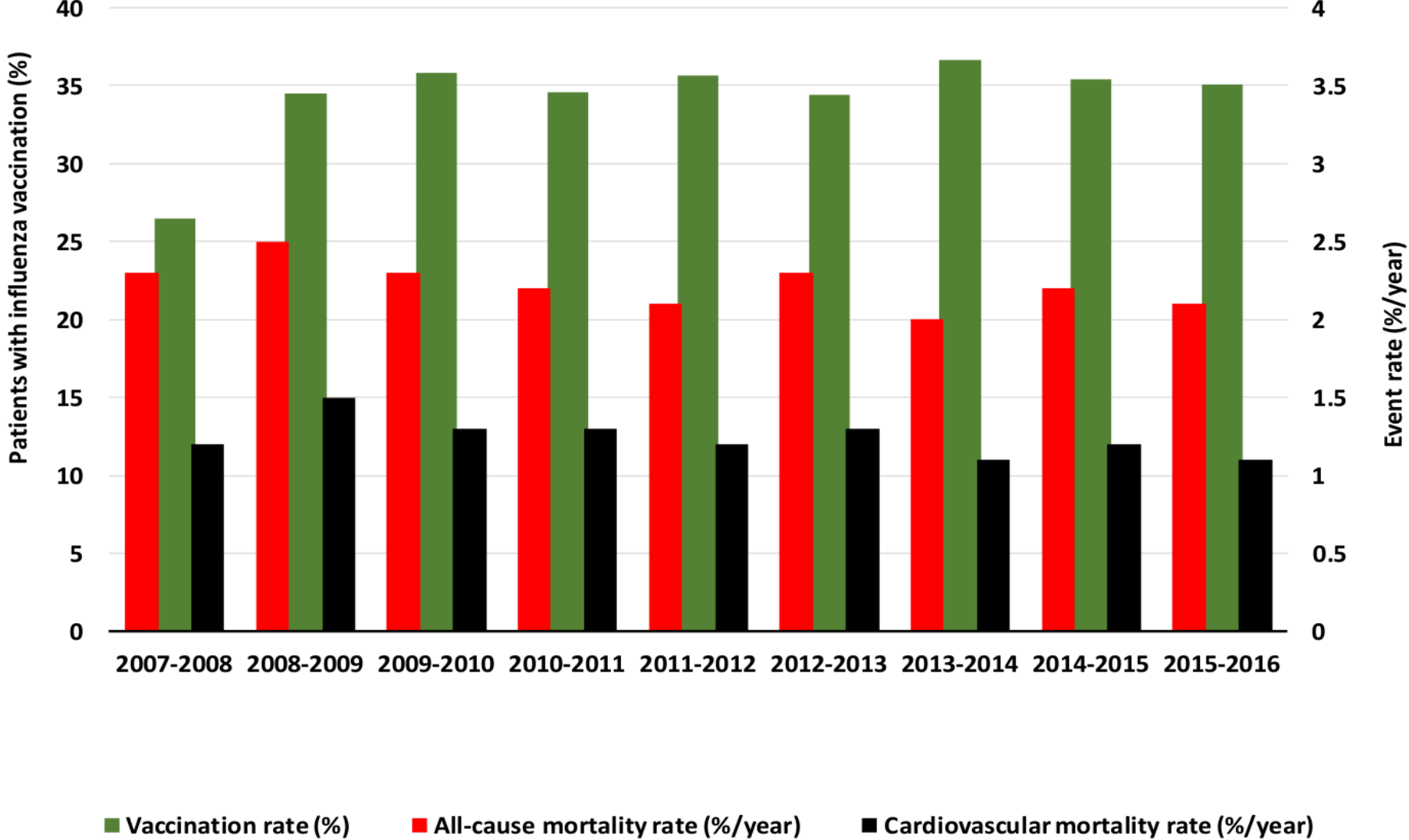
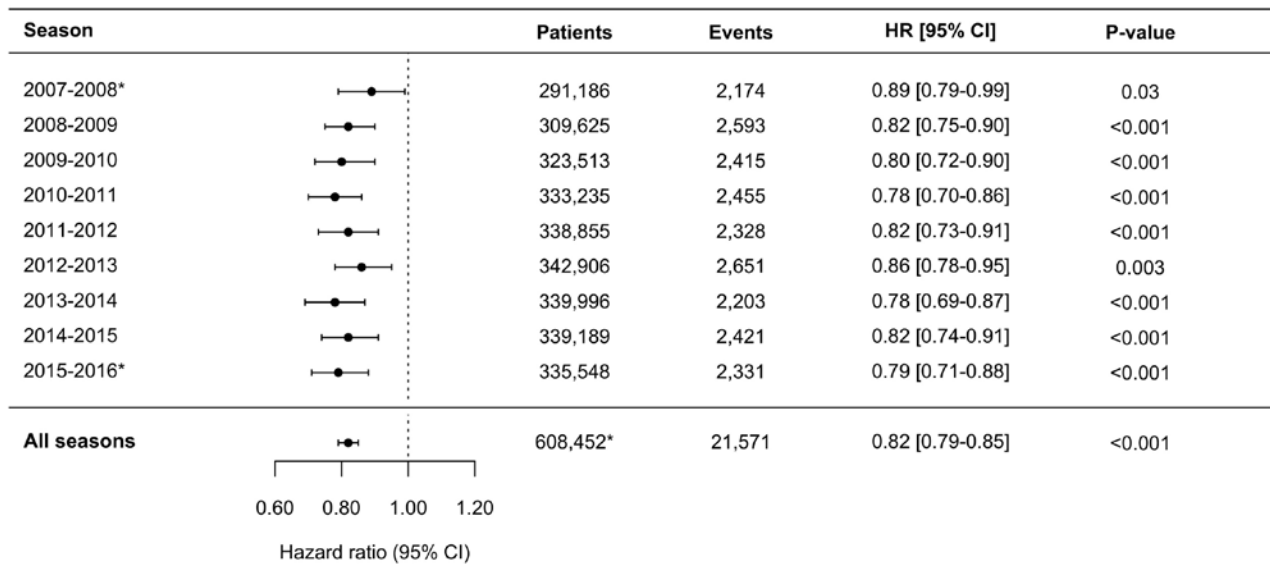


Figure S1 Legend: Vaccination coverage, all-cause mortality rate and cardiovascular mortality rate in each season included in the study. A season denotes the period December 1 until April 1 the following year. For example, in this figure, “2007-2008” denotes the period December 1, 2007 – April 1, 2008.

FIGURE S2

All-cause Death



Cardiovascular death

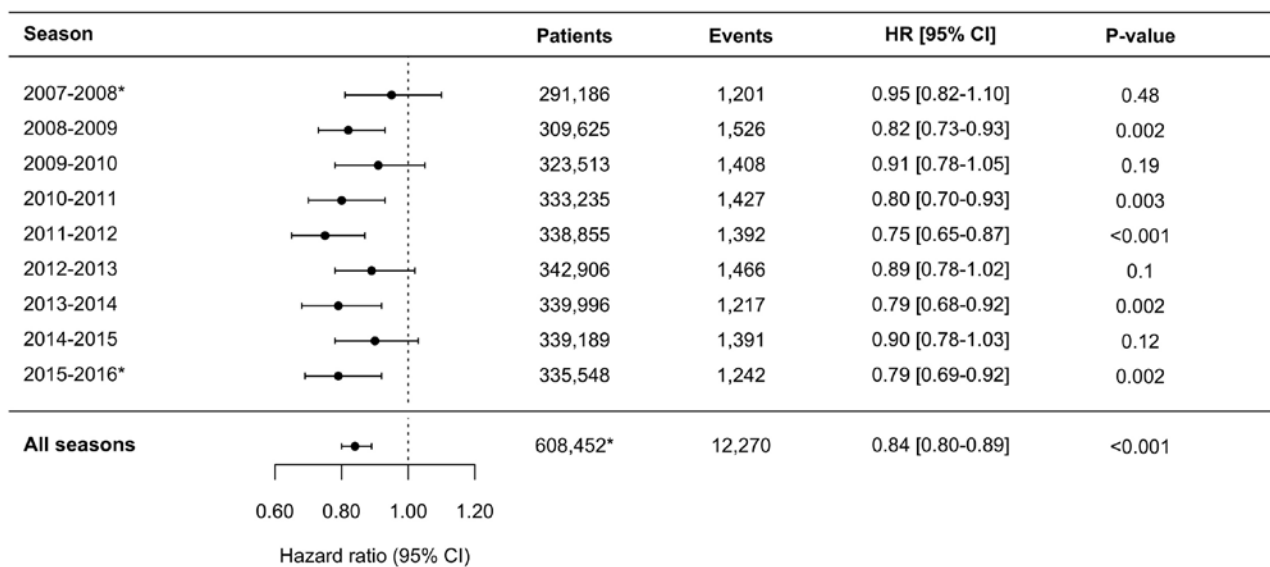


Figure S2 legend: Landmark analyses assessing the association between influenza vaccination and outcome in each separate influenza season included in the study. In all analyses the reference is no vaccination in the given season. For each season, follow-up was counted from December 1 and ended on April 1 the next year, encompassing the period of high influenza activity in Denmark. The Cox regression models were adjusted for all variables displayed in Table 1. *In seasons 2007-2008 and 2015-2016 partial mismatches between the influenza B vaccine strain and the circulating influenza B strain occurred. For more details, please see the Methods section, Statistical analysis and Data S1 and Data S2. *608,452 denotes the number of unique patients included in the study.

FIGURE S3

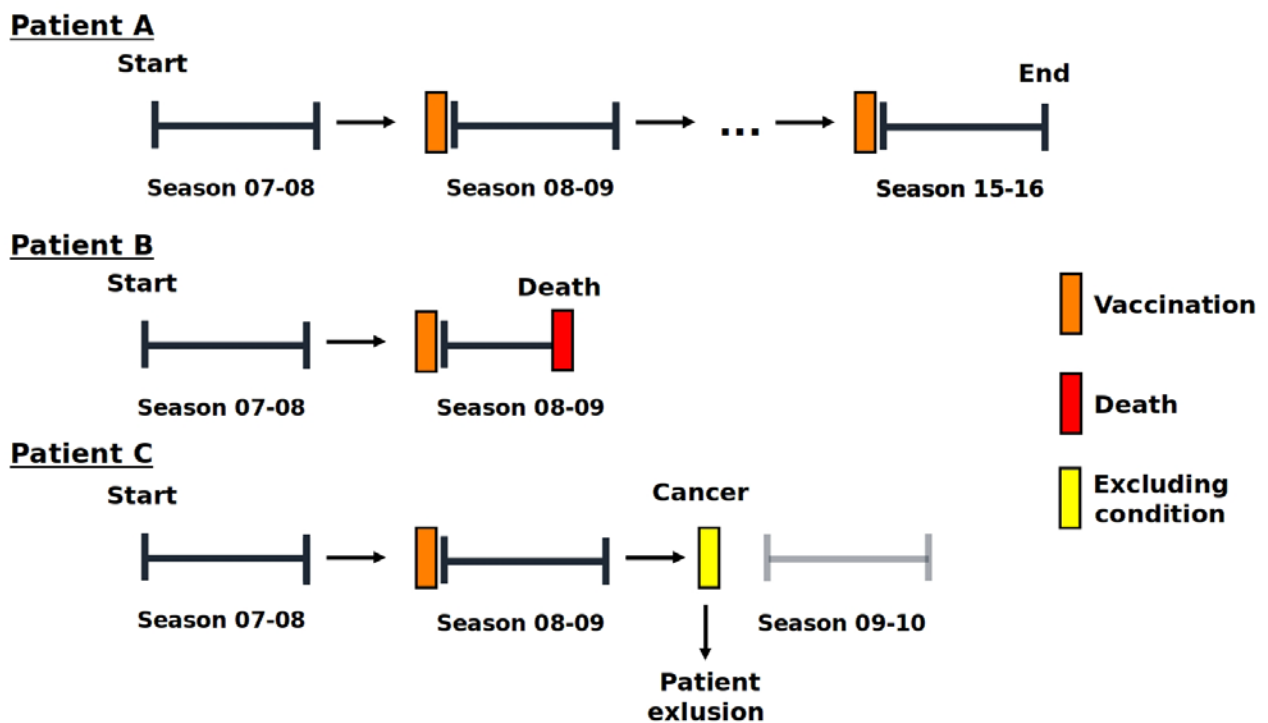


Figure S3 legend: This figure depicts the modified cohort design of the study. An influenza season is defined as the period December 1 – April 1 next year. For each season, we identified all patients living with hypertension on December 1 and followed these patients until April 1 the following year. When considering all seasons included in the study, patients could contribute with follow-up in multiple seasons. For example, consider patient A, a patient diagnosed with hypertension fulfilling inclusion criteria prior to December 1, 2007 who is included in the 2007-2008 season. Then, if the patient did not die in the 2007-2008 season, did not develop any of the exclusion criteria conditions (IHD, HF, COPD, cancer or cerebrovascular disease) and continued to receive at least 2-drug antihypertensive therapy in the 6 months prior to the index date of the next seasons the patient would also be included in following seasons, potentially until the end of the study period as shown for patient A. Patient B shows an example of a patient who was included in the 2007-2008 season, did not develop an outcome during this season and did not develop an excluding condition prior to the 2008-2009 season. Since the patient still fulfils inclusion criteria on December 1, 2008, the patient is included for another season but dies during this season. Finally, patient C displays an example of a patient who develops an excluding condition after season 2008-2009 resulting in the patient not being included in any subsequent seasons.