Influenza Vaccination Is Associated With Reduced Cardiovascular Mortality in Adults With Diabetes: A Nationwide Cohort Study

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OBJECTIVE

Recent influenza infection is associated with an increased risk of atherothrombotic events, including acute myocardial infarction (AMI) and stroke. Little is known about the association between influenza vaccination and cardiovascular outcomes in patients with diabetes.

RESEARCH DESIGN AND METHODS

We used nationwide register data to identify patients with diabetes in Denmark during nine consecutive influenza seasons in the period 2007–2016. Diabetes was defined as use of glucose-lowering medication. Patients who were not 18–100 years old or had ischemic heart disease, heart failure, chronic obstructive lung disease, cancer, or cerebrovascular disease were excluded. Patient exposure to influenza vaccination was assessed before each influenza season. We considered the outcomes of death from all causes, death from cardiovascular causes, and death from AMI or stroke. For each season, patients were monitored from December 1 until April 1 the next year.

RESULTS

A total of 241,551 patients were monitored for a median of four seasons (interquartile range two to eight seasons) for a total follow-up of 425,318 person-years. The vaccine coverage during study seasons ranged from 24% to 36%. During follow-up, 8,207 patients died of all causes (3.4%), 4,127 patients died of cardiovascular causes (1.7%), and 1,439 patients died of AMI/stroke (0.6%). After adjustment for confounders, vaccination was significantly associated with reduced risks of all-cause death (hazard ratio [HR] 0.83, $P < 0.001$), cardiovascular death (HR 0.84, $P < 0.001$), and death from AMI or stroke (HR 0.85, $P = 0.028$) and a reduced risk of being admitted to hospital with acute complications associated with diabetes (diabetic ketoacidosis, hypoglycemia, or coma) (HR 0.89, $P = 0.006$).

CONCLUSIONS

In patients with diabetes, influenza vaccination was associated with a reduced risk of all-cause death, cardiovascular death, and death from AMI or stroke. Influenza vaccination may improve outcome in patients with diabetes.

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In recent years, it has become increasingly clear that the abrupt inflammatory response associated with acute infection may trigger ischemic events such as acute myocardial infarction (AMI) or stroke (1,2). Patients with diabetes have an increased risk of developing atherosclerotic cardiovascular disease, and they suffer an increased mortality from acute myocardial infarction (AMI) and stroke compared with their counterparts without diabetes (3,4). Over the last two decades, studies have linked influenza infection with an increased risk of both AMI (2,5,6) and stroke (7). Because patients with diabetes have a high risk of AMI and stroke in addition to an increased susceptibility for influenza infection (8,9), they may be at high risk of suffering acute ischemic events secondary to influenza infection. This prompts the question of whether influenza vaccination may prevent cardiovascular mortality in patients with diabetes. If this is the case, the safety profile, cost efficiency, and feasibility of vaccination make it ideal for improving outcomes in diabetes.

Currently, influenza vaccination is recommended for all patients with diabetes by the American Diabetes Association in their *Standards of Medical Care in Diabetes* 2019 guidelines (10). However, this recommendation is made without a class of recommendation and with a low evidence level (level C, evidence based on observational studies of low quality) (10). No randomized controlled trials assessing the effect of influenza vaccination in patients with diabetes exist, and very little is known about the effect of influenza vaccination on cardiovascular mortality in diabetes (11,12). Thus, whether influenza vaccination may prevent cardiovascular mortality in diabetes is not clear. We therefore sought to assess the association between vaccination and mortality, including cardiovascular mortality, in patients with diabetes.

RESEARCH DESIGN AND METHODS

Ethics

In Denmark, informed consent and approval by a local ethics committee is not required for registry-based studies.

Data Sources

In Denmark, the government-funded health care system provides all Danish citizens with equal access to health care irrespective of socioeconomic status. The services provided are unrestricted and include primary, secondary, and tertiary care. At birth or immigration, all citizens are assigned a unique personal identification number (PIN) (13). This PIN is used throughout the Danish civil registration system, including the health care system. The PIN allows for linkage of health and administrative data at the individual level and ensures complete follow-up (14). Data for this study were retrieved from several nationwide registries. More details and an overview of the registries used in this study may be found in Supplementary Table 1.

Study Design and Diabetes Definition

We used a modified cohort design with a season-specific approach to assess the association between influenza vaccination and outcome. We assumed that a potential causal association between vaccination and improved outcome would be due to a reduced likelihood of influenza infection or a reduced severity of infection. Therefore, we confined our main study period of interest to include months December, January, February, and March, because epidemiological data have shown that almost all influenza activity in Denmark occurs in these months (15). Consequently, if a potential causal relationship between influenza vaccination and outcome exists, the strongest association is likely to be observed during this period. For the remainder of this report, the period from December 1 to April 1 the following year (spanning the 4 months of high influenza activity) will be referred to as an influenza season. In this study, we considered all influenza seasons in the period 2007–2016. Hence, we included nine seasons representing nine distinct periods of observation. For each season, we identified all patients living with diabetes on December 1 and monitored these patients until April 1 the following year (Fig. 1).

Patients with diabetes were identified as individuals who had filled at least one prescription for glucose-lowering medication (oral or insulin) in the 6 months leading up to each season (i.e., the 6 months leading up to December 1, which marked the beginning of each season) (16–18). Information on prescription use was obtained from the Danish National Prescription Register (19). The Danish National Prescription Register has recorded all prescriptions filled at Danish pharmacies since 1995. The register contains information on drug type (coded using the Anatomical Therapeutic Chemical Classification System [ATC]), date of dispense, and the PIN of the recipient. The register is used for drug cost reimbursement and is accurate (19). 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 glucose-lowering medication (ATC code: A10) (Fig. 1). It is well established that influenza vaccination is beneficial for patients with high-risk health conditions such as lung disease, heart disease, or cancer. We therefore excluded patients with common high-risk disease in an attempt to isolate the effect of vaccination in diabetes. Hence, patients who were younger than 18 years old, older than 100 years old, had ischemic heart disease, heart failure, chronic obstructive pulmonary disease, cancer, or prior cerebrovascular disease were excluded (Fig. 1). The inclusion process for the 2007–2008 season is presented in Fig. 1. An identical process was used to identify patients for the remaining eight seasons included in the study.

Patient Characteristics

Patient characteristics were assessed at the beginning of each season (December 1). For more detail, refer to the Supplementary Material.

Influenza Vaccination Status

In Denmark, seasonal influenza vaccination is offered to all patients with diabetes free of charge. Records of vaccine administration are recorded in the General Practitioners Reimbursement Register tied to the unique PIN of the vaccine recipient. General practitioners are reimbursed by the government for services rendered to citizens on a fee-by-service basis, and they rely on the accuracy of this register for reimbursement. In this study, we used the General Practitioners Reimbursement Register to assess the exposure to influenza vaccination before the beginning of each season. For a particular season, a patient was only considered vaccinated if the patient had received an influenza vaccination in the 4 months before the beginning of a season (before December 1). For instance, for a patient to be considered vaccinated in the influenza season 2008–2009, the patient must have had undergone vaccination in

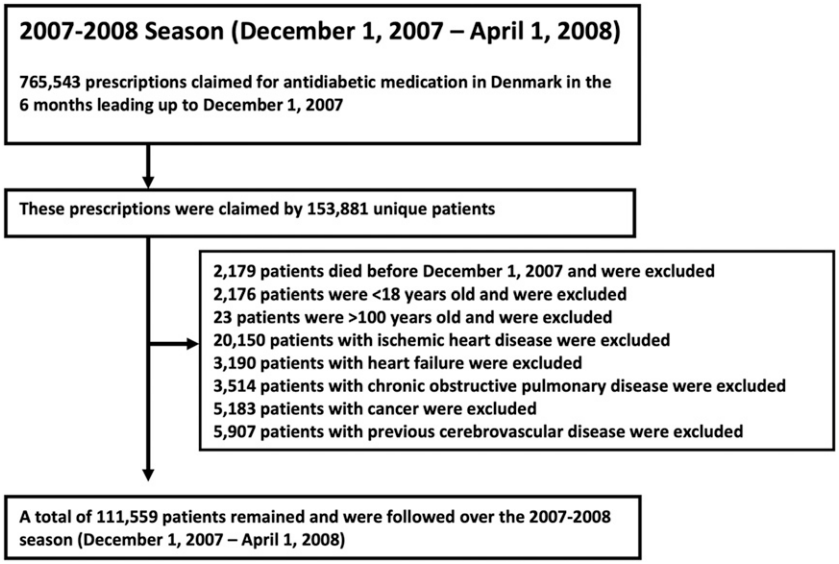

Figure 1—A flowchart of the inclusion procedure. The inclusion process for the 2007–2008 season is shown. A similar process was used for identifying patients in the remaining eight seasons from 2008 to 2016.

the 4 months leading up to the start of this season (before December 1, 2008). Then, the patient would have been considered vaccinated for the 2008–2009 season only, and not for any subsequent seasons, unless the patient underwent vaccination again before later seasons. A patient was considered vaccinated if the patient had received an influenza vaccination in the 4 months before the beginning of a season (before December 1). We chose this period because the large majority of influenza vaccines dispensed in Denmark are administered to patients in September, October, and November.

Outcomes

In each season included in the study, patients were monitored from December 1 until their death or until April 1 the following year. The primary outcomes of this study were all-cause death, cardiovascular death, and death from AMI or stroke. We defined AMI as ICD-10 codes I21-I22 and stroke as ICD-10 codes I61-I64. In addition, we assessed the incidence of a combined outcome consisting of common acute complications associated with diabetes, namely diabetic ketoacidosis (ICD-10: E101, E111, E121, E131, E141) and hospitalization for hypoglycemia or coma (ICD-10: E100, E110, E120, E130, E140, E162). To investigate the association between vaccination and influenza and/or pneumonia, we assessed the incidence of a composite outcome consisting of influenza or pneumonia during follow-up (ICD-10: J1). We also assessed the association between influenza vaccination and the risk of starting insulin therapy during follow-up for patients who did not receive insulin at study inclusion. Finally, in an attempt to assess how effective our fully adjusted models were at controlling for confounding factors, we assessed the incidence of cancer during follow-up (ICD-10 codes: C00-C97). It is highly unlikely that influenza vaccination would increase cancer rates. Thus, any association between vaccination and cancer rates is likely to represent residual confounding. For example, if vaccination is associated with a higher risk of cancer in unadjusted analysis, this would suggest that vaccination is associated with a sicker patient. Then, if the association between vaccination and cancer is fully attenuated by multivariable adjustment, this suggests that the multivariable model is able to at least partly control for confounding factors affecting the association between influenza vaccination and outcome (20).

Statistical Analysis

In this study, when considering all nine seasons, patients could contribute with follow-up in multiple seasons. For instance, a patient with diabetes fulfilling the inclusion criteria before December 1, 2007 would be 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 (ischemic heart disease, heart failure, chronic obstructive pulmonary disease, cancer, or cerebrovascular disease), and continued to receive at least one glucose-lowering drug in the 6 months before the index date of the next season (December 1, 2008), the patient would also be included in the 2008–2009 season. Hence, in Table 1, we stratified patients according to whether they received at least one influenza vaccination in at least one season during the study period. In addition, we listed characteristics in Table 1 corresponding to patient characteristics at the time of their first inclusion into the study.

To assess the association between vaccination and outcome we used survival analysis. When considering all seasons, we used stratified multivariable Cox regression models stratified by season with multiple follow-up intervals per patient. We adjusted these models for all variables in Table 1 (referred to as "fully adjusted results" from here on). In these models, we used a clustered variance estimator to calculate cluster-robust SEs to account for multiple observation periods per patient. The follow-up period for each season began on December 1 and ended at the time of death or April 1 of the following year, allowing a contribution of up to 120 days per patient per season. Because it is accepted that the effect of influenza vaccination varies with each season and is highly dependent on matching between vaccine strains and circulating strains (21), we also conducted analyses stratified by season to capture interseasonal differences. To assess whether the association between vaccination and outcome was modified by age, we assessed the significance of an age-vaccination interaction term in our fully adjusted models. We reassessed and updated patient characteristics (comorbidities, medications, household income, and vaccination status) on the index date of each season (December 1) to account for season-to-season changes. We also conducted an analysis assessing the association between mortality and vaccination in the "off-season" months (April 1–December 1 the following year). For this analysis, we extended the follow-up from the 4-month "in-season" period (December 1–April 1 the following year) to 1 full year (December 1–December 1 the following year).

Table 1—Characteristics of patients who were vaccinated at least once in at least one season and patients who never received a vaccination at the time of inclusion into their first season in the study

Demographics	All patients $N = 241,551$	No vaccine $n = 122,154$	Ever vaccinated in study $n = 119,397$	P value
Age, mean (SD) (years)	58.7 (15.5)	53.2 (15.7)	64.3 (13.2)	<0.001
Male	127,659 (52.9)	64,490 (52.3)	63,169 (52.9)	0.58
Household income quartile				<0.001
First quartile	NA	26,881 (22.0)	32,571 (27.3)	
Second quartile	NA	25,878 (21.1)	33,574 (28.1)	
Third quartile	NA	30,182 (24.7)	29,270 (24.1)	
Fourth quartile	NA	36,277 (29.7)	23,175 (19.4)	
Highest education level				
Basic school	94,394 (39.1)	42,700 (35.0)	51,694 (43.3)	
High school	9,617 (3.4)	6,571 (5.4)	3,046 (2.6)	
Vocational education	83,360 (34.5)	43,117 (35.3)	40,243 (33.7)	
Short-cycle tertiary or bachelor's degree	30,898 (12.8)	17,205 (14.1)	13,693 (11.5)	
Master's degree or higher	8,703 (3.6)	4,938 (4.0)	3,765 (3.2)	
Unknown	14,579 (6.0)	7,623 (6.2)	6,956 (5.8)	
Vaccination in previous season	39,652 (16.4)	2,177 (1.8)	37,475 (31.4)	<0.001
Comorbidities				
Hypertension	82,103 (34.0)	53,974 (29.6)	28,129 (48.0)	<0.0013
Valvular disease	1,709 (0.7)	567 (0.5)	1,142 (1.0)	<0.001
Systemic embolus	982 (0.4)	446 (0.4)	536 (0.5)	0.001
Atrial fibrillation or flutter	6,815 (2.8)	2,167 (1.8)	4,648 (3.9)	<0.001
Chronic renal failure	1,811 (0.8)	785 (0.6)	1,026 (0.9)	<0.001
Anemia	3,448 (1.4)	1,382 (1.1)	2,066 (1.7)	<0.001
Peripheral vascular disease	3,346 (1.4)	1,251 (1.0)	2,095 (1.8)	<0.001
Liver disease	2,818 (1.2)	1,441 (1.2)	1,377 (1.2)	0.55
Rheumatic disease	2,787 (1.2)	1,007 (0.8)	1,780 (1.5)	<0.001
Peptic ulcer	4,909 (2.0)	1,958 (1.6)	2,951 (2.5)	<0.001
Medications				
Number of antidiabetic drugs				<0.001
1 drug	197,024 (81.6)	104,658 (85.7)	92,366 (77.4)	
2 drugs	41,152 (17.0)	16,197 (13.3)	24,955 (20.9)	
≥3 drugs	3,375 (1.4)	1,299 (1.1)	2,076 (1.7)	
Insulin	50,923 (21.1)	23,949 (19.6)	26,974 (22.6)	<0.001
Insulin monotherapy	35,787 (15.9)	28,967 (17.0)	6,820 (12.4)	<0.001
Oral antidiabetics and insulin	15,136 (6.3)	11,033 (6.1)	4,103 (6.9)	<0.001
Oral antidiabetics only	190,628 (78.9)	142,364 (78.1)	48,264 (81.5)	<0.001
Metformin	177,173 (73.3)	92,448 (75.7)	84,725 (71.0)	<0.001
Sulfonylurea	51,399 (21.3)	19,446 (15.9)	31,953 (26.8)	<0.001
DPP-4 inhibitor	4,269 (1.8)	2,077 (1.7)	2,192 (1.8)	0.011
SGLT-2 inhibitor	195 (0.1)	142 (0.1)	53 (<0.1)	<0.001
GLP-1 agonist	1,795 (0.7)	1,198 (1.0)	597 (0.5)	<0.001
Glitazone	1,035 (0.4)	360 (0.3)	675 (0.6)	<0.001
Renin-angiotensin system inhibitor	117,440 (48.6)	49,446 (40.5)	67,994 (57.0)	<0.001
β-Blocker	39,318 (16.3)	15,101 (12.4)	24,217 (20.3)	<0.001
Diuretic	62,352 (25.8)	23,209 (19.0)	39,143 (32.8)	<0.001
Loop diuretic	21,569 (8.9)	7,220 (5.9)	14,349 (12.0)	<0.001
Calcium antagonist	50,310 (20.8)	19,826 (16.2)	30,484 (25.5)	<0.001
Statin	121,115 (50.1)	51,056 (41.8)	70,059 (58.7)	<0.001
Antithrombotic	69,808 (28.9)	24,289 (19.9)	45,519 (38.1)	<0.001
Spironolactone	5,832 (2.4)	2,323 (1.9)	3,509 (2.9)	<0.001
Digoxin	5,765 (2.4)	1,603 (1.3)	4,162 (3.5)	<0.001
Aspirin	60,857 (25.2)	21,312 (17.5)	39,545 (33.1)	<0.001
Opioid	26,022 (10.8)	10,252 (8.4)	15,770 (13.2)	<0.001
Antipsychotic	10,794 (4.5)	4,737 (3.9)	6,057 (5.1)	<0.001
Antidepressant	30,745 (12.7)	12,973 (10.6)	17,772 (14.9)	<0.001
Antiepileptic	8,412 (3.5)	3,555 (2.9)	4,857 (4.1)	<0.001
Systemic glucocorticoid	8,224 (3.4)	3,124 (2.6)	5,100 (4.3)	<0.001
Proton-pump inhibitor	32,161 (13.3)	13,087 (10.7)	19,074 (16.0)	<0.001

Data are presented as *n* (%) unless indicated otherwise. DPP-4, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide 1; SGLT-2, sodium–glucose cotransporter 2; NA, not applicable. Percentages may not sum to 100% due to rounding.

We also investigated whether vaccination may be more beneficial for patients with diabetes than people without diabetes. In this analysis, we matched patients with diabetes 1:1 by age and sex with people without diabetes sourced from the Danish general background population in each season (defined as no prescriptions glucose-lowering medications in the 6 months before each season and otherwise identical inclusion criteria). After the matching procedure, we assessed the fully adjusted association between vaccination and outcome in both groups. Then we used the fully adjusted Cox regression estimates to calculate the adjusted number needed to treat (NNT) to prevent one death in a single season associated with influenza vaccination for patients with diabetes and patients without diabetes (22). Finally, to assess the possibility of season-to-season differences, the association between vaccination and death in each separate season included in the study was examined.

Data and Resource Availability

The authors were allowed full access to raw, anonymized data stored in nationwide administrative registries by Statistics Denmark (Central Authority on Danish Statistics).

RESULTS

Study Subjects and Characteristics

During the period 2007–2016, over nine consecutive influenza seasons, we included 241,551 patients with diabetes (Fig. 1). Most patients were included before the first season (2007–2008). At inclusion, 190,628 patients (78.9%) were treated with oral antidiabetics only, 35,787 patients (15.9%) were treated with insulin only, and 15,136 patients (6.3%) were treated with oral antidiabetics and insulin in combination. Patient characteristics at the time of first entry into the study are summarized in Table 1. Patients who were vaccinated at least once during the study period were older, had lower income, lower educational level, and had more comorbidities (Table 1). In addition, they were more likely to use multiple antidiabetic drugs and displayed a higher use of most medications (Table 1).

Vaccination Coverage

During the study period, the vaccine coverage ranged from 24% to 36%, with an overall average of 33% when considering all seasons (Supplementary Fig. 1).

Follow-up and Outcome

When considering all seasons, patients were monitored for a total of 425,318 person-years of follow-up. Patients were monitored for a median of four seasons (interquartile range two to eight). During follow-up, 8,207 patients died (3.4%) of all causes, 4,127 patients (1.7%) died of cardiovascular causes, and 1,439 patients (0.6%) died of stroke/AMI. In addition, 5,755 patients (2.4%) were admitted to the hospital with acute complications associated with diabetes (diabetic ketoacidosis, hospitalization for hypoglycemia or diabetic coma), and 7,764 patients (3.2%) were hospitalized for influenza or pneumonia.

In unadjusted analysis, vaccination was significantly associated with a higher risk of death from all causes (hazard ratio [HR] 1.73, 95% CI 1.65–1.80, $P < 0.001$), cardiovascular causes (HR 1.92, 95% CI 1.80–2.04, $P < 0.001$), and stroke/AMI (HR 1.97, 95% CI 1.78–2.19, $P < 0.001$). However, in fully adjusted analyses, vaccination was significantly associated with a reduced risk of all-cause death (HR 0.83, 95% CI 0.78–0.88, $P < 0.001$), cardiovascular death (HR 0.84, 95% CI 0.77–0.91, $P < 0.001$), and stroke/AMI death (HR 0.85, 95% CI 0.74–0.98, $P = 0.028$) (Fig. 2). In fully adjusted analysis, the association between vaccination and outcome was not modified by age (all-cause death, age-vaccination interaction term: $P = 0.13$; cardiovascular death, age-vaccination interaction term: $P = 0.22$; stroke/AMI death, age-vaccination interaction term: $P = 0.21$). Also, in the fully adjusted analysis, vaccination was significantly associated with a reduced risk of being admitted to the hospital with acute complications associated with diabetes (HR 0.89, 95% CI 0.83–0.97, $P = 0.006$). Similarly, in the fully adjusted analysis, vaccination was significantly associated with a reduced risk of hospitalization for influenza or pneumonia during follow-up (HR 0.94, 95% CI 0.88–0.99, $P = 0.033$). In patients who did not receive insulin therapy at baseline, vaccination was not significantly associated with a reduced risk of starting insulin therapy during follow-up (HR 0.90, 95% CI 0.78–1.04, $P = 0.15$).

The fully adjusted NNT to prevent one death over one season associated with vaccination was 1,133 (95% CI 876–1,606). In patients without diabetes matched 1:1 with patients with diabetes on age, sex, and season, in the fully adjusted analysis, vaccination was significantly associated with reduced risks of all-cause death (HR 0.81, 95% CI 0.74–0.90, $P < 0.001$) and cardiovascular death (HR 0.77, 95% CI 0.66–0.90, $P = 0.001$). However, in patients without diabetes, the fully adjusted NNT to prevent one death over one season associated with vaccination was 2,508 (95% CI 1,832–4,766), which was significantly higher than the NNT estimate obtained in the patients with diabetes ($P < 0.001$).

When the follow-up period was extended to 1 full year, the association between vaccination and reduced mortality appeared strongest in months December–January, February–March, and April–May (Fig. 3). Stratifying our analysis by season revealed that the association between vaccination and death was strongest in seasons 2010–2011, 2011–2012, 2013–2014, and 2015–2016, while it appeared attenuated in seasons 2007–2008, 2008–2009, 2009–2010, and 2014–2015 (Supplementary Fig. 2).

Subgroup Analyses

In patients who did not receive insulin therapy at baseline, vaccination was significantly associated with a reduced risk of all-cause death (HR 0.85, 95% CI 0.79–0.91, $P < 0.001$) and cardiovascular death (HR 0.83, 95% CI 0.75–0.92, $P < 0.001$). In patients receiving insulin therapy, vaccination was also significantly associated with a reduced risk of all-cause death (HR 0.80, 95% CI 0.72–0.88, $P < 0.001$) and cardiovascular death (HR 0.86, 95% CI 0.74–0.99, $P = 0.035$). Similarly, when the analysis excluded patients with chronic renal failure, vaccination remained significantly associated with a reduced risk of all-cause death (HR 0.85, 95% CI 0.80–0.90, $P < 0.001$) and cardiovascular death (HR 0.86, 95% CI 0.79–0.94, $P = 0.001$).

Sensitivity Analysis

In unadjusted analysis, vaccination was significantly associated with an increased risk of incident cancer (HR 1.73, 95% CI 1.66–1.81, $P < 0.001$). However, in fully adjusted analysis, vaccination was not associated with an increased risk of incident cancer (HR 1.06, 95% CI 0.99–1.12, $P = 0.051$).

CONCLUSIONS

In this nationwide register-based study including >240,000 patients with diabetes, we have shown that influenza vaccination

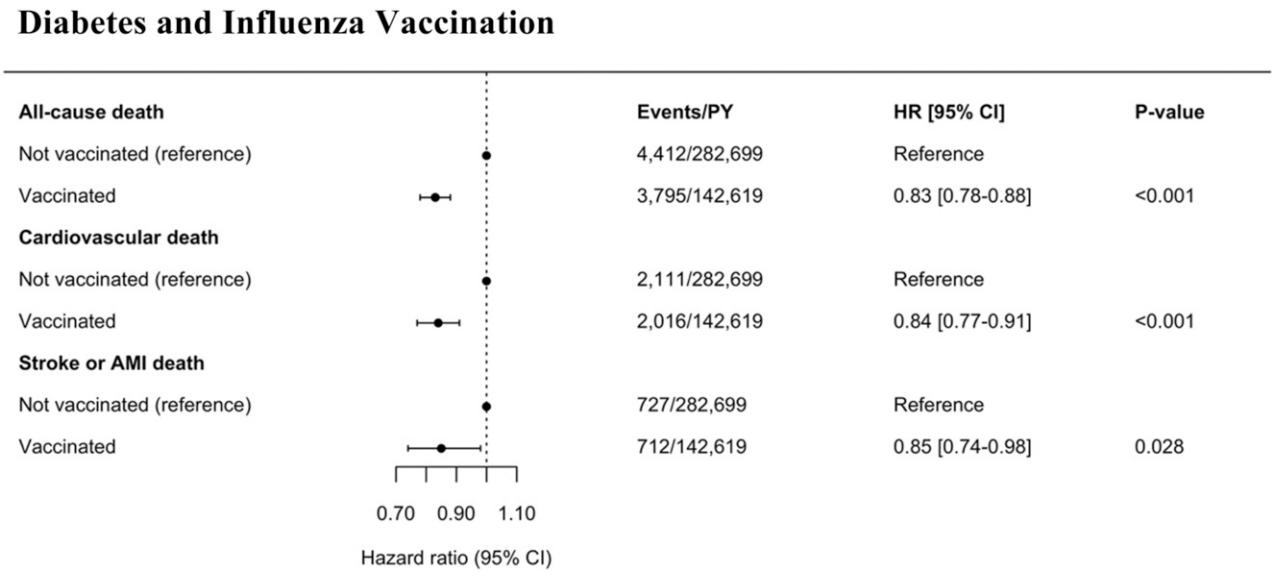

Figure 2—Forest plot of the association between influenza vaccination and the risk of death when considering all seasons included in the study. The error bars represent 95% CIs. HRs were derived from multivariable Cox regression models with patient-level cluster variances and stratified on season year. The models were adjusted for all variables from Table 1. PY, person-years.

is significantly associated with reduced risks of all-cause, cardiovascular, and stroke/AMI death despite rigorous control for confounding factors. We have also shown that vaccination is significantly associated with a reduced incidence of acute diabetes complications. To our knowledge, this is the largest study to date examining the association between influenza vaccination and outcome in patients with diabetes.

Current Recommendations and Knowledge

Patients with diabetes have an increased risk of suffering severe complications from influenza infection, including hospitalization and death (23,24). Hence, the Standards of Care 2019 guidelines published by the American Diabetes Association recommend influenza vaccination for all patients with diabetes (10). Yet, no randomized controlled trials assessing the effect of influenza vaccination in patients with diabetes exist. Currently, the evidence supporting this recommendation is based on a limited number of observational studies of varying quality (10,25–28). In a Dutch nested case-control study based on a cohort of 9,238 patients with diabetes from the 1999 to 2000 influenza season, Looijmans-Van den Akker et al. (26) found that influenza vaccination was significantly associated with a 54% reduced risk of hospitalization and a 58% reduced risk of death. In another study by Vamos et al. (29) including 124,503 patients with type 2 diabetes over a 7-year period, vaccination was significantly associated with a 15% lower incidence of pneumonia or influenza and a 24% lower incidence of death during influenza season. A few other observational cohort studies have also demonstrated associations between influenza vaccination and a reduced incidence of hospitalization and death (25,30,31). This is consistent with our findings, since we found that influenza

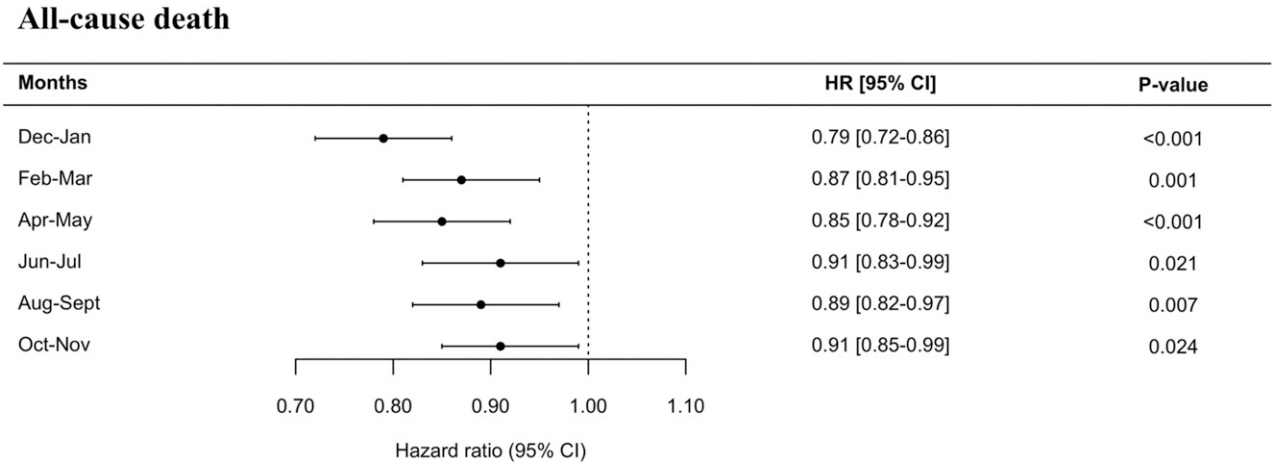

Figure 3—Landmark analyses considering all seasons with follow-up extended from the 4-month "in-season" period (December 1–April 1 the following year) to 1 full year (December 1–December 1 the following year). The association between vaccination and all-cause mortality was assessed for each 2-month period of follow-up. In all analyses, the reference is no vaccination in the given season. The Cox regression models were adjusted for all variables reported in Table 1.

vaccination was associated with an 11% reduced risk of hospitalization for acute diabetes complications and a 17% reduced risk of death during the influenza season. In summary, our findings confirm those of previous studies, and our study significantly adds to the growing body of evidence indicating beneficial effects of influenza vaccination in patients with diabetes.

Diabetes, Influenza Vaccination, and Cardiovascular Outcome

Previous studies have linked influenza infection with an increased risk of both AMI (2,5,6) and stroke (7). Potential mechanisms for this increased risk may include atherosclerotic plague destabilization, endothelial dysfunction, and hypercoagulability induced by the inflammatory response (1). The risk of atherosclerotic cardiovascular disease is increased in patients with diabetes, and acute ischemic events, such as AMI and stroke, are leading causes of morbidity and mortality in this patient population (3,4). Hence, it is possible that influenza vaccination may prevent cardiovascular mortality in patients with diabetes. To our knowledge, only one observational study has specifically assessed the association between influenza vaccination and cardiovascular outcome in patients with diabetes. Vamos et al. (29) studied 124,503 patients with type 2 diabetes from England during the period 2003–2009. In fully adjusted analysis, they found that influenza vaccination was associated with a 30% reduced risk of stroke (incidence rate ratio 0.70, 95% CI 0.53–0.91) and a nearly significant trend toward a reduced risk of AMI (incidence rate ratio 0.81, 95% CI 0.62–1.04). Although the trend toward a reduced incidence of AMI did not reach statistical significance, their results appear to concur with our findings, since we found that vaccination was significantly associated with a 16% reduced risk of cardiovascular death and a 15% reduced risk of AMI/stroke death. However, an important difference between the study inclusion criteria used by Vamos et al. (29) and our inclusion criteria must be noted: Vamos et al. did not exclude patients based on comorbidity. Since it is well known that influenza vaccination is beneficial for patients with high-risk health conditions, such as lung disease, heart disease, or cancer, we excluded patients with these conditions to isolate the effect of vaccination in diabetes. Consequently, we studied a "healthier" sample of patients with diabetes compared with the patients with diabetes studied by Vamos et al. (29). This could potentially explain differences between our results. However, when considering the results of our two studies in unison, it is reasonable to suggest that influenza vaccination may potentially improve cardiovascular outcome. Consequently, more research into the cardiovascular benefits of influenza vaccination in patients with diabetes is warranted.

Confounding, Bias, and Limitations

Our study was not randomized, and therefore, we cannot provide clear evidence of causation. Despite this, several aspects of our findings support a potential causal association between influenza vaccination and improved outcome in patients with diabetes. In unadjusted analysis, we found that vaccination was associated with a higher risk of death. Patients who underwent vaccination were older, had lower income, lower educational level, more comorbidity, and used more medication. After adjusting for these confounding factors, the association between vaccination and outcome reversed so that vaccination was significantly associated with a lower risk of death. This suggests that older, sicker patients were more likely to undergo vaccination, and once this confounding is adjusted for, a potential beneficial effect of vaccination emerges (20). These considerations are further supported by our analysis of the association between vaccination and incident cancer during follow-up. It is very unlikely that influenza vaccination would increase cancer rates. Yet, in unadjusted analysis, vaccination was associated with an increased risk of cancer, again indicating that older, sicker patients were more likely to undergo vaccination. Again, after adjusting for confounding factors, no association between vaccination and incident cancer was found, indicating that our statistical methods were effective at controlling for confounding associated with vaccination (20). When we extended the follow-up from the 4-month in-season period (December 1–April 1 the following year), the association between vaccination and a reduced risk of death was strongest in months December–May, while it appeared weaker, but not nonexistent, in the off-season months June–November. This pattern is consistent with recent reports indicating that the risk of cardiovascular events is highest during and in the short period after an acute infection, such as influenza, and then declines but remains elevated in the months after the infection before returning to preinfection levels (1,32). In summary, these findings support a potential causal association between influenza vaccination and improved outcome in patients with diabetes.

In contrast, when we conducted stratified analysis to assess the association between vaccination and outcome in each individual season, our results were less clear-cut: These analyses revealed that the association between vaccination and death was strongest in seasons 2010–2011, 2011–2012, 2013–2014, and 2015–2016, while it appeared attenuated in seasons 2007–2008, 2008–2009, 2009–2010, and 2014–2015. At first, these results may appear to contradict the remainder of our findings that support that influenza vaccination may improve outcome in diabetes. However, it is well known that the effect of influenza vaccination varies with each season and is highly dependent on matching between vaccine strains and circulating strains (21). Thus, if our results were largely due to confounding, it is probable that we would instead have found a consistent and homogenous association with reduced risks of both all-cause and cardiovascular death in all seasons included in the study, because such confounding is unlikely to vary by season. However, because our study was observational, we cannot exclude that another potential explanation for these findings is the presence of residual confounding not addressed by our statistical methods. Ideally, our results should be replicated in future clinical trials. Because diabetes is often managed in the primary care sector, and because diagnoses and test results from the primary care sector are not available in the Danish Nationwide Registers, we defined diabetes using prescriptions for antidiabetic medication. A similar approach has been used in several previous Danish Register-based studies (16–18). However, this also limits the possibility for us to confidently distinguish patients with type 1 diabetes from patients with type 2 diabetes. Finally, it would have been interesting to assess the association between vaccination and other relevant causes of death such as

cancer or respiratory disease. However, for this particular analysis, we only had access to mortality information regarding cardiovascular, AMI, and stroke death.

Conclusion

In patients suffering from diabetes, influenza vaccination was significantly associated with a reduced risk of all-cause death, cardiovascular death, and death from AMI or stroke. Influenza vaccination may improve outcome in patients with diabetes.

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