Influenza Vaccination and Outcome in Heart Failure

Israel Gotsman, MD[a,b,*], Mony Shuvy[a,b], Ilgar Tahiroglu, MD[a], Donna R. Zwas, MD[a,b], and Andre Keren, MD[a,b]

Influenza virus infection is associated with significant morbidity and mortality in patients with chronic diseases including heart failure (HF). Annual influenza vaccination is recommended to prevent infection during the winter months. Data regarding its clinical benefit in HF patients are sparse. The purpose of the study was to evaluate the effect of influenza vaccination on clinical outcome in patients with HF. Consecutive patients with HF at a health maintenance organization were evaluated for influenza vaccination status during the winter season of 2017/2018 and its association with cardiac-related hospitalizations and death during 1-year after vaccination. The study cohort included 6,435 HF patients. A total of 4,440 patient were vaccinated during the winter season (69% of the HF cohort). The vast majority (96%) were vaccinated before the winter months (September to November). Patients vaccinated were older patients with more co-morbidities. Cox regression analysis after adjustment for clinically significant predictors demonstrated that vaccination was associated with reduced mortality (hazard ratio [HR] 0.77, 95% confidence interval [CI] 0.65 to 0.91, p <0.01) as well as reduced death and cardiovascular hospitalizations (HR 0.83 95% CI 0.76 to 0.90, p <0.001). Adjustment for drug therapy demonstrated a similar result with improved outcome with influenza vaccine. Propensity score matched control analysis demonstrated that vaccination was associated with improved survival (HR 0.80, 95% CI 0.67 to 0.95, p <0.01) and reduced death and cardiovascular hospitalizations (HR 0.86, 95% CI 0.79 to 0.94, p <0.001). In conclusion, Influenza vaccination in patients with HF was associated with improved clinical outcome including improved survival and reduced death and hospitalizations. **(Am J Cardiol 2020;128:134−139)**

Heart failure (HF) has emerged as a major epidemic and is associated with considerable morbidity and mortality.[1] Respiratory infections and specifically the seasonal influenza viral infection cause significant disease in HF patients and results in increased mortality.[2] Influenza vaccination is efficient and safe[3] and can help reduce the incidence of respiratory infections, prevent HF decompensation and should improve outcome in HF patients.[4] The influenza vaccination has been shown to be associated with reduced mortality[5−8] and hospitalization[9,10] in patients with HF. Nevertheless, a large US registry[11] failed to find an association between vaccination status and reduced 1-year mortality. In addition, randomized studies are lacking. Given the limited and conflicting data regarding the vaccination on HF outcomes, we evaluated the impact of influenza vaccination on clinical outcome including mortality or cardiovascular hospitalization in a large real-world cohort of patients with chronic HF.

Methods

Clalit Health Services is the largest health maintenance organization (HMO) in Israel. It has a central computerized database in which all members have a complete digital record. The database includes demographics, comprehensive clinical data, diagnoses, and all laboratory data undertaken in a single centralized laboratory of the HMO. Natriuretic peptides are not routinely performed in Israel and were not available for analysis. We identified and retrieved electronically from the computerized database all members with a diagnosis of HF as coded by the database in Jerusalem. Analysis was performed for the winter season of 2017/2018. All patients with HF at the start of the winter season, November 2017 were included and followed for clinical events until November 1, 2018. Data on vaccination were retrieved from the start of the vaccination period, September 2017. Six thousand four hundred and thirty-five patients with a diagnosis of HF were included in the analysis. The Influenza vaccination is recommended and provided free of charge by the Ministry of Health to all persons at risk including patients with HF. The vaccine used in the winter season of 2017/2018 was the Quadrivalent influenza vaccine, split virion, inactivated including recommended A and B strains ("VaxigripTetra," Sanofi Pasteur, 2 Avenue Pont Pasteur 69007, Lyon, France). This vaccine complied with the World Health Organization recommendations (Northern Hemisphere) and European Union decision for the 2017/2018 winter season. All hospitalizations in cardiac and internal medicine departments including cardiac and internal intensive care units were retrieved and analyzed. Data on mortality were retrieved from the National Census Bureau. The Institutional Committee for Human Studies of Clalit Health Services, approved the study protocol.

Biochemical analyses were performed at the HMO single centralized core laboratory with routine standardized

[a]Heart Institute, Hadassah University Hospital, Jerusalem, Israel; and [b]Heart Failure Center, Clalit Health Services, Israel. Manuscript received April 5, 2020; revised manuscript received and accepted May 12, 2020.

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*Corresponding author: Tel: 972-2-6776564; fax: 972-2-6411028.
E-mail address: igotsman@bezeqint.net (I. Gotsman).

0002-9149/
https://doi.org/10.1016/j.amjcard.2020.05.019

methodologies on fresh samples of blood obtained after an overnight fast. Glucose levels were measured in plasma, and all other biochemical analyses were performed on serum. The laboratory is authorized to perform tests according to the international quality standard ISO-9001.

SPSS version 17.0 for Windows (SPSS Inc., Chicago, Illinois) and R Statistical Software version 3.6.1 for Windows (R Development Core Team) were used for the statistical analyses. Comparison of the clinical characteristics was performed using the Mann-Whitney U test for continuous variables and the chi-square test for categorical variables. Clinical predictors were transformed where appropriate. Log_{10} was used for logarithmic transformations with the exception of estimated glomerular filtration rate that a square root transformation was used. Follow-up time was calculated using Kaplan-Meier estimate of potential follow-up.[12] Kaplan-Meier curves, with the log-rank test, were used to compare survival according to vaccination status. Multivariate Cox proportional hazards regression analysis was used to evaluate independent variables that determined survival. Parameters included in the multivariate Cox regression analysis incorporated age, gender and other clinically significant parameters as well as significant clinical and laboratory parameters on univariable analysis with the addition of significant drug therapy in separate models. Proportionality assumptions of the Cox regression models were evaluated by log−log survival curves and with the use of Schoenfeld residuals. An evaluation of the existence of confounding or interactive effects was made between variables and their possible collinearity. Propensity score matching was performed with 2:1 ratio of vaccinated to non-vaccinated patients with R function "MatchIt," using near-neighbor matching. Matching was assessed by graphical balance diagnostics including covariate balance plots, propensity score location and distribution. A p value of <0.05 was considered statistically significant.

Results

The study cohort included 6,435 HF patients. A total of 4,440 patient were vaccinated during the winter season of 2017/2018 (69% of the HF cohort). The vast majority of these patients (96%) were vaccinated in the months September to November 2017 before the winter months (Supplemental Figure 1). Table 1 presents the demographics and clinical parameters of the patients stratified according to vaccination status. Patients vaccinated were patients with more co-morbidities including older age, diabetes, hypertension, ischemic heart disease, atrial fibrillation, peripheral vascular disease, previous stroke, dementia, and depression. These patients had lower estimated glomerular filtration rate, hemoglobin, and albumin. Patients vaccinated were treated more with furosemide.

The follow-up period was 365 days. The overall mortality rate during this period was 13%. Influenza vaccination was not associated with survival or event-free survival from death and cardiovascular hospitalization by unadjusted Cox regression survival analysis (Figure 1). Multivariable Cox regression analysis after adjustment for significant predictors demonstrated that influenza vaccination was a significant predictor of reduced mortality (Table 2). After adjustment for other significant predictors, influenza vaccination was associated with reduced mortality (Figure 1). Inclusion of HF medications demonstrated a similar result, with reduced mortality with the influenza vaccination (Figure 1). Influenza vaccination was also associated with a significant reduction in the combined end point of death and cardiovascular hospitalization after adjustment for significant predictors. Multivariable Cox regression analysis demonstrated that influenza vaccination was a significant predictor of reduction in the combined end point (Figure 1).

We performed a propensity score matching analysis to further evaluate the impact of vaccination on clinical outcome. We used a 2:1 ratio matched control of vaccinated versus nonvaccinated patients (n = 3,376/1,688). Covariates included in the propensity score were variables used in the multivariable regression model. The groups were well balanced for all the covariates included. Survival rate by Kaplan-Meier analysis using the propensity score matched groups demonstrated that influenza vaccination was associated with increased survival (Figure 2) as well as increased event-free survival from death and cardiovascular hospitalization (Figure 2). Cox regression analysis using the propensity score-matched groups demonstrated that influenza vaccination was significantly associated with reduced mortality (HR 0.80, 95% CI 0.67-0.95, $p < 0.01$) and with reduced death and cardiovascular hospitalizations (hazard ratio [HR] 0.86, 95% confidence interval [CI] 0.79 to 0.94, $p < 0.001$).

Subgroup analysis of clinical effect of the influenza vaccine analysis did not demonstrate any significant interactions. However, the association with better outcome was greater in older patients. Adjustment for other covariates demonstrated that influenza vaccination was associated with a greater reduction in mortality in older patients (Figure 3). A similar tendency was seen with mortality and cardiovascular hospitalization.

Discussion

In this cohort of real-world HF patients, we found that the influenza vaccine was associated with a ∼20% relative risk reduction in mortality as well as a reduction in death and cardiovascular hospitalizations. This association was evident by Cox regression analysis as well as by propensity score matching analysis. A larger benefit was seen in older patients.

Recent data has shown that influenza infection has a significant impact on clinical outcome in HF, with increased mortality in HF patients.[13] Furthermore, influenza activity coincides with increased HF hospitalizations.[14] Analyzing the survival and event-free survival curves in the present study demonstrate that the clinical benefit was evident after 90 days of follow-up. Based on the European Centre for Disease Prevention and Control 2017 to 2018 seasonal influenza report,[15] influenza activity peaked in late December 2017 and continued until end of March 2018. As mentioned, divergence in the clinical outcome in the HF patients vaccinated started approximately 90 days after start of follow-up, early February 2018, which coincided with the peak influenza activity of the 2017/2018 winter season. This pattern suggests that the benefit of the vaccination

Table 1
Demographics and clinical characteristics of patients with heart failure according to Influenza vaccination status

Variable	Influenza vaccination		Total (n = 6,435)	p Value
	No (n = 1,995)	Yes (n = 4,440)		
Age (Years)	74 (62-83)	77 (67-85)	76 (66-85)	<0.001
Men	1025 (51%)	2384 (54%)	3409 (53%)	0.09
New York Heart Association Class III/IV	499 (35%)	1318 (38%)	1817 (37%)	0.11
Heart Failure Type				
Reduced ejection fraction	584 (29%)	1188 (27%)	1772 (28%)	0.11
Preserved ejection fraction	754 (38%)	1720 (39%)	2474 (38%)	
Not-specified	657 (33%)	1532 (35%)	2189 (34%)	
Diabetes mellitus	960 (48%)	2455 (55%)	3415 (53%)	<0.001
Hypertension	1546 (77%)	3745 (84%)	5291 (82%)	<0.001
Hyperlipidemia	1706 (86%)	4028 (91%)	5734 (89%)	<0.001
Coronary heart disease	1215 (61%)	2992 (67%)	4207 (65%)	<0.001
Prior myocardial infarction	795 (40%)	1904 (43%)	2699 (42%)	0.02
Prior coronary bypass surgery	40 (2%)	74 (2%)	114 (2%)	0.34
Atrial fibrillation	650 (33%)	1743 (39%)	2393 (37%)	<0.001
Prior stroke/ transient ischemic attack	406 (20%)	1053 (24%)	1459 (23%)	0.003
Peripheral vascular disease	229 (11%)	673 (15%)	902 (14%)	<0.001
Chronic obstructive lung disease	365 (18%)	1003 (23%)	1368 (21%)	<0.001
Charlson Score	6.0 (4.0-7.0)	6.0 (5.0-8.0)	6.0 (5.0-8.0)	<0.001
Depression	316 (16%)	831 (19%)	1147 (18%)	0.005
Dementia	200 (10%)	628 (14%)	828 (13%)	<0.001
Dialysis	82 (4%)	237 (5%)	319 (5%)	0.04
Body mass index (kg/m^2)	29 (25-33)	29 (25-33)	29 (25-33)	0.53
Pulse (beats per minute)	73 (65-81)	72 (64-80)	72 (64-80)	<0.001
Systolic blood pressure (mmHg)	128 (118-140)	128 (118-138)	128 (118-139)	0.17
Diastolic blood pressure (mmHg)	72 (66-80)	71 (64-79)	71 (65-80)	<0.001
Creatinine (mg/dL)	0.9 (0.8-1.2)	1.0 (0.8-1.3)	1.0 (0.8-1.3)	<0.001
Estimated glomerular filtration rate (mL/min per 1.73m^2)*	74 (52-95)	69 (49-92)	70 (50-93)	<0.001
Urea (mg/dL)	43 (32-60)	46 (35-64)	45 (34-63)	<0.001
Sodium (mEq/L)	140 (138-142)	140 (138-142)	140 (138-142)	0.16
Potassium (mEql/L)	4.6 (4.3-4.9)	4.6 (4.3-4.9)	4.6 (4.3-4.9)	0.30
Hemoglobin (g/dL)	12.9 (11.5-14.3)	12.7 (11.5-14.0)	12.7 (11.5-14.1)	<0.001
White blood count (x109/L)	7.3 (6.0-8.9)	7.3 (6.0-8.8)	7.3 (6.0-8.8)	0.40
Red Cell Distribution Width (%)	15 (14-16)	15 (14-16)	15 (14-16)	0.002
Glucose (mg/dL)	105 (93-131)	107 (94-134)	106 (94-133)	0.13
Hemoglobin A1c (%)	6.1 (5.6-7.1)	6.1 (5.6-7.1)	6.1 (5.6-7.1)	0.06
Uric Acid (mg/dL)	6.2 (5.1-7.4)	6.3 (5.1-7.6)	6.2 (5.1-7.5)	0.20
TSH (mIU/L)	2.3 (1.4-3.4)	2.2 (1.5-3.3)	2.2 (1.5-3.4)	0.25
Iron (μg/dL)	60 (42-79)	59 (43-78)	59 (43-78)	0.53
Transferrin (mg/dL)	248 (217-290)	249 (214-287)	249 (215-288)	0.71
Transferrin Saturation (%)	17 (12-24)	17 (12-23)	17 (12-23)	0.44
Ferritin (ng/ml)	84 (39-173)	79 (38-165)	80 (38-168)	0.32
Calcium (mg/dL)	9.3 (9.0-9.6)	9.3 (8.9-9.6)	9.3 (8.9-9.6)	0.06
Phosphorus (mg/dL)	3.5 (3.1-3.9)	3.5 (3.1-3.9)	3.5 (3.1-3.9)	0.54
Magnesium (mg/dL)	2.1 (1.9-2.3)	2.1 (1.9-2.3)	2.1 (1.9-2.3)	0.34
Triglycerides (mg/dL)	122 (89-173)	120 (89-169)	121 (89-169)	0.28
Low-density lipoprotein (mg/dL)	87 (67-112)	81 (64-103)	83 (65-106)	<0.001
Albumin (g/dL)	4.0 (3.7-4.2)	3.9 (3.6-4.2)	3.9 (3.6-4.2)	0.02
C-Reactive Protein (mg/dL)	0.6 (0.2-1.6)	0.6 (0.2-1.5)	0.6 (0.2-1.5)	0.98
Alanine transaminase (IU)	16 (11-22)	16 (12-22)	16 (12-22)	0.61
Alkaline Phosphatase (IU)	89 (73-112)	88 (71-111)	88 (71-111)	0.03
Total Bilirubin (mg/dL)	0.6 (0.5-0.8)	0.6 (0.4-0.8)	0.6 (0.4-0.8)	0.12
Gamma-glutamyltransferase (IU)	26 (18-43)	25 (17-42)	25 (17-42)	0.20
Medication				
RAS Inhibitors **	1508 (76%)	3481 (78%)	4989 (78%)	0.01
Beta blockers	1471 (74%)	3320 (75%)	4791 (74%)	0.38
Spironolactone	687 (34%)	1591 (36%)	2278 (35%)	0.28
Furosemide	1234 (62%)	2992 (67%)	4226 (66%)	<0.001
Thiazide	267 (13%)	616 (14%)	883 (14%)	0.6
Digoxin	97 (5%)	292 (7%)	389 (6%)	0.008
Amiodarone	271 (14%)	733 (17%)	1004 (16%)	0.003

(*continued*)

Table 1 (***Continued***)

Variable	Influenza vaccination		Total (n = 6,435)	p Value
	No (n = 1,995)	Yes (n = 4,440)		
Aspirin	1099 (55%)	2489 (56%)	3588 (56%)	0.47
New oral anticoagulants***	471 (24%)	1228 (28%)	1699 (26%)	<0.001
Vitamin K antagonists	235 (12%)	693 (16%)	928 (14%)	<0.001

Data is presented as median (inter-quartile range) for continuous variables and counts (percentages) for categorical variables. P value by the Kruskal Wallis Test for continuous variables and the chi-square test for categorical variables.

Diabetes mellitus defined as fasting plasma glucose ≥126 mg/dl or glucose lowering treatment, hypertension as blood pressure >140/90 mm Hg measured on several occasions or antihypertensive treatment and hyperlipidemia as low-density lipoprotein >130 mg/dl, fasting serum triglycerides >200 mg/dl or lipid lowering treatment.

* Estimated Glomerular Filtration Rate was calculated using the modified Modification of Diet in Renal Disease (MDRD) equation (175 * serum creatinine$^{-1.154}$ * age$^{-0.203}$. For females a correction factor is used multiplying by 0.742.)

** Angiotensin converting enzyme inhibitor, Angiotensin receptor blocker, Angiotensin receptor-neprilysin inhibitor.

*** Dabigatran, Rivaroxaban or Apixaban.

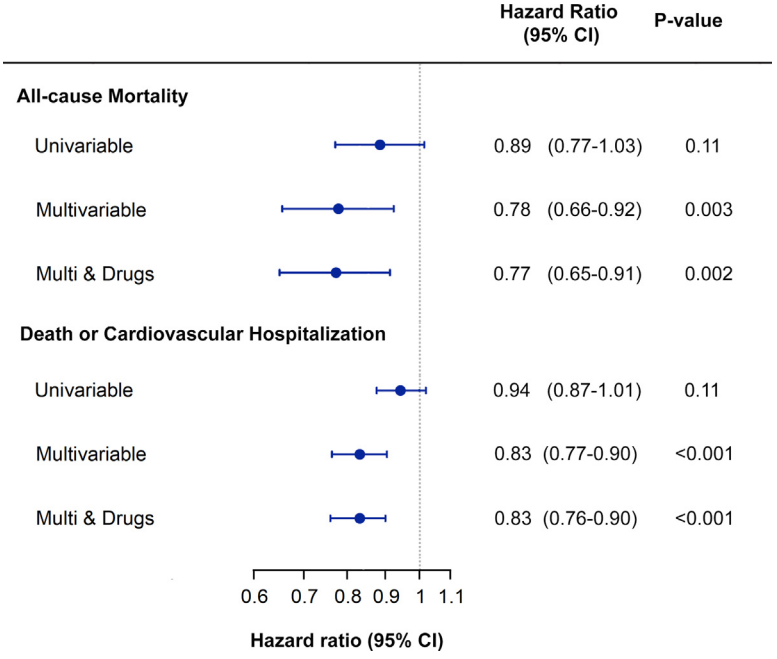

Figure 1. Cox regression analysis of outcome based on vaccination status.
Cox regression demonstrated that influenza vaccination was a significant predictor of reduced mortality as well reduced combined end point of death and cardiovascular hospitalizations. Parameters included in the multivariable model included age, gender, NYHA class, diabetes, hypertension, ischemic heart disease, atrial fibrillation, log-transformed body mass index, log-transformed serum urea levels, square root-transformed estimated glomerular filtration rate, hemoglobin, and serum sodium. Parameters that were included in the multivariable and drugs analysis included the above parameters and drug treatment with angiotensin-converting enzyme inhibitor/angiotensin receptor blocker/sacubitril-valsartan, beta blocker, furosemide, and spironolactone.

could be related to the winter season and its respiratory infections and more specifically, to influenza viral activity of that season.

The data in the present study demonstrate that influenza vaccination had a beneficial effect on clinical outcome in a large real-world cohort of HF population. This is consistent with several studies demonstrating that the influenza vaccination is associated with reduced mortality in patients with acute HF[5] as well as chronic HF[6–8] and is associated with reduced hospitalization.[9,10] Two meta-analysis[16,17] of these observational studies found that the influenza vaccination was associated with a reduced mortality risk in HF patients. A large Danish observational study[8] demonstrated that the influenza vaccination was associated with a reduced risk of both all-cause and cardiovascular death. In addition, the Danish study demonstrated that frequent vaccination and vaccination earlier in the year were associated with larger reductions in the risk of death. However, a large US registry[11] failed to show clinical benefit of the vaccination. There are several differences in the methodology of the US study in comparison to other studies. The present study included chronic HF patients similar to the Danish study. The US study included hospitalized HF patients and clinical outcome was available in a proportion of the patients.

Table 2
Predictors of mortality by Cox regression analysis

	Univariable		Multivariable	
	Hazard ratio (95% CI)	p Value	Hazard ratio (95% CI)	p Value
Age (years)	1.05 (1.05-1.06)	<0.001	1.04 (1.03-1.05)	<0.001
Gender (Male)	0.77 (0.67-0.89)	<0.001	1.14 (0.96-1.35)	0.13
NYHA III/IV	1.73 (1.49-2.02)	<0.001	1.25 (1.05-1.48)	0.01
Diabetes Mellitus	1.19 (1.04-1.37)	0.01	1.18 (1.00-1.39)	0.05
Hypertension	2.38 (1.86-3.03)	<0.001	1.29 (0.97-1.72)	0.08
Ischemic Heart Disease	1.00 (0.86-1.15)	0.96	0.83 (0.70-0.98)	0.03
Atrial Fibrillation	1.71 (1.49-1.96)	<0.001	1.33 (1.14-1.55)	<0.001
Body mass index* (kg/m^2)	0.14 (0.06-0.33)	<0.001	0.17 (0.07-0.42)	<0.001
Urea (mg/dL)*	7.95 (5.87-10.78)	<0.001	3.27 (1.84-5.83)	<0.001
eGFR** (mL/min per $1.73m^2$)	0.85 (0.83-0.88)	<0.001	0.98 (0.92-1.05)	0.60
Sodium (mEq/L)	0.94 (0.92-0.96)	<0.001	0.95 (0.93-0.98)	<0.001
Hemoglobin (g/dL)	0.78 (0.75-0.81)	<0.001	0.87 (0.83-0.91)	<0.001
Influenza Vaccination	0.89 (0.77-1.03)	0.11	0.78 (0.66-0.92)	0.003

Data is presented as hazard ratio (95% confidence interval), p value.
* Log-transformed.
** Square root-transformed.

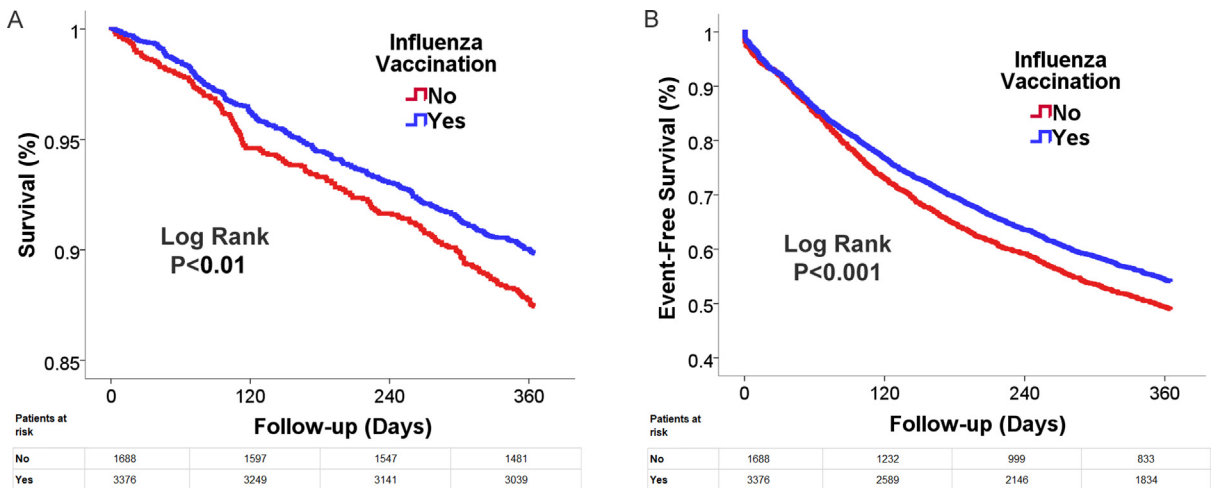

Figure 2. Kaplan-Meier survival analysis according to vaccination status in the propensity score matching analysis.
(A) Influenza vaccination was associated with increased survival (87.4 ± 0.8% vs 89.8 ± 0.5%, p <0.01)
(B) Influenza vaccination was associated with increased event-free survival from death or cardiovascular-hospitalizations. (48.9 ± 1.2% vs 54.0 ± 0.9%, p <0.001).

Definite beneficial considerations of the vaccination in preventing clinical deterioration due to the viral infection as well observational studies including the present study strongly support influenza vaccination as a strategy to improve outcome in HF [18]. Randomized studies are needed to provide evidence-based definitive recommendations.

In the present study, 69% of the HF cohort received an influenza vaccine and the majority received it before the winter season as recommended. This proportion was higher than most published studies with an average of less than 50% vaccine coverage, however, this is similar to that seen in the large US registry.[11] For comparison, the Israeli center for disease control reported approximately a 60% influenza vaccination rate in persons aged 65 years or older in the 2017/2018 season.[19] This would suggest that HF patients are preferentially receiving the vaccination, although not all HF patients. Patients that received the vaccination were older, with more co-morbidities and were treated more with diuretics. This suggests that these patients were sicker patients perhaps with more medical surveillance and were more likely to be vaccinated. This pattern of vaccination was also seen in a large study in Denmark with a similar health coverage system.[8] The present study suggests that younger, perhaps less advanced HF patients were less likely to be vaccinated but could benefit from the vaccination. This population should be targeted to further increase vaccination coverage.

The present study was an observational study and causality cannot be determined. Data regarding clinical parameters and drug therapy was based on a digitized database. Although this database was validated and found to be highly accurate, not all data could be verified. While we tried to adjust for clinically relevant parameters, it is impossible to adjust for all variables that may affect outcome. In particular, data on socioeconomic status and natriuretic

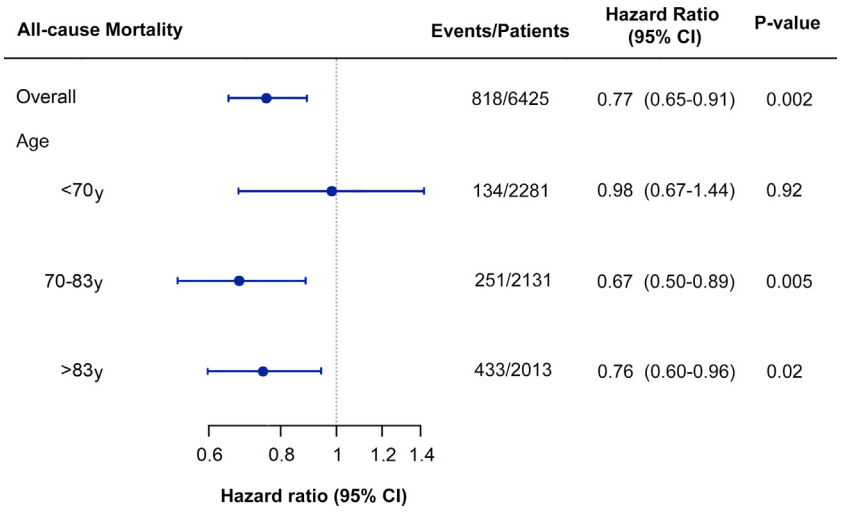

Figure 3. Multivariable Cox regression analysis of vaccination status according to three age groups. Older patients demonstrated a greater benefit. Parameters included in the analysis were parameters described for the multivariable analysis outlined in Figure 1, including medication.

peptide levels were not available. In addition, the cohort was a community-based cohort and the findings may not be applicable in more advanced or hospital-based HF cohorts.

In conclusion, Influenza vaccination in patients with HF was associated with improved outcome including improved survival and reduced death and hospitalizations.

CRediT author statement

Israel Gotsman: Conceptualization, Writing - Original Draft, Visualization.
Mony Shuvy: Writing - Review & Editing
Ilgar Tahiroglu: Investigation
Dona Zwas: Writing - Review & Editing
Andre Keren: Supervision

Disclosures

The authors have no conflicts of interest to disclose.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2020.05.019.

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