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The effect of influenza vaccination on mortality and hospitalization in patients with heart failure: a systematic review and meta-analysis

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Abstract

Influenza infection is associated with increased risk for mortality and hospitalization in heart failure patients. Although there are no published randomized controlled trials examining the effect of influenza vaccination on clinical outcomes in heart failure patients, the effect has been examined in observational cohort studies. Nevertheless, results are inconsistent due partly to limited power with small sample sizes and use of different definitions of outcomes. We therefore aimed to conduct a systematic review and meta-analysis of the effect of influenza vaccination on mortality and hospitalization in heart failure patients. The search of electronic databases identified 6 observational cohort studies with 22,486 patients examining the effect of influenza vaccination on mortality and hospitalization in heart failure patients. Pooled analysis of confounder-adjusted hazard ratio showed that influenza vaccination was associated with reduced risk of mortality during 1-year follow-up (risk ratio [95% CI] = 0.76 [0.63–0.92], $P_{fix} < 0.01$) and during long-term (up to 4 years) follow-up (0.80 [0.71–0.90], $P_{fix} < 0.001$). Furthermore, influenza vaccination was associated with reduced risk of mortality during influenza season (risk ratio [95% CI] = 0.52 [0.39–0.69], $P_{random} < 0.001$) and during non-influenza season (0.79 [0.69–0.90], $P_{fix} < 0.001$). Only a few studies reported the effect of influenza vaccination on hospitalization, which did not permit us to perform pooled analysis. In conclusion, our meta-analysis showed that influenza vaccination was associated with reduced risk of mortality in heart failure patients. Large-scale and adequately powered randomized controlled trials should be planned to confirm our observed potential survival benefit of influenza vaccination in these patients.

Keywords Heart failure · Influenza · Vaccine · Prognosis · Meta-analysis

Introduction

Heart failure is a major public health problem, with a prevalence of more than 5.8 million in the USA and more than 23 million worldwide [1]. Although there have been significant advances in the management of heart failure, the mortality in patients with heart failure remains high and the survival estimates are about 50% at 5 years [1].

Heart failure patients are susceptible to influenza-related complications including acute heart failure exacerbations and secondary infections such as pneumonia, both of which lead to significant morbidity and mortality [2–4]. Although there are no published randomized controlled trials (RCTs) examining the effect of influenza vaccination on clinical outcomes in heart failure patients, the effect has been reported in observational cohort studies [5–10]. Nevertheless, the results are inconsistent due partly to limited power with small sample sizes and use of different definitions of outcomes. We therefore aimed to conduct a systematic review and meta-analysis of the effect of influenza vaccination on mortality and hospitalization in heart failure patients.

Methods

This meta-analysis was performed and reported according to the preferred reporting items for systematic reviews and meta-

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analyses (PRISMA) [11] and the reporting meta-analyses of observational studies in epidemiology (MOOSE) [12].

Studies on the effect of influenza vaccination in patients with heart failure published until June 31, 2017, were identified using PubMed and EMBASE databases. For search of the eligible studies, the following key words and Medical Subject Heading were used: *influenza* and *heart failure*. Our literature search was limited to studies involving human subjects and those published in English. Additionally, we manually searched the references that were cited in other relevant publications.

Inclusion criteria for the present meta-analysis included (1) assessment of the effectiveness of influenza vaccination in patients with heart failure, and (2) observational cohort study that provided information on the mortality and/or hospitalization. Primary outcome of interest was all-cause mortality. Secondary outcome of interest was hospitalization.

Information on the study and patient characteristics, methodological quality, and intervention strategies was systematically extracted separately by two reviewers (TG and KW). Disagreements were resolved by consensus. The quality of the included studies was evaluated by Newcastle-Ottawa Scale tool (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp).

For each outcome, confounder-adjusted hazard ratios were pooled and the heterogeneity was assessed using Cochran's Q chi-square test and I^2 statistic; for Cochran's Q chi-square test and I^2 statistic, a p value of < 0.1 and $I^2 > 50\%$ were considered significant, respectively [13]. When there was significant heterogeneity, the data were pooled using a random-effects model, otherwise a fixed-effects model was used. A two-tailed $P < 0.05$ was considered statistically significant. Data were analyzed by Review Manager (version 5.3.5, the Cochrane Collaboration) and Comprehensive Meta Analysis Software version 2 (Biostat, Englewood, NJ, USA).

Results

The article identification and selection process is summarized in Fig. 1. A total of 6 observational studies with 22,486 patients were included in this meta-analysis.

Characteristics of included studies are summarized in Table 1. Among the included studies, 2 studies were conducted in Europe, 2 in Asia, and 1 in the USA; 1 study was a retrospective analysis of the PARADIGM-HF [14], an international clinical trial. Among the included studies, all studies reported the effect of influenza vaccination on mortality and 2 studies reported the effect on hospitalization. Among the included studies, 2 studies reported the effect of influenza vaccination on mortality during 1-year follow-up; 2 reported the effect on mortality during long-term (up to 4 years) follow-up; 3 reported the effect on mortality during influenza season and non-influenza season separately. The follow-up duration ranged from 1 to 4 years. The influenza vaccine rate ranged from 26 to 86%. The score assessed by the Newcastle-Ottawa Scale for the included studies ranged from 6 to 8 (supplement Table 1).

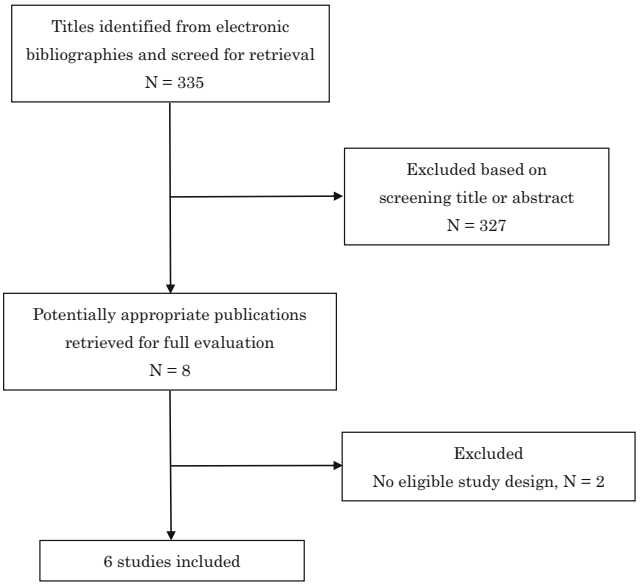

Fig. 1 Selection process for articles included in meta-analysis

Baseline patient characteristics of the included studies are summarized in Table 2. Mean age ranged from 64 to 76 years and the prevalence of male sex ranged from 38 to 98%.

The effect of influenza vaccination on mortality is shown in Figs. 2, 3, 4 and 5. Pooled analysis of confounder-adjusted hazard ratio showed that influenza vaccination was associated with reduced risk of mortality during 1-year follow-up (risk ratio [95% CI] = 0.76 [0.63–0.92], $P_{fix} < 0.01$; Fig. 2) and during long-term (up to 4 years) follow-up (0.80 [0.71–0.90], $P_{fix} < 0.001$; Fig. 3). Furthermore, influenza vaccination was associated with reduced risk of mortality during influenza season (risk ratio [95% CI] = 0.52 [0.39–0.69], $P_{random} < 0.001$; Fig. 4) and during non-influenza season (0.79 [0.69–0.90], $P_{fix} < 0.001$; Fig. 5).

The effect of influenza vaccination on hospitalization is shown in Figs. 6 and 7. Among the included studies, one study reported the effect of influenza vaccination on cardiovascular hospitalization during influenza season [6] and one study reported the effect on all-cause hospitalization during a median follow-up of 27 months [9]. Influenza vaccination was associated with reduced risk for cardiovascular hospitalization but not for all-cause hospitalization (Figs. 6 and 7).

Discussion

Although there are no published RCTs examining the effect of influenza vaccination on clinical outcomes in heart failure patients, the effect has been reported in observational cohort studies [5–10]. Nevertheless, results are inconsistent across

Table 1 Study characteristics

Source, year	Country	Study design	Inclusion criteria	Follow-up duration	Outcome	Study size, Vaccinated/unvaccinated, *n*
De Diego C et al. [5] 2009	Spain	Retrospective cohort study	Chronic heart disease (including HF or CAD)†	40 months	ACD*	480/860
Liu IF et al. [6] 2012	Taiwan	Retrospective cohort study	Congestive HF, myocardial infarction, and CAD who had undergone coronary revascularization‡	4 years	ACD*, CV hospitalization*	2760/2288
Kopel E et al. [7] 2014	Israel	Prospective cohort study	Hospitalized with a diagnosis of HF (acute or chronic)§	1 year, 4 years	ACD	501/1453
Wu WC et al. [8] 2014	USA	Retrospective cohort study	HF patients were included either ischemic and non-ischemic#	1 year	ACD	2087/429
Vardeny et al. [9] 2016	International	Retrospective cohort study	HF patients were included either ischemic and non-ischemic¶	27 months (median)	ACD, All-cause hospitalization	1769/6630
Blaya-Novakova et al. [10] 2016	Spain	Retrospective cohort study	HF patients were included either ischemic and non-ischemic‖	4 years	ACD*	1016/2213

ACD all-cause mortality, *CAD* coronary artery disease, *CV* cardiovascular, *HF* heart failure

*Analysis was performed separately for during influenza season and non-influenza season

† In these inclusion criteria, patients with CAD with or without HF were included. Patients included as HF were either ischemic or non-ischemic. The left ventricular (LV) ejection fraction (EF) was not described. HF patients with reduced LVEF and preserved LVEF were included

‡In these inclusion criteria, only patients with HF and ischemic were included. The LVEF was not stated. HF patients with reduced LVEF and preserved LVEF were included

§In these inclusion criteria, patients with HF were either ischemic or non-ischemic. The percentage of patients with LVEF < 50% was described. HF patients with reduced LVEF and preserved LVEF were included

LVEF was assessed, both reduced LVEF, and preserved LVEF patients were included

¶ LVEF was assessed, only reduced LVEF patients were included (average LVEF ~ 30%)

‖ LVEF was stated. HF patients with reduced LVEF and preserved LVEF were included

studies due to a variety of potential reasons including limited power, different definitions of outcomes, different inclusion criteria, different heart failure definition, various vaccine types, and diverse types of heart failure (ischemic vs. non-ischemic, reduced left ventricular [LV] ejection fraction [EF] vs. preserved LVEF, etc.). In the present meta-analysis of the observational cohort studies, we found that influenza vaccination was associated with reduced risk of mortality during 1-year and long-term follow-ups. Furthermore, influenza vaccination was associated with reduced risk of mortality during influenza season and non-influenza season. To our knowledge, the present study is the first meta-analysis of the effect of influenza vaccination on mortality in heart failure patients.

Although the studies included in our meta-analysis consistently reported the favorable effect of influenza vaccination in heart failure patients during influenza season, the effect of influenza vaccination during non-influenza season was conflicting due partly to limited power. Our meta-analysis is

Table 2 Patient characteristics

Source, year	Mean age, years	Men	White race	Ischemic etiology	LVEF < 50%	Respiratory diseases	Obesity	Diabetes	Smoker	Hypertension	Cancer
De Diego C et al. [5] 2009	76	47%	NR	NR	NR	19%	22%	32%	7%	65%	3%
Liu IF et al. [6] 2012	75	55%	NR	NR	NR	36%	NR	54%	NR	79%	13%
Kopel E et al. [7] 2014	75	55%	NR	34%	53%	NR	24%	45%	30%	72%	NR
Wu WC et al. [8] 2014	70	98%	72%	NR	NR	NR	NR	NR	NR	NR	NR
Vardeny et al. [9] 2016	64	79%	68%	62%	100%	NR	NR	36%	NR	70%	NR
Blaya-Novakova et al. [10] 2016	74	38%	NR	NR	NR	64%	20%	24%	NR	62%	12%

LVEF left ventricular ejection fraction, *NR* not reported

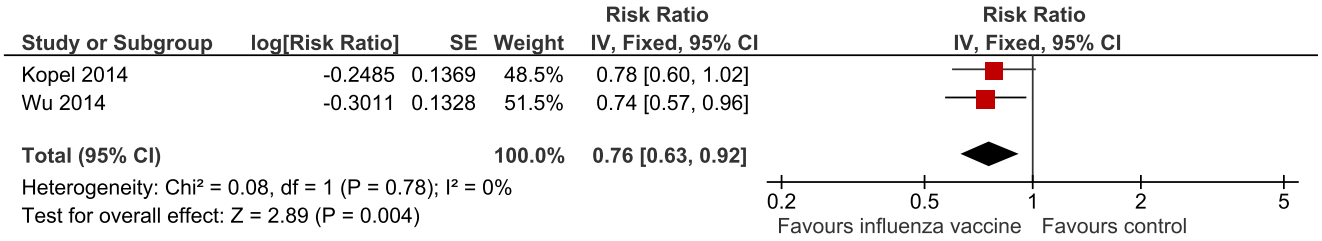

Fig. 2 Forest plot showing the effect of influenza vaccination on mortality during 1-year follow-up

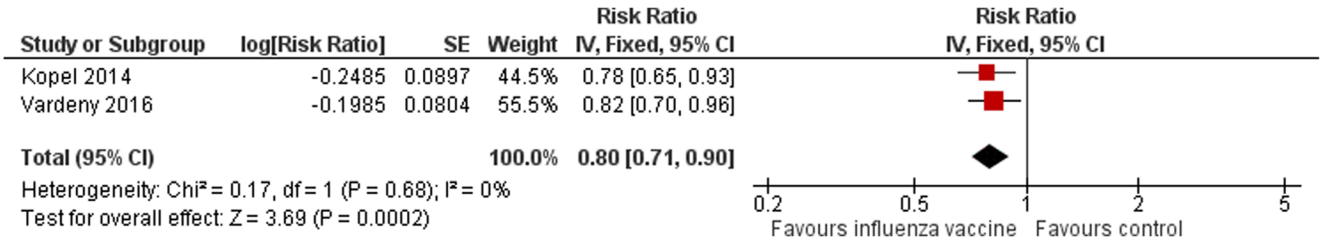

Fig. 3 Forest plot showing the effect of influenza vaccination on mortality during long-term follow-up

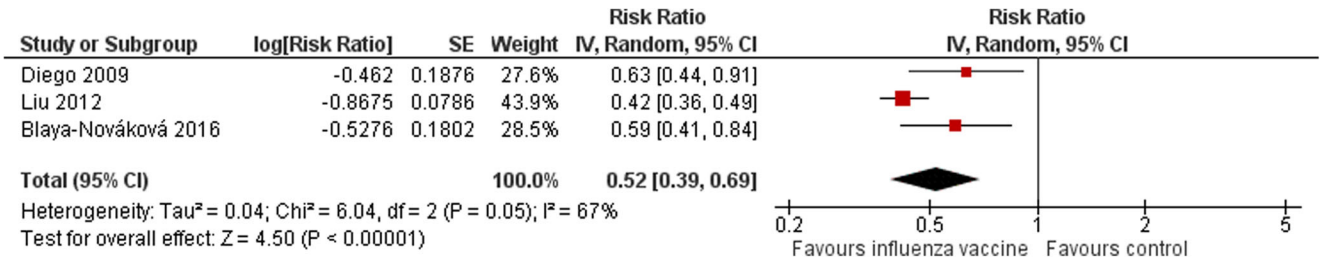

Fig. 4 Forest plot showing the effect of influenza vaccination on mortality during influenza season

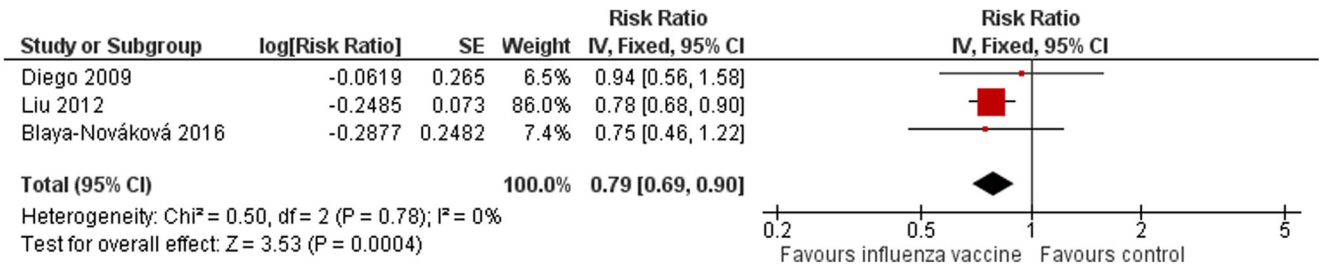

Fig. 5 Forest plot showing the effect of influenza vaccination on mortality during non-influenza season

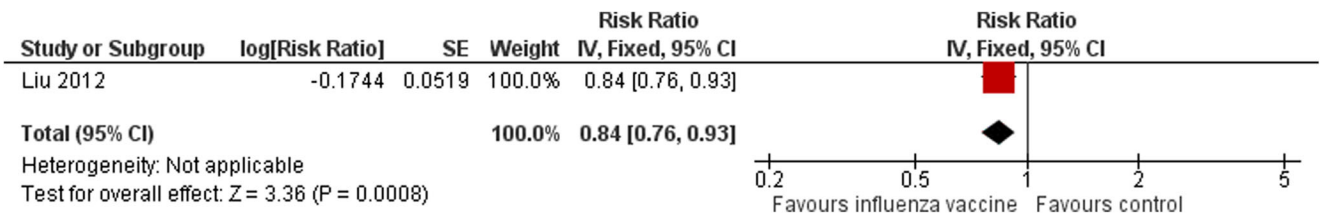

Fig. 6 Forest plot showing the effect of influenza vaccination on cardiovascular hospitalization during influenza season

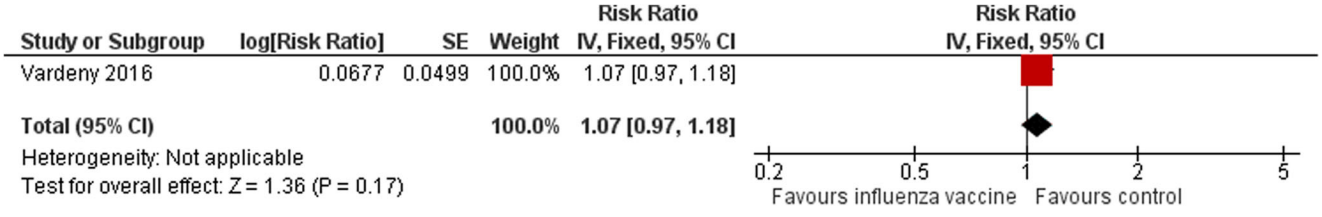

Fig. 7 Forest plot showing the effect of influenza vaccination all-cause hospitalization during long-term follow-up

significant in showing the potential mortality benefit of influenza vaccination in heart failure patients not only during influenza season but also during non-influenza season.

Although the present meta-analysis does not provide the mechanisms for the observed association of influenza vaccination with decreased mortality risk in heart failure patients, there are several potential explanations. First, studies have reported that respiratory infections including influenza and pneumonia are the important precipitating cause of heart failure and are associated with increased risk of mortality [2–4]. Thus, influenza vaccination may reduce the incidence and/or severity of respiratory infection, and thereby prevent heart failure exacerbations, hospitalization, and associated mortality in heart failure patients. Second, a meta-analysis of RCTs on the effect of influenza vaccination on clinical outcomes in patients with coronary artery disease reported that influenza vaccination reduced the risk of major cardiovascular events including hospitalization for myocardial infarction and unstable angina [15–17]. Since ischemic heart disease is a major cause of heart failure and acute coronary events are associated with increased risk of mortality in heart failure patients [18–21], our observed association of influenza vaccination with reduced risk of mortality may be due to the protective effect of influenza vaccination against acutely triggered ischemic coronary events.

Although our pooled analysis showed the potential mortality benefit of influenza vaccination in heart failure patients, there was a trend toward higher all-cause hospitalization in patients who received influenza vaccine (Fig. 7). It is possible that influenza vaccination was a potential surrogate for higher level of and improved access to health care for any given severity of illness.

The influenza vaccine rate among the studies included in our meta-analysis varied and ranged from 26 to 86%. The observed variation in the vaccine rate among the included studies may be due to limited guideline recommendations for influenza vaccination in heart failure patients. Specifically, in the guidelines of Heart Failure Society of America, annual influenza vaccination is recommended in all heart failure patients in the absence of known contraindications (Level of Evidence: B) [22], while the ACC/AHA and ESC guidelines do not make such specific recommendations in heart failure patients [18, 19]. Although our meta-analysis supports a wider use of influenza vaccine in heart failure patients, large-scale and adequately powered RCTs are necessary to confirm our observed potential mortality benefit of influenza vaccination in these patients.

There are several limitations to the present study. Most importantly, all the studies included in our meta-analysis are observational studies. Although all the included studies reported the hazard ratio adjusted for differences in baseline clinical features and other predictors for death (Supplement Table 2), it is possible that patients who received influenza vaccine were more likely to be adherent to their medical regimen than those who did not, thus introducing bias. Although the present study performed pooled analysis of the confounder-adjusted hazard ratio, our observed potential benefit of influenza vaccination might reflect other unmeasured factors that are related to improved survival. Second, cause-specific mortality benefit of influenza vaccination was not examined because none of the included studies reported the association of influenza vaccination with cause of death. Third, only a few studies reported the effect of influenza vaccination on hospitalization, which did not permit us to perform pooled analysis. Further studies are necessary to examine the effect of influenza vaccination on hospitalization in heart failure patients. Forth, the effect of different dose of influenza vaccine on clinical outcomes was not determined. Heart failure patients have been reported to exhibit reduced antibody responses to influenza vaccine [23] and a small pilot study have reported that heart failure patients who received double dose influenza vaccine showed higher antibody titers compared with those who received standard dose vaccine [24]. Further studies are warranted to examine the effect of higher doses of influenza vaccine on clinical outcomes in these patients. Finally, LVEF was not consistently reported in the included studies, which did not allow us to examine the potential different effect of influenza vaccination in heart failure with reduced EF and preserved EF.

In conclusion, our meta-analysis of observational studies showed that influenza vaccination was associated with reduced risk of mortality in heart failure patients. Large-scale and adequately powered RCTs should be planned not only to confirm our observed potential survival benefit of influenza vaccination but also to examine the cause-specific mortality benefit in these patients.

Compliance with ethical standards

Conflict of interest Dr. Ohte has received lecture fees from Takeda Pharmaceutical Co. Ltd., Daiichi Sankyo Co., Ltd., Bayer GA, AstraZeneca plc, and Boehringer Ingelheim and grant support from Takeda Pharmaceutical Co. Ltd., Bayer GA, Daiichi Sankyo Co., Ltd., MSD, Novartis International AG, Boehringer Ingelheim, Astellas Pharma Inc., and Otsuka Pharmaceutical Co., Ltd. No other disclosures were reported.

Ethical approval This article does not contain any studies with human participants performed by any of the authors.

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