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ORIGINAL ARTICLE
Heart Failure

Influenza Vaccination and Cardiovascular Events in Japanese Patients With Heart Failure
— Findings From the PARALLEL-HF Trial —

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Background: Influenza is associated with an increased risk for cardiovascular events in patients with heart failure (HF). This study aimed to investigate the prevalence of influenza vaccination among Japanese patients with HF enrolled in the PARALLEL-HF (Prospective comparison of ARNI with ACEi to determine the noveL beneficiaL trEatment vaLue in Japanese Heart Failure patients) trial and the association between receiving influenza vaccination and cardiovascular events including death or HF hospitalization.

Methods and Results: In PARALLEL-HF, in which 223 patients with HF and reduced ejection fraction (HFrEF) were randomized to the angiotensin-receptor neprilysin inhibitor (sacubitril/valsartan) or enalapril, 97 (43%) received influenza vaccination. Influenza vaccination tended to be associated, though statistically not significant, with a lower risk for all-cause death (adjusted hazard ratio [HR]: 0.67; 95% confidence interval [CI]: 0.32–1.39) and cardiopulmonary or influenza-related hospitalization or death (adjusted HR: 0.72; 95% CI: 0.46–1.11) in propensity score-adjusted models.

Conclusions: The influenza vaccination rate in Japanese patients with HFrEF who were well managed on guideline-directed medical therapy was suboptimal despite recommendations from clinical practice guidelines. However, importantly, it could be associated with better clinical benefits.

Key Words: Cardiovascular events; Heart failure; Influenza; Japanese; Vaccination

Influenza infection is a severe hazard for patients with heart failure (HF) such as an increased risk of hospitalization and death.[1] They are especially susceptible to influenza-related complications including acute exacerbations and secondary infections such as pneumonia, both of which increase hospitalizations.[2,3]

Influenza vaccination has been shown to effectively prevent infection as well as reduce the risk of hospitalization and death among patients with HF.[4,5] Pooled data from 6 cohort studies reported a 17% reduction in all-cause death with influenza vaccination in patients with HF.[5] Recently, a randomized controlled trial (RCT), the IVVE (Influenza Vaccine to Prevent Adverse Vascular Events) trial, reported that influenza vaccination reduced all-cause hospitalization by 16% and community-acquired pneumonia by 42% in patients with HF during periods of peak influenza circulation.[6] The reduction in all-cause hospitalization was largely due to the effect of the vaccine reducing HF hospitalizations and pneumonia. When events during peak influenza circulation periods were analyzed, the first co-primary composite outcome of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke was also reduced in participants assigned to influenza vaccine. Influenza vaccination is therefore recommended for patients with HF according to clinical practice guidelines by the Japanese Circulation Society (JCS)/Japanese Heart Failure Society (JHFS), the European Society of Cardiology (ESC), and the American College of Cardiology/American Heart Association/Heart Failure Society of America (AHA/ACC/HFSA).[7–9]

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Table 1. Baseline Characteristics in Patients With and Without Influenza Vaccination

	No influenza vaccination (n=126; 57%)	Influenza vaccination (n=97; 43%)	P value
Age, years	66.8±10.5	69.1±10.2	0.0973
Female sex	20 (15.9)	11 (11.3)	0.4353
Body mass index, kg/m^2	24.97±4.44	23.81±3.69	0.0392
Ischemic etiology	59 (46.8)	47 (48.5)	0.8925
Systolic blood pressure, mmHg	124.3±16.8	119.8±15.1	0.0395
Diastolic blood pressure, mmHg	73.7±13.3	71.7±11.6	0.2504
Heart rate, beats/min	73.0±13.0	73.1±13.1	0.9749
NYHA functional class			0.4380
I	0 (0.0)	0 (0.0)	
II	120 (95.2)	90 (92.8)	
III	6 (4.8)	7 (7.2)	
IV	0 (0.0)	0 (0.0)	
Left ventricular ejection fraction, %	28.29±5.26	28.01±5.35	0.6995
NT-proBNP (median, IQR), pg/mL	1,070.0 (763.0–1,860.0)	1,240.0 (789.0–1,920.0)	0.2133
eGFR, mL/min/1.73 m^2	59.86±15.80	55.51±16.45	0.0461
History of HF hospitalization	91 (72.2)	71 (73.2)	0.8810
History of hypertension	87 (69.0)	66 (68.0)	0.7701
History of diabetes	53 (42.1)	51 (52.6)	0.1370
History of myocardial infarction	52 (41.3)	45 (46.4)	0.4964
History of respiratory disease	12 (9.5)	10 (10.3)	1.0000
Use of ICD	10 (7.9)	5 (5.2)	0.5911
Use of CRT	11 (8.7)	16 (16.5)	0.0979
Baseline medications			
ACE inhibitors	74 (58.7)	66 (68.0)	0.1648
ARBs	52 (41.3)	31 (32.0)	0.1648
β-blockers	120 (95.2)	93 (95.9)	1.0000
MRAs	73 (57.9)	60 (61.9)	0.5839
Diuretics	103 (81.7)	83 (85.6)	0.4737
Digoxin	7 (5.6)	12 (12.4)	0.0907

Values are mean±SD, n (%), or median (interquartile range). ACE, angiotensin-converting enzyme; ARBs, angiotensin-receptor blockers; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; ICD, implantable cardioverter-defibrillator; IQR, interquartile range; MRAs, mineralocorticoid receptor antagonists; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association.

However, previous reports have found that vaccination uptake is suboptimal in HF patients.[10,11] The PARADIGM-HF (Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial reported that influenza vaccination rates were as low as 21% in patients with HF and reduced rejection fraction (HFrEF), which did not include Japanese patients.[10] The PARALLEL-HF trial enrolled only Japanese patients with HFrEF and queried them about receipt of influenza vaccination during the past 12 months at the time of enrolment, similar to PARADIGM-HF.[12,13] Thus, this analysis sought to determine the prevalence of influenza vaccination among Japanese patients enrolled in the PARALLEL-HF trial and investigate the association between receiving influenza vaccination and cardiovascular outcomes including death or HF hospitalization, all-cause hospitalization, and cardiopulmonary or influenza-related hospitalization.

Methods

Study Design

PARALLEL-HF was a multicenter, randomized, double-blind study that assessed the efficacy and safety of sacubitril/valsartan 200 mg twice daily (b.i.d.) vs. enalapril 10 mg bid on reduction in cardiovascular death and HF hospitalization in Japanese patients with HFrEF (ClinicalTrials.gov NCT02468232). The detailed study design and results for PARALLEL-HF have been published elsewhere.[12,13]

The study enrolled only Japanese patients with symptomatic chronic HFrEF (New York Heart Association [NYHA] class II–IV; left ventricular ejection fraction [LVEF] ≤35%) and elevated NT-pro B-type natriuretic peptide (BNP) levels (≥600 pg/mL or ≥400 pg/mL for those who had been hospitalized for HF within the last 12 months).

Patients were asked if they had received the seasonal influenza vaccine during the previous 12 months, and this information was recorded in the case report form. Cardiopulmonary and influenza-related hospitalizations were recorded through investigator reporting of causes of hospitalization on the case report form.

The study was conducted according to the Declaration of Helsinki and the International Conference on Harmonization (ICH) and Good Clinical Practice guidelines,[14] and complied with all local regulatory requirements. All patients gave written informed consent prior to participation. The

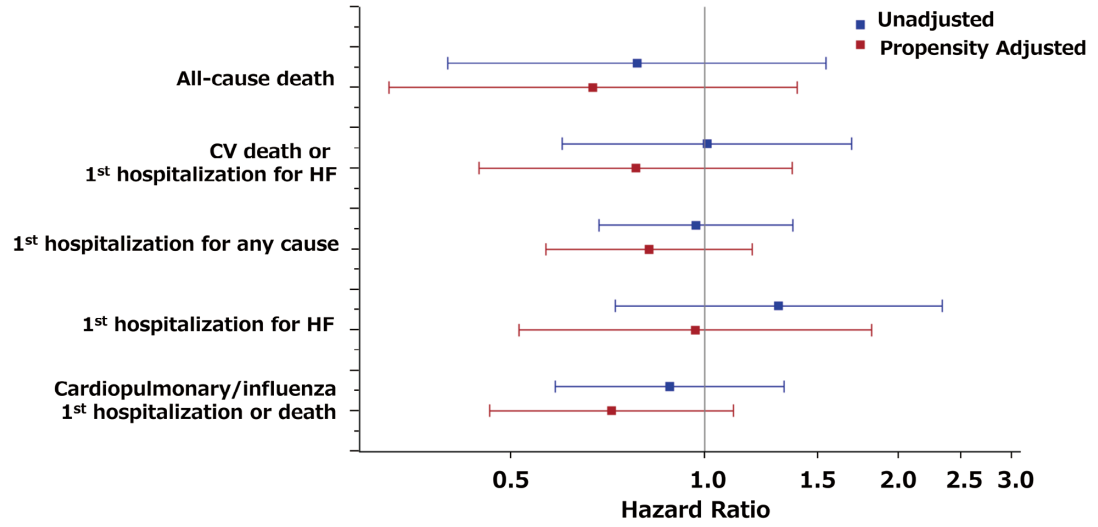

Figure 1. Crude and propensity score-adjusted hazard ratio of influenza vaccination for all-cause death, cardiovascular (CV) death or first hospitalization for heart failure (HF) (primary endpoint), first hospitalization for any cause, first hospitalization for HF, and cardiopulmonary/influenza-related first hospitalization or death.

executive committee designed and oversaw the conduct of the trial. The study was monitored by an independent data safety monitoring committee. The Consolidated Standards of Reporting Trials guidelines were followed.

Objectives

The objectives of this post hoc analysis of the PARALLEL-HF trial were to evaluate the prevalence of and baseline clinical characteristics associated with influenza vaccination, as well as outcomes in those who did and did not receive influenza vaccination. We hypothesized that influenza vaccination would be associated with better outcomes in patients with HFrEF.

Statistical Analysis

Baseline characteristics were analyzed to compare patients who received influenza vaccination and those who did not. Between-group assessments were performed using t-tests for continuous variables except for NT-proBNP, Wilcoxon rank sum test for NT-proBNP, and chi-square or Fisher's exact tests, as appropriate, for categorical variables. Two-sided P values were provided. To investigate associations of influenza vaccination with the risk for all-cause death, cardiovascular death or first hospitalization for HF, first hospitalizations for any cause, first hospitalization for HF, and cardiopulmonary/influenza-related first hospitalization or death, Cox proportional hazard models were constructed in an unadjusted model as well as a propensity score-adjusted model. The propensity score was created for receipt of influenza vaccination based on the logistic regression model including the following covariates: age, sex, body mass index (BMI), systolic blood pressure, NYHA functional class, LVEF, history of diabetes, history of myocardial infraction, history of respiratory disease, estimated glomerular filtration rate (eGFR), use of cardiac resynchronization therapy (CRT), use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs), use of β-blockers, use of mineralocorticoid receptor antagonists (MRA), use of diuretics, and sacubitril/valsartan treatment assignment.

Patients were stratified into 5 strata based on similarity in propensity scores, with the same number of patients who received influenza vaccination in each stratum. The strata were used as a stratification factor in the Cox models. The hazard ratios (HR) between patients who received influenza vaccination vs. those who did not, and the corresponding 95% confidence interval (CI) were provided. Finally, the same logistic regression model used for the creation of the propensity score was used to examine associations between baseline characteristics and receipt of the influenza vaccination. All analyses were performed using SAS 9.4 (SAS Institute, Cary, NC, USA).

Results

Of 223 patients in the PARALLEL-HF trial, 97 (43 %) had received influenza vaccination within a 12-month period while enrolled in the study. Baseline characteristics of the study patients according to influenza vaccination status are shown in **Table 1**. Patients who received vaccination tended to be older (69.1 vs. 66.8 years, P=0.0973) and had a lower mean BMI (23.8 vs. 25.0 kg/m^2, P=0.0392), lower systolic blood pressure (119.8 vs. 124.3 mmHg, P=0.0395), and lower eGFR (55.5 vs. 59.9 mL/min/1.73 m^2, P=0.0461) at screening compared with those who did not (**Table 1**). However, NYHA functional class, LVEF, and median NT-proBNP level at screening were similar between patients who did or did not receive vaccination (**Table 1**). Most of the patients who did or did not receive vaccination were receiving guideline-directed medical therapy, including ACE inhibitors (68.0 vs. 58.7%, P=0.1648), ARBs (32.0 vs. 41.3%, P=0.1648), β-blockers (95.9 vs. 95.2%, P=1.000), MRAs (61.9 vs. 57.9%, P=0.5839), and diuretics (85.6 vs. 81.7%, P=0.4737) (**Table 1**).

The multivariate analysis of receiving vaccination did not show a statistically significant association with any of

Table 2. Association Between Influenza Vaccination and Outcomes

	No influenza vaccination		Influenza vaccination		Unadjusted		Propensity score-adjusted	
	n/N	%	n/N	%	HR	95% CI	HR	95% CI
All-cause death	21/126	16.7	14/97	14.4	0.785	0.399–1.545	0.670	0.323–1.391
Cardiovascular death or first hospitalization for HF	32/126	25.4	26/97	26.8	1.009	0.601–1.693	0.782	0.446–1.369
First hospitalization for any cause	72/126	57.1	57/97	58.8	0.969	0.685–1.373	0.820	0.567–1.186
First hospitalization for HF	22/126	17.5	23/97	23.7	1.303	0.726–2.338	0.968	0.515–1.819
Cardiopulmonary/influenza first hospitalization or death	54/126	42.9	40/97	41.2	0.882	0.585–1.328	0.717	0.463–1.109

CI, confidence interval; HF, heart failure; HR, hazard ratio.

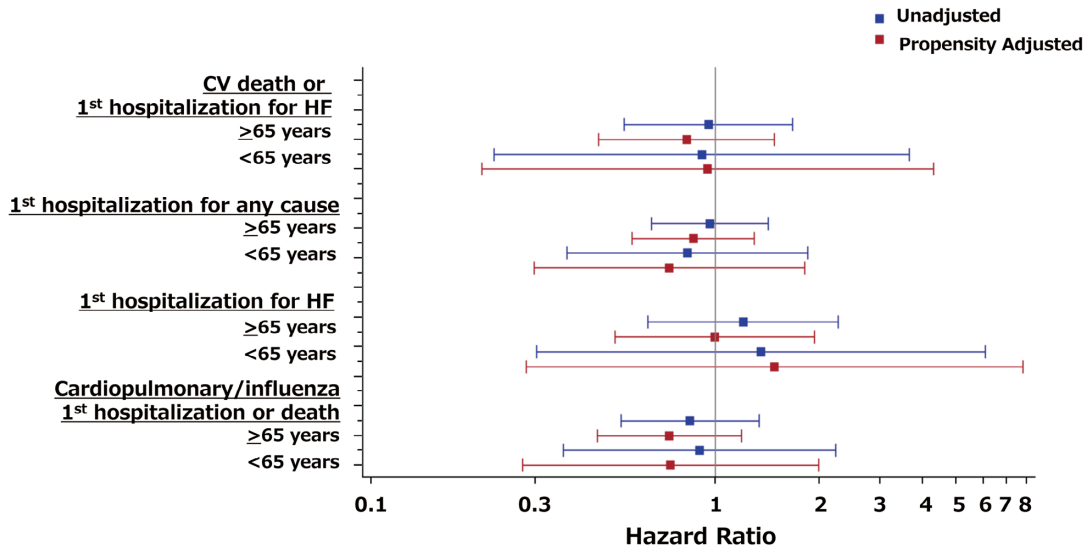

Figure 2. Crude and propensity score-adjusted hazard ratio of influenza vaccination for cardiovascular (CV) death or first hospitalization for heart failure (HF) (primary endpoint), first hospitalization for any cause, first hospitalization for HF, and cardiopulmonary/influenza-related first hospitalization or death according to the age of 65 years. Data on all-cause death is not shown because no deaths occurred in the subgroup of patients aged <65 years with influenza vaccination.

the baseline characteristics except for BMI.

Influenza vaccination tended to be associated with a lower risk for all-cause death compared with no vaccination in the unadjusted (HR 0.785, 95% CI 0.399–1.545) and propensity score-adjusted models (HR 0.670, 95% CI: 0.323–1.391) (**Figure 1**, **Table 2**), but did not reach statistical significance. Vaccination also tended to be associated with lower rates of cardiopulmonary/influenza-related hospitalization and death in the unadjusted (HR 0.882, 95% CI 0.585–1.328) and propensity score-adjusted models (HR 0.717, 95% CI 0.463–1.109) (**Figure 1**, **Table 2**), but did not reach statistical significance.

The subgroup analysis divided by the age of 65 years demonstrated that influenza vaccination was associated with similar clinical outcomes irrespective of the age (**Figure 2**).

Discussion

This is the first report to show that the influenza vaccination rate was 43% in Japanese patients with HFrEF. Influenza vaccination tended to be associated with better clinical outcomes including all-cause death, in agreement with the findings reported from the PARADIGM-HF trial.[10]

There has not been a previous report on influenza vaccination rates in patients with HF in Japan. The present study demonstrated that the vaccination rate was higher among Japanese HFrEF patients in PARALLEL-HF than in the global population of PARADIGM-HF (43% vs. 21%). The major reason for this difference between these trials, despite similar study design, might be the enrolment of global patients, because the major factor to receiving vaccination was found to be 'country' in the PARADIGM-HF.[10] In fact, the vaccination rate of 43% among Japanese HFrEF patients in PARALLEL-HF was higher than in other Asian countries such as Thailand (0%), India (0.2%), China (0.6%), Philippines (4.0%), Taiwan (5.8%), Hong Kong (8.7%), Singapore (9.3%), and Korea (20.7%), but substantially lower than in European countries such as the Netherlands (77.5%), Great Britain (77.2%), and Belgium (67.6%) and in the USA (55.1%).[10] Therefore, the vaccina-

tion rate in Japanese patients with HF found in the present study is definitely suboptimal despite the JCS/JHFS HF guideline advocating for annual influenza vaccination in HF patients.[7] Moreover, annual influenza vaccination is recommended for all persons aged ≥65 years in the international guidelines developed by the World Health Organization.[15] In Japan, the Immunization Act in 2001 mandated municipalities to subsidize annual influenza vaccination for persons aged ≥65 years. Nevertheless, the influenza vaccination rate was reported to be as low as 48.2% in 2017.[16] Therefore, the vaccination uptake rate in the present study is also suboptimal despite recommendations from public health organizations advocating for annual immunization in this high-risk population. The reasons for poor uptake of influenza vaccine in HF patients in Japan remain unclear, but may include factors such as fear of adverse reactions, limited knowledge regarding the benefits of vaccination, cost of vaccination, or reduced access to vaccination. Strategies including reinforcing existing HF practice guidelines, providing education to both patients and physicians, combating misinformation, and incorporating influenza vaccination into the disease management program of HF are needed to improve the vaccine rate in Japan.[17]

In PARALLEL-HF, vaccination was associated with lower BMI, lower systolic blood pressure, and lower eGFR at screening (**Table 1**), consistent with findings from PARADIGM-HF.[10] However, it was not associated with the severity of HF such as NYHA functional class, LVEF, and NT-proBNP level. In PARADIGM-HF, the factors significantly associated with vaccination included the enrolling country, white race, receipt of an implantable cardioverter-defibrillator device, older age, lower NYHA functional class, lower heart rate, and a history of diabetes mellitus.[10] In PARALLEL-HF, the multivariate analysis results could not identify any significant association between vaccination uptake and these factors, which might be due to its small sample size (223 patients in PARALLEL-HF vs. 8,442 patients in PARADIGM-HF).

The present study demonstrated that numerically fewer HF patients who received influenza vaccination experienced all-cause death (HR 0.67) (**Figure 1**, **Table 2**), although this did not reach statistical significance. However, these findings are in agreement with the results from the PARADIGM-HF trial (HR 0.81, P=0.015) and also with prior retrospective and prospective observational studies in which influenza vaccination was associated with lower rates of death.[18,19] It is also supported by the IVVE trial published in 2022, a large, randomized, double-blinded, placebo-controlled trial assessing the effect of influenza vaccine on the incidence of cardiovascular events in patients with HF. That trial randomized 5,129 patients with symptomatic HF to 3 consecutive years of influenza vaccine or placebo and followed cardiovascular outcomes over 3 years.[6] The primary endpoint of first cardiovascular death, myocardial infarction, stroke and HF hospitalization did not reach statistical significance by the intention-to-treat analyses (14.8% vs. 16.0 %; HR 0.93, 95% CI 0.81–1.07; P=0.30). However, influenza vaccination significantly reduced this outcome (HR 0.82, 95% CI 0.68–0.99) in a sensitivity analysis considering periods of high influenza activity. In addition, a recent systematic review and meta-analysis of 6 RCTs including the IVVE trial with a total of 9,340 patients with ischemic heart disease (4,211 patients) and/or HF (5,129 patients) also demonstrated that influenza vaccination significantly reduced a composite of cardiovascular death, acute coronary syndrome, stent thrombosis, coronary revascularization, and stroke or HF hospitalization (15.5% vs. 18.4%; HR 0.74, 95% CI 0.63–0.88; P<0.001) as well as the secondary endpoints of cardiovascular mortality (HR 0.63, 95% CI 0.42–0.95; P=0.028) and all-cause death (HR 0.72, 95% CI 0.54–0.95; P=0.023).[20] This meta-analysis included multiple geographical regions including Africa, Asia, Australia, Europe, the Middle East, and South America, which could enhance the generalizability of the findings regarding the clinical benefits of influenza vaccination. Therefore, although the association between influenza vaccination and the primary outcome was not statistically significant in PARALLEL-HF, there might be a certain clinical benefit for Japanese patients with HF. Furthermore, taken together with previous observational studies and clinical trials, the collective data support the clinical benefits of influenza vaccination in HF patients.[21]

Study Limitations

Several potential limitations should be acknowledged. First, this report is a post hoc analysis of the PARALLEL-HF trial. Therefore, observed rates of influenza vaccination may not be a true representation of real-world patients with HF because their characteristics may differ from those enrolled in a clinical trial. In addition, we could not present any scientific conclusions with statistical significance because of the small number of study patients (n=223) in the PARALLEL-HF trial. Second, the observed association between influenza vaccination and potential clinical benefits could not prove direct effects on mortality in this population. Third, there is the possibility that unmeasured confounding factors, which could not be adjusted, might contribute to the observed findings among influenza vaccine recipients. Fourth, vaccination information was collected during a 12-month period in the trial, and the effects of multiple years of receipt of influenza vaccination on outcomes could not be investigated. In addition, detailed information regarding the types of vaccine (e.g., maker, type, strain) was not collected. Therefore, the mechanisms responsible for the clinical benefit over a longer term remain unexplored. It may simply indicate better access to healthcare, including annual receipt of vaccination, or better general health status of vaccine recipients, and does not prove its inhibitory effects on infection or chronic inflammation. Fifth, even though the outcomes in the present study included cardiopulmonary or influenza-related hospitalizations or death, we could not assess the association between influenza vaccination and infection because data on pneumonia specifically caused by influenza were not collected.

Conclusions

The influenza vaccination rate in Japanese patients with HFrEF who were well managed on guideline-directed medical therapy was suboptimal despite well-publicized recommendations from clinical practice guidelines as well as public health organizations advocating for annual immunization in this high-risk population. Consistent with the benefits of influenza vaccination in HF shown by the PARADIGM-HF trial, influenza vaccination could be associated with better clinical outcomes also in Japanese patients.

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IRB Information

The study protocol and all amendments were reviewed and approved by the Independent Ethics Committee or Institutional Review Board (IRB) for each center, e.g., Nihon University Hospitals Joint IRB (reference number: 5010005002382).

Author Contributions

All authors participated in the development and writing of the paper, reviewed and critically revised the manuscript for content, and approved the final version of the manuscript for submission.

Data Availability

The deidentified participant data will not be shared.

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