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Research Letter | Public Health

Risk of Myocarditis or Pericarditis With High-Dose vs Standard-Dose Influenza Vaccine

A Prespecified Secondary Analysis of the Randomized DANFLU-2 Trial

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Introduction

Influenza infection is associated with an increased risk of myocarditis and pericarditis.[1] Although such cardiac complications are rare and usually mild, they may lead to cardiogenic shock or cardiac tamponade. The high-dose inactivated influenza vaccine (HD-IIV) significantly reduces the incidence of laboratory-confirmed influenza infection compared with standard-dose IIVs (SD-IIVs) among older adults.[2] However, it is unknown whether HD-IIV reduces the risk of myocarditis or pericarditis, and it has not previously been possible to explore this hypothesis given the large sample size needed. This prespecified analysis of the trial A Pragmatic Randomized Trial to Evaluate the Effectiveness of High-Dose Influenza Vaccine vs Standard-Dose Influenza Vaccine in Older Adults (DANFLU-2)[3] examined the risk of myocarditis or pericarditis with HD-IIV vs SD-IIV.

Methods

This prespecified secondary analysis of a randomized clinical trial used data from the DANFLU-2 trial,[3] as did another secondary analysis.[4] The trial is registered (NCT05517174), and the protocol indicating prespecification of this analysis is included in Supplement 1. In brief, DANFLU-2 was a pragmatic (ie, with broadened generalizability via more representative populations studied in routine settings), registry-based, open-label, randomized clinical trial of adults aged 65 years or older conducted in Denmark during the 2022-2023, 2023-2024, and 2024-2025 influenza seasons. Participants were randomized 1:1 to HD-IIV or SD-IIV. The trial was approved by the Danish Medical Research Ethics Committees and Danish Medicines Agency. All participants provided informed consent, granting access to registry data and medical records. Approval and consent extend to this study, which is reported according to the CONSORT reporting guideline.

Baseline and outcome data were collected through linkage to nationwide health registries. During each study season, participants were followed up from day 14 after vaccination through May 31 the following year. The primary outcome was hospitalization for influenza or pneumonia. As an exploratory outcome, this study examined the risk of hospitalization for myocarditis (defined as *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* [*ICD-10*] codes I40-I41) or pericarditis (defined as *ICD-10* codes I30-I31) in the 2 randomization groups. Relative vaccine effectiveness ([1 − relative risk] × 100%) based on first events was reported, with 95% CIs constructed using the exact Clopper-Pearson method for binomial proportions. Events occurring before 14 days after vaccination were included in a sensitivity analysis. Consistency of the treatment effect was assessed across baseline characteristics and conditions, with no adjustment for multiplicity. Interactions were assessed

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using the Cochran-Mantel-Haenszel test for homogeneity. We considered 2-sided *P* values < .05 statistically significant. Statistical analysis was performed using SAS version 9.4 (SAS Institute), Stata MP version 19.5 (StataCorp), and R version 4.3.3 (R Project for Statistical Computing).

Results

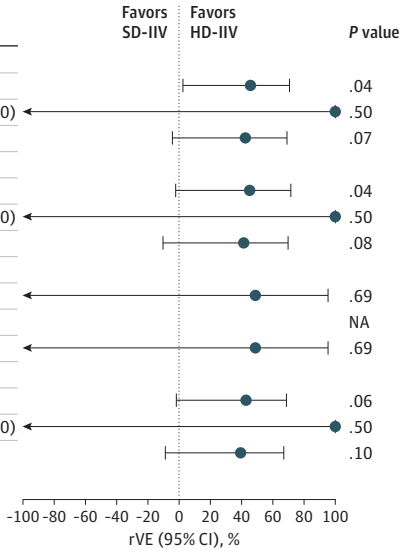
Of 332 438 participants randomized, 1295 (mean [SD] age, 74.2 [5.7] years; 884 men [68.3%]) had a prior history of myocarditis or pericarditis, including 97 with prior myocarditis and 1218 with prior pericarditis, and 331 143 did not (mean [SD] age, 73.7 [5.8] years; 170 016 men [51.3%]) (**Table**).

Table. Participant Baseline Characteristics

Characteristic	Participants, No. (%) (N = 332 438)		*P* value
	No prior myocarditis or pericarditis (n = 331 143)	Prior myocarditis or pericarditis (n = 1295)	
Age, mean (SD), y	73.7 (5.8)	74.2 (5.7)	.001
Gender			
Men	170 016 (51.3)	884 (68.3)	<.001
Women	161 127 (48.7)	411 (31.7)	<.001
Comorbidities			
Hypertension	63 416 (19.2)	491 (37.9)	<.001
Diabetes	43 639 (13.2)	242 (18.7)	<.001
Chronic cardiovascular disease	90 086 (27.2)	940 (72.6)	<.001
Ischemic heart disease	30 718 (9.3)	394 (30.4)	<.001
Cerebrovascular disease	16 300 (4.9)	81 (6.3)	.03
Peripheral artery disease	2956 (0.9)	23 (1.8)	<.001
Heart failure	10 212 (3.1)	198 (15.3)	<.001
Atrial fibrillation	33 550 (10.1)	535 (41.3)	<.001
Chronic lung disease	26 948 (8.1)	204 (15.8)	<.001
Chronic kidney disease	46 452 (14.0)	336 (25.9)	<.001
Chronic liver disease	4950 (1.5)	38 (2.9)	<.001
Cancer	45 693 (13.8)	225 (17.4)	<.001
Immunodeficiency	14 193 (4.3)	122 (9.4)	<.001
Coadministration with COVID-19 vaccine	203 916 (61.6)	807 (62.3)	.59

Figure. Risk of Myocarditis or Pericarditis Among Patients Receiving High-Dose vs Standard-Dose Influenza Vaccine

Outcome	Participants, No./total No.		rVE (95% CI), %	*P* value
	HD-IIV	SD-IIV		
All participants				
Myocarditis or pericarditis	19/166 218	35/166 220	45.71 (2.46 to 70.67)	.04
Myocarditis	0/166 218	2/166 220	100.00 (-432.46 to 100.00)	.50
Pericarditis	19/166 218	33/166 220	42.42 (-4.27 to 69.07)	.07
Participants without prior myocarditis or pericarditis				
Myocarditis or pericarditis	17/165 578	31/165 565	45.17 (-2.19 to 71.53)	.04
Myocarditis	0/165 578	2/165 565	100.00 (-432.41 to 100.00)	.50
Pericarditis	17/165 578	29/165 565	41.38 (-10.30 to 69.78)	.08
Participants with prior myocarditis or pericarditis				
Myocarditis or pericarditis	2/640	4/655	48.83 (-257.05 to 95.37)	.69
Myocarditis	0/640	0/655	NA	NA
Pericarditis	2/640	4/655	48.83 (-257.05 to 95.37)	.69
All participants (including the first 14 d after vaccination)				
Myocarditis or pericarditis	20/166 218	35/166 220	42.86 (-1.76 to 68.74)	.06
Myocarditis	0/166 218	2/166 220	100.00 (-432.46 to 100.00)	.50
Pericarditis	20/166 218	33/166 220	39.39 (-8.80 to 67.04)	.10



HD-IIV indicates high-dose inactivated influenza vaccine; NA, not applicable; rVE, relative vaccine effectiveness; SD-IIV, standard-dose inactivated influenza vaccine.

Baseline characteristics were balanced across HD-IIV and SD-IIV groups. Individuals with prior myocarditis or pericarditis were older, more often men, and had a higher prevalence of comorbidities. The incidence of myocarditis or pericarditis was lower among participants randomized to HD-IIV vs SD-IIV (19 vs 35 events; relative vaccine effectiveness, 45.71%; 95% CI, 2.46%-70.67%; $P = .04$) (**Figure**). Results were consistent when events occurring before 14 days were included. No interactions were detected.

Discussion

In this prespecified analysis of the DANFLU-2 trial, the risk of incident myocarditis or pericarditis was lower among individuals randomized to HD-IIV vs SD-IIV. Despite sporadic reports of myocarditis and pericarditis associated with influenza vaccination,[5] the consistency of our results with vs without inclusion of events occurring immediately after vaccination negates a dose-response association and a causal link. Study limitations include the small number of events, lack of knowledge regarding the etiology and severity of each event, and inability to compare the effects of vaccines vs no vaccine. Implications for myocarditis are unclear given that only 2 such events occurred. The generalizability to younger individuals, who typically have a higher risk of inflammatory cardiac conditions, is also unknown.[6] HD-IIV was associated with protection against myocarditis or pericarditis compared with SD-IIV in the largest individually randomized trial of an enhanced influenza vaccine.

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Supervision: Dalager-Pedersen, Claggett, Sengeløv, Solomon, Køber, Sivapalan, Jensen, Biering-Sørensen.

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SUPPLEMENT 1.
Trial Protocol and Statistical Analysis Plan

SUPPLEMENT 2.
Data Sharing Statement