JAMA Internal Medicine | Original Investigation | AGING AND HEALTH

High-Dose vs Standard-Dose Influenza Vaccine in Older Adults With Diabetes

A Secondary Analysis of the DANFLU-2 Randomized Clinical Trial

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IMPORTANCE Influenza infection poses a substantial risk of severe complications, particularly in older adults and high-risk populations, such as individuals with diabetes. The high-dose inactivated influenza vaccine (HD-IIV) has demonstrated superior efficacy against influenza infection compared with the standard-dose inactivated influenza vaccine (SD-IIV) among adults 65 years or older. However, there is limited evidence on its effectiveness in preventing severe respiratory and cardiovascular outcomes in individuals with diabetes.

OBJECTIVE To investigate the relative vaccine effectiveness (rVE) of HD-IIV vs SD-IIV against severe respiratory and cardiovascular outcomes according to diabetes status and across diabetes subgroups.

DESIGN, SETTING, AND PARTICIPANTS This was a prespecified secondary analysis of DANFLU-2, a pragmatic, open-label, individually randomized clinical trial conducted in Denmark during the 2022/2023 to 2024/2025 influenza seasons. Adults 65 years or older were eligible for inclusion regardless of comorbidities. Data were obtained from nationwide health registries and analyzed from June to October 2025.

INTERVENTIONS Participants were randomly allocated 1:1 to receive HD-IIV or SD-IIV.

MAIN OUTCOMES AND MEASURES Outcomes included respiratory and cardiovascular hospitalizations. The potential effect modification by diabetes status and across diabetes subgroups was tested.

RESULTS Among 332 438 participants (mean [SD] age, 73.7 [5.8] years; 161 538 female individuals [48.6%]), 43 881 (13.2%) had diabetes. Overall, HD-IIV compared with SD-IIV was associated with reduced cardiorespiratory hospitalization, cardiovascular hospitalization, and influenza hospitalization. Effect estimates were similar for participants with and without diabetes for cardiorespiratory hospitalization (diabetes: rVE, 7.4%; 95% CI, −2.5% to 16.3%; no diabetes: rVE, 5.3%; 95% CI, 0.4%-10.0%; interaction P = .69), cardiovascular hospitalization (diabetes: rVE, 12.0%; 95% CI, −0.9% to 23.3%; no diabetes: rVE, 6.0%; 95% CI, −0.4% to 12.0%; interaction P = .38), and influenza hospitalization (diabetes: rVE, 41.6%; 95% CI, 5.0%-64.7%, vs no diabetes: rVE, 44.3%; 95% CI, 25.3%-58.7%; interaction P = .87). Duration of diabetes appeared to modify the effect of HD-IIV vs SD-IIV for cardiorespiratory hospitalization, with suggested benefit of HD-IIV in participants with diabetes duration longer than 5 years (rVE, 20.4%; 95% CI, 5.3%-33.1%), but not in those with shorter duration (rVE, −0.4%; 95% CI, −13.8% to 11.5%; interaction P = .03).

CONCLUSIONS AND RELEVANCE The trial results suggest that, among adults 65 years or older, HD-IIV provided consistent benefit for cardiorespiratory, cardiovascular, and influenza hospitalizations compared with SD-IIV, regardless of diabetes status.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT05517174

JAMA Intern Med. doi:10.1001/jamainternmed.2025.7286
Published online January 12, 2026.

Supplemental content

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Influenza infection causes substantial global morbidity and mortality, particularly burdening older adults and individuals with chronic conditions, such as diabetes, who face elevated risk of severe influenza-related complications.[1-3] While seasonal influenza vaccination remains the primary preventive measure against influenza and associated adverse outcomes, the standard-dose inactivated influenza vaccine (SD-IIV) may elicit suboptimal immune responses and insufficient protection, particularly for susceptible populations, such as older adults and individuals with diabetes.[4-6] Given the substantial burden of influenza in these vulnerable populations, optimizing vaccination strategies is crucial.

The high-dose inactivated influenza vaccine (HD-IIV), which contains 4 times the antigen content of SD-IIV, was developed to better protect older adults.[4] The relative efficacy of HD-IIV compared with SD-IIV against laboratory-confirmed influenza has been demonstrated in older adults,[7] and its use is currently preferentially recommended compared with SD-IIV for adults 65 years or older in the US.[8] However, there is limited evidence from individually randomized trials on the relative vaccine effectiveness (rVE) of HD-IIV compared with SD-IIV against severe clinical outcomes in individuals with diabetes. Therefore, this prespecified secondary analysis of the DANFLU-2 randomized clinical trial aimed to evaluate the rVE of HD-IIV vs SD-IIV against severe respiratory and cardiovascular outcomes according to diabetes status and across key diabetes subgroups in adults 65 years or older.

Key Points

Question Does the high-dose inactivated influenza vaccine (HD-IIV) provide superior protection against severe respiratory and cardiovascular outcomes in older adults compared with the standard-dose inactivated influenza vaccine (SD-IIV), and does relative vaccine effectiveness differ among older adults with and without diabetes?

Findings In this prespecified secondary analysis of the DANFLU-2 randomized clinical trial of 332 438 older adults, including 43 881 with diabetes, HD-IIV was associated with reduced cardiorespiratory, cardiovascular, heart failure, influenza, and laboratory-confirmed hospitalizations compared with SD-IIV, irrespective of diabetes status.

Meaning The trial results suggest that HD-IIV may offer incremental protection compared with SD-IIV against cardiovascular and influenza-related outcomes in individuals with and without diabetes, although these findings are exploratory and must be interpreted in this context.

Methods

Trial Design

This was a prespecified secondary analysis of DANFLU-2, a pragmatic, registry-based, open-label, active-controlled, individually randomized clinical trial conducted in Denmark during the 2022/2023, 2023/2024, and 2024/2025 influenza seasons. The trial design and primary results have previously been published.[9,10] The trial used nationwide Danish administrative health registries to obtain baseline, end point, and safety data. Only 1 study visit was required for randomization and vaccination.

DANFLU-2 was approved as a low-intervention clinical trial (EU CT 2022-500657-17-00) by the Medical Research Ethics Committees in Denmark and the Danish Medicines Agency and was approved by the data authority in the Capital Region of Denmark. All participants provided informed consent. The trial protocol and statistical analysis plan are available in Supplement 1. This report followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines.

Participants

Adults 65 years or older were eligible for inclusion, regardless of comorbidities. No formal exclusion criteria were specified. In each season, up to 1 000 000 Danish citizens 65 years or older were invited through electronic invitations delivered via the Danish governmental electronic letter system (Digital Post).[11] After scheduling the trial visit, participants could provide informed consent online or in person at the trial visit.

Group Allocation and Interventions

Participants were randomly allocated in 1:1 to receive HD-IIV or SD-IIV. Randomization was performed during the trial visit through a tablet application linked to a centralized randomization algorithm. Participants re-enrolling in subsequent seasons underwent rerandomization and were treated as unique observations.[12] Treatment allocation was open label for participants and study staff.

In each season, participants received a single intramuscular injection of quadrivalent HD-IIV (Fluzone High-Dose Quadrivalent/Efluelda/Efluelda Tetra; Sanofi) or quadrivalent SD-IIV (VaxigripTetra; Sanofi). HD-IIV contains 60 µg of hemagglutinin antigen for each strain, whereas SD-IIV contains 15 µg for each. The trial allowed for coadministration with other seasonal vaccines as per local recommendations and guidelines.

Data Collection and Baseline Information

Minimal data were collected at the trial visit, comprising identifying information, consent, and information on randomization and vaccine administration. All other data were obtained primarily from the nationwide administrative health registries, which contain data from all inpatient and outpatient hospital contacts within the universal Danish public health system.[13] Baseline characteristics and end points were identified using prespecified definitions.[9]

Baseline diabetes was defined as at least 1 inpatient or outpatient hospital encounter registered in the Danish National Patient Registry with an *International Classification of Diseases, 10th Revision* (*ICD-10*) code for diabetes (E10-E14) as the primary or secondary discharge diagnosis within 10 years before randomization, or at least 1 laboratory measurement of glycated hemoglobin (HbA_{1c}) of 6.5% (48 mmol/mol) or greater (to convert to the total proportion of hemoglobin, multiply by 0.01) within 5 years before randomization. Baseline HbA_{1c} levels were reported as the most recent measured HbA_{1c} level within 5 years of randomization. As HbA_{1c} was measured as

part of usual care in primary care or hospitals, it was not systematically available for all participants. Baseline definitions for diabetes subgroups are described in the eMethods in Supplement 2.

End Points

In each season, follow-up extended from 14 days after vaccination through May 31 of the following year. The primary end point of DANFLU-2 was hospitalization for influenza or pneumonia, for which the results, including by diabetes status, have been reported.[10] This analysis evaluated the following prespecified severe cardiovascular and respiratory end points: (1) hospitalization for any cardiorespiratory disease, (2) hospitalization for any cardiovascular disease, (3) hospitalization for any respiratory disease, (4) hospitalization for influenza, (5) laboratory-confirmed influenza hospitalization, (6) hospitalization for heart failure, (7) hospitalization for myocardial infarction, (8) hospitalization for stroke, (9) major adverse cardiovascular events (MACE), defined as a composite of myocardial infarction, stroke, heart failure hospitalization, or cardiovascular death, and (10) cardiovascular death. The prespecified end points were evaluated according to diabetes status and across diabetes subgroups. Hospitalization-based events with an associated COVID-19 *ICD-10* discharge diagnosis code (B34.2, B97.2) were not considered end points. In addition to the prespecified end points, nonprespecified end points of incident diabetes and incident diabetes-related complications were evaluated, with definitions provided in the eMethods in Supplement 2.

Statistical Analysis

For each end point, absolute risks were calculated separately for participants with and without diabetes. Risk ratios comparing these 2 groups were estimated using log-binomial regression models and presented with 95% CIs.

rVE was calculated as 1 minus the relative risk of the end point and presented as a percentage, with *P* values calculated using binomial tests and 95% CIs determined using the Clopper-Pearson method.[14] To test for effect modification by diabetes status, rVE was calculated for each stratum, and interaction *P* values were calculated using the Cochran-Mantel-Haenszel test for homogeneity.

The number needed to vaccinate (NNV) was estimated as the reciprocal of the absolute risk difference between SD-IIV and HD-IIV for end points, with an overall benefit of HD-IIV. All comparisons of HD-IIV vs SD-IIV were performed according to the intention-to-treat principle and were limited to the first occurrence of each end point. A sensitivity analysis was performed to account for within-participant correlation among participants enrolled in more than 1 season. A description of statistical analyses within diabetes subgroups is available in the eMethods in Supplement 2.

P values of <.05 were considered statistically significant; no adjustments were made for multiple comparisons. Statistical analyses were performed using SAS, version 9.4 (SAS Institute); Stata MP, version 19.5 (StataCorp); and R, version 4.3.3 (R Foundation for Statistical Computing).

Results

Participants

Among a total of 332 438 included participants, 166 218 (50.0%) were randomly assigned to receive HD-IIV and 166 220 (50.0%) to SD-IIV. A total of 43 881 participants (13.2%) had diabetes at baseline, of whom 21 929 (50.0%) were randomly assigned to receive HD-IIV and 21 952 (50.0%) to SD-IIV. A study flow diagram is available in eFigure 1 in Supplement 2. Among participants with diabetes, the mean (SD) age was 74.1 (5.9) years, 16 379 (37.3%) were female, and the median HbA_{1c} level was 6.5% (IQR, 6.2%-7.0%). Of the participants with diabetes, 41 889 (95%) were identified by HbA_{1c} levels, 19 528 (45%) by *ICD-10* codes, and 17 546 (40%) met both criteria. Among participants registered with an *ICD-10* code for diabetes, 2052 (11%) were classified as having type 1 diabetes and 15 233 (78%) as having type 2 diabetes. Baseline comorbidities were more prevalent among participants with diabetes than in those without (**Table 1**). The median diabetes duration was 4.6 years (IQR, 2.9-6.2), and a diabetes-related complication was present in 7562 participants with diabetes (17%). Baseline characteristics were balanced across randomization groups in participants with diabetes (eTable 1 in Supplement 2).

End Points by Diabetes Status

The risk of experiencing the evaluated cardiovascular and respiratory end points was generally higher for participants with diabetes than for those without, with relative risks ranging from 1.34 (95% CI, 1.13-1.59) for stroke hospitalizations to 3.26 (95% CI, 2.69-3.94) for heart failure hospitalizations (**Figure 1**).

During follow-up, a total of 1903 participants (4.3%) with diabetes and 8543 participants (3.0%) without diabetes were tested for influenza. Among those tested, 170 participants (8.9%) with diabetes and 840 (9.8%) without diabetes had a positive test result (*P* = .23).

The rVE of HD-IIV vs SD-IIV against all examined end points was consistent regardless of diabetes status (**Table 2**). There was no evidence of effect modification by diabetes status on the overall lower incidence of hospitalization for any cardiorespiratory disease in the HD-IIV group compared with the SD-IIV group (diabetes: rVE, 7.4%; 95% CI, −2.5% to 16.3%; no diabetes: rVE, 5.3%; 95% CI, 0.4%-10.0%; interaction *P* = .69).[15] Similar consistent findings were observed for the overall lower incidence of hospitalization for any cardiovascular disease (diabetes: rVE, 12.0%; 95% CI, −0.9% to 23.3%; no diabetes: rVE, 6.0%; 95% CI, −0.4% to 12.0%; interaction *P* = .38), while no difference in hospitalization for any respiratory disease was observed, which was consistent by diabetes status (diabetes: rVE, 1.7%; 95% CI, −13.7% to 15.0%; no diabetes: rVE, 4.3%; 95% CI, −3.4% to 11.3%; interaction *P* = .75).

Of the examined individual components of hospitalization for any cardiovascular disease, hospitalization for heart failure was lower with HD-IIV compared with SD-IIV in the overall population, with no evidence of effect modification by diabetes status (diabetes: rVE, 19.2%; 95% CI, −11.7% to 41.8%; no diabetes: rVE, 19.7%; 95% CI, −0.7% to 36.0%; interaction *P* = .98).

Table 1. Baseline Characteristics According to Diabetes Status

Characteristic	Participants, No. (%)[a]		
	Overall (N = 332 438)	With diabetes[b] (n = 43 881)	Without diabetes[b] (n = 288 548)
Age, mean (SD), y	73.7 (5.8)	74.1 (5.9)	73.6 (5.8)
Sex			
Female	161 538 (48.6)	16 379 (37.3)	145 153 (50.3)
Male	170 900 (51.4)	27 502 (62.7)	143 395 (49.7)
Presence of at least 1 chronic disease	177 769 (53.5)	43 881 (100.0)	133 888 (46.4)
Chronic cardiovascular disease	91 026 (27.4)	17 326 (39.5)	73 700 (25.5)
Ischemic heart disease	31 112 (9.4)	7473 (17.0)	23 639 (8.2)
Myocardial infarction	9405 (2.8)	2110 (4.8)	7295 (2.5)
Atrial fibrillation	34 085 (10.3)	6578 (15.0)	27 507 (9.5)
Heart failure	10 410 (3.1)	2914 (6.6)	7496 (2.6)
Cerebrovascular disease	16 381 (4.9)	3102 (7.1)	13 279 (4.6)
Peripheral vascular disease	2979 (0.9)	938 (2.1)	2041 (0.7)
Chronic lung disease	27 152 (8.2)	4860 (11.1)	22 292 (7.7)
Chronic obstructive lung disease	13 488 (4.1)	2844 (6.5)	10 644 (3.7)
Chronic kidney disease	46 788 (14.1)	16 234 (37.0)	30 554 (10.6)
Immunodeficiency	14 315 (4.3)	2382 (5.4)	11 933 (4.1)
Cancer	45 918 (13.8)	6869 (15.7)	39 049 (13.5)
Coadministration with COVID-19 vaccine	204 723 (61.6)	27 440 (62.5)	177 283 (61.4)
HbA_{1c} level, median (IQR), %[c]	5.6 (5.4-5.9)	6.5 (6.2-7.0)	5.6 (5.4-5.8)

Abbreviation: HbA_{1c}, glycated hemoglobin.

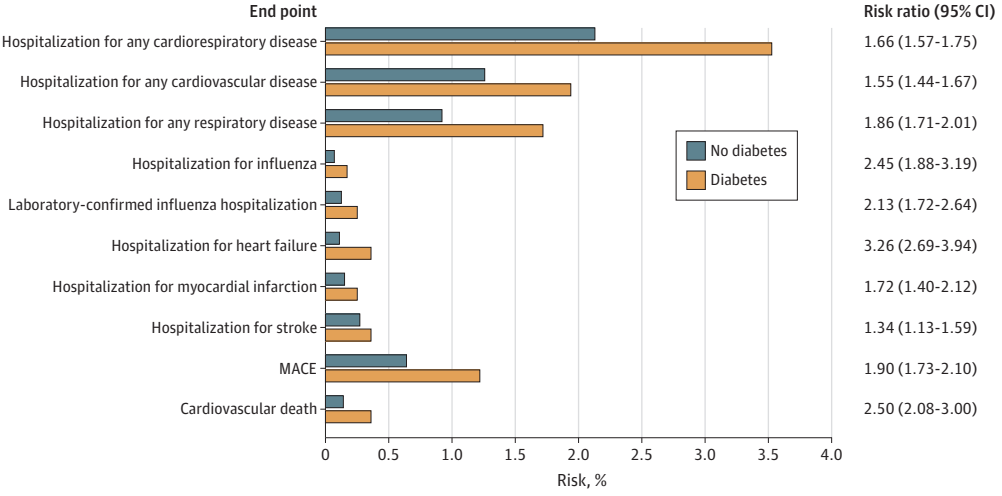
SI conversion factor: to convert HbA_{1c} to the proportion of total hemoglobin, multiply by 0.01 (to convert to mmol/mol, multiply by 10.93 and subtract 23.5).

[a] Baseline characteristics were sourced from nationwide administrative health registries using prespecified definitions. Nine individuals (8 in season 2, 1 in season 3) of the total 332 438 randomized withdrew consent after randomization and did not contribute any other baseline data than age and sex.

[b] All *P* values for the comparison of participants with and without diabetes were <.001.

[c] HbA_{1c} level was missing for 25 858 participants (7.8%) (24 [0.1%] with diabetes and 25 825 [9.0%] without diabetes).

Figure 1. Risks of End Points by Diabetes Status



Risks of evaluated end points according to baseline diabetes status. Risk ratios with 95% CIs that compared participants with and without diabetes were estimated using a log-binomial regression. MACE indicates major adverse cardiovascular events.

HD-IIV compared with SD-IIV was also consistently associated with reduced hospitalization for influenza (diabetes: rVE, 41.6%; 95% CI, 5.0%-64.7%; no diabetes: rVE, 44.3%; 95% CI, 25.3%-58.7%; interaction *P* = .87) and laboratory-confirmed influenza hospitalization (diabetes: rVE, 29.2%; 95% CI, −4.9% to 52.5%; no diabetes: rVE, 37.9%; 95% CI, 22.4%-50.5%; interaction *P* = .55), irrespective of diabetes status. Analyses that accounted for within-participant correlation among those enrolled in more than 1 season yielded similar results (eTable 2 in Supplement 2).

Across outcomes favoring HD-IIV, NNVs were generally lower among individuals with diabetes. For cardiorespiratory hospitalization, the NNV was 371 for individuals with diabetes and 861 for those without diabetes. For cardiovascular hospitalization, the NNV was 402 for individuals with diabetes and 1284 for those without. For heart failure hospitalization, the NNV was 1297 for individuals with diabetes and 4119 for those without. For influenza hospitalization, the NNV was 1099 for individuals with diabetes and 2487 for those without. For laboratory-confirmed influenza hospitalization, the

Table 2. Relative Vaccine Effectiveness of HD-IIV vs SD-IIV Against Prespecified End Points According to Diabetes Status

End point[a]/diabetes status	Events, No. (%)		Relative vaccine effectiveness, % (95% CI)	*P* value for interaction
	HD-IIV	SD-IIV		
Hospitalization for any cardiorespiratory disease				
All participants	3735 (2.3)	3962 (2.4)	5.7 (1.4 to 9.9)	.69
Diabetes	744 (3.4)	804 (3.7)	7.4 (−2.5 to 16.3)	
No diabetes	2991 (2.1)	3158 (2.2)	5.3 (0.4 to 10.0)	
Hospitalization for any cardiovascular disease				
All participants	2156 (1.3)	2323 (1.4)	7.2 (1.5 to 12.5)	.38
Diabetes	399 (1.8)	454 (2.1)	12.0 (−0.9 to 23.3)	
No diabetes	1757 (1.2)	1869 (1.3)	6.0 (−0.4 to 12.0)	
Hospitalization for any respiratory disease				
All participants	1677 (1.0)	1742 (1.0)	3.7 (−3.0 to 10.0)	.75
Diabetes	373 (1.7)	380 (1.7)	1.7 (−13.7 to 15.0)	
No diabetes	1304 (0.9)	1362 (0.9)	4.3 (−3.4 to 11.3)	
Hospitalization for influenza				
All participants	101 (0.1)	179 (0.1)	43.6 (27.6 to 56.2)	.87
Diabetes	28 (0.1)	48 (0.2)	41.6 (5.0 to 64.7)	
No diabetes	73 (0.1)	131 (0.1)	44.3 (25.3 to 58.7)	
Laboratory-confirmed influenza hospitalization				
All participants	177 (0.1)	276 (0.2)	35.9 (22.3 to 47.2)	.55
Diabetes	46 (0.2)	65 (0.3)	29.2 (−4.9 to 52.5)	
No diabetes	131 (0.1)	211 (0.2)	37.9 (22.4 to 50.5)	
Hospitalization for heart failure				
All participants	214 (0.1)	266 (0.2)	19.5 (3.3 to 33.1)	.98
Diabetes	71 (0.3)	88 (0.4)	19.2 (−11.7 to 41.8)	
No diabetes	143 (0.1)	178 (0.1)	19.7 (−0.7 to 36.0)	
Hospitalization for myocardial infarction				
All participants	265 (0.2)	265 (0.2)	0.0 (−19.0 to 16.0)	.66
Diabetes	57 (0.3)	53 (0.2)	−7.7 (−59.5 to 27.2)	
No diabetes	208 (0.1)	212 (0.2)	1.9 (−19.3 to 19.4)	
Hospitalization for stroke				
All participants	458 (0.3)	485 (0.3)	5.6 (−7.5 to 17.1)	.82
Diabetes	79 (0.4)	81 (0.4)	2.4 (−34.8 to 29.3)	
No diabetes	379 (0.3)	404 (0.3)	6.2 (−8.2 to 18.7)	
MACE				
All participants	1158 (0.7)	1224 (0.7)	5.4 (−2.6 to 12.8)	.55
Diabetes	266 (1.2)	269 (1.2)	1.0 (−17.7 to 16.8)	
No diabetes	892 (0.6)	955 (0.7)	6.6 (−2.4 to 14.9)	
Cardiovascular death				
All participants	291 (0.2)	279 (0.2)	−4.3 (−23.4 to 11.8)	.06
Diabetes	90 (0.4)	67 (0.3)	−34.5 (−87.3 to 3.1)	
No diabetes	201 (0.1)	212 (0.2)	5.2 (−15.5 to 22.2)	

Abbreviations: HD-IIV, high-dose inactivated influenza vaccine; MACE, major adverse cardiovascular events; SD-IIV, standard-dose inactivated influenza vaccine.

[a] End points occurring between 14 days after vaccination and May 31 the following year were defined as eligible for analysis. End points were ascertained using data from nationwide administrative health registries using prespecified definitions.

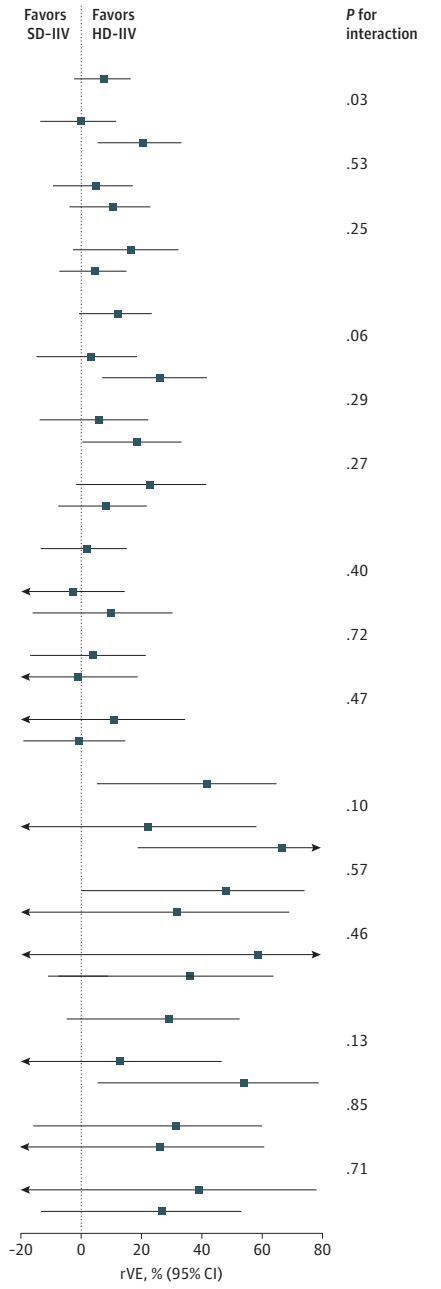
NNV was 1158 for individuals with diabetes and 1803 for those without.

rVE According to Diabetes Subgroups

The rVE of HD-IIV vs SD-IIV was evaluated across diabetes subgroups, as stratified by diabetes duration (less than or more than 5 years), median HbA_{1c} level, the presence of a diabetes-related complication, and diabetes type. Diabetes duration appeared to modify the effect of HD-IIV vs SD-IIV against hospitalization for any cardiorespiratory disease, with lower incidence observed among participants with diabetes duration longer than 5 years (rVE, 20.4%; 95% CI, 5.3%-33.1%), but not in those with shorter duration (rVE, −0.4%; 95% CI, −13.8% to 11.5%; interaction *P* = .03) (**Figure 2**). Similar suggested effect modification by diabetes duration was observed for hospitalization for heart failure (duration >5 years: rVE, 51.3%; 95% CI, 13.7%-73.4%; ≤5 years: rVE, −6.3%; 95% CI, −60.4% to 29.4%; interaction *P* = .02), hospitalization for stroke (duration >5 years: rVE, 42.0%; 95% CI, −7.1% to 69.4%; ≤5 years: rVE, −22.2%; 95% CI, −81.3% to 17.3%; interaction *P* = .03), and MACE (duration >5 years: rVE, 27.8%; 95% CI, 3.5%-46.3%; ≤5 years: rVE, −19.0%; 95% CI, −48.4% to 4.5%; interaction *P* = .005) (**Figure 3**). The presence of a diabetes-related complication at baseline seemed to modify the effect for heart

Figure 2. Relative Vaccine Effectiveness Across Subgroups of Participants With Diabetes

Variable	HD-IIV No./Total No. (%)	SD-IIV No./Total No. (%)	rVE, % (95% CI)	*P* for interaction
Cardiorespiratory hospitalization				
Overall	744/21 929 (3.4)	804/21 952 (3.7)	7.4 (-2.5 to 16.3)	
Diabetes duration, y				.03
≤ 5	505/15 412 (3.3)	504/15 437 (3.3)	-0.4 (-13.8 to 11.5)	
> 5	239/6517 (3.7)	300/6515 (4.6)	20.4 (5.3 to 33.1)	
HbA_{1c}				.53
≤ Median 6.5%	405/11 364 (3.6)	426/11 403 (3.7)	4.6 (-9.6 to 16.9)	
> Median 6.5%	339/10 550 (3.2)	378/10 540 (3.6)	10.4 (-4.0 to 22.9)	
Diabetes-related complication				.25
Yes	173/3799 (4.6)	205/3763 (5.5)	16.4 (-2.8 to 32.1)	
No	571/18 130 (3.2)	599/18 189 (3.3)	4.4 (-7.4 to 14.9)	
Cardiovascular hospitalization				
Overall	399/21 929 (1.8)	454/21 952 (2.1)	12.0 (-0.9 to 23.3)	
Diabetes duration, y				.06
≤ 5	269/15 412 (1.8)	278/15 437 (1.8)	3.1 (-15.0 to 18.3)	
> 5	130/6517 (2.0)	176/6515 (2.7)	26.2 (6.8 to 41.6)	
HbA_{1c}				.29
≤ Median 6.5%	216/11 364 (1.9)	230/11 403 (2.0)	5.8 (-14.0 to 22.1)	
> Median 6.5%	183/10 550 (1.7)	224/10 540 (2.1)	18.4 (0.3 to 33.2)	
Diabetes-related complication				.27
Yes	96/3799 (2.5)	123/3763 (3.3)	22.7 (-1.8 to 41.4)	
No	303/18 130 (1.7)	331/18 189 (1.8)	8.2 (-7.7 to 21.7)	
Respiratory hospitalization				
Overall	373/21 929 (1.7)	380/21 952 (1.7)	1.7 (-13.7 to 15.0)	
Diabetes duration, y				.40
≤ 5	253/15 412 (1.6)	247/15 437 (1.6)	-2.6 (-22.8 to 14.2)	
> 5	120/6517 (1.8)	133/6515 (2.0)	9.8 (-16.3 to 30.1)	
HbA_{1c}				.72
≤ Median 6.5%	200/11 364 (1.8)	209/11 403 (1.8)	4.0 (-17.1 to 21.3)	
> Median 6.5%	173/10 550 (1.6)	171/10 540 (1.6)	-1.1 (-25.6 to 18.7)	
Diabetes-related complication				.47
Yes	83/3799 (2.2)	92/3763 (2.4)	10.6 (-21.6 to 34.4)	
No	290/18 130 (1.6)	288/18 189 (1.6)	-1.0 (-19.3 to 14.5)	
Influenza hospitalization				
Overall	28/21 929 (0.1)	48/21 952 (0.2)	41.6 (5.0 to 64.7)	
Diabetes duration, y				.10
≤ 5	21/15 412 (0.1)	27/15 437 (0.2)	22.1 (-43.1 to 58.1)	
> 5	7/6517 (0.1)	21/6515 (0.3)	66.7 (18.6 to 88.0)	
HbA_{1c}				.57
≤ Median 6.5%	15/11 364 (0.1)	29/11 403 (0.3)	48.1 (0.0 to 74.1)	
> Median 6.5%	13/10 550 (0.1)	19/10 540 (0.2)	31.6 (-45.9 to 69.0)	
Diabetes-related complication				.46
Yes	5/3799 (0.1)	12/3763 (0.3)	58.7 (-25.9 to 88.6)	
No	23/18 130 (0.1)	36/18 189 (0.2)	35.9 (-11.2 to 63.7)	
Laboratory-confirmed influenza hospitalization				
Overall	46/21 929 (0.2)	65/21 952 (0.3)	29.2 (-4.9 to 52.5)	
Diabetes duration, y				.13
≤ 5	34/15 412 (0.2)	39/15 437 (0.3)	12.7 (-42.0 to 46.5)	
> 5	12/6517 (0.2)	26/6515 (0.4)	53.9 (5.3 to 78.8)	
HbA_{1c}				.85
≤ Median 6.5%	26/11 364 (0.2)	38/11 403 (0.3)	31.3 (-16.1 to 60.0)	
> Median 6.5%	20/10 550 (0.2)	27/10 540 (0.3)	26.0 (-37.0 to 60.6)	
Diabetes-related complication				.71
Yes	8/3799 (0.2)	13/3763 (0.4)	39.0 (-58.7 to 78.1)	
No	38/18 130 (0.2)	52/18 189 (0.3)	26.7 (-13.6 to 53.1)	

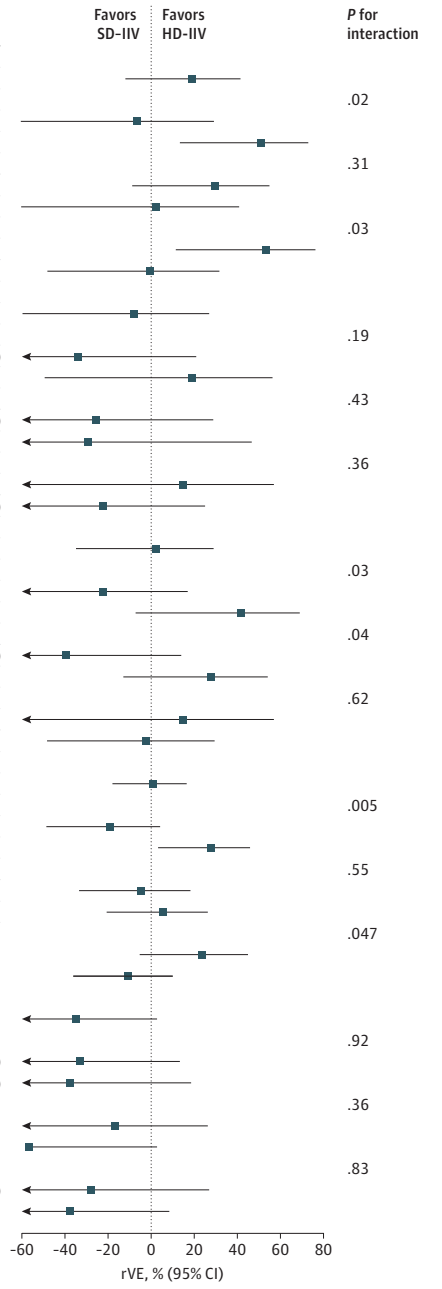


Diabetes subgroup analyses by diabetes duration, glycated hemoglobin (HbA_{1c}; to convert HbA_{1c} to the proportion of total hemoglobin, multiply by 0.01 [to convert to mmol/mol, multiply by 10.93 and subtract 23.5]), and the presence of a diabetes-related complication at baseline against hospitalizations for any cardiorespiratory disease, any cardiovascular disease, any respiratory disease, influenza, and laboratory-confirmed influenza. Relative vaccine effectiveness was calculated as 1 minus the relative risk. Interaction *P* values were estimated using the Cochran-Mantel-Haenszel test for homogeneity. HD-IIV indicates high-dose inactivated influenza vaccine; rVE, relative vaccine effectiveness; SD-IIV, standard-dose inactivated influenza vaccine.

failure hospitalization, in which HD-IIV vs SD-IIV was associated with reduced heart failure hospitalization in participants with a diabetes-related complication (rVE, 53.6%; 95% CI, 11.7%-76.6%) but not in those without (rVE, −0.3%; 95% CI, −48.0% to 32.0%; interaction *P* = .03). A similar suggested treatment heterogeneity was observed for the presence of a diabetes-related complication against MACE (individuals with a complication: rVE, 24.1%; 95% CI, −5.1% to 45.3%; individuals without a complication: rVE, −10.4%; 95% CI, −35.9% to 10.3%; interaction *P* = .047) and between strata of HbA_{1c} for hospitalization for stroke (rVE, 28.1%; 95% CI, −12.6% to 54.5% in individuals with HbA_{1c} >6.5%; rVE, −39.2%; 95% CI, −128.5% to 14.3% in individuals with HbA_{1c} ≤6.5%; interaction *P* = .04) (Figure 3). Treatment ef-

Figure 3. Relative Vaccine Effectiveness Against Specific Cardiovascular End Points Across Subgroups of Participants With Diabetes

Variable	HD-IIV No./Total No. (%)	SD-IIV No./Total No. (%)	rVE, % (95% CI)	P for interaction
Hospitalization for heart failure				
Overall	71/21 929 (0.3)	88/21 952 (0.4)	19.2 (-11.7 to 41.8)	
Diabetes duration, y				.02
≤ 5	52/15 412 (0.3)	49/15 437 (0.3)	-6.3 (-60.4 to 29.4)	
> 5	19/6517 (0.3)	39/6515 (0.6)	51.3 (13.7 to 73.4)	
HbA_{1c}				.31
≤ Median 6.5%	37/11 364 (0.3)	53/11 403 (0.5)	29.9 (-8.6 to 55.3)	
> Median 6.5%	34/10 550 (0.3)	35/10 540 (0.3)	2.9 (-60.2 to 41.3)	
Diabetes-related complication				.03
Yes	15/3799 (0.4)	32/3763 (0.9)	53.6 (11.7 to 76.6)	
No	56/18 130 (0.3)	56/18 189 (0.3)	-0.3 (-48.0 to 32.0)	
Hospitalization for myocardial infarction				
Overall	57/21 929 (0.3)	53/21 952 (0.2)	-7.7 (-59.5 to 27.2)	
Diabetes duration, y				.19
≤ 5	36/15 412 (0.2)	27/15 437 (0.2)	-33.5 (-128.7 to 21.2)	
> 5	21/6517 (0.3)	26/6515 (0.4)	19.3 (-49.2 to 56.8)	
HbA_{1c}				.43
≤ Median 6.5%	30/11 364 (0.3)	24/11 403 (0.2)	-25.4 (-124.2 to 29.1)	
> Median 6.5%	27/10 550 (0.3)	29/10 540 (0.3)	7.0 (-62.8 to 47.0)	
Diabetes-related complication				.36
Yes	18/3799 (0.5)	21/3763 (0.6)	15.1 (-67.4 to 57.4)	
No	39/18 130 (0.2)	32/18 189 (0.2)	-22.3 (-101.6 to 25.4)	
Hospitalization for stroke				
Overall	79/21 929 (0.4)	81/21 952 (0.4)	2.4 (-34.8 to 29.3)	
Diabetes duration, y				.03
≤ 5	61/15 412 (0.4)	50/15 437 (0.3)	-22.2 (-81.3 to 17.3)	
> 5	18/6517 (0.3)	31/6515 (0.5)	42.0 (-7.1 to 69.4)	
HbA_{1c}				.04
≤ Median 6.5%	43/11 364 (0.4)	31/11 403 (0.3)	-39.2 (-128.5 to 14.3)	
> Median 6.5%	36/10 550 (0.3)	50/10 540 (0.5)	28.1 (-12.6 to 54.5)	
Diabetes-related complication				.62
Yes	18/3799 (0.5)	21/3763 (0.6)	15.1 (-67.4 to 57.4)	
No	61/18 130 (0.3)	60/18 189 (0.3)	-2.0 (-48.2 to 29.8)	
MACE				
Overall	266/21 929 (1.2)	269/21 952 (1.2)	1.0 (-17.7 to 16.8)	
Diabetes duration, y				.005
≤ 5	183/15 412 (1.2)	154/15 437 (1.0)	-19.0 (-48.4 to 4.5)	
> 5	83/6517 (1.3)	115/6515 (1.8)	27.8 (3.5 to 46.3)	
HbA_{1c}				.55
≤ Median 6.5%	137/11 364 (1.2)	132/11 403 (1.2)	-4.1 (-33.3 to 18.6)	
> Median 6.5%	129/10 550 (1.2)	137/10 540 (1.3)	5.9 (-20.5 to 26.6)	
Diabetes-related complication				.047
Yes	69/3799 (1.8)	90/3763 (2.4)	24.1 (-5.1 to 45.3)	
No	197/18 130 (1.1)	179/18 189 (1.0)	-10.4 (-35.9 to 10.3)	
Cardiovascular death				
Overall	90/21 929 (0.4)	67/21 952 (0.3)	-34.5 (-87.3 to 3.1)	
Diabetes duration, y				.92
≤ 5	53/15 412 (0.3)	40/15 437 (0.3)	-32.7 (-105.4 to 13.6)	
> 5	37/6517 (0.6)	27/6515 (0.4)	-37.0 (-134.0 to 18.8)	
HbA_{1c}				.36
≤ Median 6.5%	43/11 364 (0.4)	37/11 403 (0.3)	-16.6 (-86.1 to 26.6)	
> Median 6.5%	47/10 550 (0.5)	30/10 540 (0.3)	-56.5 (-156.3 to 3.1)	
Diabetes-related complication				.83
Yes	31/3799 (0.8)	24/3763 (0.6)	-27.9 (-127.8 to 27.3)	
No	59/18 130 (0.3)	43/18 189 (0.2)	-37.7 (-108.9 to 8.6)	



Diabetes subgroup analyses by diabetes duration, glycated hemoglobin (HbA_{1c}; to convert HbA_{1c} to the proportion of total hemoglobin, multiply by 0.01 [to convert to mmol/mol, multiply by 10.93 and subtract 23.5]), and the presence of a diabetes-related complication at baseline against hospitalization for heart failure, myocardial infarction, and stroke, as well as major adverse cardiovascular events (MACE) and cardiovascular death. Relative vaccine effectiveness was calculated as 1 minus the relative risk. Interaction *P* values were estimated using the Cochran-Mantel-Haenszel test for homogeneity. HD-IIV indicates high-dose inactivated influenza vaccine; rVE, relative vaccine effectiveness; SD-IIV, standard-dose inactivated influenza vaccine.

fects were consistent across these diabetes subgroups for the remaining examined end points (interaction $P \geq .05$) (Figure 2 and Figure 3). In addition, treatment effects were consistent by diabetes type for all end points (interaction $P \geq .05$).

The consistency of the rVE of HD-IIV vs SD-IIV was also evaluated across the continuous spectrum of diabetes duration and HbA_{1c}. Treatment heterogeneities were suggested for continuous diabetes duration against MACE (interaction $P = .046$), and for continuous HbA_{1c} against hospitalization for any cardiovascular disease (interaction $P = .04$), hospitalization for myocardial infarction (interaction $P = .007$), hospitalization for stroke (interaction $P = .04$), and MACE (interaction $P = .02$). In these cases, longer duration and higher HbA_{1c} levels were associated with higher rVE (eFigure 2 in

Supplement 2). No further suggested effect modification by continuous diabetes duration or HbA_{1c} was observed (interaction $P \geq .05$).

Exploratory Diabetes-Related End Points

There was no difference in incident diabetes between HD-IIV and SD-IIV (66 of 144 287 participants [0.05%] in the HD-IIV group vs 69 of 144 261 participants [0.05%] in the SD-IIV group; rVE, 4.4%; 95% CI, −36.0% to 32.8%; $P = .80$). Incident diabetes-related complications in the overall population were numerically lower in the HD-IIV group but did not reach statistical significance (147 of 162 417 participants [0.1%] in the HD-IIV group vs 181 of 162 450 participants [0.1%] in the SD-IIV group; rVE, 18.8%; 95% CI, −1.5% to 35.1%; $P = .07$). No evidence of effect modification by baseline diabetes was observed (diabetes: HD-IIV, 0.7% vs SD-IIV, 0.9%; rVE, 17.7%; 95% CI, −4.1% to 35.0%, vs no diabetes: HD-IIV, 0.01% vs SD-IIV, 0.01%; rVE, 27.8%; 95% CI, −55.9% to 67.5%; interaction $P = .73$).

Discussion

In this prespecified secondary subgroup analysis of the large-scale, pragmatic, randomized clinical DANFLU-2 trial, HD-IIV compared with SD-IIV was associated with reductions in hospitalization for any cardiorespiratory disease, any cardiovascular disease, heart failure, influenza, and laboratory-confirmed influenza, with consistent treatment effects in individuals with and without diabetes. Across these outcomes that favored HD-IIV, NNVs were generally lower among individuals with diabetes compared with those without diabetes, reflecting their higher baseline risk and suggesting greater absolute benefit for these end points in this population. To our knowledge, DANFLU-2 is the largest individually randomized influenza vaccine trial conducted to date, with 332 438 randomized participants, including 43 881 with diabetes, thus constituting the largest randomized sample of individuals with diabetes in an influenza vaccine trial.

Annual influenza vaccination has been widely recommended by major public health authorities and medical associations, particularly for individuals with chronic conditions, such as diabetes, as they are more susceptible to complications, including cardiovascular complications.[3,16] In this analysis, we observed higher end point rates in participants with diabetes compared with those without, underlining the importance of optimizing preventive strategies for this high-risk population. Although a higher proportion of participants with diabetes were tested for influenza than those without, test positivity among those tested was similar between groups, likely reflecting more frequent health care contacts and closer clinical monitoring of this population. Among individuals with diabetes, the consistent benefits of HD-IIV vs SD-IIV against hospitalizations for cardiorespiratory disease, cardiovascular disease, and heart failure support the case for using influenza vaccination not only to prevent influenza infection but also to reduce related cardiovascular events. Further, our findings suggest that HD-IIV may offer superior protection against these severe outcomes in this vulnerable population through a single annual intervention that imposes no additional burden on the individual compared with SD-IIV.

Analyses of participants with diabetes suggested treatment heterogeneity across diabetes characteristics, such that HD-IIV vs SD-IIV was associated with reduced risk of heart failure hospitalization only among participants with a diabetes-related complication. Similarly, there was a signal of greater benefit of HD-IIV vs SD-IIV against MACE, cardiorespiratory, heart failure, and stroke hospitalizations in participants with diabetes duration longer than 5 years, with attenuated effects in those with shorter duration. When diabetes duration was treated as a continuous variable, suggested effect modification was observed for MACE, whereas no evidence of effect modification was observed for cardiorespiratory, heart failure, or stroke hospitalizations. Treatment heterogeneity was also suggested for continuous and dichotomized HbA_{1c} in relation to hospitalization for stroke, with seemingly greater benefit at higher compared with lower HbA_{1c} levels, despite no overall benefit for this end point. A similar pattern of suggested greater benefit at higher continuous HbA_{1c} levels was observed for MACE, cardiovascular, and myocardial infarction hospitalizations. Participants with a diabetes-related complication also appeared to derive greater protection against MACE compared with those without. Although exploratory and requiring confirmation in future research, these findings could imply that for certain end points, the protective benefits of HD-IIV compared with SD-IIV may be more prominent in individuals with more advanced diabetes. This could reflect a potentially more pronounced suboptimal immune response to SD-IIV among individuals with greater disease burden, in addition to the increased susceptibility to influenza-related complications associated with longer disease duration and comorbidity burden.[6,17,18] Although body mass index data were not available, obesity is likely common in this population and may be more prevalent among participants with greater disease burden, potentially contributing to suboptimal responses to SD-IIV and the greater relative benefit of HD-IIV.[19]

While several previous studies have suggested the benefits of seasonal influenza vaccination compared with no vaccination in individuals with diabetes,[20,21] the DANFLU-1 exploratory post hoc analysis (1162 of 12 477 [9.3%] with diabetes) is the only previous study to report data on the rVE of HD-IIV vs SD-IIV specifically in this population.[22] Conducted as a pilot trial to assess the feasibility of large-scale vaccine trials in real-world settings, DANFLU-1 found that HD-IIV vs SD-IIV was associated with a lower risk of a composite of all-cause death or hospitalization for pneumonia or influenza, as well as reduced rates of all-cause hospitalizations, regardless of diabetes status.[22] Additionally, no effect of HD-IIV vs SD-IIV was observed on incident diabetes or change in HbA_{1c} levels. Similar to the present study, participants with diabetes had a greater burden of comorbidities and higher event rates than participants without diabetes. The DANFLU-1 post hoc analysis and this prespecified analysis of DANFLU-2 found no evidence of effect modification by diabetes status for the clinical outcomes investigated, although the specific end points assessed differed between the studies. However, as neither DANFLU-1 nor this subgroup analysis was adequately pow-

ered to draw definitive conclusions for this population, further investigation is warranted.

Limitations

This study had several limitations. First, DANFLU-2 was not specifically powered for subgroup analyses; therefore, the study's findings were exploratory and should be considered hypothesis generating. Furthermore, our findings must be interpreted in the context of the trial's neutral primary end point of hospitalization for influenza or pneumonia. While this diabetes subgroup analysis was prespecified in the protocol (Supplement 1), the exploratory diabetes-related end points and analyses across diabetes subgroups by disease duration, HbA_{1c} levels, diabetes-related complications, and diabetes type were not prespecified and were based on relatively few events for some end points. Diabetes duration was defined based on the first recorded indication of diabetes within 10 years of randomization using *ICD-10* codes or the first elevated HbA_{1c} measurement within 5 years of randomization. Thus, some participants may have received their diagnoses earlier than these time windows, which could lead to an underestimation of diabetes duration. Additionally, reliance on *ICD-10* codes limited the assessment of diabetes type and the presence of diabetes-related complications to only 39% and 45% of the diabetes population, respectively.

Treatment allocation was open label. However, risk of bias was considered low, as trial investigators were not involved in subsequent treatment of participants, and end points were severe clinical events that were objectively assessed using passively collected data from the Danish nationwide health registries using prespecified definitions.

Data collected from the registries may include imprecise data but should be balanced between the randomization groups. HbA_{1c} levels were not systematically available, and no systematic influenza or immunogenicity testing was performed due to the pragmatic nature of this trial. However, we had access to all tests conducted as part of routine clinical practice. The trial did not have access to follow-up laboratory data, such as follow-up HbA_{1c} levels, or to the Danish prescription registries, which limited the ability to include data on filled prescriptions in baseline or end point definitions. Thus, treatment patterns, including use of glucose-independent cardiorenal protective and weight-lowering agents, such as glucagon-like peptide 1 receptor agonists and sodium-glucose cotransporter-2 inhibitors, and the balance between groups could not be determined.

Conclusions

In this prespecified secondary subgroup analysis of the DANFLU-2 randomized clinical trial, our findings suggest that the effects of HD-IIV vs SD-IIV against severe respiratory and cardiovascular outcomes remain consistent regardless of diabetes status. HD-IIV vs SD-IIV was associated with reduced cardiorespiratory hospitalization, cardiovascular hospitalization, heart failure hospitalization, influenza hospitalization, and laboratory-confirmed influenza hospitalization, irrespective of diabetes. These findings, while exploratory, underscore the importance of influenza vaccination and suggest potential benefit of HD-IIV compared with SD-IIV in individuals with diabetes.

ARTICLE INFORMATION

Accepted for Publication: November 12, 2025.

Published Online: January 12, 2026. doi:10.1001/jamainternmed.2025.7286

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Author Contributions: Drs Nielsen and Biering-Sørensen had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
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Obtained funding: Davidovski, Biering-Sørensen.
Administrative, technical, or material support: C. Larsen, Dalager-Pedersen, Bernholm, Davidovski, Dons, Duus, Fussing, Reimer Jensen, Gislason, Køber, Martel, Biering-Sørensen.
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Other - safety reporting: Espersen.

Conflict of Interest Disclosures: Dr Loiacono reported being a full-time employee of Sanofi. Dr Harris reported personal fees from, employment with, and shares held in Sanofi during the conduct of the study. Dr Dufournet being an employee of Sanofi during the conduct of the study and stock options in Sanofi outside the submitted work. Dr Claggett reported personal fees from Alnylam, Cardior, Cardurion, Cytokinetics, CVRx, Intellia, Rocket, Eli Lilly, and Alexion outside the submitted work. Dr Bartholdy reported grants from the Danish Cardiovascular Academy outside the submitted work. Dr Langhoff reported personal fees from Novo Nordisk outside the submitted work. Dr Lassen reported personal fees from Pfizer outside the submitted work. Dr Skaarup reported personal fees from Sanofi and travel support from AstraZeneca outside the submitted work. Dr Pareek reported personal fees from AstraZeneca, Bayer, Boehringer Ingelheim, Janssen-Cilag, and Novo Nordisk and grants from the Danish Cardiovascular Academy and Danish Heart Foundation outside the submitted work. Dr Müller-Wieland reported personal fees from GlaxoSmithKlines and Sanofi outside the submitted work. Dr Solomon reported grants from Alexion, Alnylam, Applied Therapeutics, AstraZeneca, Bellerophon, Bayer, BMS, Boston Scientific, Cardior, Cytokinetics, Edgewise, BridgeBio, Gossamer, GSK, Ionis, Lilly, National Institutes of Health/National Heart, Lung, and Blood Institute, Novartis, NovoNordisk, Respicardia, Sanofi Pasteur, Tenaya, Theracos, and US2.AI and personal fees from Abbott, Action, Akros, Alexion, Alnylam, Amgen, Arena, Askbio, AstraZeneca, Bayer, BMS, Bridgebio, Cardior, Cardurion, Corvia, Cytokinetics, GSK, Intellia, Lilly, Novartis, Roche, Theracos, Quantum Genomics, Tenaya, Sanofi-Pasteur, Dinaqor, Tremeau, CellProThera, Moderna, American Regent, Sarepta, Lexicon, Anacardio, Akros, Valo, Synhale, and Recordati outside the submitted work. Dr Landray reported grants from Novartis, Boehringer Ingelheim, Sanofi, Moderna, GSK, and Regeneron outside the submitted work. Dr Køber reported personal fees from Novo, Novartis, AstraZeneca, and Boehringer outside the submitted work. Dr Jensen reported research support from Sanofi outside the submitted work. Dr Biering-Sørensen reported grants from Sanofi during the conduct of the study as well as grants from Sanofi, GSK, Novo Nordisk, AstraZeneca Research, Boston Scientific, GE Healthcare, Novartis, Moderna, and Bayer and personal fees from IQVIA, Sanofi, GSK, Parexel, Amgen, CSL Seqirus, GE Healthcare, Novartis, AstraZeneca, and Bayer outside the submitted work. No other disclosures were reported.

Funding/Support: This externally sponsored collaboration was funded by Sanofi. Dr Nielsen was supported by a research grant from the Danish Cardiovascular Academy, which is funded by the Novo Nordisk Foundation (grant NNF20SA0067242) and the Danish Heart Foundation.

Role of the Funder/Sponsor: Sanofi contributed to the design of the study; review and approval of the manuscript; and the decision to submit the manuscript for publication, but had no responsibilities in the conduct of the study; collection, management, analysis, or interpretation of the data; or preparation of the manuscript. The trial was sponsored by the academic research group at the Center for Translational Cardiology and Pragmatic Randomized Trials at the Department of Cardiology, Copenhagen University Hospital–Herlev and Gentofte, Copenhagen, Denmark, who assumes full responsibility for trial conduct.

Data Sharing Statement: See Supplement 3.

Additional Contributions: We thank all personnel at European LifeCare Group for collaborating and assisting with study procedures. We also thank the following personnel at Sanofi for their contributions: Sandrine Samson, PhD; Ayman Chit, PhD; Robertus van Aalst, PhD; Martin Ryser, MD; Marion Fournier, MSc; and Tamala Moore, MD (scientific advice), Camille Salamand, MSc (biostatistics advice), and Pierre Bourron, MSc, and Marie-Caroline Guichard, MSc (administrative and dose provision logistical support). They were not compensated for this work outside of their usual salaries.

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