High-Dose vs. Standard-Dose Influenza Vaccine in Heart Failure: A Prespecified Analysis of the DANFLU-2 Trial

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Short title: High-dose influenza vaccine in heart failure

Word Count: 3,273 (exclusive of title page, abstract, references, figure legends, and tables).

Trial Registration: NCT05517174, registered August 24, 2022

(https://clinicaltrials.gov/study/NCT05517174)

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Abstract

Background:

Influenza contributes substantially to disease burden in individuals with heart failure (HF) and is an established trigger of cardiovascular (CV) and HF events. Standard-dose inactivated influenza vaccine (SD-IIV) is recommended for HF, though immune responses may be attenuated. High-dose IIV (HD-IIV) was developed to enhance immunogenicity, but its effectiveness compared with SD-IIV against hospitalization for influenza and CV disease by HF status remains uncertain.

Methods:

This was a prespecified analysis of a pragmatic, prospective, individually randomized, open-label trial with registry-based endpoint-evaluation conducted in Denmark across the 2022/2023 to 2024/2025 influenza seasons. Citizens ≥65 years were randomized 1:1 to HD-IIV or SD-IIV. Outcomes included hospitalization for influenza-related illness, laboratory-confirmed influenza (LCI), any CV disease, cardio-respiratory disease, and HF, assessed by HF status. Effect of HD-IIV vs. SD-IIV in reducing risk of outcomes assessed was expressed as risk ratios (RR).

Results:

The trial randomized 332,438 participants (48.6% female, mean age 73.7±5.8 years), including 10,410 with HF at baseline (27.4% female, mean age 76.0±6.3 years). Overall, HD-IIV was associated with a statistically significant lower incidence of hospitalization for influenza-related illness, LCI, cardio-respiratory disease, CV disease, and HF compared with SD-IIV. In participants with HF, effect estimates were similar: RR for influenza-related hospitalization was 0.48 (95%CI, 0.20-1.06; $p_{interaction}$=0.64), for LCI hospitalization 0.55 (95%CI, 0.29-1.02; $p_{interaction}$=0.59), for cardio-respiratory hospitalization 0.89 (95%CI, 0.77-1.02; $p_{interaction}$=0.34), for CV hospitalization

0.86 (95%CI, 0.72-1.02; $p_{interaction}$=0.34), and for HF hospitalization 0.82 (95%CI, 0.61-1.11; $p_{interaction}$=0.83). Findings were consistent across HF subgroups by disease duration, recency of hospitalization, most recent N-terminal pro-B-type natriuretic peptide, and presence of device therapy.

Conclusions:

In this prespecified exploratory analysis of the largest individually randomized influenza vaccine trial ever conducted, HD-IIV was associated with lower rates of influenza and CV hospitalizations compared with SD-IIV, with effect estimates similar across HF status at baseline and HF subgroups.

Trial Registration:

NCT05517174, registered August 24, 2022, https://clinicaltrials.gov/study/NCT05517174.

Keywords:

Randomized controlled trial; influenza; vaccination; high dose; pragmatic; registry; heart failure.

Clinical Perspectives

What is new?

- This prespecified exploratory analysis of the DANFLU-2 trial, that individually randomized 332,438 older adults, including 10,410 with heart failure (HF), to receive high-dose vs. standard-dose influenza vaccination, assessed the potential benefit of high-dose against severe clinical outcomes by HF status and across major HF subgroups
- High-dose influenza vaccination was associated with lower rates of influenza-related, laboratory-confirmed influenza, cardio-respiratory, cardiovascular, and HF hospitalizations.
- No significant effect modification of vaccine effectiveness by HF status or across HF subgroups was observed.

What are the clinical implications?

- High-dose influenza vaccination may offer incrementally improved protection compared with standard-dose vaccination in both those with and without HF; however, findings should be interpreted as exploratory and in context of previous randomized trials with patients with HF.
- Pragmatic, registry-based randomized trials can provide unique large-scale evidence on preventive strategies in cardiovascular populations.

Non-standard Abbreviations and Acronyms

HF: Heart failure

CV: Cardiovascular

HD-IIV: High-dose inactivated influenza vaccine

SD-IIV: Standard-dose inactivated influenza vaccine

LCI: Laboratory-confirmed influenza

ICD-10: International Classification of Diseases, 10th Revision

NT-proBNP: N-terminal pro-B-type natriuretic peptide

Introduction

Influenza infection is a common cause of hospital admission among individuals with heart failure (HF), who are at increased risk of severe complications, including death.[1,2] Approximately 2.6% of all deaths and 5% of all hospitalizations in patients with HF have been attributed to influenza.[3] Influenza infection has also been linked to an elevated risk of cardiovascular (CV) events, including HF hospitalization.[4,5] Annual influenza vaccination has been demonstrated to reduce the risk of major adverse CV events.[6,7] Accordingly, the European Society of Cardiology (ESC) guidelines for HF recommend that influenza vaccination should be considered (class IIa) to prevent HF hospitalization.[8] The American Heart Association and American College of Cardiology likewise state that vaccination against respiratory illnesses is reasonable to reduce mortality.[9] However, individuals with HF may exhibit attenuated immune responses to influenza vaccination, even after accounting for age-related factors.[10] High-dose inactivated influenza vaccine (HD-IIV), which contains four times the antigen content of standard-dose inactivated influenza vaccine (SD-IIV), was developed to enhance immunogenicity in individuals with reduced immune responses.[11]

A previous randomized trial comparing HD-IIV with SD-IIV in individuals with HF or prior myocardial infarction found no difference in the primary endpoint of cardiopulmonary hospitalizations or all-cause mortality.[12] However, the effectiveness of HD-IIV vs. SD-IIV against HF hospitalizations in the general elderly population and for laboratory-confirmed influenza (LCI) hospitalization and specific CV outcomes in individuals with HF remains uncertain. The DANFLU-2 trial (A Pragmatic Randomized Trial to Evaluate the Effectiveness of High-Dose Influenza Vaccine vs. Standard-Dose Influenza Vaccine in Older Adults) randomized 332,438 individuals to receive HD-IIV or SD-IIV.[13] HD-IIV did not significantly reduce the composite primary endpoint of hospitalization due to pneumonia or influenza. Within this composite endpoint, limited effect

was seen for pneumonia hospitalizations, but clear reductions were observed for influenza hospitalizations. HD-IIV was associated with a lower risk of the powered 1st secondary endpoint of cardio-respiratory hospitalization. The DANFLU-2 trial enabled a dedicated evaluation of HD-IIV in individuals with and without HF. In this prespecified analysis, we evaluated the effectiveness of HD-IIV vs. SD-IIV against prespecified respiratory hospitalizations, including severe influenza, and CV outcomes, by HF status and across major HF subgroups.

Methods

Data Availability Statement

Individual-level participant data stemming from the nationwide Danish health registries cannot be shared according to Danish law. Summarized data can be made available upon reasonable request.

Trial Design and Oversight

This was a prespecified exploratory analysis of the DANFLU-2 trial, a pragmatic, registry-based, open-label, active-controlled, individually randomized trial of HD-IIV vs. SD-IIV in older adults (≥65 years) conducted in Denmark across three consecutive influenza seasons from 2022/2023 through 2024/2025. The trial design and primary results have been published.[13,14]

The trial was approved as a low-intervention clinical trial under the EU Clinical Trials Regulation 536/2014 (EU CT number: 2022-500657-17-00) by the Danish Medical Research Ethics Committees and the Danish Medicines Agency. Data protection approval was granted by the Capital Region of Denmark (approval number: P-2021-841). This report adhered to the CONSORT 2025 reporting guidelines, and the completed checklist is provided in the Supplements.

DANFLU-2 enrolled individuals aged 65 years and older, irrespective of comorbidity. There were no formal exclusion criteria. Participants were recruited primarily through digital invitation letters. Each season, up to 1,000,000 randomly selected Danish citizens ≥65 years were invited through the governmental electronic letter system.[15] The digital invitations directed recipients to a dedicated website, where they could schedule a trial visit and optionally provide asynchronous consent after reviewing study information in written and video formats. Informed consent could also be provided in person at the trial visit.

Group Allocation and Vaccines

Participants were individually randomized 1:1 to receive either HD-IIV or SD-IIV at the trial visit. Randomization was conducted using a central unstratified randomization algorithm. Participants who re-enrolled in subsequent seasons were re-randomized and considered independent observations in the analyses.[16]

Participants and study staff were not blinded to treatment allocation. However, investigators were not involved in participant care, and outcomes were severe hospitalization events assessed through routinely collected registry data; therefore, risk of bias was considered minimal.

Each season, participants received a single dose of either quadrivalent HD-IIV (Fluzone® High-Dose Quadrivalent/Efluelda®/Efluelda Tetra®; Sanofi) or quadrivalent SD-IIV (VaxigripTetra; Sanofi). HD-IIV contains 60 mg of HA antigen for each strain, while SD-IIV contains 15 mg. All study vaccines contained the four strains recommended by the World Health Organization for the corresponding season.

Data Collection

Baseline characteristics, outcome and safety surveillance were primarily collected from the nationwide Danish administrative health registries using prespecified definitions.[14] These registries contain routinely collected data from all hospital encounters (both in- and out-patient contacts) within the Danish public health system.[17]

HF status was defined according to prespecified criteria of at least one hospital encounter (inpatient or outpatient) with an International Classification of Diseases, 10th Revision (ICD-10) code of I50 recorded in either the primary or secondary position within the past 10 years prior to baseline. Utilization of ICD-10 code to identify individuals with HF has recently been validated in the Danish National Patient Registry.[18]

To characterize HF status the following variables were defined: (1) Time since HF diagnosis, measured as the interval from the date of first recorded HF diagnosis to the date of randomization. (2) Time since most recent HF hospitalization, measured as the interval from the most recent overnight inpatient hospitalization with a primary discharge diagnosis of HF (ICD-10 code I50) to the date of randomization. In an alternative definition, those without an overnight hospitalization for HF were included by using the date of HF diagnosis as a proxy. (3) The most recent measurement of N-terminal pro-B-type natriuretic peptide (NT-proBNP) was obtained using Nomenclature, Properties, and Units codes NPU2571 and NPU26811. (4) Presence of device therapy, either implantable cardioverter-defibrillator or cardiac resynchronization therapy, was identified using procedure codes (implantable cardioverter-defibrillator: BFCB0, BFCB00-04, BFCB6, BFCB60-63; cardiac resynchronization therapy: BFCA04-BFCA06, BFCA21, BFCA63, BFCB03, BFCB21), and was recorded only if no extraction codes were present at a later point.

HF subgroups were defined as dichotomous subsets of the above variables: by medians for (time since diagnosis and NT-proBNP), within 1 year for (time since HF hospitalization), and by presence or absence for (device therapy). When available, continuous versions of the variables were also analyzed.

The primary endpoint in DANFLU-2 was the composite of hospitalization for influenza or pneumonia, which has been reported separately.[13] In the present analysis, we conducted a prespecified evaluation of respiratory hospitalizations, including influenza hospitalization, and CV outcomes among participants with and without HF, and across major HF subgroups. The prespecified endpoints were hospitalization for: a) influenza-related disease, b) LCI, c) cardio-respiratory disease, d) any CV disease, and e) HF. LCI hospitalization was defined as an overnight hospitalization with a positive influenza test within 14 days before to 3 days after admission, irrespective of ICD-10 code, in accordance with standard Center for Disease Control and Prevention definition.[19] For each influenza season, follow-up was defined as the period from 14 days after vaccination until May 31 of the subsequent year. Hospitalizations with a concurrent COVID-19 ICD-10 discharge diagnosis code (B34.2 or B97.2) were excluded from all endpoint definitions.

Statistical Analysis

Risk ratios (RRs) for each endpoint in those with vs. without HF were estimated using log-binomial regression and presented with 95% confidence intervals (95%CI). Effectiveness of HD-IIV vs. SD-IIV was expressed as RRs and presented with 95%CI calculated using the Clopper-Pearson method.[20] Adjusted RRs and 95%CIs for sensitivity analyses were estimated using multivariable log-binomial regression. For subgroup analyses, RRs were estimated within each stratum, and interaction P values were calculated using the Cochran-Mantel-Haenszel test for homogeneity. Numbers needed to vaccinate to prevent a first event were calculated as the reciprocal of the absolute risk difference between the SD-IIV and HD-IIV groups, stratified by HF status. Effect modification by continuous variables of HF characteristics (log2-transformed if right-skewed) were assessed in restricted cubic spline curves using log-binomial regression models with group-by-

variable interaction term. Number of knots was chosen according to lowest Akaike Information Criterion. As prespecified, no replacement or imputation was performed for missing data.

All comparisons between HD-IIV and SD-IIV were conducted according to the intention-to-treat principle. The trial was not powered to detect treatment heterogeneity across subgroups, and no adjustments were made for multiple comparisons.

P values <0.05 were considered statistically significant. Analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC), Stata MP version 19.5 (StataCorp, College Station, TX), and R version 4.3.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Participant Characteristics

A total of 332,438 participants were randomized in DANFLU-2 across the 2022/2023, 2023/2024 and 2024/2025 influenza seasons, including 10,410 (3.1%) with HF at baseline. Among those with HF, 5,201 were allocated to receive HD-IIV and 5,209 to SD-IIV. A study flow diagram is available in the Supplements (**Figure S1**). Mean age of participants with HF was 76.0 years ± 6.3 and 2,838 (27.4%) were female. Median time from HF diagnosis to randomization was 4.5 years (interquartile range [IQR], 2.1-7.3). For those with a previous HF hospitalization, the median time since most recent HF hospitalization was 5.5 years (IQR, 2.7-7.4) and 420 (4.0%) had been hospitalized with HF within 1 year prior to randomization. Baseline characteristics stratified by HF status are presented in **Table 1**. Participants with HF were older, less often female, and had a higher burden of other comorbidities than those without. Characteristics according to randomization group among participants with HF were well balanced and available in **Supplementary Table S1**. A comparison of participants with HF in DANFLU-2 to those with HF ≥65 years in the general population identified by the same definition in Danish registries is shown in **Supplementary Table S2**.

Among those without HF, 125,545 (57.2%) participated once, 85,392 (38.9%) twice, and 8,652 (3.9%) in all three seasons, while among those with HF, 4,630 (63.6%) participated once, 2,433 (33.4%) twice, and 216 (3.0%) in all three seasons.

Clinical Outcomes

Risks of assessed outcomes in participants with and without HF are shown in **Figure 1**. Baseline diagnosis of HF was associated with significantly higher risk of severe influenza and CV outcomes. The most pronounced relative differences were observed for HF hospitalizations, while relative

risks for influenza, LCI, cardio-respiratory and CV hospitalizations were comparable, although absolute risks were lower for influenza events.

Effectiveness of HD-IIV vs. SD-IIV According to Heart Failure Status

HD-IIV vs. SD-IIV was associated with risk reductions in the overall study population for hospitalization against influenza-related illness and LCI, with no sign of effect modification by HF status for either outcome. Effect estimates for all outcomes in the overall population and stratified by HF status, together with p values for interaction and numbers needed to vaccinate, are listed in **Table 2**. For influenza-related hospitalization, RR was 0.48 (95%CI, 0.20 to 1.06; $p_{interaction}$=0.64) in those with HF. For LCI hospitalization, RR was 0.55 (95%CI, 0.29 to 1.02; $p_{interaction}$=0.59) in participants with HF.

In the overall study population, incidences of hospitalization for cardio-respiratory disease, CV disease, and HF were lower in the HD-IIV group than the SD-IIV group. No statistically significant treatment heterogeneity by HF status was observed for these three outcomes, as reported elsewhere.[21] Among participants with HF, RR for cardio-respiratory hospitalization was 0.89 (95%CI, 0.77 to 1.02; $p_{interaction}$=0.34), for CV hospitalization 0.86 (95%CI, 0.72 to 1.02; $p_{interaction}$=0.34), and for HF hospitalization 0.82 (95%CI, 0.61 to 1.11; $p_{interaction}$=0.83).

Endpoints by study season in participants with and without HF are provided in **Supplementary Table S3**.

In a sensitivity analysis excluding participants with a recent HF diagnosis (within 1 year), effect estimates were overall similar to those in the total HF population (**Supplementary Table S4**).

Additionally, for HF hospitalization among participants with HF, adjustment for age, sex, and presence of ASCVD (history of ischemic heart disease, stroke, or peripheral artery disease) yielded a RR of 0.83 (95% CI, 0.62 to 1.10), consistent with the unadjusted estimate.

Effectiveness of HD-IIV vs. SD-IIV Across Heart Failure Subgroups

The RRs of HD-IIV vs. SD-IIV against hospitalization for influenza-related, LCI, cardio-respiratory disease, CV disease, and HF were evaluated across subgroups within the population with HF. Treatment effects were consistent among participants with a time since HF diagnosis duration above vs. below the median of 4.5 years, with vs. without a HF hospitalization within 1 year of randomization; with or without device therapy, and with most recent NT-proBNP levels above vs. below the median of 685 pg/mL (**Figure 2-3**).

Relative risk reductions were also evaluated across the continuous spectrum of HF duration, time since most recent HF hospitalization, and NT-proBNP. No evidence of treatment heterogeneity was observed across HF-related characteristics (**Figure 4**).

Discussion

This prespecified exploratory analysis of the DANFLU-2 trial included the largest sample to date of individuals with HF randomized to receive HD-IIV or SD-IIV. HD-IIV was associated with substantive reductions in influenza-related and LCI hospitalizations, as well as cardio-respiratory, CV and HF hospitalizations. Effect estimates were similar according to HF status and across key HF subgroups. Numbers needed to vaccinate were lower in participants with HF than in those without for all outcomes, indicating higher baseline risk and greater absolute benefit.

The European Society of Cardiology recently issued a clinical consensus statement highlighting the role of vaccination, particularly influenza vaccination, in CV prevention, consistent with its recommendation in the most recent HF guidelines that influenza vaccination should be considered.[22] The present findings provide further nuance to this recommendation, with effect estimates for reductions in HF and broader CV hospitalizations of moderate magnitude comparable to those observed in contemporary trials of daily-administered HF therapies.[23–27] These observations raise the possibility that HD-IIV may offer incremental protection relative to SD-IIV, even beyond prevention of influenza-related hospitalization, especially considering that the only prior randomized trial of SD-IIV vs. placebo in patients with HF, the IVVE (Influenza Vaccine to Prevent Adverse Vascular Events) trial (n=5,129), was inconclusive for its primary endpoint of major adverse CV events.

These findings must also be interpreted in the context of the INVESTED (INfluenza Vaccine to Effectively Stop Cardio Thoracic Events and Decompensated heart failure) trial, which compared HD-IIV and SD-IIV in 5,260 adults recently hospitalized for HF (n=3,289) or myocardial infarction (n=1,960).[12] HD-IIV did not reduce the risk of cardiopulmonary hospitalization or all-cause death in

that trial. The authors of INVESTED speculated that the high event burden in this very high-risk population may have limited the ability to detect a differential benefit of HD-IIV, and that such a benefit might be more apparent in lower-risk populations. This may also partially account for the differing results observed in the present analysis as our broad inclusion criteria, requiring only a single HF diagnosis code during a hospital contact (inpatient or outpatient) within the past 10 years, likely captured a wider spectrum of diagnosed HF. Participants in INVESTED were at higher risk, with 1,729 (32.9%) first cardio-pulmonary hospitalizations among 5,260 participants, compared with 824 (7.9%) cardio-respiratory events among 10,410 individuals with HF in DANFLU-2. This difference likely reflects the broader HF case definition used to identify participants with HF at baseline in DANFLU-2. Although participants with HF in DANFLU-2 were older than those in INVESTED (mean age: 76.0 vs. 65.5 years), only 7.8% had been hospitalized for HF within two years prior to randomization. In contrast, INVESTED required recent hospitalization for HF (within two years) or myocardial infarction (within one year), along with at least one additional CV risk factor as inclusion criteria. Further differences include how participants were identified: INVESTED enrolled individuals during hospitalization or identified them through electronic health records. In DANFLU-2, HF was defined based on any recorded discharge diagnosis (primary or secondary position) during inpatient or outpatient contact within the prior 10 years. Finally, influenza was recorded as the cause of only 18 hospitalizations in INVESTED, which may have further limited the ability of HD-IIV to reduce the overall hospitalization and mortality burden in that population, despite potential non-specific protective effects.[28]

This analysis provides the first randomized evidence that HD-IIV vs. SD-IIV was associated with a reduction in LCI hospitalization in individuals with HF. Findings for the LCI hospitalization endpoint in participants with HF were consistent with the substantial relative risk reductions

observed in those without HF. Similar findings were observed for ICD-10 coded influenza. Furthermore, the additional reduction in HF hospitalizations during the trial associated with HD-IIV compared to SD-IIV was consistent regardless of prior HF history, raising the hypothesis that HD-IIV may exert similar relative effects in reducing the risk of recurrent HF worsening and in preventing development of first HF events. Therefore, HD-IIV may offer additional protection over SD-IIV against HF outcomes not only in individuals with HF, but also in those without.

It must be stressed that, despite being based on a prespecified analysis, the present findings are exploratory and should be interpreted with appropriate caution. They warrant further investigation and should be viewed in the context of the trial's inconclusive primary endpoint. For some endpoints, assessments of effectiveness across HF subgroups were based on a relatively low number of events, further underscoring the need for careful interpretation. Nevertheless, they are based on the largest individually randomized sample to date evaluating HD-IIV in individuals with HF, a scale that may not be easily replicated.

This study has limitations. First, the trial was open-label, and participants and their providers were not blinded to vaccination received. However, this is unlikely to have influenced severe hospitalization outcomes substantially. Second, registry-based data collection of baseline and follow-up data may have introduced some misclassification. However, the outcome algorithms used in the Danish registries have been validated,[18,29] and any residual bias would be expected to be equally distributed between the groups due to randomization, and therefore unlikely to affect between-group comparisons. Third, as discussed, the broad HF case definition may limit generalizability to other HF populations, particularly those with more severe disease. This is underscored by the INVESTED trial, which primarily enrolled high-risk HF patients and found no

difference in outcomes between those randomized to HD-IIV vs. SD-IIV. However, stratified analyses based on HF characteristics reflecting disease severity showed relatively consistent results across subpopulations. Additionally, some degree of healthy volunteer bias must be acknowledged, as participants with HF were slightly younger, had fewer comorbidities, and included fewer females compared with the overall HF population identified in Danish registries, although these differences were not pronounced. While no treatment heterogeneity was observed across HF subgroups for any investigated endpoints, this trial was not powered to detect treatment interaction, and the potential of incremental benefit of HD-IIV for individuals with HF must be interpreted in light of this. The registry-based HF-definition also did not permit classification by HF phenotype (preserved vs. reduced ejection fraction). The absence of ejection fraction data is a significant limitation that precludes evaluation of whether treatment effects may differ across HF phenotypes and is not overcome by examining other features of patients with HF. Additionally, NT-proBNP measurements were obtained from registries and reflected clinical testing performed at the discretion of the treating clinician, which may introduce bias regarding who had these measured. Analyses including NT-proBNP should therefore be interpreted with caution. Due to national data protection laws, the trial did not have access to medication data, which could have provided additional insight into baseline risk and treatment effect. Data on race and ethnicity were not available, and the study population likely had limited diversity, which may limit generalizability to other countries' populations. Finally, systematic influenza testing was not performed.

Conclusions

In the DANFLU-2 trial HD-IIV was associated with a lower incidence of influenza-related and LCI hospitalizations, as well as cardio-respiratory, CV, and HF hospitalizations, compared with SD-IIV. Effect estimates were similar regardless of HF diagnosis at baseline and across HF subgroups.

While exploratory, these findings support the importance of influenza vaccination in individuals with HF and raise the possibility that HD-IIV may offer incremental protection.

Disclosures

KGS has served on an advisory board for Sanofi and received financial support for congress participation from AstraZeneca. MML, RCH, and MD are full-time employees of Sanofi and may own shares and/or stock options in the company. CSL has received speaker fees and served on advisory boards for GSK, MSD, Pfizer, Takeda, and Valneva. BLC has received consulting fees from Amgen, Cardurion, Corvia, Myokardia, and Novartis. SDS has received research grants from Actelion, Alnylam, Amgen, AstraZeneca, Bellerophon, Bayer, BMS, Celladon, Cytokinetics, Eidos, Gilead, GSK, Ionis, Lilly, Mesoblast, MyoKardia, NIH/NHLBI, Neurotronik, Novartis, Novo Nordisk, Respicardia, Sanofi, Theracos, US2.AI and consulted for Abbott, Action, Akros, Alnylam, Amgen, Arena, AstraZeneca, Bayer, Boehringer Ingelheim, BMS, Cardior, Cardurion, Corvia, Cytokinetics, Daiichi-Sankyo, GSK, Lilly, Merck, Myokardia, Novartis, Roche, Theracos, Quantum Genomics, Cardurion, Janssen, Cardiac Dimensions, Tenaya, Sanofi, Dinaqor, Tremeau, CellProThera, Moderna, American Regent, Sarepta, Lexicon, Anacardio, Akros, and Puretech Health. MJL reports institutional research grants from Novartis, Sanofi, Regeneron, Moderna, GSK and Boehringer Ingelheim. LK has received speaker fees from Novo Nordisk, Novartis, AstraZeneca, Boehringer Ingelheim, and Bayer. AM received research contracts from 4TEEN4, Roche, Sphingotec, Abbott Diagnostics, Windtree; consultation fee from Roche, Corteria, Adrenomed, Fire, Johnson&Johnson; honorarium for lecture from Merck, Novartis, Roche, Bayer; is co-inventor of patent on combined therapies to treat dyspnea, owned by S-Form Pharma; member of Committee of trials for Secret-HF, sponsored by the French Government, for S-Form Pharma, for 4TEEN4, Echosens and Implicity. TB-S has received research grants from Bayer, Novartis, Pfizer, Sanofi Pasteur, GSK, Novo Nordisk, AstraZeneca, Boston Scientific, and GE Healthcare, consulting fees from Novo Nordisk, IQVIA, Parexel, Amgen, CSL Seqirus, GSK, and Sanofi

Pasteur, and lecture fees from AstraZeneca, Bayer, Novartis, Sanofi Pasteur, GE Healthcare, and GSK. All other authors declare no competing interests.

Acknowledgements

The authors thank the personnel at European LifeCare Group for their collaboration and support with the study procedures. The authors would also like to thank personnel at Sanofi for their contributions: Ayman Chit, Sandrine Samson, Robertus van Aalst, Martin Ryser, Marion Fournier, and Tamala Moore (scientific advice), Camille Salamand (biostatistics advice), as well as Pierre Bourron and Marie-Caroline Guichard (administrative and dose provision logistical support).

Funding

The trial was funded by Sanofi who participated in the study design, protocol development phase, and manuscript review, but have no responsibilities in trial conduct, data collection, or data analysis. KGS was financed by a research grant from the Danish Cardiovascular Academy, which is funded by the Novo Nordisk Foundation and The Danish Heart Foundation (NNF20SA0067242).

Supplementary Material:

Trial protocol and statistical analysis plan

Tables S1-S4

Figure S1

Consort 2025 checklist

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Table 1. Baseline Characteristics of participants with and without heart failure

Characteristic	No HF n = 322,019	HF n =10,410
Age, mean (SD)	73.6 (5.8)	76.0 (6.3)
Female sex, n (%)	158,684 (49.3)	2,848 (27.4)
Chronic cardiovascular disease, n (%)	80,616 (25.0)	10,410 (100)
Ischemic heart disease, n (%)	26,381 (8.2)	4,731 (45.4)
History of myocardial infarction, n (%)	7,385 (2.3)	2,020 (19.4)
History of atrial fibrillation, n (%)	29,013 (9.0)	5,072 (48.7)
Cerebrovascular disease, n (%)	15,421 (4.8)	960 (9.2)
Diabetes, n (%)	40,967 (12.7)	2,914 (28.0)
Hypertension, n (%)	59,822 (18.6)	4,085 (39.2)
Chronic kidney disease, n (%)	42,220 (13.1)	4,568 (43.9)
Liver disease, n (%)	4,719 (1.5)	269 (2.6)
Chronic lung disease, n (%)	25,214 (7.8)	1,938 (18.6)
Cancer, n (%)	44,132 (13.7)	1,786 (17.2)
Immunodeficiency, n (%)	13,653 (4.2)	662 (6.4)
Influenza vaccination in previous season, n (%)	311,891 (96.9)	10,166 (97.7)
Co-administration with COVID-19 vaccine, n (%)	198,379 (61.6)	6,344 (60.9)
RSV-vaccination in same season, n (%)	25,212 (7.8)	711 (6.8)
Pneumococcal vaccination in same season, n (%)	4,733 (1.5)	221 (2.1)
Device therapy, n (%)	601 (0.2)	1,720 (16.5)
Most recent NT-proBNP, pg/mL (IQR)*	157 (78-377)	685 (287-1,568)
Years since HF diagnosis, (IQR)	-	4.5 (2.1-7.3)
Years since most recent HF hospitalization (IQR)†	-	5.5 (2.7-7.4)
Recency of HF hospitalization, n (%)		
- 0-30 days	-	25 (0.2)
- 30-90 days	-	62 (0.6)
- 90-180 days	-	112 (1.1)
- 180-365 days	-	221 (2.1)
- >1 year	-	3,963 (38.1)

- No HF hospitalization	6,027 (57.9)

Nine individuals of the 332,438 randomized, withdrew consent following randomization, and are omitted from this table. Baseline characteristics were sourced from nationwide administrative health registries using prespecified definitions. SD, standard deviation; IQR, interquartile range; HF, heart failure; RSV, respiratory syncytial virus; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

*NT-proBNP was not available in 305,794 individuals (301,154 without HF and 4,640 with HF)

†A total of 4,383 individuals were hospitalized overnight and discharged with HF as the primary diagnosis within 10 years before randomization.

Table 2. Effectiveness of High-Dose vs. Standard-Dose Influenza Vaccine Against Prespecified Endpoints According to Heart Failure Status

Endpoint/HF status (no.)	HD-IIV No. (%)	SD-IIV No (%)	Risk ratio (95% CI)	p for interaction	Numbers needed to vaccinate
Influenza-related hospitalization					
All participants (332,438)	101 (0.1)	179 (0.1)	0.56 (0.44 to 0.72)	0.64	
HF (10,410)	10 (0.2)	21 (0.4)	0.48 (0.20 to 1.06)		475
No HF (322,019)	91 (0.1)	158 (0.1)	0.58 (0.44 to 0.75)		2403
LCI hospitalization					
All participants (332,438)	177 (0.1)	276 (0.2)	0.64 (0.53 to 0.78)	0.59	
HF (10.410)	17 (0.3)	31 (0.6)	0.55 (0.29 to 1.02)		373
No HF (322,019)	160 (0.1)	245 (0.2)	0.65 (0.53 to 0.80)		1894
Cardio-respiratory hospitalization					
All participants (332,438)	3,735 (2.3)	3,962 (2.4)	0.94 (0.90 to 0.99)	0.34	
HF (10.410)	387 (7.4)	437 (8.4)	0.89 (0.77 to 1.02)		106
No HF (322,019)	3,348 (2.1)	3,525 (2.2)	0.95 (0.91 to 1.00)		909
Cardiovascular hospitalization					
All participants (332,438)	2,156 (1.3)	2,323 (1.40)	0.93 (0.87 to 0.98)	0.34	
HF (10.410)	242 (4.7)	282 (5.4)	0.86 (0.72 to 1.02)		132
No HF (322,019)	1,914 (1.2)	2,041 (1.3)	0.94 (0.88 to 1.00)		1267
HF hospitalization					
All participants (332,438)	214 (0.1)	266 (0.16)	0.80 (0.67 to 0.97)	0.83	
HF (10.410)	84 (1.6)	102 (2.0)	0.82 (0.61 to 1.11)		292
No HF (322,019)	130 (0.1)	164 (0.1)	0.79 (0.62 to 1.00)		4735

Discrepancy in the sum of individuals with and without HF and total number of participants are due to nine individuals withdrawing consent following randomization, and thus, does not contribute with data beyond randomization group. Endpoints occurring between 14 days after vaccination and May 31 the following year were defined as eligible for analysis. Endpoints were ascertained using data from nationwide administrative health registries. HD-IIV, high-dose inactivated influenza vaccine; SD-IIV, standard-dose inactivated influenza vaccine; HF, heart failure; 95%CI, 95% confidence intervals LCI, laboratory-confirmed influenza.

Figure Legends

Figure 1

Title: Outcomes in Participants with and Without Heart Failure at Baseline

Caption: Risks of evaluated outcomes according to heart failure status at baseline with risk ratios with 95% confidence intervals for participants with heart failure vs. no heart failure at baseline.

Abbreviations: HF, heart failure; RR, risk ratio; 95%CI, 95% confidence interval.

Figure 2

Title: Effectiveness of High-Dose vs. Standard-Dose Influenza Vaccine Against Influenza Endpoints Across Major Heart Failure Subgroups

Caption: To explore potential treatment heterogeneity of high-dose inactivated influenza vaccine across major heart failure subgroups, we evaluated hospitalization for influenza-related and laboratory-confirmed influenza by duration of heart failure diagnosis, recency of heart failure hospitalization, history of device therapy, and most recent N-terminal proB-type natriuretic peptide. Effectiveness of HD-IIV vs. SD-IIV is expressed as risk ratios for each outcome. P for interaction values were estimated using the Cochran-Mantel-Haenszel test for homogeneity.

Abbreviations: HD-IIV, high-dose inactivated influenza vaccine; SD-IIV, standard-dose inactivated influenza vaccine; HF, heart failure; 95%CI, 95% confidence interval; LCI, laboratory-confirmed influenza; ICD, implantable cardioverter-defibrillator; cardiac resynchronization therapy, CRT; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

Figure 3

Title: Effectiveness of High-Dose vs. Standard-Dose Influenza Vaccine Against Cardiovascular Endpoints Across Major Heart Failure Subgroups

Caption: To explore potential treatment heterogeneity of high-dose inactivated influenza vaccine across major heart failure subgroups, we evaluated hospitalization for cardio-respiratory disease, cardiovascular disease, and heart failure according to duration of heart failure diagnosis, recency of heart failure hospitalization, history of device therapy, and most recent N-terminal pro-B-type natriuretic peptide. Effectiveness of HD-IIV vs. SD-IIV is expressed as risk ratios for each outcome. P for interaction values were estimated using the Cochran-Mantel-Haenszel test for homogeneity.

Abbreviations: HD-IIV, high-dose inactivated influenza vaccine; SD-IIV, standard-dose inactivated influenza vaccine; HF, heart failure; 95%CI, 95% confidence interval; ICD, implantable cardioverter-defibrillator; cardiac resynchronization therapy, CRT; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

Figure 4:

Title: Effectiveness According to Continuous Markers Reflecting Heart Failure Characteristic Among Participants with Heart Failure.

Caption: Risk ratios for the comparison of HD-IIV vs. SD-IIV for each assessed influenza-related and cardiovascular endpoint according to continuous markers reflecting heart failure characteristics among participants with heart failure. Effect modification by continuous variables was assessed in restricted cubic spline modeling using a log-binomial regression model with an interaction term between group assignment and continuous variable evaluated. Number of knots was chosen according to lowest Akaike Information Criterion. Solid lines indicate estimated risk ratios with a reference line at 1, and dashed lines indicate 95% confidence intervals. Histograms show the distribution of each continuous marker. For the heart failure hospitalization endpoint, an alternative definition of time since most recent heart failure hospitalization was used, as no participants

hospitalized overnight with heart failure prior to randomization were subsequently hospitalized for heart failure during follow-up. HD-IIV, high-dose inactivated influenza vaccine; SD-IIV, standard-dose inactivated influenza vaccine; LCI, laboratory-confirmed influenza vaccine; HF, heart failure; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

Figure 1: Outcomes in Participants with and Without Heart Failure at Baseline

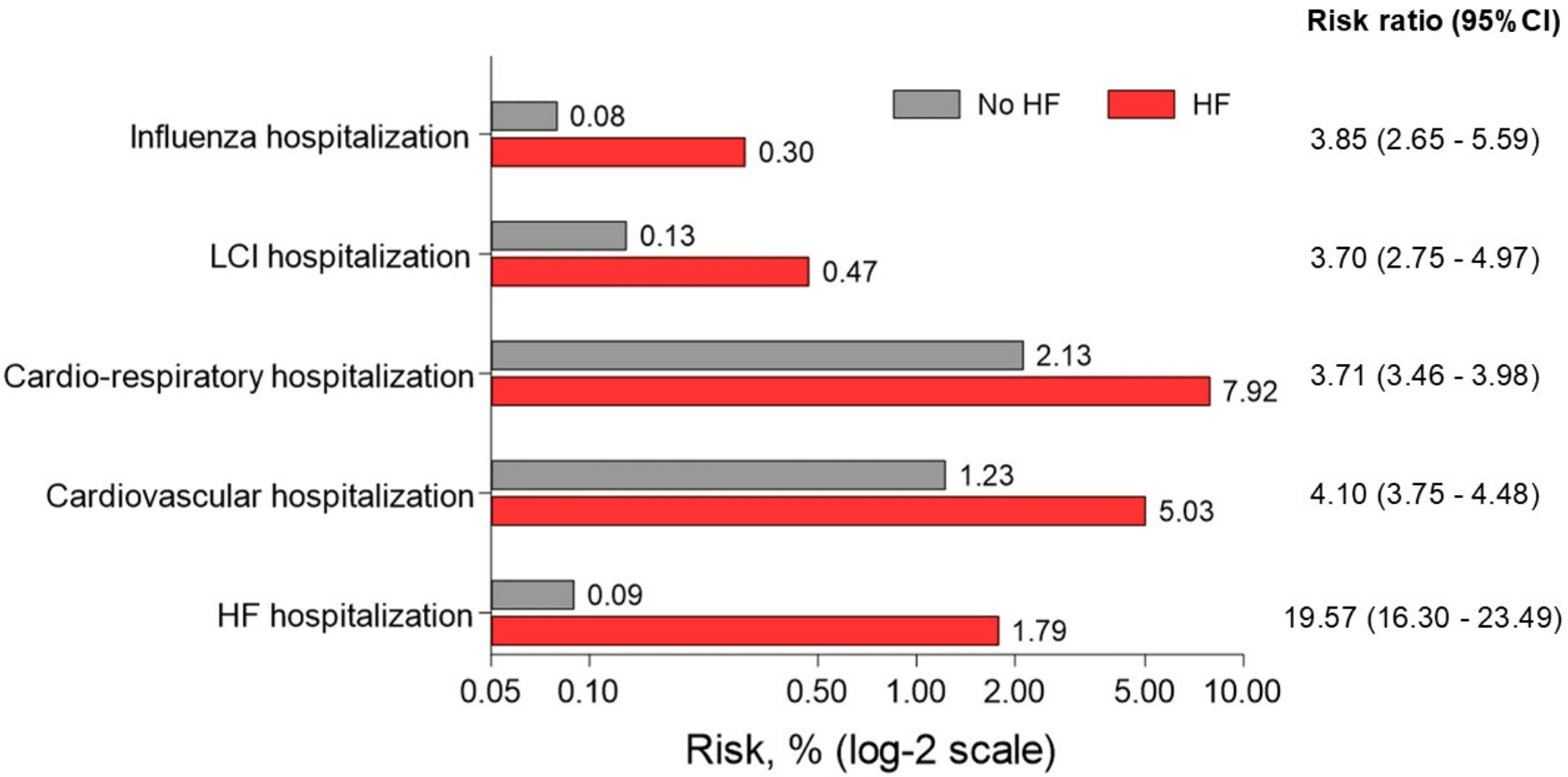

Figure 2: Effectiveness of High-Dose vs. Standard-Dose Influenza Vaccine Against Influenza Endpoints Across Major Heart Failure Subgroups

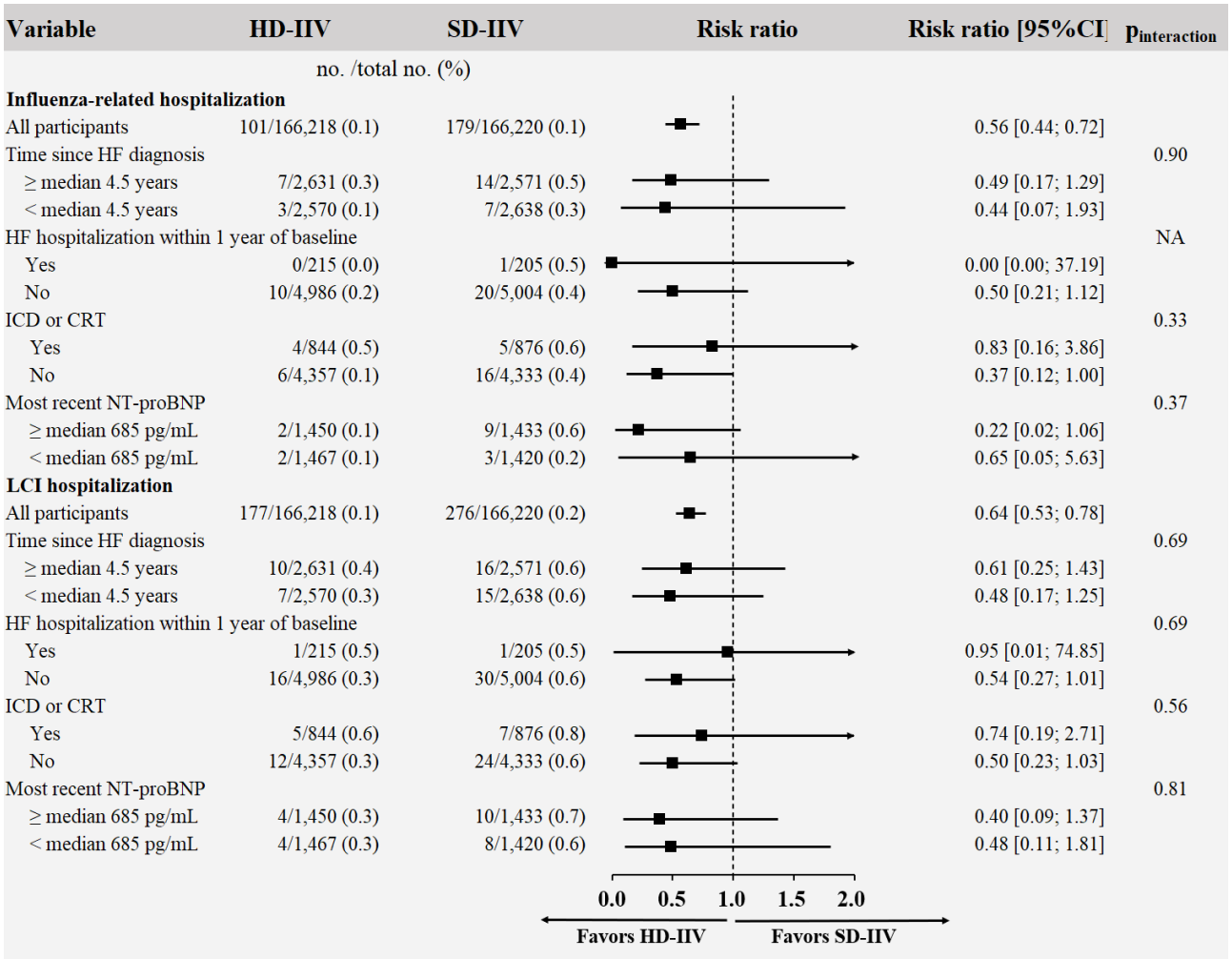

Figure 3: Effectiveness of High-Dose vs. Standard-Dose Influenza Vaccine Against Cardiovascular Endpoints Across Major Heart Failure Subgroups

Figure 4: Effectiveness According to Continuous Markers Reflecting Heart Failure Characteristic Among Participants with Heart Failure