ESC European Society of Cardiology

European Heart Journal (2025) **46**, 4299–4301
https://doi.org/10.1093/eurheartj/ehaf697

EDITORIAL
Clinical trials

Respiratory viruses, vaccines, and the heart: lessons from DANFLU-2, DAN-RSV, and beyond

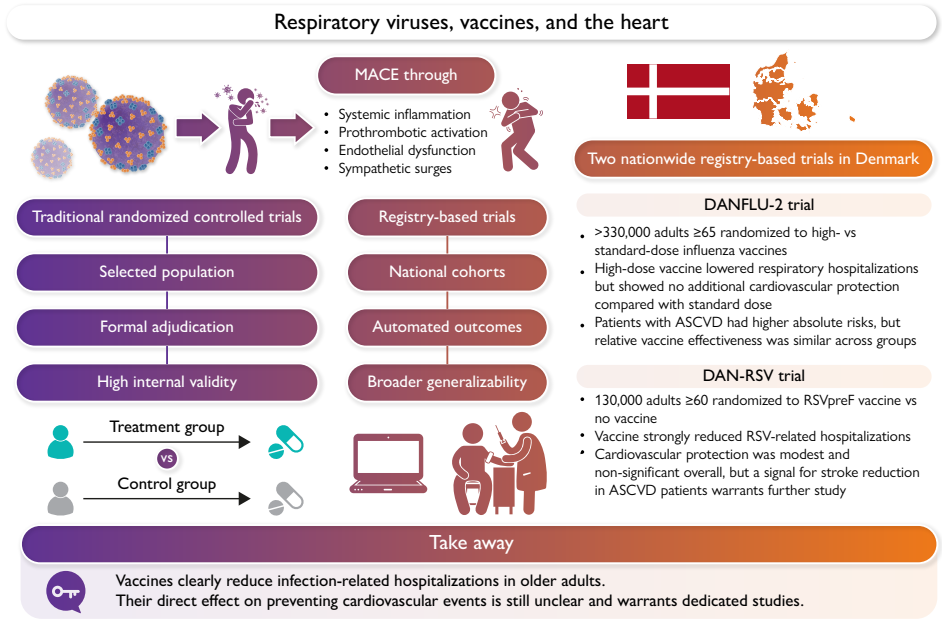
Bettina Heidecker [1,2,3,*] **and Thomas F. Lüscher** [4,5]

[1]Deutsches Herzzentrum der Charité, Universitätsmedizin Berlin, Hindenburgdamm 30, D-12203 Berlin, Germany; [2]Berlin Institute of Health (BIH) at Charité—Universitätsmedizin Berlin, Berlin, Germany; [3]DZHK (German Center for Cardiovascular Research), Germany; [4]Heart Division, Royal Brompton Hospital, King's College and Imperial College, London, UK; and [5]Center for Molecular Cardiology, University of Zurich, Schlieren, Zurich, Switzerland

Online publish-ahead-of-print 30 August 2025

This editorial refers to 'High-dose vs. standard-dose inactivated influenza vaccine and cardiovascular outcomes in persons with or without pre-existing atherosclerotic cardiovascular disease: the DANFLU-2 trial', by M. Pareek *et al.*, https://doi.org/10.1093/eurheartj/ehaf678 and 'Effectiveness of bivalent respiratory syncytial virus prefusion F protein-based vaccine in individuals with or without atherosclerotic cardiovascular disease: the DAN-RSV trial', by M. Pareek *et al.*, https://doi.org/10.1093/eurheartj/ehaf679.

Graphical Abstract



Cardiovascular outcomes after influenza and RSV vaccination in Denmark: Two nationwide registry-based study.

The opinions expressed in this article are not necessarily those of the Editors of the *European Heart Journal* or of the European Society of Cardiology.

* Corresponding author. Tel: +49 30 450 513 638, Email: bettina.heidecker@gmail.com

Influenza virus and respiratory syncytial virus (RSV) have long been regarded primarily as respiratory pathogens. However, a growing body of evidence reveals their substantial impact on cardiovascular health, particularly among vulnerable populations, including older adults and those with atherosclerotic cardiovascular disease (ASCVD).[1–4] Indeed, acute viral infections are potent triggers of major cardiovascular events (MACE) such as myocardial infarction, stroke, and heart failure, as the COVID-19 pandemic has revealed on a broad scale.[5–8] Preventive strategies that mitigate infection-related pathways thus hold great promise in reducing cardiovascular events.[2,9–11] In a recent European Society of Cardiology consensus document, we have emphasized vaccination as an emerging pillar of cardiovascular prevention.[1]

Increasing evidence suggests that vaccination will become an important cornerstone of prevention of cardiovascular disease.[2,9–12] As a result, a critical unanswered question has lingered: Do novel influenza vaccines or newly developed RSV vaccines provide cardiovascular protection in high-risk patients beyond their benefits of reducing the risk for respiratory infections? Two major pragmatic, nationwide randomized trials from Denmark—the DANFLU-2[13] and DAN-RSV[14]—published in this issue of the *European Heart Journal*, address this important clinical question.

A distinctive strength of both DANFLU-2 and DAN-RSV lies in their unprecedented design and scale. Leveraging Denmark's nationwide health registries and centralized vaccination infrastructure, virtually the entire eligible population ≥60 years was reached. Participants were primarily recruited using electronic invitation letters sent through the Danish governmental digital mailing system. This pragmatic, registry-based design minimized loss to follow-up and made these the largest randomized vaccine trials ever conducted in older adults for influenza and RSV (*Graphical Abstract*).

In DANFLU-2, >330 000 adults aged ≥65 years were randomized to receive either high- or standard-dose influenza vaccination over three consecutive influenza seasons, in order to assess potential differences in vaccine effectiveness. The primary outcome was hospitalization for influenza or pneumonia. In addition, the study compared vaccine effectiveness in patients with and without ASCVD in a pre-specified exploratory analysis.

Consistent with prior literature, patients with ASCVD experienced markedly higher absolute rates of respiratory hospitalizations and MACE. Yet, the relative vaccine effectiveness (rVE) of high-dose vs standard-dose vaccination for the primary outcome, i.e. hospitalization for influenza or pneumonia, was similar in both groups, with ∼7% in those without ASCVD and ∼5% in those with (no significant interaction).

Subgroup analyses revealed that the rates of both hospitalization for influenza and laboratory-confirmed influenza were lower in the high-dose influenza vaccine group than in the standard-dose inactivated influenza group. Therefore, in summary, older adults with ASCVD carried higher risk and thus higher absolute MACE rates, but high-dose influenza vaccine did not appear to provide incremental cardiovascular benefit beyond standard-dose vaccination in the current study.

While influenza has long been implicated in cardiovascular risk, RSV is a relative newcomer in that discussion. Indeed, RSV infection has emerged as an under-recognized trigger for hospitalization and adverse outcomes in older adults. The DAN-RSV trial randomized >130 000 adults ≥60 years to receive either a bivalent RSV prefusion F protein-based vaccine (RSVpreF) or no vaccine.

Again, patients with ASCVD had substantially higher baseline event rates. Vaccine effectiveness against the primary outcome—RSV-related hospitalization—was robust (80% in those without ASCVD, 100% in those with ASCVD, albeit with wide confidence intervals due to relatively few events). For cardiovascular outcomes, protection against MACE was modest and non-significant in both groups (9%–12%). Importantly, a signal for stroke reduction emerged in the ASCVD subgroup, although this was hypothesis-generating given the small number of events and warrants confirmation in future studies. Overall, the DAN-RSV trial underscores that RSV vaccination can substantially reduce respiratory hospitalizations. Further research will be necessary to explore its potential benefits in reducing cardiovascular events.

The biological plausibility for vaccination as cardiovascular prevention is strong.[1,5] Acute respiratory infection induces systemic inflammation, prothrombotic activation, endothelial dysfunction, and sympathetic surges—all potential triggers for myocardial infarction and stroke. There is mounting evidence that viral infections provoke cytokine cascades that destabilize vascular plaques and impair myocardial energetics.[1,5] By preventing infection or attenuating its systemic inflammatory consequences, vaccines may indirectly reduce cardiovascular events.[1,5]

Lessons from DANFLU-2 and DAN-RSV for the practizing cardiologist are:[1] risk stratification matters. Patients with ASCVD consistently had higher absolute risks for MACE.[2] The relative benefits of these vaccines are not amplified by ASCVD. Both trials found consistent rVE/VE across cardiovascular stratification.[3] The signals for protection deserve further exploration. The trend for fewer respiratory hospitalizations in the influenza vaccine group, and the signal in the RSV vaccine group for stroke reduction, hint at potential cardiovascular effects that trials with longer follow-up may detect.[4] The public health impact of vaccination in the elderly population is substantial. Even in the absence of direct cardiovascular protection, preventing respiratory hospitalizations in older adults has clear implications for healthcare utilization, morbidity, and potentially mortality.

Taken together, the data describe the complex relationship between viral infection, vaccines, and the heart: vaccination effectively reduces infection; whether it directly prevents cardiovascular events depends on context, timing, and host factors, and probably the duration of follow-up.

With regards to limitations, both trials were pragmatic and registry based, maximizing generalizability, but with inherent caveats: DANFLU-2 did not include a placebo arm, most probably as current ESC guidelines recommend vaccination against influenza, pneumococcal disease, and other widespread infections such as COVID-19 for patients with chronic coronary syndromes.[15] Similarly, the AHA/ACC guidelines for the management of chronic coronary artery disease recommend influenza vaccine.[16] Under these circumstances, withholding vaccination for a placebo group would not have been ethically justifiable.

DAN-RSV had overall low event rates and wide confidence intervals, as a result limiting statistical power for cardiovascular outcomes. Both trials were based on registry definitions of comorbidities and outcomes. As in any registry study without central chart review by the investigators or endpoint adjudication committee, coding errors, variations in clinical practice, or incomplete capture can occur.

Despite the inherent limitations of registry-based outcome definitions and the absence of formal adjudication, the investigators deserve recognition for implementing an innovative, large-scale pragmatic approach that enabled the enrolment and follow-up of entire national cohorts. This strategy has yielded uniquely valuable real-world evidence at a scale previously unattainable in cardiovascular vaccine research.

The DANFLU-2 and DAN-RSV trials advance our understanding of the interplay of infectious disease and cardiovascular disease prevention. Although the expectation that high-dose influenza or new RSV vaccines might yield disproportionate cardiovascular benefit has not

yet been realized, it is important to recognize that these trials were not primarily powered to detect reductions in individual cardiovascular events following vaccination. Therefore, studies powered to explore exactly these endpoints will be needed in the future, in particular with the hints at cardiovascular protective effects obtained from these data. Future research will serve to refine our strategies, test combined approaches, and integrate mechanistic insights into clinical trial design.

Declarations

Disclosure of Interest

B.H. is an inventor on patents that use RNA for the diagnosis of myocarditis and on a patent protection that is in process for magnetocardiography for the diagnosis and measurement of treatment response in inflammatory cardiomyopathy; has received speaker fees from Pfizer, Bayer, Sanofi-Aventis, Novartis, and Astra Zeneca unrelated to this topic; and has received research funding from Pfizer unrelated to this topic. T.F.L. has, outside this work, received research and educational grants to the institution from Abbott, Anylam, Amgen, AstraZeneca, Bayer Healthcare, Boehringer-Ingelheim, Cytokinetics, Daichi-Sankyo, Eli Lilly, Novartis, Novo Nordisk, Pfizer, Roche Diagnostics, Sanofi, and Vifor. He no longer accepts honoraria from industry partners, but has consulted with GSK on vaccines without any financial involvement.

References

1. Heidecker B, Libby P, Vassiliou VS, Roubille F, Vardeny O, Hassager C, *et al.* Vaccination as a new form of cardiovascular prevention: a European Society of Cardiology clinical consensus statement. *Eur Heart J* 2025;**46**:3518–31. https://doi.org/10.1093/eurheartj/ehaf384
2. Fröbert O, Götberg M, Erlinge D, Akhtar Z, Christiansen EH, MacIntyre CR, *et al.* Influenza vaccination after myocardial infarction: a randomized, double-blind, placebo-controlled, multicenter trial. *Circulation* 2021;**144**:1476–84. https://doi.org/10.1161/CIRCULATIONAHA.121.057042
3. Modin D, Claggett B, Johansen ND, Solomon SD, Trebbien R, Grove Krause T, *et al.* Excess mortality and hospitalizations associated with seasonal influenza in patients with heart failure. *J Am Coll Cardiol* 2024;**84**:2460–7. https://doi.org/10.1016/j.jacc.2024.08.048
4. Woodruff RC, Melgar M, Pham H, Sperling LS, Loustalot F, Kirley PD, *et al.* Acute cardiac events in hospitalized older adults with respiratory syncytial virus infection. *JAMA Intern Med* 2024;**184**:602–11. https://doi.org/10.1001/jamainternmed.2024.0212
5. Libby P, Luscher T. COVID-19 is, in the end, an endothelial disease. *Eur Heart J* 2020;**41**:3038–44. https://doi.org/10.1093/eurheartj/ehaa623
6. Bhatt AS, Jering KS, Vaduganathan M, Claggett BL, Cunningham JW, Rosenthal N, *et al.* Clinical outcomes in patients with heart failure hospitalized with COVID-19. *JACC Heart Fail* 2021;**9**:65–73. https://doi.org/10.1016/j.jchf.2020.11.003
7. Suwalski P, Violano M, Müller M, Patriki D, Thibeault C, Quedenau C, *et al.* Male carriers of HLA-C*04:01 have increased risk of cardiac injury in COVID-19. *J Cardiovasc Aging* 2022;**2**:33. https://doi.org/10.20517/jca.2022.19
8. Heidecker B, Dagan N, Balicer R, Eriksson U, Rosano G, Coats A, *et al.* Myocarditis following COVID-19 vaccine: incidence, presentation, diagnosis, pathophysiology, therapy, and outcomes put into perspective. A clinical consensus document supported by the Heart Failure Association of the European Society of Cardiology (ESC) and the ESC Working Group on myocardial and pericardial diseases. *Eur J Heart Fail* 2022;**24**:2000–18. https://doi.org/10.1002/ejhf.2669
9. Phrommintikul A, Kuanprasert S, Wongcharoen W, Kanjanavanit R, Chaiwarith R, Sukonthasarn A. Influenza vaccination reduces cardiovascular events in patients with acute coronary syndrome. *Eur Heart J* 2011;**32**:1730–5. https://doi.org/10.1093/eurheartj/ehr004
10. Gurfinkel EP, Leon de la Fuente R, Mendiz O, Mautner B. Flu vaccination in acute coronary syndromes and planned percutaneous coronary interventions (FLUVACS) Study. *Eur Heart J* 2004;**25**:25–31. https://doi.org/10.1016/j.ehj.2003.10.018
11. Ciszewski A, Bilinska ZT, Brydak LB, Kepka C, Kruk M, Romanowska M, *et al.* Influenza vaccination in secondary prevention from coronary ischaemic events in coronary artery disease: FLUCAD study. *Eur Heart J* 2008;**29**:1350–8. https://doi.org/10.1093/eurheartj/ehm581
12. Modin D, Lassen MCH, Claggett B, Johansen ND, Keshtkar-Jahromi M, Skaarup KG, *et al.* Influenza vaccination and cardiovascular events in patients with ischaemic heart disease and heart failure: a meta-analysis. *Eur J Heart Fail* 2023;**25**:1685–92. https://doi.org/10.1002/ejhf.2945
13. Pareek M, Johansen ND, Modin D, Loiacono MM, Harris RC, Dufournet M, *et al.* High-dose vs. standard-dose inactivated influenza vaccine and cardiovascular outcomes in persons with or without pre-existing atherosclerotic cardiovascular disease: the DANFLU-2 trial. *Eur Heart J* 2025;**46**:4282–90. https://doi.org/10.1093/eurheartj/ehaf678
14. Pareek M, Lassen MCH, Johansen ND, Christensen SH, Aliabadi N, Skaarup KG, *et al.* Effectiveness of bivalent respiratory syncytial virus prefusion F protein-based vaccine in individuals with or without atherosclerotic cardiovascular disease: the DAN-RSV trial. *Eur Heart J* 2025;**46**:4291–8. https://doi.org/10.1093/eurheartj/ehaf679
15. Vrints C, Andreotti F, Koskinas KC, Rossello X, Adamo M, Ainslie J, *et al.* 2024 ESC guidelines for the management of chronic coronary syndromes. *Eur Heart J* 2024;**45**:3415–537. https://doi.org/10.1093/eurheartj/ehae177
16. Virani SS, Newby LK, Arnold SV, Bittner V, Brewer LC, Demeter SH, *et al.* 2023 AHA/ACC/ACCP/ASPC/NLA/PCNA Guideline for the management of patients with chronic coronary disease: a report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines. *Circulation* 2023;**148**:e9–119. https://doi.org/10.1161/CIR.0000000000001168