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Association of Influenza Vaccination With Cardiovascular Risk
A Meta-analysis

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Abstract

IMPORTANCE Influenza infection is associated with increased cardiovascular hospitalization and mortality. Our prior systematic review and meta-analysis hypothesized that influenza vaccination was associated with a lower risk of cardiovascular events.

OBJECTIVE To evaluate, via an updated meta-analysis, if seasonal influenza vaccination is associated with a lower risk of fatal and nonfatal cardiovascular events and assess whether the newest cardiovascular outcome trial results are consistent with prior findings.

DATA SOURCES A previously published meta-analysis of randomized controlled trials (RCTs) and a large 2021 cardiovascular outcome trial.

STUDY SELECTION Studies with RCTs published between 2000 and 2021 that randomized participants to either influenza vaccine or placebo/control. Eligible participants were inpatients and outpatients recruited for international multicenter RCTs and randomized to receive either influenza vaccine or placebo/control.

DATA EXTRACTION AND SYNTHESIS PRISMA guidelines were followed in the extraction of study details, and risk of bias was assessed using the Cochrane Collaboration tool. Trial quality was evaluated using Cochrane criteria. Data were analyzed January 2020 and December 2021.

MAIN OUTCOMES AND MEASURES Random-effects Mantel-Haenszel risk ratios (RRs) and 95% CIs were derived for a composite of major adverse cardiovascular events and cardiovascular mortality within 12 months of follow-up. Where available, analyses were stratified by patients with and without recent acute coronary syndrome (ACS) within 1 year of randomization.

RESULTS Six published RCTs comprising a total of 9001 patients were included (mean age, 65.5 years; 42.5% women; 52.3% with a cardiac history). Overall, influenza vaccine was associated with a lower risk of composite cardiovascular events (3.6% vs 5.4%; RR, 0.66; 95% CI, 0.53-0.83; $P < .001$). A treatment interaction was detected between patients with recent ACS (RR, 0.55; 95% CI, 0.41-0.75) and without recent ACS (RR, 1.00; 95% CI, 0.68-1.47) (P for interaction = .02). For cardiovascular mortality, a treatment interaction was also detected between patients with recent ACS (RR, 0.44; 95% CI, 0.23-0.85) and without recent ACS (RR, 1.45; 95% CI, 0.84-2.50) (P for interaction = .006), while 1.7% of vaccine recipients died of cardiovascular causes compared with 2.5% of placebo or control recipients (RR, 0.74; 95% CI, 0.42-1.30; P = .29).

CONCLUSIONS AND RELEVANCE In this study, receipt of influenza vaccination was associated with a 34% lower risk of major adverse cardiovascular events, and individuals with recent ACS had a 45%

(continued)

Key Points

Question Is seasonal influenza vaccination associated with lower rates of adverse cardiovascular events?

Findings In this meta-analysis of 6 randomized clinical trials including 9001 adults who were randomized to influenza vaccination vs matching placebo or standard care, 3.6% of vaccinated patients developed a major adverse cardiovascular event within 12 months compared with 5.4% of those who received placebo or control, a 1.8% significant difference translating into a number needed to vaccinate of 56 patients to prevent 1 event. Higher-risk patients with recent acute coronary syndrome had 45% reduced risk.

Meaning These results suggest that clinicians and policy makers should continue to counsel high-risk patients on the cardiovascular benefits of seasonal influenza vaccination.

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Abstract (continued)

lower risk. Given influenza poses a threat to population health during the COVID-19 pandemic, it is integral to counsel high-risk patients on the cardiovascular benefits of influenza vaccination.

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Introduction

Viral respiratory infections, including those due to the influenza virus, increase the risk for pneumonia and systemic illness that can precipitate fatal and nonfatal cardiovascular events.[1,2] Underlying cardiovascular disease is also a risk factor for influenza infection, downstream cardiopulmonary complications, and mortality from respiratory infections.[3] In a prior systematic review and meta-analysis, we found that influenza vaccination was associated with a lower risk of fatal and nonfatal cardiovascular events within a year. A larger risk reduction was seen in patients with recent acute coronary syndrome (ACS).[4] In this study, we assessed whether new randomized trial data of influenza vaccination from the Influenza Vaccination After Myocardial Infarction (IAMI) trial[5] was consistent with the findings of our prior meta-analysis and provided further refinement of the cardiovascular risk reduction associated with influenza vaccination.

Methods

Our analyses focused on published (between 2000 and 2021) randomized clinical trials (RCTs) comparing influenza vaccination with either placebo or control and collecting cardiovascular-related outcomes as primary and/or secondary (including safety) end points. Trial data were included per the Cochrane Collaboration and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guideline.

Levels of influenza activity, estimated according to the Centers for Disease Control and Prevention and World Health Organization reports, were categorized as without activity, sporadic, local, regional, and/or widespread.[6] Risk of bias for each included trial was evaluated by the method of randomization; allocation concealment; patient, investigator, and outcome assessor masking; outcome reporting and ascertainment; and other potential sources of bias as recommended by the Cochrane Collaboration.[7] Trial quality was determined as high quality by the Cochrane criteria if at least the first 3 criteria were accounted for, low quality if any aspect of the first 3 criteria was unaccounted for, or of uncertain risk of material bias.

Statistical Analysis

A random-effects Mantel-Haenszel model was used to calculate summary risk ratios (RRs), absolute risk reduction (ARR), and 95% CIs, which used a weighting scheme that depends on the effect measure being used. Our primary outcome was a composite of major adverse cardiovascular events (ie, cardiovascular death or hospitalization for myocardial infarction, unstable angina, stroke, heart failure, or urgent coronary revascularization) within 12 months of follow-up. If unavailable, nonfatal and fatal myocardial infarction and stroke events were used. Our secondary outcome was cardiovascular mortality within 12 months of follow-up. The threshold for significance was $P < .05$ in 2-sided tests. If an outcome achieved statistical significance, the number needed to treat (NNT) to avoid 1 event were derived from the inverse of the pooled estimated ARR. Where available, analyses were stratified by patients with and without recent ACS within 1 year of randomization. Statistical analyses were performed with RevMan version 5.4.1 (Cochrane Training).

Results

In a total of 6 published RCTs, 2890 patients were randomly assigned to receive an intramuscular injection of standard influenza vaccination, 1620 to receive an intranasal live attenuated vaccine, 2504 to receive intramuscular placebo, 1622 to receive intranasal placebo, and 365 to receive no treatment (**Table**). A total of 9001 participants (mean age, 65.5 years; 3828 women [42.5%]; 4704 participants [52.3%] with a cardiac history) were followed up for a mean duration of 9 months (range, 0.1-12.2 months). Half of the trials were conducted with rigorous randomization, allocation concealment, and masking that met the Cochrane criteria for high quality (ie, low risk of bias) (**Figure 1**). The remaining studies were considered of uncertain or low quality.

Among the 4510 patients who received influenza vaccine, 162 patients (3.6%) developed a major adverse cardiovascular event compared with 242 (5.4%) of the 4491 patients who received placebo or control within 1 year of follow-up (RR, 0.66; 95% CI, 0.53-0.83; I^2 = 19%; P < .001) (Figure 1). This association represented an ARR of 1.8% (95% CI, 0.9%-2.7%; P < .001) or an NNT of 56 patients (95% CI, 38-107) to prevent 1 cardiovascular event. A significant treatment interaction was detected in a subgroup analysis of patients with recent ACS (3313 patients; 6.5% vaccine vs 11% placebo/control; RR, 0.55; 95% CI, 0.41-0.75; I^2 = 33%; P < .001) and stable outpatients (5688 patients; 1.7% for both vaccine and placebo/control; RR, 1.00; 95% CI, 0.68-1.47; I^2 = 0%; P = .98; P for interaction = .02) (**Figure 2**). For patients vaccinated with a recent ACS, the ARR was 4.5% (95% CI, 2.6%-6.4%; P < .001) or an NNT of 23 patients (95% CI, 16-39 patients) to prevent 1 cardiovascular event.

Furthermore, 76 of the 4510 patients who received influenza vaccine (1.7%) died due to cardiovascular causes compared with 111 of the 4491 patients (2.5%) who received placebo or control within 1 year of follow-up, although this result was not significant (RR, 0.74; 95% CI, 0.42-1.30 I^2 = 62%; P = .29). However, in a subgroup analysis of patients with recent ACS (3313 patients; 2.6% vaccine vs 5.4% placebo/control; RR, 0.44; 95% CI, 0.23-0.85; I^2 = 43%; P = .01) and stable outpatients (5688 patients; 1.1% vaccine vs 0.8% placebo/control; RR, 1.45; 95% CI, 0.84-2.50; I^2 = 0%; P = .18), a significant treatment interaction was found (P for interaction = .006) (**Figure 3**). Therefore, for recent ACS, the ARR was 2.8% or an NNT 36 (95% CI, 15-100) patients to prevent 1 cardiovascular death.

Discussion

Our prior meta-analysis underpinned the need for a large multicenter trial, powered for cardiovascular outcomes, to confirm our findings. Subsequently, the IAMI trial[5] randomized 2532 patients with recent myocardial infarction to influenza vaccine or placebo and showed a lower risk of composite cardiovascular events. Although the study was terminated early because of the COVID-19 pandemic, with approximately 60% of planned randomization, IAMI (hazard ratio, 0.72) prospectively confirmed our meta-analysis (RR, 0.64) while reducing the percentage of variation across the included studies because of heterogeneity (I^2) to 19%. Another recent outcome trial, Influenza Vaccine to Effectively Stop Cardio Thoracic Events and Decompensated Heart Failure,[13] demonstrated no difference in efficacy between a high-dose trivalent vs a standard-dose quadrivalent vaccine in patients with recent hospitalization for heart failure or myocardial infarction. However, the lack of a placebo arm limited its incorporation here.

With the addition of the most recent RCT data, we now also observe a significant interaction between the benefits of influenza vaccination for reducing cardiovascular mortality based on underlying cardiovascular risk. Specifically, among patients with a recent ACS, the risk reduction of cardiovascular death is over 50% among those who received seasonal influenza vaccine. The effect sizes reported here for major adverse cardiovascular events and cardiovascular mortality (in patients

Table. Characteristics of Studies Included in the Meta-analysis

Source	Patient cohort	Age, mean (SD), y[a]	Women, No. (%)	Men, No. (%)	No. with cardiac disease (%)	Follow-up, mean (range), mo	Control therapy	No. in control cohort	Vaccine therapy	No. in intervention cohort	Influenza activity[b]	Trial quality	Region
Efficacy trials (influenza vaccine vs placebo/control)													
Gurfinkel et al,[8] 2004	Inpatients with ACS or outpatients with stable CAD and planned PCI	65 (NR)	62 (20.6)	239 (79.4)	301 (100)	12 (1.0-12.0)	No treatment	147	IM TIV	145	Sporadic	Low	Argentina
Ciszewski et al,[9] 2008	Outpatients with recent ACS or stable CAD with planned PCI	60 (10)	181 (27.5)	477 (72.5)	658 (100)	9.8 (0.1-12.2)	IM placebo	333	IM TIV	325	Regional	High	Poland
Phrommintikul et al,[10] 2011	Inpatients with recent ACS	66 (9)	193 (44)	246 (56)	439 (100)	11.8 (0.1-12.0)	No treatment	218	IM TIV	221	Sporadic and widespread	Low	Thailand
Frøbert et al,[5] 2021	Inpatients and outpatients with recent ACS, coronary angiography or PCI, or stable CAD (high-risk)	59.9 (11.2)	462 (18.2)	2070 (81.8)	2532 (100)	12 (NR)	IM placebo	1260	IM TIV and IM QIV	1272	Sporadic, local, regional, and widespread	High	Sweden, Denmark, Norway, Latvia, UK, Czechia, Bangladesh, Australia
Safety trials (influenza vaccine vs placebo/control)													
Govaert et al,[11] 1994	Outpatients	67 (NR)	969 (52.7)	869 (47.3)	249 (13.5)	5.0 (2.5-5.0)	IM placebo	911	IM QIV	927	Regional	Uncertain	The Netherlands
De Villiers et al,[12] 2009	Outpatients	70 (7)	1961 (60.5)	1281 (39.5)	525 (16.2)	8.0 (0.1-8.0)	INL placebo	1622	INL LAIV	1620	Sporadic	High	South Africa

Abbreviations: ACS, acute coronary syndrome; CAD, coronary artery disease; INL, intranasal; IM, intramuscular; LAIV, live attenuated influenza vaccine; NR, not reported; PCI, percutaneous coronary intervention; QIV, quadrivalent inactivated influenza vaccine; TIV, trivalent inactivated influenza vaccine.

[a] Some results are without SD due to the mean data derived from distribution of participants within age categories or group means being reported without SD.

[b] Sporadic describes isolated laboratory-confirmed influenza cases or a laboratory-confirmed outbreak in 1 institution, with no increase in activity. Local describes increased incidence of influenza-like illness (ILI), or less than 1 institutional outbreak of ILI or laboratory-confirmed influenza in 1 region with recent laboratory evidence of influenza in that region; virus activity no greater than sporadic in other regions. Regional describes outbreaks of ILI or laboratory-confirmed influenza in more than 1 region with a combined population of less than 50% of the state's total population. Widespread describes outbreaks of ILI or laboratory-confirmed influenza in more than 50% of the regions in the state.

with and without recent ACS) are comparable with—if not greater than—those seen with guideline-recommended mainstays of cardiovascular therapy, such as aspirin, angiotensin-converting enzyme inhibitors, β-blockers, statins, and dual antiplatelet therapy.[14]

Limitations

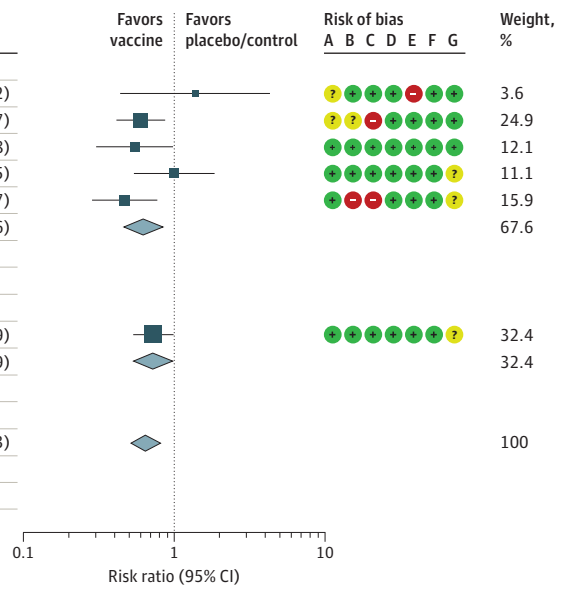
Our study had several limitations. Smaller studies are at risk of selection, performance, or attrition bias, requiring circumspection against overinterpretation. Therefore, it is integral to continue to update future meta-analyses with the results of at least 3 other ongoing large cardiovascular outcome trials (placebo- and active-controlled) that examine various patient populations across the spectrum of cardiovascular disease in other jurisdictions, during contemporary influenza seasons, and using the latest available formulations of seasonal influenza vaccines.[15-17]

Conclusion

Influenza continues to pose a substantial threat to population health during the COVID-19 pandemic, which is why new viral respiratory vaccine research prominently features combination formulations with influenza.[18-20] It is also well established that limitations of the current egg-based mass production systems for seasonal influenza vaccines have curbed the effectiveness of existing vaccines to date.[1] Alternative vaccine platforms, such as those based in mRNA and other technology, continue to progress toward the end goal of a universal influenza vaccine.[14] At the same time, patients with cardiovascular disease have also demonstrated an inadequate immune response postvaccination due to processes such as immunosenescence and inflammaging.[1] Despite potential suboptimal vaccine effectiveness and immune response, the potential risk reduction in major adverse cardiovascular events and cardiovascular mortality with an influenza vaccine is already

Figure 1. Major Adverse Cardiovascular Events for Influenza Vaccine vs Control When Comparing 2021 Large Cardiovascular Outcome Trial With Previous Meta-analysis

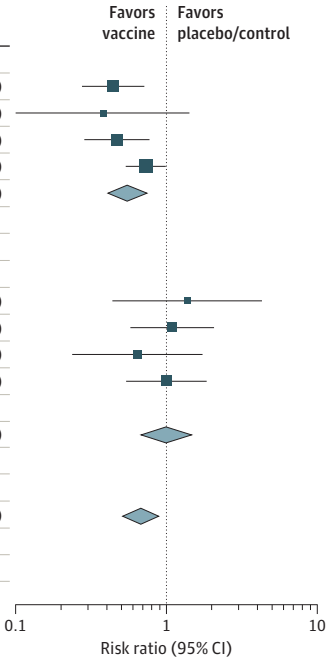
Study or subgroup	Vaccine Events	Vaccine Total	Placebo/control Events	Placebo/control Total	Risk ratio, (95% CI)	Weight, %
Previous trials						
Govaert et al,[22] 1994	7	927	5	911	1.38 (0.44-4.32)	3.6
Gurfinkel et al,[19] 2004	32	145	54	147	0.60 (0.41-0.87)	24.9
Ciszewski et al,[20] 2008	16	325	30	333	0.55 (0.30-0.98)	12.1
De Villiers et al,[23] 2009	20	1620	20	1622	1.00 (0.54-1.85)	11.1
Phrommintikul et al,[21] 2011	20	221	42	218	0.47 (0.29-0.77)	15.9
Total events	95	3238	151	3231	0.64 (0.48-0.86)	67.6
Heterogeneity: $\tau^2 = 0.03$; $\chi^2 = 5.59$, df = 4 ($P = .23$); $I^2 = 28\%$						
Test for overall effect: z = 2.93 ($P = .003$)						
Large cardiovascular outcome trial						
Frøbert et al,[7] 2021	67	1272	91	1260	0.73 (0.54-0.99)	32.4
Total events	67	1272	91	1260	0.73 (0.54-0.99)	32.4
Heterogeneity: not applicable						
Test for overall effect: z = 2.02 ($P = .04$)						
Total events	162	4510	242	4491	0.66 (0.53-0.83)	100
Heterogeneity: $\tau^2 = 0.01$; $\chi^2 = 6.19$, df = 5 ($P = .29$); $I^2 = 19\%$						
Test for overall effect: z = 3.66 ($P = .0003$)						
Test for subgroup differences: $\chi^2 = 0.35$; df = 1 ($P = .55$); $I^2 = 0\%$						



Square data markers represent risk ratios; horizontal lines, 95% CIs, with marker size reflecting the statistical weight of the study using random-effects meta-analysis. Diamond data markers represent each subgroup and overall risk ratio with 95% CIs for the outcome of interest. Evaluated using the random-effects Mantel-Haenszel test. Heterogeneity variance τ^2 calculated using the DerSimonian-Laird estimator. Risk of bias evaluated using standard Cochrane criteria: A, random sequence generation (selection bias); B, allocation concealment (selection bias); C, masking of participants and personnel (performance bias); D, masking of outcome assessment (detection bias); E, incomplete outcome data (attrition bias); F, selective reporting (reporting bias); G, other bias. Red indicates high risk of bias, yellow indicates unclear risk of bias, and green indicates low risk of bias.

Figure 2. Major Adverse Cardiovascular Events Comparing Influenza Vaccine vs Control Stratified by History of Recent Acute Coronary Syndrome (ACS)

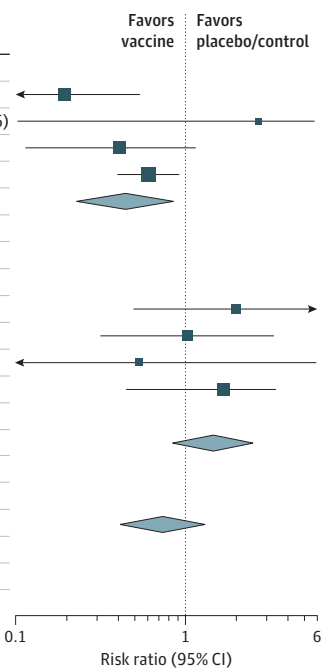
Study or subgroup	Vaccine Events	Vaccine Total	Placebo/control Events	Placebo/control Total	Risk ratio, (95% CI)	Weight, %
Recent ACS						
Gurfinkel et al,[19] 2004	18	96	41	97	0.44 (0.28-0.71)	17.5
Ciszewski et al,[20] 2008	3	83	7	74	0.38 (0.10-1.42)	3.9
Phrommintikul et al,[21] 2011	20	221	42	218	0.47 (0.29-0.77)	16.7
Frøbert et al,[7] 2021	67	1266	91	1258	0.73 (0.54-0.99)	25.2
Total events	108	1666	181	1647	0.55 (0.41-0.75)	63.4
Heterogeneity: $\tau^2 = 0.03$; $\chi^2 = 4.50$, df = 3 ($P = .21$); $I^2 = 33\%$						
Test for overall effect: $z = 3.78$ ($P < .001$)						
Stable outpatients						
Govaert et al,[22] 1994	7	927	5	911	1.38 (0.44-4.32)	5.0
Gurfinkel et al,[19] 2004	14	49	13	50	1.10 (0.58-2.09)	12.3
Ciszewski et al,[20] 2008	6	242	10	259	0.64 (0.24-1.74)	6.4
De Villiers et al,[23] 2009	20	1620	20	1622	1.00 (0.54-1.85)	13.0
Frøbert et al,[7] 2021	0	6	0	2	Not estimable	
Total events	47	2844	48	2844	1.00 (0.68-1.47)	36.6
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 1.14$, df = 3 ($P = .77$); $I^2 = 0\%$						
Test for overall effect: $z = 0.02$ ($P = .98$)						
Total events	155	4510	229	4491	0.68 (0.52-0.90)	100
Heterogeneity: $\tau^2 = 0.05$; $\chi^2 = 11.27$, df = 7 ($P = .13$); $I^2 = 38\%$						
Test for overall effect: $z = 2.73$ ($P = .006$)						
Test for subgroup differences: $\chi^2 = 5.65$; df = 1 ($P = .02$); $I^2 = 82.3\%$						



Square data markers represent risk ratios; horizontal lines, the 95% CIs with marker size reflecting the statistical weight of the study using random-effects meta-analysis. Diamond data markers represent each subgroup and overall risk ratio and 95% CIs for the outcome of interest. Evaluated using the random-effects Mantel-Haenszel test. Heterogeneity variance τ^2 calculated using the DerSimonian-Laird estimator.

Figure 3. Cardiovascular Mortality Comparing Influenza Vaccine vs Control Stratified by History of Recent Acute Coronary Syndrome (ACS)

Study or subgroup	Vaccine Events	Vaccine Total	Placebo/control Events	Placebo/control Total	Risk ratio, (95% CI)	Weight, %
Recent ACS						
Gurfinkel et al,[19] 2004	4	96	21	97	0.19 (0.07-0.54)	14.1
Ciszewski et al,[20] 2008	1	83	0	74	2.68 (0.11-64.76)	2.9
Phrommintikul et al,[21] 2011	5	221	12	218	0.41 (0.15-1.15)	14.2
Frøbert et al,[7] 2021	34	1266	56	1258	0.60 (0.40-0.92)	22.8
Total events	44	1666	89	1647	0.44 (0.23-0.85)	54.0
Heterogeneity: $\tau^2 = 0.18$; $\chi^2 = 5.29$, df = 3 ($P = .15$); $I^2 = 43\%$						
Test for overall effect: $z = 2.45$ ($P = .01$)						
Stable outpatients						
Govaert et al,[22] 1994	6	927	3	911	1.97 (0.49-7.84)	10.3
Gurfinkel et al,[19] 2004	5	49	5	50	1.02 (0.32-3.31)	12.4
Ciszewski et al,[20] 2008	1	242	2	259	0.54 (0.05-5.86)	4.7
De Villiers et al,[23] 2009	20	1620	12	1622	1.67 (0.82-3.40)	18.5
Frøbert et al,[7] 2021	0	6	0	2	Not estimable	
Total events	32	2844	22	2844	1.45 (0.84-2.50)	46.0
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 1.35$, df = 3 ($P = .72$); $I^2 = 0\%$						
Test for overall effect: $z = 1.35$ ($P = .18$)						
Total events	76	4510	111	4491	0.74 (0.41-1.30)	100
Heterogeneity: $\tau^2 = 0.33$; $\chi^2 = 16.55$, df = 7 ($P = .02$); $I^2 = 58\%$						
Test for overall effect: $z = 1.05$ ($P = .29$)						
Test for subgroup differences: $\chi^2 = 7.52$; df = 1 ($P = .006$); $I^2 = 86.7\%$						



Square data markers represent risk ratios; horizontal lines, the 95% CIs with marker size reflecting the statistical weight of the study using random-effects meta-analysis. Diamond data markers represent each subgroup and overall risk ratio and 95% CIs for the outcome of interest. Evaluated using the random-effects Mantel-Haenszel test. Heterogeneity variance τ^2 calculated using the DerSimonian-Laird estimator.

sizeable. Therefore, it is likely that the forthcoming improved vaccine technologies have the potential to increase this protective benefit.

It is important to evaluate new influenza vaccine platforms for their potential impact on cardiovascular outcomes. Until then, we urge clinicians to continue counselling their high-risk patients on the cardiovascular benefits of seasonal influenza vaccination, especially given the historically low uptake of this low-cost and well-tolerated intervention.[21-23]

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Author Contributions: Ms Behrouzi and Dr Udell had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: All authors.

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Drafting of the manuscript: Behrouzi.

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Supervision: Cannon, Vardeny, Lee, Solomon, Udell.

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REFERENCES

1. Behrouzi B, Araujo Campoverde MV, Liang K, et al. Influenza vaccination to reduce cardiovascular morbidity and mortality in patients with COVID-19: JACC state-of-the-art review. *J Am Coll Cardiol*. 2020;76(15):1777-1794. doi:10.1016/j.jacc.2020.08.028

2. Corrales-Medina VF, Madjid M, Musher DM. Role of acute infection in triggering acute coronary syndromes. *Lancet Infect Dis*. 2010;10(2):83-92. doi:10.1016/S1473-3099(09)70331-7

3. Chow EJ, Rolfes MA, O'Halloran A, et al. Acute cardiovascular events associated with influenza in hospitalized adults: a cross-sectional study. *Ann Intern Med*. 2020;173(8):605-613. doi:10.7326/M20-1509

4. Udell JA, Zawi R, Bhatt DL, et al. Association between influenza vaccination and cardiovascular outcomes in high-risk patients: a meta-analysis. *JAMA*. 2013;310(16):1711-1720. doi:10.1001/jama.2013.279206

5. Fröbert O, Götberg M, Erlinge D, et al. Influenza vaccination after myocardial infarction: a randomized, double-blind, placebo-controlled, multicenter trial. *Circulation*. 2021;144(18):1476-1484. doi:10.1161/CIRCULATIONAHA.121.057042

6. World Health Organization Global Influenza Surveillance and Response System (GISRS). Influenza Laboratory Surveillance Information. Published 2022. Accessed September 30, 2021. https://apps.who.int/flumart/Default?ReportNo=7

7. Higgins JPT, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928-d5928. doi:10.1136/bmj.d5928

8. 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(1):25-31. doi:10.1016/j.ehj.2003.10.018

9. Ciszewski A, Bilinska ZT, Brydak LB, et al. Influenza vaccination in secondary prevention from coronary ischaemic events in coronary artery disease: FLUCAD study. *Eur Heart J*. 2008;29(11):1350-1358. doi:10.1093/eurheartj/ehm581

10. 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(14):1730-1735. doi:10.1093/eurheartj/ehr004

11. Govaert TM, Thijs CT, Masurel N, Sprenger MJ, Dinant GJ, Knottnerus JA. The efficacy of influenza vaccination in elderly individuals: a randomized double-blind placebo-controlled trial. *JAMA*. 1994;272(21):1661-1665. doi:10.1001/jama.1994.03520210045030

12. De Villiers PJT, Steele AD, Hiemstra LA, et al; LAIV Elderly Study Trial Network. Efficacy and safety of a live attenuated influenza vaccine in adults 60 years of age and older. *Vaccine*. 2009;28(1):228-234. doi:10.1016/j.vaccine.2009.09.092

13. Vardeny O, Kim K, Udell JA, et al; INVESTED Committees and Investigators. Effect of high-dose trivalent vs standard-dose quadrivalent influenza vaccine on mortality or cardiopulmonary hospitalization in patients with high-risk cardiovascular disease: a randomized clinical trial. *JAMA*. 2021;325(1):39-49. doi:10.1001/jama.2020.23649

14. Behrouzi B, Udell JA. Universal flu vaccines: a shot at lifelong cardioprotection? *Nat Rev Cardiol*. 2022;19(3):145-146. doi:10.1038/s41569-021-00670-w

15. Hollingsworth R, Palmu A, Pepin S, et al. Effectiveness of the quadrivalent high-dose influenza vaccine for prevention of cardiovascular and respiratory events in people aged 65 years and above: rationale and design of a real-world pragmatic randomized clinical trial. *Am Heart J*. 2021;237:54-61. doi:10.1016/j.ahj.2021.03.007

16. Loeb M, Dokainish H, Dans A, et al; IVVE investigators. Randomized controlled trial of influenza vaccine in patients with heart failure to reduce adverse vascular events (IVVE): rationale and design. *Am Heart J*. 2019;212:36-44. doi:10.1016/j.ahj.2019.02.009

17. Feasibility of randomizing Danish citizens aged 65-79 years to high-dose quadrivalent influenza vaccine vs standard-dose quadrivalent influenza vaccine in a pragmatic registry-based setting (DANFLU-1). ClinicalTrials.gov identifier: NCT05048589. Updated October 8, 2021. Accessed October 11, 2021. https://clinicaltrials.gov/ct2/show/NCT05048589

18. Toback S, Galiza E, Cosgrove C, et al; 2019nCoV-302 Study Group. Safety, immunogenicity, and efficacy of a COVID-19 vaccine (NVX-CoV2373) co-administered with seasonal influenza vaccines: an exploratory substudy of a randomised, observer-blinded, placebo-controlled, phase 3 trial. *Lancet Respir Med*. 2022;10(2):167-179. doi:10.1016/S2213-2600(21)00409-4

19. Massare MJ, Patel N, Zhou B, Maciejewski S, Flores R, Guebre-Xab M. Combination respiratory vaccine containing recombinant Sars-CoV-2 spike and quadrivalent seasonal influenza hemagglutinin nanoparticles with matrix-m adjuvant. *bioRxiv*. Preprint posted May 5, 2021. doi:10.1101/2021.05.05.442782

20. Moderna announces significant advances across industry-leading mRNA portfolio at 2021 R&D Day. Moderna press release. Published September 9, 2021. Accessed February 7, 2022. https://investors.modernatx.com/news/news-details/2021/Moderna-Announces-Significant-Advances-Across-Industry-Leading-mRNA-Portfolio-at-2021-RD-Day-09-09-2021/default.aspx

21. Bhatt AS, Liang L, DeVore AD, et al. Vaccination trends in patients with heart failure: insights from get with the guidelines-heart failure. *JACC Heart Fail*. 2018;6(10):844-855. doi:10.1016/j.jchf.2018.04.012

22. Panhwar MS, Kalra A, Gupta T, et al. Effect of influenza on outcomes in patients with heart failure. *JACC Heart Fail*. 2019;7(2):112-117. doi:10.1016/j.jchf.2018.10.011

23. Tripathi B, Kumar V, Kalra A, et al. Influence of influenza infection on in-hospital acute myocardial infarction outcomes. *Am J Cardiol*. 2020;130:7-14. doi:10.1016/j.amjcard.2020.05.045