ORIGINAL ARTICLE

Effect of Influenza Vaccination in Patients with Cardiovascular Disease: An Updated Meta-Analysis of Randomized Controlled Trials

Efecto de la vacunación contra la influenza en pacientes con enfermedad cardiovascular: un metaanálisis actualizado de ensayos clínicos controlados aleatorizados

LUCRECIA M. BURGOS[1], EZEQUIEL J. ZAIDEL[MTSAC, 2], ÁLVARO SOSA LIPRANDI[MTSAC,2], ADRIÁN BARANCHUK[3]

ABSTRACT

Background: Influenza is a major cause of morbidity and mortality in patients with cardiovascular disease (CVD). The aim of this updated systematic review and meta-analysis was to evaluate the effect of influenza vaccination (IV) on morbidity and morbidity in adult patients with CVD.
Methods: We conducted a systematic review and meta-analysis (PubMed, Cochrane Library, International Clinical Trials Registry Platform, and manual search of conference presentations) of randomized clinical trials published up to April 2022 analyzing whether IV reduced all-cause mortality in adult patients with CVD, including heart failure (HF) and coronary artery disease (CAD), compared with patients who were not vaccinated.
Results: A total of six clinical trials comprising 9316 patients were analyzed. Five trials included CAD patients, and one trial included HF patients. Mean follow-up was 16 ± 9.7 months. Influenza vaccine was associated with a reduction of mortality compared to controls: relative risk (RR) 0.67, 95% confidence interval (95% CI), 0.47-0.95; p = 0.03; I^2 = 53%, and with reduction of cardiovascular death compared to controls: RR 0.64; 95% CI 0.44-0.94; p = 0.02; I^2 = 54%. There was a non-statistically significant reduction in myocardial infarction compared to control: RR 0.82, 95% CI 0.60-1.12; p = 0.57; I^2 = 0%.
Conclusion: In this meta-analysis of six randomized controlled clinical trials, IV was associated with a 33% and 36% relative risk reduction of all-cause mortality and cardiovascular death, respectively, in patients with CVD. We sought to promote consensus about the persistent benefits of influenza vaccination in patients with CVD by including two new clinical trials in CAD and HF, confirming the association of vaccination with risk reduction in subjects with CVD.

Keywords: Influenza - Influenza Vaccines - Cardiovascular Diseases/Mortality - Myocardial Infarction

RESUMEN

Introducción: La influenza es una causa importante de morbilidad y mortalidad en pacientes con enfermedades cardiovasculares (ECV). El objetivo de esta revisión sistemática actualizada y metaanálisis fue evaluar los efectos de la vacunación contra la influenza (VI) sobre la mortalidad y morbilidad en pacientes adultos con ECV.
Métodos: Se realizó una revisión sistemática y un metaanálisis (PubMed, Cochrane Library, International Clinical Trials Registry Platform, y búsqueda manual en presentaciones en congresos de la especialidad), de ensayos clínicos aleatorizados publicados hasta abril de 2022 que investigaron si la VI reduce la mortalidad por todas las causas en pacientes adultos con ECV, incluyendo insuficiencia cardíaca (IC) y enfermedad de las arterias coronarias (EAC), en comparación con pacientes que no fueron vacunados.
Resultados: Se analizaron un total de seis ensayos clínicos, que incluyeron 9316 pacientes. Cinco ensayos incluyeron pacientes con EAC, y uno con IC. El seguimiento medio fue de 16 ± 9,7 meses. La VI se asoció con una reducción de la mortalidad en comparación con el control, cociente de riesgos (RR) 0,67, intervalo de confianza del 95% (IC95%) 0,47-0,95; , p = 0,03; I^2 = 53%; y con una reducción de la mortalidad cardiovascular en comparación con el control, RR 0,64; IC95% 0,44-0,94; p = 0,02; I^2 = 54%. El uso de la VI se asoció con una reducción no estadísticamente significativa de infarto de miocardio en comparación con el control, RR 0,82; IC95% 0,60-1,12; p = 0,57; I^2 = 0%.
Conclusión: En este metaanálisis de seis ensayos controlados aleatorizados, la VI se asoció con una reducción del riesgo relativo del 33% y del 36% de la mortalidad por todas las causas y cardiovascular, respectivamente, en pacientes con ECV. Intentamos promover un consenso con respecto a los beneficios persistentes de la vacuna contra la influenza en pacientes con ECV, incluyendo dos nuevos ensayos clínicos en EAC e IC, donde se confirma la asociación de la vacunación con la reducción de riesgo en sujetos con ECV.

Palabras clave: Gripe Humana - Vacunas contra la Influenza - Enfermedades Cardiovasculares/Mortalidad - Infarto del Miocardio

Argent J Cardiol 2023;91:5-17. http://dx.doi.org/10.7775/rac.v91.i1.20605

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Received: 11/22/2022 – *Accepted:* 12/13/2022

Address for reprints: Lucrecia María Burgos. lburgos@icba.com.ar. Instituto Cardiovascular de Buenos Aires, Blanco Encalada 1543, CABA. CP1428

[1] Department of Heart Failure, Pulmonary Hypertension and Heart Transplantation, Instituto Cardiovascular de Buenos Aires, Argentina
[2] Department of Cardiology. Sanatorio Güemes, Argentina, and School of Medicine, University of Buenos Aires.
[3] Department of Cardiology, Kingston Health Science Center, Queen's University, Kingston, Ontario, Canada
This article received the Dr. Pedro Cossio Award in the 48º Argentine Congress of Cardiology

INTRODUCTION

Although influenza is primarily considered a viral infection usually limited to the respiratory system, several cardiovascular complications have been described. (1) Cardiovascular disease (CVD) and influenza have been associated for a long time due to an overlap in the peak incidence of each disease in the winter months. (2) Epidemiological studies observed an increase in cardiovascular (CV) mortality during influenza outbreaks, indicating that CV complications of influenza, including exacerbation of heart failure (HF), acute ischemic heart disease, and, less often, other CV manifestations (stroke, cardiac arrhythmias, venous thromboembolism, or myocarditis), are important contributors to morbidity and mortality during influenza virus infection. (3)

The connection between heart disease and influenza is complex: it can occur via the inflammation-thrombosis pathway, direct effects of the virus on the myocardium, or exacerbation of pre-existing CV disease. (4) The mechanisms postulated to explain the increased risk of vascular events include precipitating plaque rupture, endothelial dysfunction, triggering of other latent infections contributing to plaque rupture, triggering of the procoagulant pathway, tachycardia and vasodilation associated with fever, and infection-related metabolic disorders, including elevated triglyceride and blood glucose levels. (5,6)

Influenza vaccination (IV) is a well-established strategy for reducing influenza-related morbidity and mortality patients with CVD. (7,8) Based on observational studies and randomized clinical trials, vaccination has been associated with significant reductions in all-cause mortality and major adverse cardiovascular events. (9-12)

Currently, the World Health Organization, the Centers for Disease Control and Prevention, the American Heart Association/American College of Cardiology, and the European Society of Cardiology recommend annual influenza vaccination for patients with established CVD. (13-15) In 2021, the Inter-American Society of Cardiology published a consensus statement on IV and CVD, (16) citing the most recent meta-analysis with 4 randomized clinical trials that showed that IV was associated with a reduction in cardiovascular events, (17) and another meta-analysis based on observational data from HF patients, which had consistent findings. (18)

Because two new clinical trials have been recently published in the last two years, we decided to perform an updated meta-analysis of randomized clinical trials on the impact of IV on CV mortality and outcomes in patients with CVD.

OBJECTIVE

Our primary objective was to perform a systematic review and meta-analysis of randomized clinical trials to evaluate the effect of IV on mortality in patients with CVD. The secondary objective was to evaluate the effect of IV on CV mortality, myocardial infarction, and major adverse cardiovascular events (MACE) in patients with HF and coronary artery disease (CAD).

METHODS

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist was used to perform and report this systematic review. (19)

Search method for identification of studies

A systematic search was conducted to identify articles published up to April 2022 in MEDLINE (PubMed database), the Cochrane Library, and the International Clinical Trials Registry Platform. We searched the following keywords or MESH terms in the title or abstract: "influenza," "influenza vaccine," "vaccine," "myocardial infarction," "coronary artery disease," "acute coronary syndrome," "heart failure," and "congestive heart disease".

We performed manual searches checking the reference list of all the relevant publications to ensure complete collection of relevant articles, and we also reviewed recent presentations at international cardiovascular congresses.

Selection of relevant studies for inclusion

Two reviewers (LMB, EJZ) independently screened titles and abstracts to identify potentially relevant articles. Any discrepancy in the data collected was resolved via discussion. Full-text articles were included in this review if they met all the following inclusion criteria: (1) randomized clinical trials comparing influenza vaccination with placebo or no intervention when data on one of the outcomes were reported; (2) articles providing data on the effectiveness of influenza vaccination in patients with HF or CAD compared with an unvaccinated control group; (3) influenza vaccination was administered within one year after study enrollment; (4) articles published in English or Spanish language.

We excluded duplicates, studies that included patients with different doses of influenza vaccination but without an unvaccinated arm, and all nonrandomized controlled trials.

Type of participants

Participants >18 years with established CVD; HF or (CAD stable or unstable angina and ST-segment elevation or non-ST-elevation myocardial infarction) were included in the study.

Outcome measures

The primary outcome measure was all-cause mortality, while the secondary outcome measure was CV mortality, myocardial infarction, and major adverse cardiovascular events (MACE) among vaccinated and unvaccinated patients with HF and CAD.

Data collection and management

Two reviewers independently extracted data and all disagreements were resolved by discussion or arbitration. The following data were systematically extracted:

- Trial characteristics: design, duration, region, scope, year of publication.
- Intervention: type and method of vaccination, control intervention.
- Participants: number of participants, inclusion and exclusion criteria, total number and number in comparison groups, baseline characteristics (age, sex, cardiovascular

risk factors, cardiovascular medication).
- Results: primary and secondary outcomes according to trial, myocardial infarction or reinfarction, unstable angina, cardiovascular death, and related outcomes.

Any discrepancy in data extraction was resolved via discussion with another author (ASL).

Subgroup analysis
A subgroup analysis was performed to compare the effects of vaccination on mortality in patients with HF and CAD.

Bias assessment
Bias was independently assessed by two investigators. We assessed evidence of bias of randomized controlled trials with the Cochrane risk of bias tool, (20,21) with evaluation of the following criteria: random sequence generation (adequate method), allocation concealment, blinding of participants and personnel, management of incomplete outcome data, loss to follow-up or withdrawal from the study, intention-to-treat analysis, selective reporting, similarity in baseline characteristics, any other observed biases.

Measures of treatment effect
All outcome measures were dichotomous results and were presented as risk ratios (RR) at the last follow-up reported.

Heterogeneity assessment
Heterogeneity between trials was quantified with the I^2 statistics, which is independent of the number of studies in a meta-analysis, and with the chi-square test, with significance levels set at a value of $p = 0.1$. An I^2 value > 50% meant significant heterogeneity between studies. (22)

Data synthesis
Based on heterogeneity test, the pooled RR was calculated using fixed effects model when there was no heterogeneity and random effects model in case of heterogeneity.

Statistical analysis
All outcome measures were dichotomous results and were presented as risk ratios (RR) and 95% confidence intervals (95% CI) at the last follow-up reported.

Two-tailed p value < 0.05 was considered statistically significant.

Publication bias was estimated in case there were more than 10 studies by visual assessment in the funnel plot. Egger's regression test was used to examine the asymmetry of the funnel plot. (23)

The selection process was carried out using the Reference Manager Rayyan QCRI. (24) All data extracted from the included studies were entered into Review Manager (RevMan 5.3).

Ethical considerations
This review does not contain any direct interaction with human participants.

RESULTS
Search results
A total of 957 studies were identified through literature search; 527 studies were selected and 486 were excluded after an initial screening of titles and abstracts. The remaining 41 publications were reviewed in full text and evaluated according to the inclusion criteria. Finally, 6 trials were selected for the quantitative analysis. (25-30)

The search and selection process is represented in a PRISMA flow diagram (Figure 1).

Characteristics the studies included
A total of six clinical trials comprising 9316 patients were analyzed. Five trials included CAD patients (FLUVACS, FLUCAD, IVCAD, IAMI and Phrommintikul et al.), and the IVVE trial included HF patients. Mean follow-up was 16 ± 9.7 months. Table 1 summarizes the main general characteristics of the trials. A description of each study included in the meta-analysis can be found in Table 1 of the supplementary material.

Risk of bias in included studies
Risk of bias across studies is shown in Figure 1 of the supplementary material, and risk of bias within studies is shown in Figure 2 of the supplementary material.

Effects of influenza vaccination
Primary outcome measure: All-cause mortality.

Influenza vaccine was associated with lower mortality compared to control: RR 0.67, 95% CI 0.47-0.95; $p = 0.03$; $I^2 = 53\%$ (Figure 2)..

Secondary outcome measure: Cardiovascular death, myocardial infarction and MACE

Influenza vaccine was associated with lower cardiovascular death compared to control: RR 0.64, 95% CI 0.44-0.94; $p = 0.02$; $I^2 = 54\%$ (Figure 3), and with reduction of MACE: RR 0.69, 95% CI 0-53-0.90; $p = 0.007$; $I^2 = 68\%$ (Figure 4). There was a non-statistically significant reduction in myocardial infarction compared to control: RR 0.82, 95% CI 0.60-1.12; $p = 0.57$; $I^2 = 0\%$ (Figure 5).

Subgroup analysis

A subanalysis of overall mortality was performed comparing IV vs. control, stratified by history of CAD and HF. This effect was not consistent between the two study populations: in HF, RR 0.91 (95% CI 0.80-1.02; $p = 0.1$) and in CAD RR 0.56 (95% CI 0.41-0.76; $p = 0.0002$), p for interaction = 0.004. (Figure 3 of the supplementary material).

DISCUSSION
In this updated meta-analysis of controlled clinical trials including 9316 patients with CAD or HF, IV was associated with a significant reduction in all-cause mortality, cardiovascular death, and MACE. Vaccinated patients presented a non-significant reduction in the incidence of acute myocardial infarction.

The information about the association of influenza and CVD is conclusive, but its mechanisms are still under study. Yet, the inflammation-thrombosis model seems to be the most widely accepted one. Other fac-

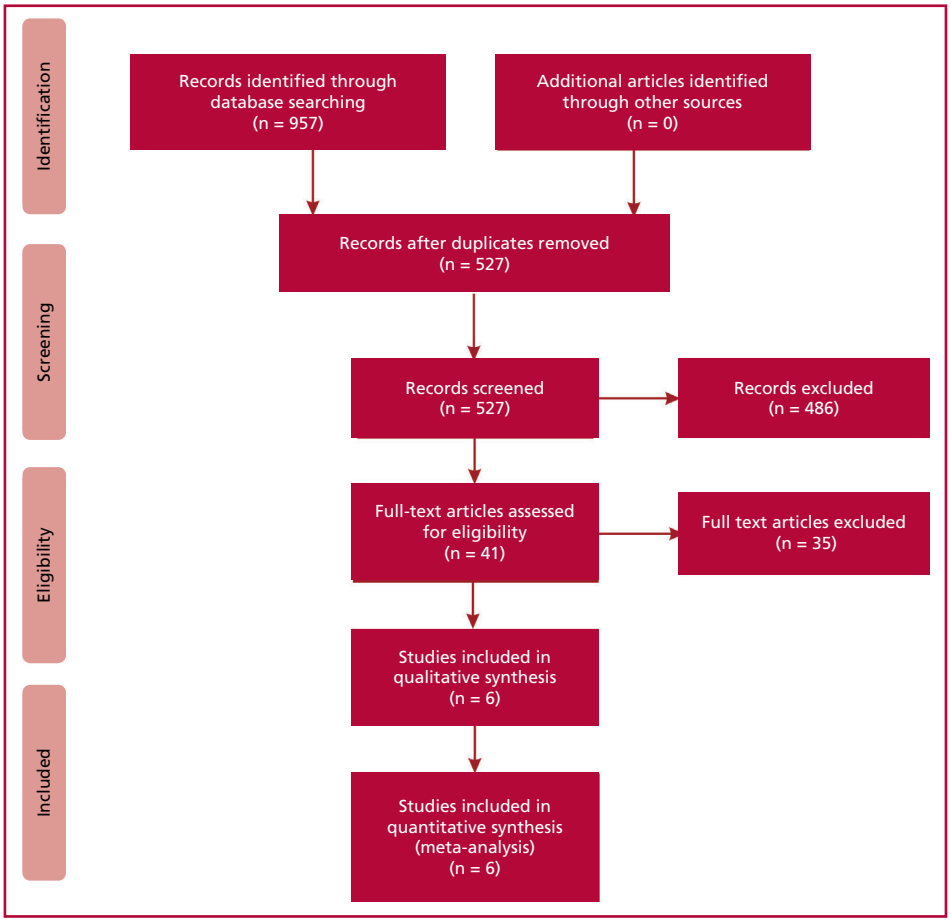

Fig. 1. PRISMA flow diagram for the selection procedure for elegible studies.

tors, such as increased metabolic demand due to the adrenergic surges and hyperdynamic CV response, and hypoxia secondary to pulmonary infection also seem to play an important role. (31,32)

Since the pioneering study conducted in Argentina by Gurfinkel et al. was published in 2004 (25) and then incorporated as the main and only evidence in the CDC guidelines in the United States in 2009, (33) IV has been gradually established as a prevention strategy for CV events.

Some recognized limitations to broaden the use of IV include uncertainty about external validity, reproducibility in different regions, climates, and high and low resource countries, and the safe use in the setting of an acute event or its efficacy in subjects with HF. These factors led to the development of the new clinical trials evaluated here.

In addition, although the recommendation for IV is not new, it is still sub-optimally accepted. In the United States, only 50% of patients with CAD received IV, with important disparities according to socioeconomic determinants. (34) Similarly, one third of those hospitalized for HF did not receive IV. (35)

We compared the results of our meta-analysis with those of previous publications. A Cochrane review published in 2015 of four secondary prevention trials included 1682 patients with CVD and reported reduction in CV mortality (RR 0.45; 95% CI, 0.26- 0.76), but not in AMI. (36) More recently, in 2021 a meta-analysis of these four randomized trials and 12 observational studies including more than 237 000 patients with CVD, reported that influenza vaccination was associated with significant reductions in the risk of all-cause mortality, CV mortality, and MACE at a median follow-up of 20 months. (17)

We believe that the main findings of this meta-analysis are confirming that the benefit of reducing all-cause mortality and cardiovascular death and the trend towards a reduction in the risk of myocardial infarction remains after including new randomized clinical trials involving more than 7000 subjects. The benefit in reducing events is also maintained when two populations that were not previously evaluated are included in the meta-analysis: subjects with a recent coronary event (IAMI trial) and subjects with heart failure (IVVE trial).

As for the IAMI study, (29) the indication of IV in subjects with coronary artery disease was supported by different clinical trials and previous meta-analyses; however, the authors proposed the strategy of indicating IV during hospitalization due to an acute coronary event, demonstrating the safety and efficacy of this

Table 1. Characteristics of the studies included in the meta-analysis.

Studies	Patients	Age, mean (SD)	Men, %	Follow-up, months	N° in the control cohort	N° in the control cohort	N° in the intervention group	Region
FLUVACS 2004 (25)	ACS (66%) or stable CAD and planned PCI (34%)	65 (NR)	79.4%	12	147	147	145	Argentina
FLUCAD 2008 (26)	56% with stable CAD, 24% with PCI for ACS, 20% with PCI for stable angina	60 (10)	72.5%	12	333	333	325	Poland
IVCAD 2009 (27)	Hospitalized patients and outpatients with recent ACS or stable CAD	55 (9)	66%	12	131	131	135	Iran
Phrommintikul et al., 2011 (28)	47%, 36% STEMI, 16% with unstable angina	66 (9)	56%	12	218	218	221	Thailand
IAMI 2021 (29)	Hospitalized patients and outpatients with recent ACS (STEMI 54.4%, NSTEMI 45.3%) or high-risk stable CAD (0.3%) Symptomatic NYHA	59,9 (11,2)	81.8%	12	1260	1260	1272	Sweden, Denmark, Norway, Latvia, United Kingdom, Czechia, Bangladesh, Australia
IVVE 2022 (30)	functional class II-IV heart failure	57 (NR)	49%	36	2569	2569	2560	India, China, Africa

ACS: acute coronary syndrome; CAD: coronary artery disease; NR: not reported; NSTEMI: non-ST-segment elevation myocardial infarction; NYHA: New York Heart Association; PCI: percutaneous coronary intervention; SD: standard deviation; STEMI: ST-segment elevation myocardial infarction.

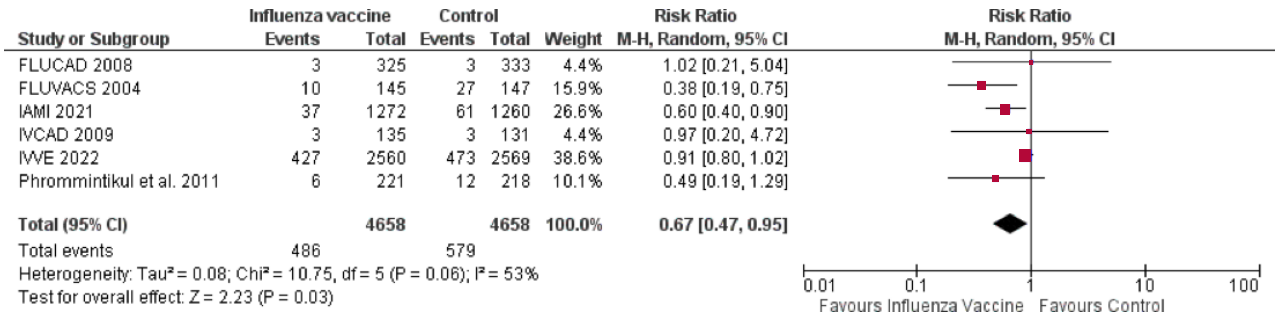

Fig. 2. Forest plot of the effect of influenza vaccine versus placebo on all-cause mortality

strategy. The indication of vaccination during hospitalization is a well-known strategy to increase adherence to vaccination, and in a previous study we have evaluated that this strategy was associated with a higher effective vaccination rate compared to office-based prescription. (37) Therefore, a possible key strategy to increase adherence would be to include influenza vaccination as part of the acute coronary syndrome discharge checklist. Checklists provide evidence-based prescribing of pharmacotherapies, (38) and adding the vaccine is key to establishing vaccination as part of standard-of-care therapy.

Our meta-analysis showed a trend towards a reduction in myocardial infarction in subjects receiving IV. The clinical trials included showed the same trend in this outcome. Possibly, one of the limitations to definitely confirm the association is the number of subjects evaluated in the clinical trials.

One of the main limitations in producing evidence about the usefulness of IV in subjects with HF was the overlap with other formal indications, mainly age: three quarters of subjects with HF have an indication for IV only because they 65 years old or greater, and at the other extreme, only 3-6% of subjects with HF are < 50 years. (39) The IVVE is the most recently presented study that is part of this meta-analysis, (30) in which the investigators included more than 5129 patients with HF with particular features: the

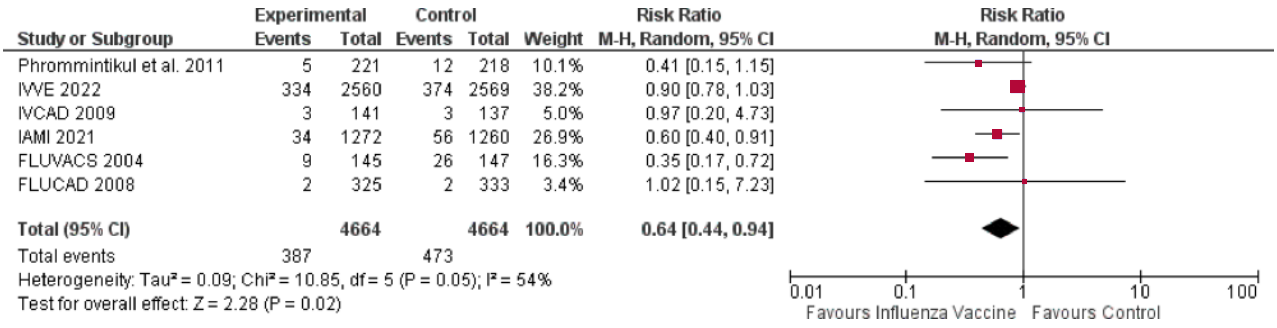

Fig. 3. Forest plot of the effect of influenza vaccine versus placebo on cardiovascular death.

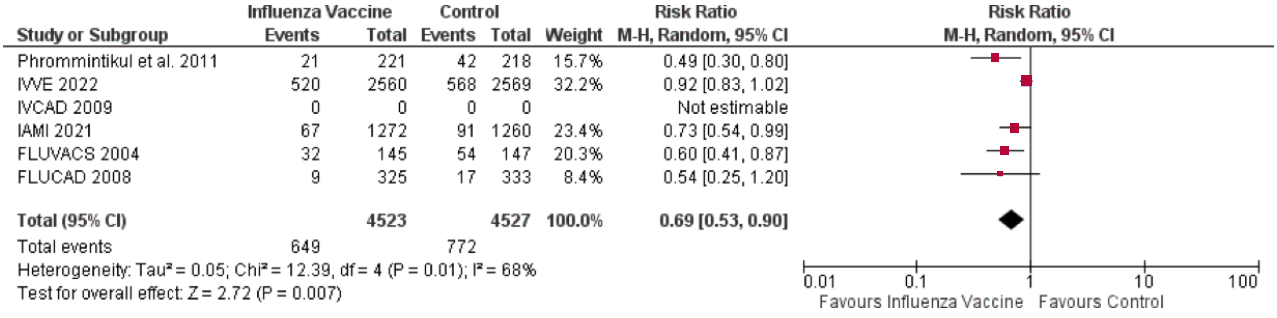

Fig. 4. Forest plot of the effect of influenza vaccine versus placebo on MACE.

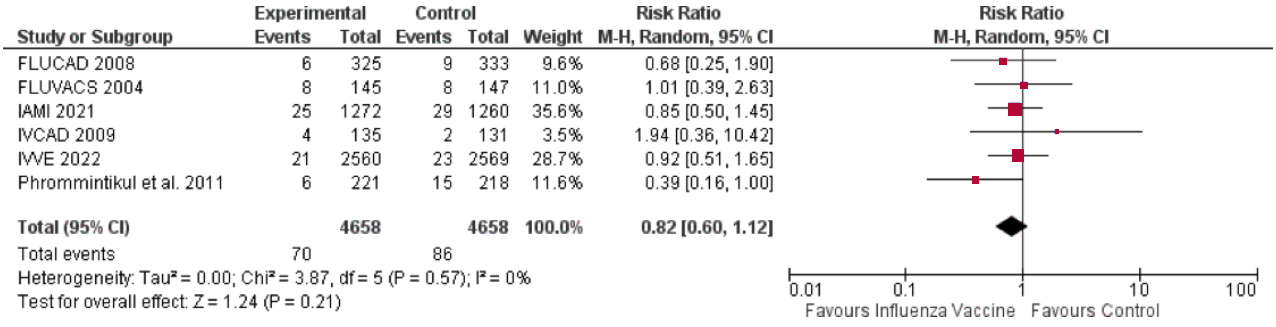

Fig. 5. Forest plot of the effect of influenza vaccine versus placebo on myocardial infarction.

average age was 57 years, and the patients came from low- and middle-income countries in Asia and Africa. The authors of the IVVE study reported a reduction in outcomes as all-cause mortality, cardiovascular death, and MACE during periods of peak circulation of influenza, and a trend towards a reduction in events throughout the duration of the study. Rather than a neutral result, this finding reinforces the pathophysiological association and strengthens the indication for IV in this population. When the overall results of this study were included in our meta-analysis, the benefits in reducing events had the same direction and magnitude of effect.

The characteristics mentioned above could explain the differences found in the stratified analysis of subgroups according to baseline CV disease. However, through this meta-analysis we cannot distinguish how many of the subjects recruited for CAD had concomitant HF and vice versa, or whether the benefit is greater or not in subjects with both clinical conditions.

To become aware of the magnitude of the findings on the effectiveness of IV in reducing events in patients with CVD, the results can be compared with those of traditional pharmacological treatments such as statins, beta-blockers and angiotensin-converting enzyme inhibitors (ACE inhibitors). (40) Cardiovascular death decreased with each treatment in the meta-analyses of the main trials: RR was 24% for statins, (41) 23% for beta-blockers, (42) and 16% for ACE inhibitors. (43) Similarly, smoking cessation reduces the

risk of CVD by 39%. (44)

The strengths of this review are the extensive systematic review of the literature performed and the inclusion of only randomized clinical trials with low risk of bias. We found low heterogeneity in the primary and secondary outcomes analyzed, probably due to the similar trial design, population included, and definition of outcomes.

However, this review has limitations. We could not assess publication bias due to the low number of studies included in the meta-analysis. The COVID-19 pandemic had an impact on recruitment, follow-up, and influenza circulation, which affected the last two large randomized clinical trials; however, the benefit in reducing major events was sustained. Few clinical trials have been included, and there is great variability in the number of subjects included and in their baseline characteristics. Nevertheless, the reduction in events was in the same direction, although with a significant difference in the magnitude of the effect. Finally, the data from the IVVE study have not been published yet in an indexed journal at the time this analysis was completed and come from the presentation at a scientific congress; therefore, the results could be modified or have a different interpretation than the one we have used for this analysis.

CONCLUSION

In this updated meta-analysis of six randomized controlled clinical trials, influenza vaccination was associated with a 33% and 36% relative risk reduction of all-cause mortality and cardiovascular death, respectively, in patients with CVD.

Over the past few decades, considerable evidence has accumulated about the cardioprotective effects of influenza vaccination in patients with established cardiovascular disease.

We sought to promote consensus based on the highest level of evidence about the persistent benefits of influenza vaccination in patients with CVD by including two new clinical trials in CAD and HF, confirming the association of vaccination with risk reduction in subjects with CVD. The present meta-analysis may help health care workers to strongly recommend influenza vaccination for secondary prevention of cardiovascular events.

Conflicts of interest

None declared.

(See authors conflicts of interest forms in the website/ Supplementary material)

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SUPPLEMENTARY MATERIAL

Supplementary material Table 1. Characteristics of the studies

FLUCAD 2008	Methods	Setting: Poland; single-center; hospitalized patients within 1 week of the coronary artery intervention before hospital discharge; outpatients vaccinated during visits to the cardiologist office. Design: individually randomized, double-blind, parallel groups.
	Participants	N:658 (325/352) completed in the intervention group and 333/333 in the control group. Patients between 30 to 80 years with coronary artery disease confirmed by angiography with ≥ 50% stenosis of 1 epicardial coronary artery. Age: Intervention group: 58.8 years (range 35 to 80); control: 58.1 years (range 32 to 80) Sex (% men): Intervention group: 71.1%; control: 73.9%.
	Interventions	Intervention group (n = 325): intramuscular single inactivated subunit influenza vaccine containing 0.5 mL dose (15 mg) hemagglutinin of each of the following strains: A/NewCaledonia/20/99 (H1N1), A/Christchurch/28/03 (H3N2), B/Jiangsu/10/03. Control group (n = 333): placebo containing all vaccine compounds except viral antigens.
	Results	Primary outcome: cardiovascular death within 12 months after vaccination Secondary outcomes: major adverse cardiac events (MACE) which was the composite of cardiovascular death, acute myocardial infarction (or coronary revascularization) and coronary ischemic event defined as a combination of MACE or hospitalization for myocardial ischaemia (MACE or hospitalization for myocardial ischemia) at 12 months), coronary revascularization, hospitalization for myocardial ischemia, myocardial infarction, adverse events.
	Notes	The study was financed by the Grant of Polish Ministry of Education and Science No. 2P05B 01627. Solvay Pharmaceuticals B.V. provided influenza vaccine and placebo vaccine.
FLUVACS 2004	Methods	Setting: Argentina; 6 centers Design: individually randomized, parallel groups
	Participants	N: 301 (292/301 /200 completed the study). Inclusion criteria: > 21 years; 2 groups: (1) patients with or without ST-segment elevation myocardial infarction (MI) within the previous 72 hours; (2) patients undergoing percutaneous coronary intervention (PCI).
	Interventions	Intervention group (n = 100 MI, 51 PCI): single intramuscular vaccination containing 0.5 ml of A/Moscow/10/99-like virus, A/New Caledonia/20/99 (H1N1)-like virus, and AB/Sichuan/379/99-like virus. Control group (100 MI, 50 PCI): saline.
	Results	Primary outcome: cardiovascular death. Secondary outcomes: composite double or triple outcome measure of cardiovascular death, non-fatal myocardial infarction, and re-hospitalization for severe recurrent ischemia.
	Notes	

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IAMI 2021	Methods	Investigator-initiated, randomized, double-blind trial. 30 centers in 8 countries (Sweden, Denmark, Norway, Latvia, United Kingdom, Czechia, Bangladesh, and Australia) from October 2016 to February 2020.
	Participants	Patients with recent MI or PCI were randomly assigned in a 1:1 ratio to receive either influenza vaccine (n = 1272) or placebo with saline (n = 1260). The trial was stopped early because of the COVID-19 pandemic on March 1, 2020 Inclusion criteria: Age ≥ 18 years. ST-segment–elevation myocardial infarction (STEMI) or non–ST-segment–elevation myocardial infarction (NSTEMI) and had completed coronary angiography or PCI. Patients with stable coronary artery disease if they were ≥75 years, and had additional risk factors Mean age of patients: 60 years. Percentage of women: 18.2%. Other outstanding features/characteristics: 35.5% current smokers. 54.5 % with STEMI, 45.2% with NSTEMI, 0.3% with stable CAD, 74.3% treated with PCI.
	Interventions	Influenza vaccine content was consistent with World Health Organization recommendations according to season and hemisphere; trivalent inactivated vaccine (Vaxigrip) in the 2016 Northern Hemisphere season and quadrivalent inactivated vaccine (Vaxigrip Tetra or FluQuadri) in the following seasons (Table I in the Data Supplement). Influenza vaccine was provided by Sanofi Pasteur, which had no role in the design or conduct of the study or in preparation or review of the article. Placebo was sterile 0.9% normal saline solution.
	Results	The primary end point was the composite of all-cause death, MI, or stent thrombosis at 12 months after randomization, assessed during a telephone interview with participants or relatives. The 3 components of the primary composite end point plus cardiovascular death, all at 12 months, were considered key secondary efficacy end points. Secondary exploratory end points included unplanned revascularization; stroke, or transient ischemic attack; the composite of cardiovascular death, MI, or stent thrombosis; and hospitalization for heart failure or for arrhythmia.
	Notes	
IVCAD 2009	Methods	Setting: Iran; medical center, inpatient and outpatient care. Design: individually randomized, parallel groups
	Participants	N: 278 (135/141 completed follow-up in the intervention group and 131/137 in the control group). Inclusion criteria: adults ≥ 25 years with stable angina and coronary artery stenosis confirmed by coronary angiography or acute, evolving or recent myocardial infarction (after recovery from the acute phase) Age: intervention group: 54.9 ± 9.0 years; control group: 54.5 ± 9.2 years. Sex (% men): intervention group: 66%, control group: 67%.
	Interventions	Intervention group (n = 141): 0.5-mL intramuscular dose of the trivalent anti-influenza vaccine (Influvac, Solvay Pharma). The vaccine contained 15 g hemagglutinin of each of the three strains, namely Solomon Islands/3/2006 (H1N1), Wisconsin/67/2005 (H3N2), and Malaysia/2506/2004 (B) according to the World Health Organization guidelines for the anti-influenza vaccination campaign of 2007–2008. Control group (n = 137): 0.5-mL intramuscular dose of placebo.
	Results	Primary outcome: acute coronary syndrome (including myocardial infarction and unstable angina), coronary revascularization, cardiovascular death. Secondary outcomes: number of influenza episodes, physiological variables, adverse events.
	Notes	

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IVVE 2022	Methods	Setting: countries in China (14%), India (23%), and Africa (40%) Design: randomized controlled trial.
	Participants	Patients >18 years with clinical diagnosis of heart failure and NYHA functional class II, III and IV. Mean age of patients: 57 years. Percentage of women: 51%. Percentage with diabetes: 23%. NYHA class II: 69%, III 26%, IV 4%. Left ventricular function: ≤ 30%: 32%, 31-39%: 24%. Previous myocardial infarction (MI): 2 1%.
	Interventions	Inactivated influenza vaccine 0.5 ml intramuscularly (n = 2560) or matching placebo (n = 2569).
	Results	Primary outcome: composite outcome of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, and heart failure hospitalizations. Secondary outcomes: cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, heart failure hospitalizations, all-cause hospitalizations, or all-cause mortality.
	Notes	Funding: Joint Global Health Trials Scheme of the UK Department for International Development, Medical Research Council, National Institute for Health Research, and the Wellcome Trust. Sanofi Pasteur provided influenza vaccine for the trial.
Phrommintikul et al. 2011	Methods	Setting: Thailand; Department of Internal Medicine, no details provided. Design: individually randomized, parallel groups. Dates and follow-up: recruitment from November 2007 to October 2008; 12-month follow-up.
	Participants	N: 442 (220/221 completed the trial in the intervention group and 217/218 in the control group). Inclusion criteria: patients > 50 years admitted with acute coronary syndrome within 8 weeks. Age: intervention group: 65 ± 9 years; control group: 67 ± 9 years. Sex (men%): intervention group: 61%; control group: 52%.
	Interventions	Intervention group (n = 221): Single-dose intramuscular injection of 0.5 mL of split, inactivated influenza vaccine (no further data provided). Control group (n = 218): absence of intervention.
	Results	Primary outcomes: cardiovascular outcomes (myocardial infarction, unstable angina, hospitalization for acute coronary syndrome, heart failure or stroke, cardiovascular death). Secondary outcomes: not reported.
	Notes	

COVID-19: coronavirus disease-2019, MACE: major adverse cardiovascular event, MI: myocardial infarction, PCI: percutaneous coronary intervention.

Supplementary material

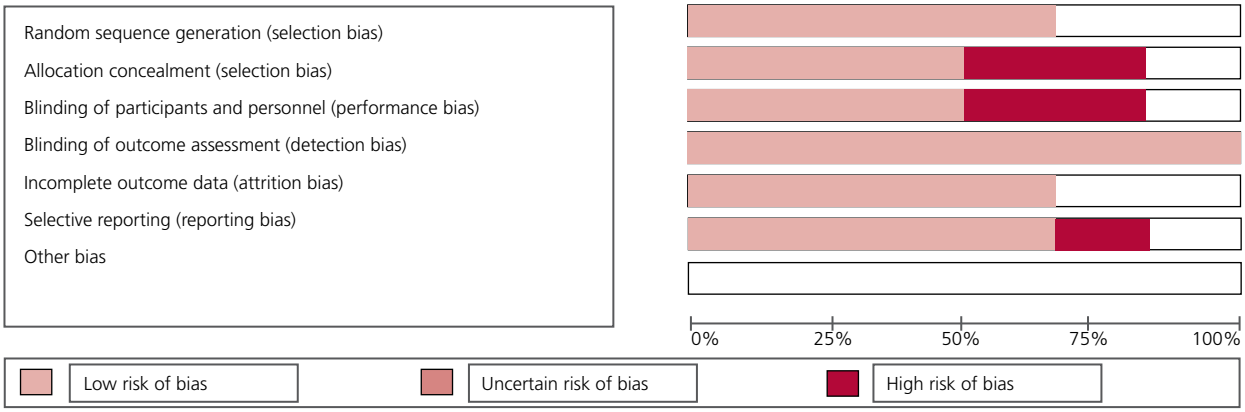

Fig. 1. Element of risk of bias in all the studies included.

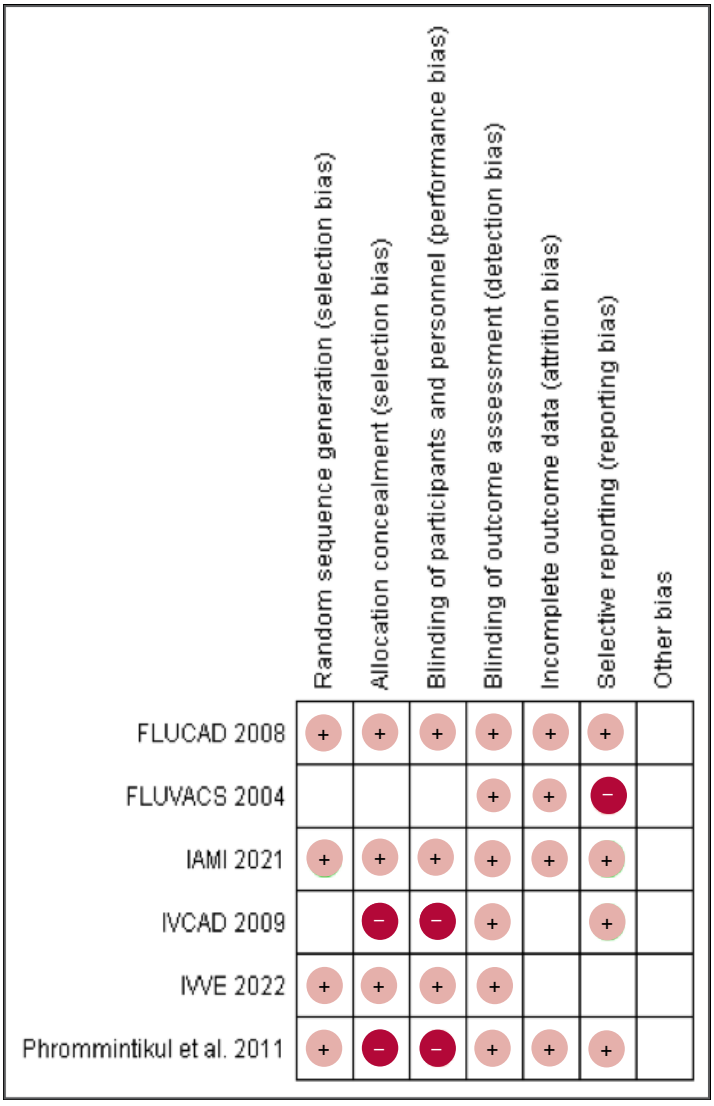

Fig. 2. Risk of bias for each study included.

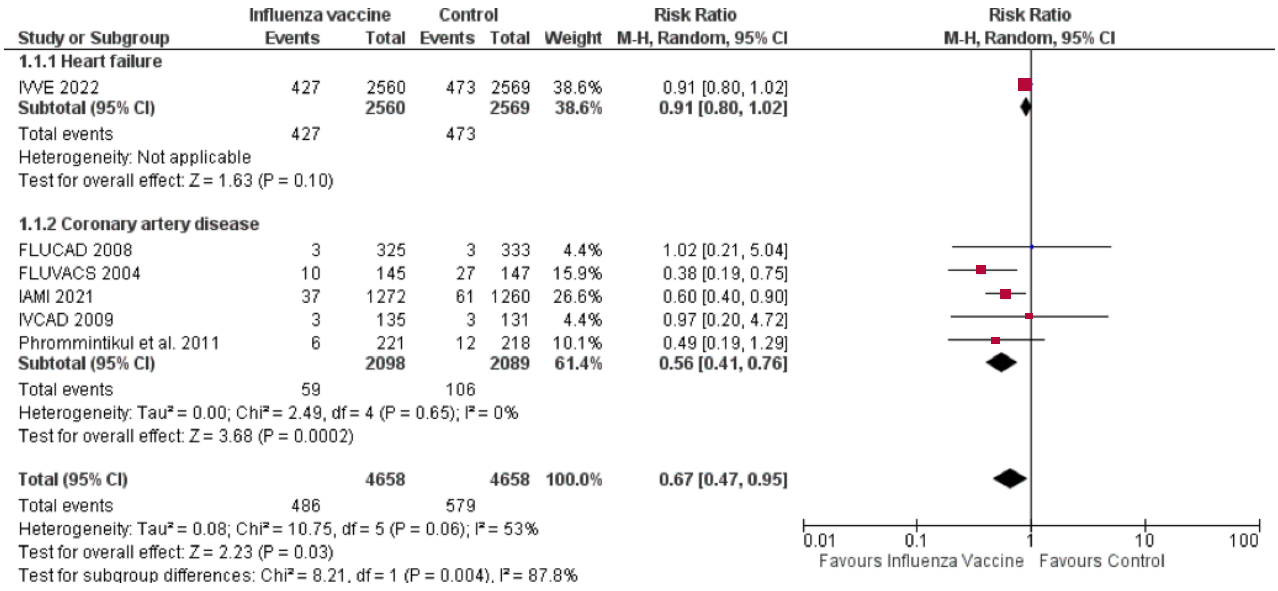

Fig. 3. Forest plot of the effect of influenza vaccination versus placebo on all-cause mortality in patients with heart failure and coronary artery disease.