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Influenza Vaccination for Cardiovascular Prevention: Further Insights from the IAMI Trial and an Updated Meta-analysis

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Abstract

Purpose of Review Influenza infection is a significant, well-established cause of cardiovascular disease (CVD) and CV mortality. Influenza vaccination has been shown to reduce major adverse cardiovascular events (MACE) and CV mortality. Therefore, major society guidelines have given a strong recommendation for its use in patients with established CVD or high risk for CVD. Nevertheless, influenza vaccination remains underutilized. Historically, influenza vaccination is administered to stable outpatients. Until recently, the safety and efficacy of influenza vaccination among patients with acute myocardial infarction (MI) had not been established.

Recent Findings The recently published Influenza Vaccination after Myocardial Infarction (IAMI) trial showed that influenza vaccination within 72 h of hospitalization for MI led to a significant 28% reduction in MACE and a 41% reduction in CV mortality, without any excess in serious adverse events. Additionally, we newly performed an updated meta-analysis of randomized clinical trials (RCTs) including IAMI and the recent Influenza Vaccine to Prevent Adverse Vascular Events (IVVE) trial. In pooled analysis of 8 RCTs with a total of 14,420 patients, influenza vaccine, as compared with control/placebo, was associated with significantly lower risk of MACE at follow-up [RR 0.75 (95%CI 0.57–0.97), I^2 56%].

Summary The recent IAMI trial showed that influenza vaccination in patients with recent MI is safe and efficacious at reducing CV morbidity and mortality. Our updated meta-analysis confirms a 25% reduction in MACE. The influenza vaccine should be strongly encouraged in all patients with CVD and incorporated as an essential facet of post-MI care and secondary CVD prevention.

Keywords Influenza vaccine · Cardiovascular disease prevention · Myocardial infarction · IAMI · COVID vaccine · Cardiovascular events

Introduction

Influenza has been a significant contributor to morbidity and mortality globally. The World Health Organization has estimated that seasonal influenza can result in 290,000 to 650,000 deaths each year from respiratory causes alone, which does not take to account deaths from other causes like cardiovascular disease (CVD) which can be influenza-related [1]. In the United States (U.S.), the Centers for Disease Control and Prevention (CDC) estimates that between the years of 2010–2020 that influenza resulted in 9 to 41 million illnesses, 140,000 to 710,000 hospitalizations, and 12,000 to 52,000 deaths annually [2].

Influenza infection is a significant, well-established cause of CVD and cardiovascular (CV) mortality [3–15]. There is growing recognition that the influenza vaccine is a key tool in CVD prevention [16, 17, 18•, 19, 20]. As such, influenza

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vaccination is recommended by the American Heart Association (AHA) and the American College of Cardiology (ACC) with a class I recommendation for all patients with established coronary artery disease (CAD) [21•]. The CDC has a similar recommendation [22]. Typically influenza vaccination is ordered in the outpatient setting among stable patients. However, until recently, no randomized controlled trial (RCT) had shown the safety and efficacy of the influenza vaccination in reducing CV events and deaths in patients with acute CVD. The recently published Influenza Vaccination after Myocardial Infarction (IAMI) trial showed that influenza vaccination within 72 h of hospitalization for acute myocardial infarction (MI) led to reductions in CV mortality and a composite of all-cause mortality, MI, and stent thrombosis [23••, 24•].

Herein, we will review prior studies on influenza vaccination, discuss key takeaways from the IAMI trial, and issue a clarion call for influenza vaccination as a crucial, evidence-based part of the armamentarium in CVD prevention, on par with pharmacologic therapy. We also perform an updated meta-analysis of RCTs of influenza vaccination that examine CV outcomes.

Influenza and CVD

Viral illness can trigger an inflammatory response that leads to cardiac injury via multiple mechanisms, with a suspected role for proinflammatory cytokines and endothelial damage [10, 25–28]. Influenza is a common cause of myocarditis, with clinical courses varying from subclinical disease to fulminant infection and death [8, 29, 30]. Inflammation from influenza infection can also exacerbate underlying atherosclerosis and directly induce acute plaque rupture leading to type 1 MI [6, 8, 26, 27]. Alternatively, influenza can cause myocardial damage through an acute febrile syndrome accompanied by respiratory distress, hypoxemia, and tachycardia, resulting in type 2 MI due to increased metabolic demand and oxygen supply–demand mismatch [26]. Some of the potential CV complications of influenza virus infection are depicted in Fig. 1.

There is a well-described temporal association between influenza season in temperate climates and MI incidence [27, 31]. Influenza epidemics correlate with increased MI incidence in multiple countries, regardless of climate [15, 32]. Patients requiring hospitalization for influenza are at high risk for MI. In a cross-sectional study of adults hospitalized with influenza between the 2010–2011 and 2017–2018 influenza seasons, nearly 12% of these patients had an acute CV event, most commonly acute heart failure or acute ischemic

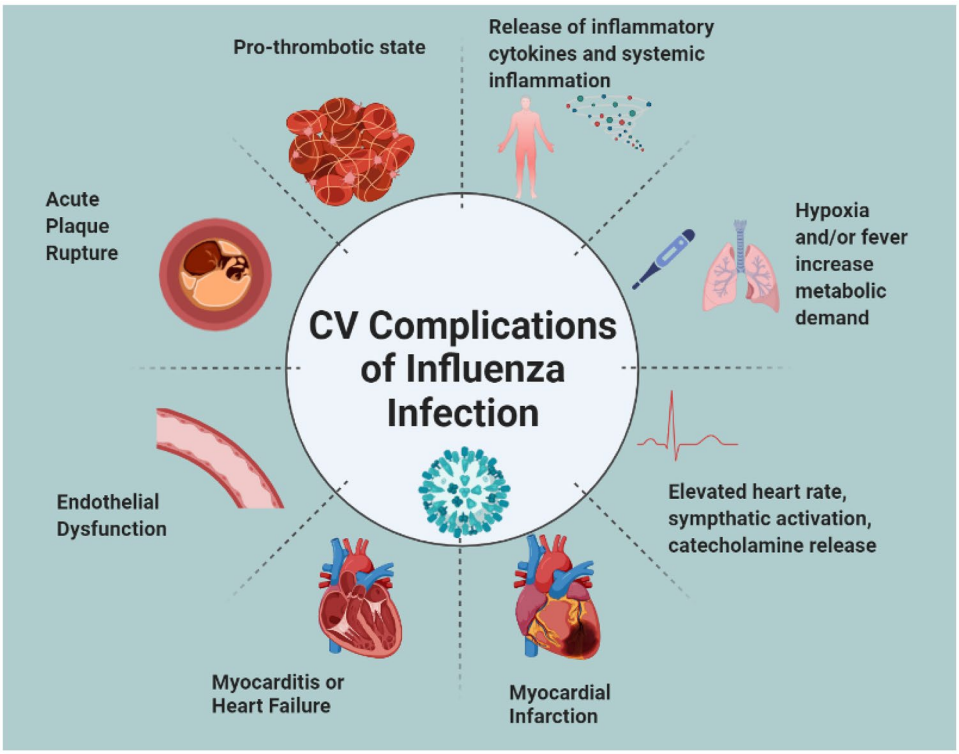


Fig. 1 Cardiovascular (CV) complications associated with influenza infection

heart disease [12]. Additionally, in a case series of over 20,000 patients with first MI, risk of MI was found to be almost 5 times higher in the 3 days after systemic respiratory tract infection including influenza [33]. In fact, a 2018 case series found that the risk of MI was over 6 times greater in the 7-day period after diagnosis of influenza, compared to a control period [5]. Patients with underlying CVD are thought to have a baseline chronic low-grade inflammatory state, which may predispose to worse outcomes with acute viral illness [17].

Influenza Vaccine and CVD Prevention

The annual influenza vaccine is a simple, effective, and low-risk intervention to prevent acute viral illness. Many observational studies have also demonstrated an association between the vaccine and improved CV outcomes [16, 18•, 34, 35]. Suggested mechanisms include prevention of acute influenza infection and its consequent increased metabolic demands as well as immunologic interactions that lead to promotion of plaque stabilization, which has been shown in murine models [17, 36].

Prior to the IAMI study, multiple smaller RCTs comparing influenza vaccination to controls in patients with CVD had been published. The Flu Vaccination Acute Coronary Syndrome (FLUVACS) study was a single-blind RCT of 301 patients with MI or stable CAD scheduled for PCI in Argentina [37]. FLUVACS found a reduced relative risk of CV death and a combined composite outcome of CV death, MI, or rehospitalization for ischemia in the vaccinated group at both 6-month and 1-year follow-up [37, 38]. However, other trials did not fully corroborate the same benefits. The Influenza Vaccination in Secondary Prevention from Coronary Ischemic Events in Coronary Artery Disease (FLUCAD) study was a double-blind RCT of 658 patients with confirmed CAD in Poland that found no improvement in CV death after influenza vaccination at 12-month follow-up, although a secondary composite endpoint of coronary ischemic events (which included CV death, MI, coronary revascularization, and hospitalization for myocardial ischemia) was significantly reduced [39]. The Efficacy of Influenza Vaccine in Reducing Cardiovascular Events in Patients with Coronary Artery Disease (IVCAD) study was a single-blind RCT of 266 patients with recent MI or stable CAD documented by angiography in Iran that found no reduction in CV death or MI at 12-month follow-up in the vaccinated group [40]. A prospective randomized open with blinded enrollment study by Phrommintikul et al. of 439 patients with recent admission for acute coronary syndrome (ACS) in Thailand showed a reduced risk of major CV events (death or hospitalization from ACS, heart failure, or stroke), but not a decrease in CV death [41].

At least four prior meta-analyses of these RCTs, other related trials studying populations without CVD, and observational studies have been published, with varying results. One meta-analysis pooled over 292,000 patients from three RCTs and two observational studies, including patients with and without CVD, and found that influenza vaccination was associated significant reductions in all-cause mortality, MI, and major adverse cardiovascular events (MACE) [42]. A 2013 meta-analysis of these randomized trials and other studies, including over 6700 patients of whom 36.2% had prior cardiac history, found that patients who received the influenza vaccine had a lower risk of a composite of MACE, with a more robust effect in those with recent ACS [16]. A 2015 Cochrane review of the four aforementioned secondary prevention trials included 1682 patients with CVD and found a reduced risk of CV mortality [Risk Ratio (RR) 0.45 (95% Confidence Interval (CI) 0.26–0.76)] but not MI [43]. More recently, in 2021 a meta-analysis of these same four RCTs as well as 12 observational studies, including a total of over 237,000 patients with CVD, found that influenza vaccination was associated with significant risk reductions in all-cause mortality, CV mortality, and MACE at median follow-up of 20 months [18•]. The discrepancy in results across these studies may be attributable to variations in median follow-up time, underlying patient populations, and total patient enrollment size.

There is evidence that elderly patients and populations with underlying CVD mount less protection from standard-dose influenza vaccination [44–46]. The Influenza Vaccine to Effectively Stop CardioThoracic Events and Decompensated Heart Failure (INVESTED) study was a recent double-blind RCT comparing standard dose to high-dose (with 4 times the amount of hemagglutinin of standard-dose) influenza vaccination in 5260 patients with recent MI or heart failure hospitalization [47]. High-dose influenza vaccine did not significantly reduce all-cause mortality or cardiopulmonary hospitalizations compared to standard dose, but influenza vaccination remains strongly indicated in this population.

The Influenza Vaccine to Prevent Adverse Vascular Events (IVVE) trial evaluated influenza vaccination among patients ($n=5129$) with symptomatic heart failure in low- to middle-income countries where influenza vaccination is not common [48]. Although not published yet, the findings were presented at the 2022 ACC Scientific Sessions [49]. It was reported that influenza vaccination did not reduce the primary outcome of 3-point MACE (composite of CV death, non-fatal MI, or non-fatal stroke) at 36 months (hazard ratio (HR) 0.93 (95% CI 0.81–1.07)]. However, hospitalizations (15.1% vs 17.6%, $p=0.01$) and pneumonia (2.4% vs 4.0%, $p=0.0006$) were lower with receipt of influenza vaccine compared to placebo. Furthermore, the primary outcome was reduced during peak influenza season.

The IAMI Study

Administering vaccination to a patient during their hospital stay may help facilitate better uptake [50]. However, it was not known whether influenza vaccination could be safely administered to patients hospitalized with an acute CV event such as in the immediate post-MI period. Although serious vaccine associated adverse events are exceedingly uncommon, there were theoretical concerns that activation of an immune response induced by vaccination could potentially worsen an already "inflamed" patient with recent plaque rupture, or increase myocardial demand by generating a low-grade fever or slight increase in heart rate. Furthermore, whether influenza vaccination early post-MI could confer additional cardio-protection on top of standard secondary prevention care was not well established.

The IAMI study, published in November 2021, was a double-blind placebo-controlled RCT of 2571 patients with recent hospitalization for MI or high-risk CAD that directly explored this question of whether influenza vaccination given early post-MI would reduce CV events [23••]. The trial, which began October 1, 2016, was stopped early in March 2020 due to the onset of the COVID-19 pandemic. In this trial, patients were administered the influenza vaccine or saline placebo within 72 h of coronary angiography or percutaneous coronary intervention for MI (99.7% of patients) or high-risk CAD. The primary outcome, a composite of all-cause death, MI, and stent thrombosis, at 12-month follow-up, was lower in the vaccine group (5.3% vs 7.2%, HR 0.72 (95% CI 0.52–0.99)). The vaccinated group also experienced fewer secondary outcomes of all-cause mortality (HR 0.59 (0.39–0.89)) and CV mortality (HR 0.59 (0.39–0.90)) (Fig. 2). The rate of MI was lower in the vaccine group as well, but not statistically significantly so, and stent thrombosis incidence was rare and not significantly different either. They subsequently pooled their results with the FLUCAD, FLUVACS, and study by Phrommintikul et al. to find a 49% reduced risk of CV mortality (HR 0.51 (0.36–0.71)).

The IAMI study confirmed the efficacy of the influenza vaccine in secondary CVD prevention. It should be noted that patients in the IAMI trial were already well-treated with contemporary medical therapy post-MI with 98% on aspirin, 97% on a $P2Y_{12}$ inhibitor, 98% on statin therapy at discharge, and there still was incremental benefit with influenza vaccination.

A couple of caveats to be noted about the trial. As mentioned, it was stopped early; early termination of a clinical trial can potentially exaggerate estimates of the effects of a study treatment. IAMI enrolled a secondary prevention population; thus all of these patients with established or newly diagnosed CAD would have been candidates for influenza

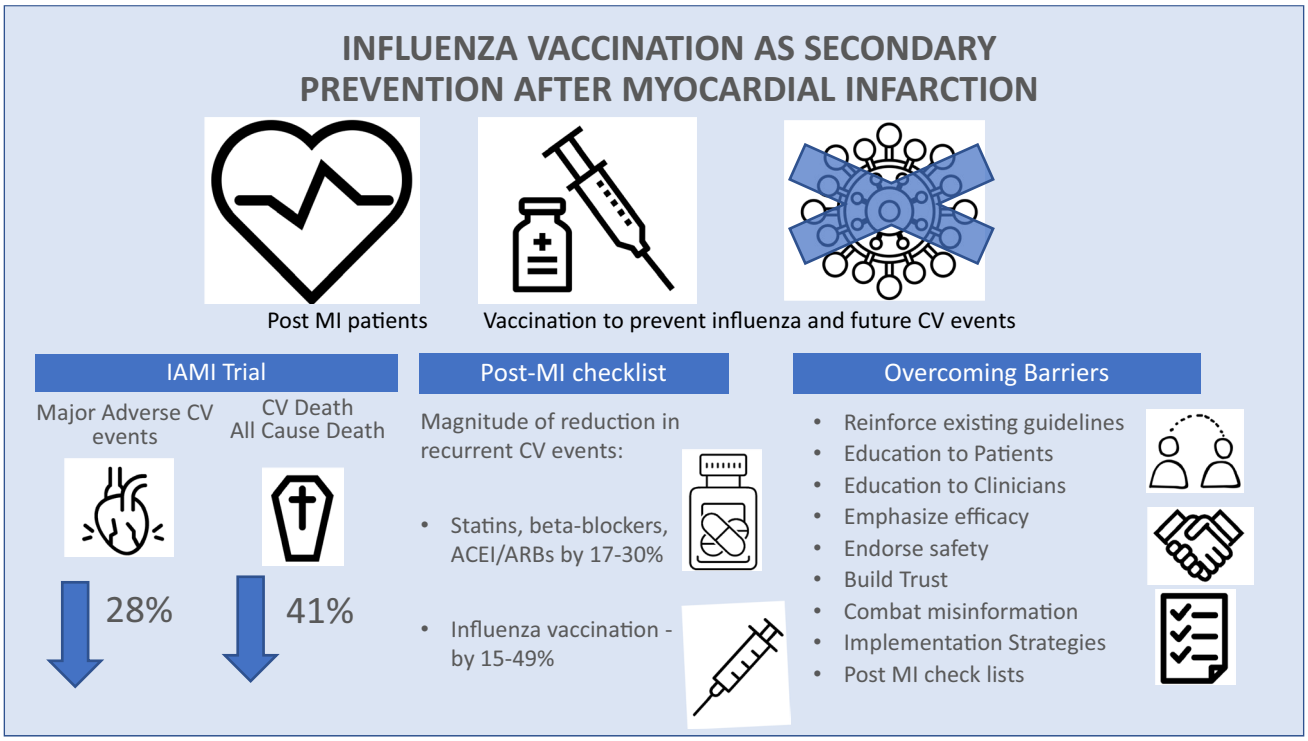


Fig. 2 Summary of key findings from the Influenza Vaccination after Myocardial Infarction (IAMI) trial

vaccination anyway per current guideline recommendations, which raises the question of whether assignment to placebo was ethical. However, the authors only enrolled patients who were not already vaccinated or planning to receive the influenza vaccination, and trial participants were still allowed to pursue vaccination outside of the trial if desired. There were 13% of individuals in the placebo arm who did cross over to vaccination treatment, but if anything, this would have biased results toward the null [23••].

The IAMI results of reduced CV mortality and all-cause mortality were consistent with the findings of the 2021 meta-analysis by Yedlapati et al. [18•, 23••]. IAMI also further demonstrated the safety of influenza vaccine administration in the post-MI period. Despite the transient immune activation generated by vaccination, no differences in significant adverse effects were found between the vaccine and control arms. These results are also corroborated by prior research that showed no increase in the risk of MI or stroke after influenza vaccination [33].

Overall, the impressive relative risk reductions in all-cause and CV mortality of 41% each are reminiscent of traditional pharmacologic therapies for secondary CVD prevention, as highlighted in a recent editorial [24•]. Medications including aspirin, $P2Y_{12}$ inhibitors, statins, beta blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers all reduce the risk of mortality by 20–41% in well-known RCTs [51–56]. Reduction in mortality with influenza appears to be of similar or even greater magnitude. While these risk reductions cannot be directly compared across trials because of differences in study design, patient population, and specific outcomes measured, the pronounced benefit afforded by influenza vaccination in addition to these proven medical therapies is remarkable.

The trial's results were consistent across many subgroups, including age, sex, diabetes history, smoking status, history of prior MI, ST-elevation vs non-ST-elevation MI, influenza season (the study was conducted over 4 seasons), institution hemisphere, and country, although this last subgroup was not prespecified in the analysis. This geographic diversity—centers spanned Europe, Asia, and Australia—lends credence and generalizability to the trial's findings. Unfortunately, as in many cardiology trials, [57] women were underrepresented at only about 19% of participants, which limits generalizability in that subgroup.

Updated Meta-analysis

Following the IAMI trial (but before IVVE was presented), another meta-analysis was recently conducted in 2022, which included 6 RCTs including IAMI with a total of 9001 patients, 53% of whom had prior CVD [58•]. Influenza vaccination reduced the composite CV outcome by 34% (HR 0.66 (0.53–0.83)), with a greater benefit seen among patients with recent ACS who experienced a 45% reduction in CV outcomes with influenza vaccination.

After IVVE was presented, we further conducted an updated meta-analysis including all RCTs that evaluated influenza vaccine and its association with CV outcomes. We searched EMBASE, PubMed, and Cochrane Library (inception through May 24, 2022) and identified eight RCTs with a total of 14,420 patients that were included in our analysis. This included both IAMI trial and the IVVE trial. Since IVVE has not been officially published, we used the IVVE results presented at the ACC Scientific Sessions [49]. We used Mantel–Haenszel method with Paule-Mandel estimator of tau^2 and Hartung-Knapp-Sidik-Jonkman adjustment (due to the small number of the included studies) to calculate the pooled RR and 95% CI. Our results confirmed that influenza vaccine, as compared with control/placebo, was associated with significantly 25% lower risk of MACE at follow-up (RR 0.75 (95% CI 0.57–0.97), $I^2 = 56\%$). There was no significant difference between influenza vaccine and placebo/control in terms of all-cause mortality (RR 0.84 (0.54–1.33), $I^2 = 50\%$), CV mortality (RR 0.77 (0.39–1.50), $I^2 = 57\%$), or MI (RR 0.75 (0.52–1.10), $I^2 = 0\%$) (Fig. 3A–D). Our meta-analysis suggests that influenza vaccine compared with control/placebo was associated with lower rates of MACE without a significant difference in the mortality or MI rates.

Future Directions

While promoting vaccinations classically has been deferred to the primary care setting, the influenza vaccine also should fall under the purview of cardiologists as a tool of CVD prevention. National and international society guidelines all recommend influenza vaccination for patients with CVD [21•, 22, 59]. The AHA/ACC joint guidelines (2006) and the European Society of Cardiology guidelines (2019) both include a Class I (Level of Evidence B) recommendation, which indicates the intervention is recommended, but that the data came from one randomized trial or multiple large non-randomized trials. With the evidence from IAMI, there are now multiple RCTs and meta-analyses supporting the use of influenza vaccination in patients with CVD, which would argue for advancing the recommendation to Class I (Level of Evidence A), the strongest possible endorsement.

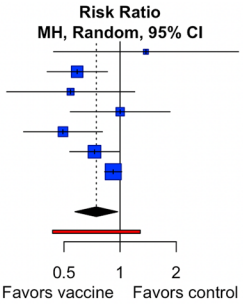
Regrettably, influenza vaccine uptake remains suboptimal, with only an estimated 50.2% of US adults vaccinated in the 2020–2021 influenza season [60]. Significant racial and geographic disparities in vaccination among patients with CVD exist, with lower vaccination rates in Black and Hispanic adults (40.4% and 38.6% in the 2020–2021 season, respectively) compared with White adults (55.5%), and in the Southeast and Southwest compared to the Northeast [60,

Fig. 3 Updated meta-analysis of randomized clinical trials, including IAMI and IVVE, examining the association of influenza vaccine, compared to placebo/control, on major adverse cardiovascular outcomes. **A** Major adverse cardiovascular events (MACE). **B** Cardiovascular mortality. **C** All-cause mortality. **D** Myocardial infarction

a Updated meta-analysis of RCTs evaluating influenza vaccine and risk of Major Adverse Cardiovascular Events

Study	Vaccine Events	Vaccine Total	Placebo Events	Placebo Total	Weight	Risk Ratio MH, Random, 95% CI
Govaret et al. 1994	7	927	5	911	3.1%	1.38 [0.44; 4.32]
Gurfinkel et al. 2004	32	151	54	150	16.8%	0.59 [0.40; 0.86]
Ciszewski et al. 2008	9	325	17	333	5.9%	0.54 [0.25; 1.20]
De Villiers et al. 2010	20	1620	20	1622	8.9%	1.00 [0.54; 1.85]
Phrommintikul et al. 2011	21	221	42	218	12.3%	0.49 [0.30; 0.80]
Frobert et al. 2021	67	1272	91	1260	20.4%	0.73 [0.54; 0.99]
Loeb et al. 2022	520	2560	568	2569	32.6%	0.92 [0.83; 1.02]
Total (95% CI)		**7076**		**7063**	**100.0%**	**0.75 [0.57; 0.97]**
Prediction interval						**[0.43; 1.28]**

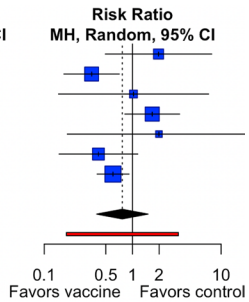
Heterogeneity: $Tau^2 = 0.0329$; $Chi^2 = 13.67$, df = 6 (P = 0.03); $I^2 = 56\%$
Test for overall effect: $t_6 = -2.72$ (P = 0.03)



b Updated meta-analysis of RCTs evaluating influenza vaccine and risk of cardiovascular mortality

Study	Vaccine Events	Vaccine Total	Placebo Events	Placebo Total	Weight	Risk Ratio MH, Random, 95% CI
Govaret et al. 1994	6	927	3	911	10.1%	1.97 [0.49; 7.84]
Gurfinkel et al. 2004	9	151	26	150	19.6%	0.34 [0.17; 0.71]
Ciszewski et al. 2008	2	325	2	333	6.1%	1.02 [0.15; 7.23]
De Villiers et al. 2010	20	1620	12	1622	19.8%	1.67 [0.82; 3.40]
Keshtkar-Jahromi et al. 2010	2	141	1	140	4.3%	1.99 [0.18; 21.65]
Phrommintikul et al. 2011	5	221	12	218	14.4%	0.41 [0.15; 1.15]
Frobert et al. 2021	34	1272	56	1260	25.7%	0.60 [0.40; 0.91]
Total (95% CI)		**4657**		**4634**	**100.0%**	**0.77 [0.39; 1.50]**
Prediction interval						**[0.18; 3.29]**

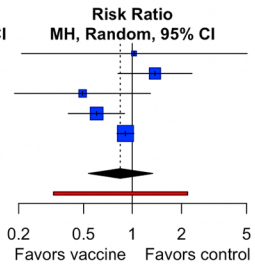
Heterogeneity: $Tau^2 = 0.2470$; $Chi^2 = 13.97$, df = 6 (P = 0.03); $I^2 = 57\%$
Test for overall effect: $t_6 = -0.97$ (P = 0.37)



c Updated meta-analysis of RCTs evaluating influenza vaccine and risk of all-cause mortality

Study	Vaccine Events	Vaccine Total	Placebo Events	Placebo Total	Weight	Risk Ratio MH, Random, 95% CI
Ciszewski et al. 2008	3	325	3	333	3.7%	1.02 [0.21; 5.04]
De Villiers et al. 2010	33	1620	24	1622	20.3%	1.38 [0.82; 2.32]
Phrommintikul et al. 2011	6	221	12	218	8.9%	0.49 [0.19; 1.29]
Frobert et al. 2021	37	1272	61	1260	26.0%	0.60 [0.40; 0.90]
Loeb et al. 2022	428	2560	473	2569	41.1%	0.91 [0.81; 1.02]
Total (95% CI)		**5998**		**6002**	**100.0%**	**0.84 [0.54; 1.33]**
Prediction interval						**[0.33; 2.18]**

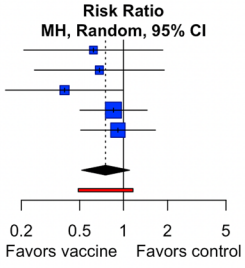
Heterogeneity: $Tau^2 = 0.0621$; $Chi^2 = 7.97$, df = 4 (P = 0.09); $I^2 = 50\%$
Test for overall effect: $t_4 = -1.03$ (P = 0.36)



d Updated meta-analysis of RCTs evaluating influenza vaccine and risk of Myocardial infarction

Study	Vaccine Events	Vaccine Total	Placebo Events	Placebo Total	Weight	Risk Ratio MH, Random, 95% CI
Gurfinkel et al. 2004	5	151	8	150	8.9%	0.62 [0.21; 1.85]
Ciszewski et al. 2008	6	325	9	333	10.2%	0.68 [0.25; 1.90]
Phrommintikul et al. 2011	6	221	15	218	12.3%	0.39 [0.16; 1.00]
Frobert et al. 2021	25	1272	29	1260	38.0%	0.85 [0.50; 1.45]
Loeb et al. 2022	21	2560	23	2569	30.6%	0.92 [0.51; 1.65]
Total (95% CI)		**4529**		**4530**	**100.0%**	**0.75 [0.52; 1.10]**
Prediction interval						**[0.49; 1.16]**

Heterogeneity: $Tau^2 = 0$; $Chi^2 = 2.66$, df = 4 (P = 0.62); $I^2 = 0\%$
Test for overall effect: $t_4 = -2.08$ (P = 0.11)



61•]. Discussions over vaccination initiatives, vaccine hesitancy, and misinformation, have taken over our discourse in the age of COVID-19, both in the healthcare setting and nationally. While these challenges persist, this new evidence should bolster clinicians' confidence when engaging cardiac patients about the influenza vaccine, especially those with underlying CVD. Building trust with patients is essential. Patient education efforts should include conversations between clinician and patient about the cardioprotective benefits of the influenza vaccine and the strength of recommendations, especially if they are strengthened, and updating patient education materials to reinforce these points. Clinicians should also place emphasis on the safety of vaccination, which was re-demonstrated in IAMI specifically for patients with recent MI.

Another key strategy to increase uptake would be to include influenza vaccination as part of the post-MI checklist, to aim for vaccination prior to discharge, similar to the structure of IAMI. Post-MI checklists already ensures prescription of evidence-based pharmacotherapies, and adding the vaccine is key to normalizing the vaccine as part of routine, standard-of-care therapy. This step would also increase clinician awareness of the strength of evidence backing influenza vaccination for these patients.

COVID-19 Vaccine and CVD Prevention

SARS-CoV-2 can also trigger acute CV events including acute MI, myocarditis, and dysrhythmias [62–64]. Some of the suspected mechanisms overlap with influenza infection, including increased metabolic demand, acute plaque rupture, and direct myocardial infection [17]. Patients with underlying CVD are at higher risk for severe outcomes from both influenza and COVID-19 [9, 64–67]. During the COVID-19 pandemic, the focus has rightly been on preventing spread of COVID-19; nonetheless, influenza vaccination should be equally emphasized [66, 67]. Influenza vaccination has been associated with improved outcomes in patients with COVID-19, and there may be an element of off-target immune benefits that requires further exploration [17, 68].

The COVID-19 vaccines are effective at reducing severe illness, hospitalizations, and death. Randomized trials need to be conducted to examine the efficacy of vaccination against COVID-19 in improving CV outcomes, in particular in high-risk patients, such as those with CVD. Observational studies for further characterization of long-term CV outcomes of COVID-19 infection are necessary. Additionally, future studies should investigate the efficacy of receiving both influenza and COVID-19 vaccines, compared to just one of the two, in preventing CV events. Influenza and COVID-19 vaccines may be co-administered safely [60].

Conclusions

Evidence for the cardioprotective effects of the influenza vaccine has been mounting for years. The recent IAMI trial showed that influenza vaccination in patients with recent MI is safe and efficacious at reducing CV morbidity and mortality. Our 2022 updated meta-analysis confirms a 25% reduction in MACE with influenza vaccination. The influenza vaccine should be strongly encouraged in all patients with CVD and incorporated as an essential facet of post-MI care and secondary CVD prevention.

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Compliance with Ethical Standards

Conflict of Interest Dr. Michos has served on advisory boards for Amarin, AstraZeneca, Bayer, Boehringer Ingelheim, Esperion, Novartis, Novo Nordisk, and Pfizer. The other authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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•• Of major importance

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