Original Investigation

Association Between Influenza Vaccination and Cardiovascular Outcomes in High-Risk Patients
A Meta-analysis

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IMPORTANCE Among nontraditional cardiovascular risk factors, recent influenzalike infection is associated with fatal and nonfatal atherothrombotic events.

OBJECTIVES To determine if influenza vaccination is associated with prevention of cardiovascular events.

DATA SOURCES AND STUDY SELECTION A systematic review and meta-analysis of MEDLINE (1946-August 2013), EMBASE (1947-August 2013), and the Cochrane Library Central Register of Controlled Trials (inception-August 2013) for randomized clinical trials (RCTs) comparing influenza vaccine vs placebo or control in patients at high risk of cardiovascular disease, reporting cardiovascular outcomes either as efficacy or safety events.

DATA EXTRACTION AND SYNTHESIS Two investigators extracted data independently on trial design, baseline characteristics, outcomes, and safety events from published manuscripts and unpublished supplemental data. High-quality studies were considered those that described an appropriate method of randomization, allocation concealment, blinding, and completeness of follow-up.

MAIN OUTCOMES AND MEASURES Random-effects Mantel-Haenszel risk ratios (RRs) and 95% CIs were derived for composite cardiovascular events, cardiovascular mortality, all-cause mortality, and individual cardiovascular events. Analyses were stratified by subgroups of patients with and without a history of acute coronary syndrome (ACS) within 1 year of randomization.

RESULTS Five published and 1 unpublished randomized clinical trials of 6735 patients (mean age, 67 years; 51.3% women; 36.2% with a cardiac history; mean follow-up time, 7.9 months) were included. Influenza vaccine was associated with a lower risk of composite cardiovascular events (2.9% vs 4.7%; RR, 0.64 [95% CI, 0.48-0.86], *P* = .003) in published trials. A treatment interaction was detected between patients with (RR, 0.45 [95% CI, 0.32-0.63]) and without (RR, 0.94 [95% CI, 0.55-1.61]) recent ACS (*P* for interaction = .02). Results were similar with the addition of unpublished data.

CONCLUSIONS AND RELEVANCE In a meta-analysis of RCTs, the use of influenza vaccine was associated with a lower risk of major adverse cardiovascular events. The greatest treatment effect was seen among the highest-risk patients with more active coronary disease. A large, adequately powered, multicenter trial is warranted to address these findings and assess individual cardiovascular end points.

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Among nontraditional cardiovascular risk factors, there remains interest in a potential association between respiratory tract infections, of which influenza and influenzalike illnesses are common causes,[1,2] and subsequent cardiovascular events.[3-9] Prior studies suggest that seasonal influenzalike illnesses may explain a major determinant of the timing of acute thrombotic vascular events in patients with previously stable coronary artery disease (CAD) and cerebrovascular disease.[3] Further supporting this hypothesis, several epidemiological studies have suggested a strong inverse longitudinal relationship between influenza vaccination and the risk of fatal and nonfatal cardiovascular events.[4,10-19] A few small randomized clinical trials (RCTs) have explicitly tested whether influenza vaccination may reduce the risk of cardiovascular events with large treatment effects.[20-24] Based largely on observational findings, medical association guidelines recommend universal vaccination in patients with, or at risk of, cardiovascular disease for protection from general influenza complications.[25-27] Cardiovascular associations specifically recommended influenza vaccination for the secondary prevention of ischemic heart disease in 2006 based on the earliest reported RCT.[28-31] Because of the potential for confounding in an observational study of this subject[32-34] and because prior meta-analyses included observational studies but omitted a systematic review of all influenza vaccination randomized trials,[7,35,36] we set out to perform a systematic review and meta-analysis of all randomized clinical trials of influenza vaccine that studied cardiovascular events as efficacy or safety outcomes.

Methods

Study Research

A systematic literature search of Ovid MEDLINE (1946-August 2013), EMBASE (1947-August 2013), and the Cochrane Library Central Register of Controlled Trials (inception through August 2013) was conducted to identify all published randomized clinical trials involving humans and comparing influenza vaccination with placebo or standard care. The search used key terms including *influenza*, *influenza vaccine*, and *cardiovascular* (eMethods in the Supplement). The search was not restricted to any language. We subsequently searched and evaluated all reference lists of eligible articles, online resources such as cardiovascular and infectious disease conference abstracts from 2000 to 2013, and clinicaltrials.gov to ensure identification of all published and unpublished studies.

Study Selection, Data Extraction, and End Points

Two investigators (J.A.U. and R.Z.) identified and scrutinized studies independently for potential inclusion. Disagreements were resolved by consensus. Baseline characteristics, outcomes, and safety events were extracted from the published articles and confirmed by contacting the corresponding investigator of each selected trial (eMethods in the Supplement). An estimate of influenza virulence during each study period was also identified and categorized into levels of activity[37] by searching the open-access online databases of the World Health Organization (WHO), Centers for Disease Control and Prevention (CDC), and the WHO FluNet registry (available at www.who.int/flunet; eTable 1 in the Supplement).[38]

The primary end point of this analysis 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). The justification to select this composite primary end point was because eligible trials included such events as either a composite primary or secondary end point (efficacy trial) or as part of severe adverse event monitoring (safety trial) in each study (eTable 2 in the Supplement). If a composite end point was indeterminable, fatal and nonfatal myocardial infarction and stroke events were used. The secondary end point was cardiovascular mortality and other individual cardiovascular events. All events occurring within 12 months of follow-up were included.

Selection Criteria

We applied the following screening criteria to determine qualitative eligibility: randomized clinical trials of adults comparing experimental or commercially approved influenza vaccinations with either placebo, control, or a strategy of more intense vs standard vaccination; short-term efficacy (duration of follow-up, 28 days to 1 year); and a sample size of at least 50 patients. A strategy of a more intense vaccination included comparisons between standard-dose intramuscular vaccines with either a higher dose or higher concentration of intramuscular vaccine, a booster of standard vaccine among poor seroresponders, experimental virosomal vaccine with higher antigenicity, or concomitant intranasal vaccine vs similar placebo (eMethods in the Supplement).

Quality Assessment

The methodological quality of each trial was evaluated for risk of bias using standard criteria: method of randomization; allocation concealment; patient, investigator, and outcome assessor blinding; selective outcome reporting; incomplete outcome ascertainment; and other potential sources of bias as recommended by the Cochrane Collaboration.[39] Studies were categorized (**Table**) as high quality if at least the first 3 criteria were clearly described and accounted for, as low quality if any aspect of the first 3 criteria was unaccounted for, or as otherwise of uncertain risk of material bias. An alternative quality score for evaluating RCTs[49] was also applied with a score of 3 or greater indicative of high quality (Table).

Statistical Analysis

Data from each trial were entered on an intention-to-treat basis according to the recommendations of the Cochrane Collaboration and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[50] Baseline characteristics were summarized, and weighted means and rates according to individual trial sample size were reported. Trials were compared with risk ratios (RRs) as the measure of effect, because accurate time-to-event data were not available in all trials. Summary RRs and 95% CIs were calculated using a random-effects model for combining results across

Table. Characteristics of Studies Included in the Meta-analysis

Source	Patient Cohort	Age, Mean (SD), y[a]	Women (%)	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 (Score)[c]	Region
Efficacy Trials: Influenza Vaccine vs Placebo/Control												
FLUVACS,[20,21] 2004	Inpatients with recent ACS or outpatients with stable CAD and planned PCI	65 (NR)	62 (31)	301 (100)	12 (1.0-12.0)	No treatment	147	IM TIV	145	Sporadic	Low (2)	Argentina
FLUCAD,[22,23] 2008	Outpatients with recent ACS or stable CAD with planned PCI	60 (10)	181 (27.5)	658 (100)	9.8 (0.1-12.2)	IM placebo	333	IM TIV	325	Regional	High (5)	Poland
IVCAD,[40] 2009[d]	Inpatients and outpatients with recent ACS or stable CAD	55 (NR)	90 (33.8)	266 (100)	12 (NR)	IM placebo	131	IM TIV	135	Unknown	Low (1)	Iran
Phrom-mintikul et al,[24] 2011	Inpatients with recent ACS	66 (9)	193 (43.7)	439 (100)	11.8 (0.1-12.0)	No treatment	218	IM TIV	221	Sporadic and Widespread	Low (3)	Thailand
Safety Trials: Influenza Vaccine vs Placebo/Control												
Govaert et al,[41] 1994	Outpatients	67 (NR)	969 (52.7)	249 (13.5)	5.0 (2.5-5.0)	IM placebo	911	IM QIV	927	Regional	Uncertain (4)	the Nether-lands
De Villiers et al,[42] 2009	Outpatients	70 (7)	1961 (60.5)	525 (16.2)	8.0 (0.1-8.0)	INL placebo	1622	INL LAIV	1620	Sporadic	High (5)	South Africa
Total		67 (7)	3456 (51.3)	2438 (36.2)	7.9		3362		3373			
Safety Trials: Experimental vs Standard Influenza Vaccine												
Jackson et al,[43] 1999	Outpatients	70 (3)	65 (32.5)	129 (64.5)	1.0 (1.0)	IM TIV plus INL placebo	100	IM TIV and INL LAIV	100	Sporadic	High (4)	United States
De Bruijn et al,[44] 2005	Outpatients	52 (NR)	205 (53.7)	203 (53.1)	6.0 (NR)	Standard IM TIV	126	Virosomal IM TIV	256	Sporadic	Low (2)	the Nether-lands
FEVER,[45] 2007	Outpatients	83 (9)	184 (66.9)	46 (16.7)	8.0 (4.0-9.0)	Standard IM TIV	142	Booster IM TIV	133	Regional	Low (3)	UK
Falsey et al,[46] 2009	Outpatients	73 (6)	2008 (52.3)	523 (13.6)[e]	6.0 (NR)	Standard IM TIV	1260	High-Dose IM TIV	2573	Regional	High (5)	United States
Forrest, et al,[47] 2011	Outpatients	69 (7)	1871 (62.2)	1908 (63.4)	8.0 (0.1-8.0)	Standard IM TIV	1501	INL LAIV	1508	Sporadic	Low (3)	South Africa
Diaz-Granados,[48] et al 2013	Outpatients	73 (6)	4915 (53.7)	2200 (24.0)	6.0 (NR)	Standard IM TIV	3050	High-Dose IM TIV	6108	Widespread	High (5)	United States
Total		72 (7)	9248 (55.8)	5009 (30.2)	6.9		6179		10 678			

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; TIV, trivalent, inactivated influenza vaccine; QIV, quadrivalent, inactivated influenza vaccine.

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

[b] Levels of influenza activity according to the Centers for Disease Control and Prevention and World Health Organization reports were categorized as (1) no activity; (2) sporadic: isolated laboratory-confirmed influenza cases or a laboratory-confirmed outbreak in 1 institution, with no increase in activity; (3) local: increased incidence of influenzalike 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; (4) regional: 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; and (5) widespread: outbreaks of ILI or laboratory-confirmed influenza in more than 50% of the regions in the state.

[c] 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 otherwise of uncertain risk of material bias. Trial scores were graded as high quality by the Jadad score criteria if the quality of reporting of the aforementioned criteria provided a score of 3 or greater. If the score was less than 3, the trial was considered low quality. Risk of bias was evaluated by the method of randomization; allocation concealment; double-blinding; outcome reporting and ascertainment; and other sources.

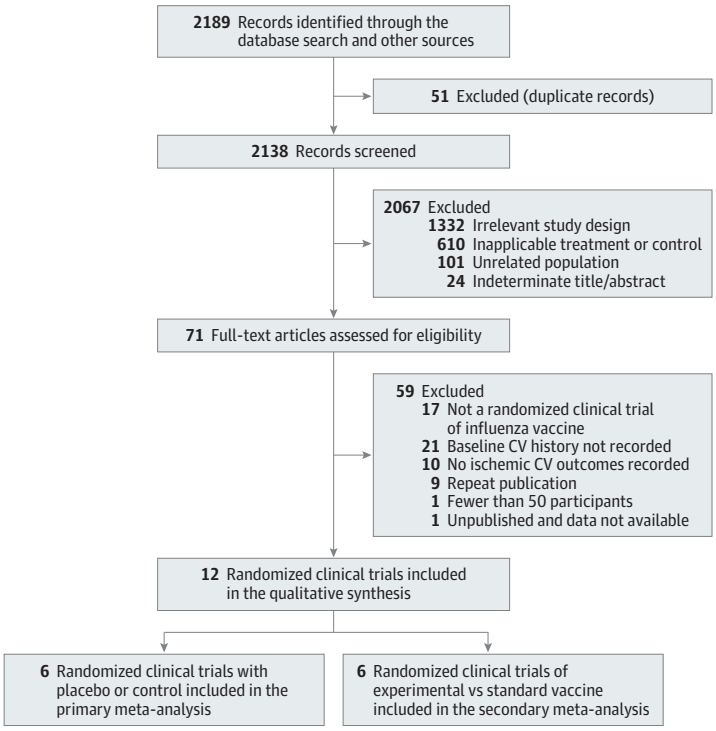
[d] Unpublished.

[e] Represents past history of coronary artery disease only.

studies, which incorporates between- and within-study variance. A random-effects model was selected because heterogeneity among patient characteristics and vaccination efficacy would unlikely result in a similar treatment effect across trials.[51] If an outcome of interest achieved pooled statistical significance, then the number needed to treat (NNT) and its 95% CI to avoid 1 event was derived from the inverse of the pooled estimated absolute-risk difference and SE.

Primary analyses focused on published trials comparing influenza vaccination with either placebo or control. When data

Figure 1. Study Flow Diagram



CV indicates cardiovascular.

were available, analyses were further stratified by patients with and without recent acute coronary syndrome (ACS) within 1 year of randomization. We focused on such patients because of the seemingly greater effect size seen in the randomized trials and the pathobiology in which a greater effect might be anticipated in these patients with more active coronary disease. Secondary analyses included published and unpublished trials. We further analyzed trials of more intense vs standard influenza vaccination to explore the consistency of association of more immune activation against influenza with cardiovascular risk.

When no events were observed within a treatment group, a 0.5 correction factor was added to all values of that end point for calculation of the RR and its variance.[52,53] To determine whether there was heterogeneity between individual trials, we assessed the *Q* statistic (a weighted index of effect estimate differences across studies assuming a χ^2 distribution) and I^2 statistic ($[Q - df]/Q \times 100$). Because the I^2 value quantifies heterogeneity on a scale of 0% to 100% and represents the extent of inconsistency among trial results rather than a sampling error independent of the number of studies, an I^2 of 75% or greater was considered representative of high heterogeneity.[54] To assess for publication bias risk, funnel plots (precision [inverse of SE] vs logarithmic RR) were evaluated. Further statistical tests for funnel plot asymmetry were not conducted given the limited specificity and power of these tests when fewer than 10 studies are included in a primary meta-analysis.[55]

Sensitivity Analysis

To test for heterogeneity among published and unpublished trials, sensitivity analyses examining the robustness of the results were explored by comparing random-effects results with both fixed-effects and Yusuf-Peto models. This was achieved by adding unpublished trial results to the pooled effect estimate, and then sequentially removing each study result from the pooled effect estimate. Heterogeneity among preplanned subgroups was further explored in patients with and without recent ACS, by trial quality, trial duration, sample size, use of placebo, circulating influenza activity, and intention to study cardiovascular efficacy or safety. Interaction terms representing these categories were tested for differences in treatment effect between subgroups.[56]

Two-sided *P* values were calculated with a *P* value less than .05 considered significant for all tests. Statistical analyses were performed with Review Manager (RevMan; Cochrane Collaboration), version 5.2.3.

Results

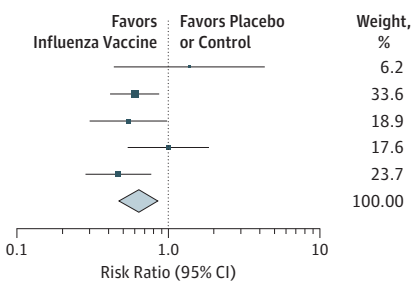
Baseline Characteristics

We screened 2189 articles for eligibility and identified 71 potentially relevant studies for further review. After excluding 59 studies, a total of 12 RCTs met our inclusion criteria for final meta-analysis (**Figure 1**).[21,23,24,40-48] Among the 6 placebo or control RCTs, 1753 patients were randomly assigned to receive 1 intramuscular injection of standard influenza vaccination, 1620 to receive a live, intranasal attenuated vaccine, 1375 to receive intramuscular placebo, 1622 to receive intranasal placebo, and 365 to receive no treatment. Five trials were previously published,[21,23,24,41,42] and 1 trial is unpublished.[40] These trials were included in the final meta-analysis of influenza vac-

Figure 2. Major Adverse Cardiovascular Events Comparing Influenza Vaccine vs Control

Study	Influenza Vaccine No. of Events	Influenza Vaccine Total Participants	Placebo or Control No. of Events	Placebo or Control Total Participants	Risk Ratio (95% CI)	Weight, %
Govaert et al,[41] 1994	7	927	5	911	1.38 (0.44-4.32)	6.2
FLUVACS,[20,21] 2004	32	145	54	147	0.60 (0.41-0.87)	33.6
FLUCAD,[22,23] 2008	16	325	30	333	0.55 (0.30-0.98)	18.9
De Villiers et al,[42] 2009	20	1620	20	1622	1.00 (0.54-1.85)	17.6
Phrommintikul et al,[24] 2011	20	221	42	218	0.47 (0.29-0.77)	23.7
Total (95% CI)	95	3238	151	3231	0.64 (0.48-0.86)	100.00

Heterogeneity: $\tau^2 = 0.03$; $\chi^2_4 = 5.59$, ($P = .23$); $I^2 = 28\%$
Test for overall effect: $Z = 2.93$ ($P = .003$)



FLUCAD indicates FLU Vaccination Coronary Artery Disease; FLUVACS, FLU Vaccination Acute Coronary Syndromes. Square data markers represent risk ratios (RRs); horizontal lines, the 95% CIs with marker size reflecting the statistical weight of the study using random-effects meta-analysis. A diamond data marker represents the overall RR and 95% CI for the outcome of interest. Evaluated using the random-effects Mantel-Haenszel test.

cine vs placebo or control and their characteristics are summarized in the Table. Overall, 6735 participants (mean age, 67 years; 51.3% women; 36.2% with a cardiac history) were followed up for a mean duration of 7.9 months. An additional 6 trials comprising 16 857 patients (mean age, 72 years; 55.8% women; 30.2% with cardiac history) randomized to various strategies of experimental (n = 6179) vs standard (n = 10 678) influenza vaccination for a mean duration of 6.9 months are described in the Table.

Among the 12 trials, 5 were conducted with rigorous randomization, allocation concealment, and double-blinding that met the Cochrane criteria for high quality (low risk of bias; Table and eFigure 1 in the Supplement). Allowing inclusion of single-blinded designs resulted in 4 more trials graded as high quality (eTable 3 in the Supplement). The remaining studies were considered low or uncertain quality. Definitions of cardiovascular outcomes were reported or provided by each efficacy trial, followed standardized cardiovascular guideline diagnostic criteria, and were generally comparable across trials. Outcome assessment varied by frequency, type of follow-up (including telephone, hospital or clinic, and home visit contact), and adjudication across trials.

Major Adverse Cardiovascular Events

For the 5 published RCTs comparing influenza vaccine with placebo or control, individual and pooled RRs for composite cardiovascular events are provided in **Figure 2**. Among the 3238 patients treated with influenza vaccine, 95 patients (2.9%) developed a major adverse cardiovascular event compared with 151 of the 3231 patients (4.7%) treated with placebo or control within 1 year of follow-up (RR, 0.64 [95% CI, 0.48-0.86]; $P = .003$; $I^2 = 28\%$; Figure 2). This association represented an absolute risk difference of 1.74% (95% CI, 0.81%-2.67%; $P = .003$) or an NNT of 58 (95% CI, 38-124) to prevent 1 major adverse cardiovascular event. The addition of the unpublished data did not materially change the results (2.9% influenza vaccine vs 4.6% placebo or control; RR, 0.64 [95% CI, 0.49-0.84]; $P = .001$; eFigure 2 in the Supplement).

In a subgroup analysis of 3 RCTs of patients with CAD, there was a significant interaction between the association of influenza vaccine and cardiovascular risk among patient cohorts with and without recent ACS (P for interaction = .02; **Figure 3**). Influenza vaccine was particularly associated with a lower risk of major adverse cardiovascular events among patients with a history of recent ACS (10.25% influenza vaccine vs 23.1% placebo or control; RR, 0.45 [95% CI, 0.32-0.63]; $P < .001$; $I^2 = 0\%$) than patients with stable CAD (6.9% influenza vaccine vs 7.4% placebo or control; RR, 0.94 [95% CI, 0.55-1.61]; $P = .81$; $I^2 = 0\%$). Among the 789 patients with a history of recent ACS, the absolute-risk difference of influenza vaccine vs placebo or control was 12.9% (95% CI, 7.75%-18.0%; $P < .001$) or an NNT of 8 (95% CI, 6-13) to prevent 1 cardiovascular event. Results were similar with the addition of unpublished data (P for interaction = .03; eFigure 3 in the Supplement).

Cardiovascular Mortality and All-Cause Mortality

In the 5 published RCTs comparing influenza vaccine with placebo or control that recorded fatal cardiovascular events, 42 of 3238 patients (1.3%) died of cardiovascular causes within 1 year of being treated with influenza vaccine compared with 55 of 3231 patients (1.7%) treated with placebo or control (RR, 0.81 [95% CI, 0.36-1.83]; $P = .61$; $I^2 = 68\%$; **Figure 4**). Subgroup analysis in trials in which data were available demonstrated no significant interaction with a recent history of ACS (2.5% influenza vaccine vs 8.4% placebo or control; RR, 0.34 [95% CI, 0.13-0.85]) compared with patients with stable CAD (2.1% influenza vaccine vs 2.3% placebo or control; RR, 0.90 [95% CI, 0.31-2.59]; P for interaction = .17; eFigure 4 in the Supplement). Results were similar with the addition of unpublished data for cardiovascular mortality overall (eFigure 5 in the Supplement) and by history of ACS (eFigure 6 in the Supplement).

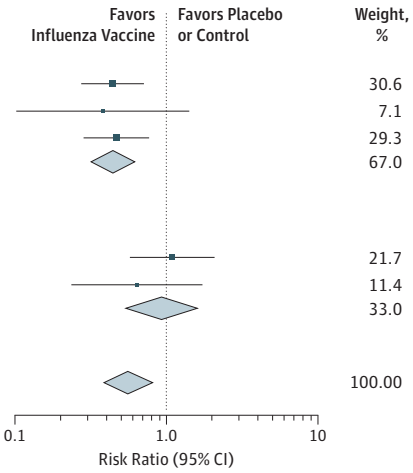
The majority of deaths observed across all 6 trials (including published and unpublished data) were considered due to a cardiovascular cause. Consequently, results were similar when influenza vaccine was compared with placebo or control for all-cause mortality (1.9% influenza vaccine vs 2.1% placebo or control; RR, 0.85 [95% CI, 0.45-1.61]; $P = .62$; $I^2 = 61\%$; eFigure 7 in the Supplement).

Other Cardiovascular Events and Active Control Trials

Individual nonfatal cardiovascular events, including myocardial infarction, stroke, heart failure, hospitalization for un-

Figure 3. Major Adverse Cardiovascular Events Comparing Influenza Vaccine vs Control Stratified by Timing of Acute Coronary Syndrome

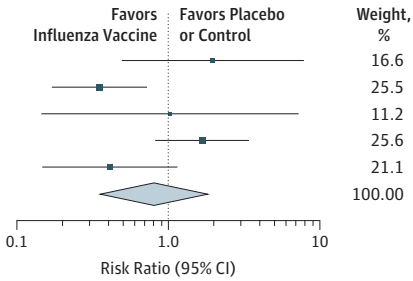
Study	Influenza Vaccine No. of Events	Influenza Vaccine Total Participants	Placebo or Control No. of Events	Placebo or Control Total Participants	Risk Ratio (95% CI)
Recent ACS					
FLUVACS,[20,21] 2004	18	96	41	97	0.44 (0.28-0.71)
FLUCAD,[22,23] 2008	3	83	7	74	0.38 (0.10-1.42)
Phrommintikul et al,[24] 2011	20	221	42	218	0.47 (0.29-0.77)
Subtotal (95% CI)	41	400	90	389	0.45 (0.32-0.63)
Heterogeneity: $\tau^2 = 0.00$; $\chi^2_2 = 0.09$, ($P = .96$); $I^2 = 0\%$ Test for overall effect: $Z = 4.68$ ($P < .001$)					
Stable CAD					
FLUVACS,[20,21] 2004	14	49	13	50	1.10 (0.58-2.09)
FLUCAD,[22,23] 2008	6	242	10	259	0.64 (0.24-1.74)
Subtotal (95% CI)	20	291	23	309	0.94 (0.55-1.61)
Heterogeneity: $\tau^2 = 0.00$; $\chi^2_1 = 0.81$, ($P = .37$); $I^2 = 0\%$ Test for overall effect: $Z = 0.23$ ($P = .82$)					
Total (95% CI)	61	691	113	698	0.57 (0.39-0.82)
Heterogeneity: $\tau^2 = 0.06$; $\chi^2_4 = 6.01$, ($P = .20$); $I^2 = 33$ Test for overall effect: $Z = 3.00$ ($P = .003$) Test for subgroup differences: $\chi^2_1 = 5.11$, ($P = .02$); $I^2 = 80.4\%$					



ACS indicates acute coronary syndrome; FLUCAD, FLU Vaccination Coronary Artery Disease; FLUVACS, FLU Vaccination Acute Coronary Syndromes. Square data markers represent risk ratios (RRs); 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 RR and 95% CI for the outcome of interest. Evaluated using the random-effects Mantel-Haenszel test.

Figure 4. Cardiovascular Mortality Comparing Influenza Vaccine vs Control

Study	Influenza Vaccine No. of Events	Influenza Vaccine Total Participants	Placebo or Control No. of Events	Placebo or Control Total Participants	Risk Ratio (95% CI)
Govaert,[41] 1994	6	927	3	911	1.97 (0.49-7.84)
FLUVACS,[20,21] 2004	9	145	26	147	0.35 (0.17-0.72)
FLUCAD,[22,23] 2008	2	325	2	333	1.02 (0.15-7.23)
De Villiers et al,[42] 2009	20	1620	12	1622	1.67 (0.82-3.40)
Phrommintikul et al,[24] 2011	5	221	12	218	0.41 (0.15-1.15)
Total (95% CI)	42	3238	55	3231	0.81 (0.36-1.83)
Heterogeneity: $\tau^2 = 0.54$; $\chi^2_4 = 12.36$, ($P = .01$); $I^2 = 68\%$ Test for overall effect: $Z = 0.50$ ($P = .61$)					



FLUCAD indicates FLU Vaccination Coronary Artery Disease; FLUVACS, FLU Vaccination Acute Coronary Syndromes; IVCAD, Influenza Vaccine for Coronary Artery Disease. Square data markers represent risk ratios (RRs); horizontal lines, the 95% CIs with marker size reflecting the statistical weight of the study using random-effects meta-analysis. A diamond data marker represents the overall RR and 95% CI for the outcome of interest. Evaluated using the random-effects Mantel-Haenszel test.

stable angina or cardiac ischemia, and urgent coronary revascularization occurred infrequently and were not universally recorded across all 6 trials. None of these individual nonfatal cardiovascular events were statistically significant (eFigures 8-12 in the Supplement). In the 6 active control trials, 42 of 10 678 patients (0.39%) developed a major adverse cardiovascular event with more potent vaccine compared with 37 of 6179 patients (0.60%) treated with standard vaccine (RR, 0.72 [95% CI, 0.42-1.13]; $P = .16$; $I^2 = 0\%$; eFigure 13 in the Supplement).

Sensitivity Analyses

No significant heterogeneity was detected for either the primary or any secondary end points. Visual inspection of funnel plots suggested no evidence of publication bias (eFigures 14-16 in the Supplement). Results for the primary end point were similar when analyses were compared with fixed-effects or Yusuf-Peto models and remained significant after removal of any trial from the pooled result (eTable 4 in the Supplement). In addition, there was no significant difference in the cardiovascular risk associated with influenza vaccine among other subgroups, level of influenza activity, or duration of follow-up (all P for interaction values ≥.14), except for the comparison of trials recording efficacy or safety events (P for interaction = .03; eTable 5 in the Supplement).

Discussion

In our meta-analysis of 6735 patients with varying degrees of cardiovascular risk, influenza vaccination was associated with a significantly lower risk of major adverse cardiovascular events. The risk associated with influenza vaccination was ro-

bust, with a greater association seen among patients with recent ACS compared with patients with stable CAD.

Influenza and Cardiovascular Risk

Although acute influenza infection is an independent risk factor for fatal and nonfatal cardiovascular events, the mechanism underlying that risk is less clear, but may relate to triggering the rupture of a vulnerable atherosclerotic plaque, fluid overload heart failure, myocarditis, arrhythmia, or the susceptibility of a frail and vulnerable patient.[4,7,9,57,58] Several observational studies support a potential association between the proximity of an acute respiratory infection and an increased risk of acute cardiac and cerebrovascular events.[3,4,8,15] Whether influenza vaccination can prevent these events remains controversial.[59] As we reviewed the literature, there appeared to be a considerable amount of evidence supporting an association between influenza vaccination and a lower risk of major clinical outcomes, such as cardiovascular mortality or nonfatal cardiovascular events, based on case-control, case-series, cohort studies, and limited prior reviews of RCTs with inherent potential for confounding and bias.[4,7,10-19,32-36] This may explain in part why less than a third of the general population in North America and less than half of high-risk patients annually consent to influenza vaccination.[60-64] Nevertheless, influenza is one of the most common, contagious, and morbid respiratory infections with a seasonal pattern of affliction during winter climate.[19,65] Several seasonal influenza vaccines are manufactured annually and universally provided with the dual goal of decreasing viral transmission and preventing influenza-related morbidity and mortality.[27,64] If severe influenza-associated morbidity and mortality is in part due to acutely triggered ischemic cardiovascular events, and a vaccine preventing influenza could decrease the risk of cardiovascular events, then this therapy could address a sizable component of residual cardiovascular risk not addressed by current therapy and provide yearlong coverage through 1 simple inoculation.

Randomized Studies of Influenza Vaccine and Cardiovascular Risk

There has been no large, adequately powered multicenter RCT testing influenza vaccination for the prevention of cardiovascular events. Several small RCTs have been conducted that either explicitly tested whether influenza vaccine compared with placebo or control may reduce cardiovascular events or carefully reported adverse events within trials of influenza vaccine for other purposes that can inform clinical practice.[20-24,40-48] Four of the 6 trials explicitly tested the cardiovascular benefit hypothesis. The FLU Vaccination Acute Coronary Syndromes (FLUVACS) trial was the first to report on 301 patients with stable CAD and myocardial infarction randomized in a single-blind manner in Argentina to either influenza vaccine or no therapy.[20,21] Vaccination reduced the RR of the primary end point of cardiovascular death and the secondary composite outcome of cardiovascular death, myocardial infarction, or unstable angina requiring coronary revascularization, which was modestly attenuated over time but remained robust at 1 year.[21] Two subsequent single-center trials studied patients with stable CAD. The Influenza Vaccination in Secondary Prevention From Coronary Ischemic Events in Coronary Artery Disease (FLUCAD) study, which randomized 658 patients in a double-blind fashion after angiography to influenza vaccine or placebo from 2004 through 2005 in Poland,[22,23] demonstrated no effect on the primary end point of cardiovascular death but a nonstatistically significant reduction in the secondary composite outcome of cardiovascular death, myocardial infarction, coronary revascularization, or cardiac ischemia driven primarily in patients with recent ACS. The Efficacy of Influenza Vaccine in Reducing Cardiovascular Events in Patients With Coronary Artery Diseases (IVCAD) study is an unpublished single-center, single-blind, 1-year outcomes trial that demonstrated no reduction in cardiovascular death or myocardial infarction in 266 randomized patients during the 2007-2008 influenza season in Iran.[40] A fourth trial of 439 patients with recent ACS without a history of prior influenza vaccination was conducted in Thailand from 2007 to 2009.[24] Patients were openly randomized before hospital discharge to receive influenza vaccination or routine care with a 1-year blinded end point ascertainment. The composite primary end point of cardiovascular death, myocardial infarction, unstable angina, heart failure, or stroke was significantly reduced in vaccinated patients.[24] Although levels of traditional influenza activity were low during this period, there was a well-publicized outbreak of a pandemic influenza A(H1N1) pdm09 virus in the latter half of the trial that had an uncertain influence on participants.[66] The inability to demonstrate a reduction in fatal events within the 2 trials that studied patients with relatively stable CAD, FLUCAD and IVCAD, may have been a result of studying a patient population with low absolute rates of subsequent fatal cardiovascular events.[22,23]

Several other RCTs of influenza vaccination recorded cardiovascular events as part of a safety evaluation throughout the past 20 years. However, in these trials it is likely that both the relative lower proportion of participants studied with acute coronary disease and the potential for selective outcome ascertainment of cardiovascular events contributed to why these studies added relatively few cardiovascular events to our analysis.[41-48] Still, despite differences in trial designs, risk of bias, sample size, cardiovascular risk of participants, circulating influenza activity, vaccination strategy, duration of follow-up, and number of observed events, our meta-analysis demonstrated a consistent association between influenza vaccination and a lower risk of cardiovascular events.

When results across trials were stratified by whether treated patients had a recent ACS, influenza vaccination was associated with the lowest risk of cardiovascular events in patients with the highest risk.[59] Our findings provide some support for current guideline recommendations for influenza vaccination of patients with ACS.[29-31]

Quality of Evidence and Limitations

Overall, our findings are based on a relatively small number of cardiovascular events (246 major adverse cardiovascular events and 97 cardiovascular deaths) among trials that varied in study design, intended primary outcomes, and patient populations. Subsequently, individual outcome analyses were of limited power. Moreover, several studies have design concerns re-

garding bias from inadequate randomization, concealment, and end point adjudication, which may limit our interpretation of the association of influenza vaccination with a lower risk of cardiovascular events.[35] For instance, a significant difference in the cardiovascular risk associated with influenza vaccine compared with placebo was detected among the subgroup of trials recording events as primary (efficacy) compared with secondary (safety) end points. This finding could suggest heterogeneity in outcome ascertainment between trials; however, it should be considered in context of multiple testing and chance of type I error. In addition, events such as unstable angina, cardiac ischemia, and coronary revascularization events included in a composite primary end point with myocardial infarction or cardiovascular death may not represent equal weighting of cardiovascular morbidity. Finally, our meta-analysis comprised a mix of both primary and secondary prevention populations, challenging our ability to distinguish the association of influenza vaccine with lower cardiovascular risk in each group.

The strengths of the current study include efforts to identify and systematically review all influenza vaccine RCTs since the inception of major biomedical literature databases, thereby limiting the likelihood of publication bias and risk of confounding from nonrandomized studies. In addition, we performed a number of sensitivity analyses that revealed no suggestion of inconsistency among trial results or missing data confirming the robustness of our primary results. In fact, funnel plots suggest potential small trials of cardiovascular benefit may remain unpublished.

Clinical and Policy Implications

The widespread influenza activity of 2012-2013 was a strong reminder of the potential cardiovascular complications that may occur in association with a severe respiratory tract infection.[67] Greater attention to prevention of cardiovascular events is therefore imperative to address the specific pathophysiology underlying this complication, particularly in elderly patients. Influenza vaccination may prevent cardiovascular events via avoidance of atherosclerotic plaque rupture or other forms of cardiac injury in a vulnerable patient and represents a simple once-annual protective therapy to reduce cardiovascular events. This finding has considerable clinical and health policy importance, given the profound underuse of vaccination among the general public and the potential impact this preventive strategy may have on high-risk patients.[60,61]

Conclusion

Within this global meta-analysis of RCTs that studied patients with high cardiovascular risk, influenza vaccination was associated with a lower risk of major adverse cardiovascular events within 1 year. Influenza vaccination was particularly associated with cardiovascular prevention in patients with recent ACS. Future research with an adequately powered multicenter trial to confirm the efficacy of this low-cost, annual, safe, easily administered, and well-tolerated therapy to reduce cardiovascular risk beyond current therapies is warranted.

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