Circulation

ORIGINAL RESEARCH ARTICLE

Influenza Vaccination After Myocardial Infarction

A Randomized, Double-Blind, Placebo-Controlled, Multicenter Trial

Ole Fröbert, MD; Matthias Götberg, MD; David Erlinge, MD; Zubair Akhtar, MPH; Evald H. Christiansen, MD; Chandini R. MacIntyre, MBBS, PhD; Keith G. Oldroyd, MBChB, MD; Zuzana Motovska, MD; Andrejs Erglis, MD; Rasmus Moer, MD; Ota Hlinomaz, MD; Lars Jakobsen, MD; Thomas Engstrøm, MD; Lisette O. Jensen, MD; Christian O. Fallesen, MD; Svend E Jensen, MD; Oskar Angerås, MD; Fredrik Calais, MD; Amra Kåregren, MD; Jörg Lauermann, MD; Arash Mokhtari, MD; Johan Nilsson, MD; Jonas Persson, MD; Per Stalby, MD; Abu K.M.M. Islam, MD; Afzalur Rahman, MD; Fazila Malik, MBBS; Sohel Choudhury, PhD; Timothy Collier, MSc; Stuart J. Pocock, PhD; John Pernow, MD

BACKGROUND: Observational and small, randomized studies suggest that influenza vaccine may reduce future cardiovascular events in patients with cardiovascular disease.

METHODS: We conducted an investigator-initiated, randomized, double-blind trial to compare inactivated influenza vaccine with saline placebo administered shortly after myocardial infarction (MI; 99.7% of patients) or high-risk stable coronary heart disease (0.3%). The primary end point was the composite of all-cause death, MI, or stent thrombosis at 12 months. A hierarchical testing strategy was used for the key secondary end points: all-cause death, cardiovascular death, MI, and stent thrombosis.

RESULTS: Because of the COVID-19 pandemic, the data safety and monitoring board recommended to halt the trial before attaining the prespecified sample size. Between October 1, 2016, and March 1, 2020, 2571 participants were randomized at 30 centers across 8 countries. Participants assigned to influenza vaccine totaled 1290 and individuals assigned to placebo equaled 1281; of these, 2532 received the study treatment (1272 influenza vaccine and 1260 placebo) and were included in the modified intention to treat analysis. Over the 12-month follow-up, the primary outcome occurred in 67 participants (5.3%) assigned influenza vaccine and 91 participants (7.2%) assigned placebo (hazard ratio, 0.72 [95% CI, 0.52–0.99]; *P*=0.040). Rates of all-cause death were 2.9% and 4.9% (hazard ratio, 0.59 [95% CI, 0.39–0.89]; *P*=0.010), rates of cardiovascular death were 2.7% and 4.5%, (hazard ratio, 0.59 [95% CI, 0.39–0.90]; *P*=0.014), and rates of MI were 2.0% and 2.4% (hazard ratio, 0.86 [95% CI, 0.50–1.46]; *P*=0.57) in the influenza vaccine and placebo groups, respectively.

CONCLUSIONS: Influenza vaccination early after an MI or in high-risk coronary heart disease resulted in a lower risk of a composite of all-cause death, MI, or stent thrombosis, and a lower risk of all-cause death and cardiovascular death, as well, at 12 months compared with placebo.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT02831608.

Key Words: influenza vaccines ■ myocardial infarction ■ randomized controlled trial

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Inflammation plays a central role in atherosclerotic progression from initiation to rupture of atherosclerotic plaques. Although the inflammatory process is multifactorial, exogenous pathogens, including influenza virus, may modulate the inflammatory response.[1] A positive association of influenza with the risk of cardiovascular

Correspondence to: Ole Fröbert, MD, PhD, Örebro University, Faculty of Health, Department of Cardiology, Södra Grev Rosengatan, 701 85 Örebro, Sweden. Email ole.frobert@regionorebrolan.se

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Clinical Perspective

What Is New?

- Observational and small randomized studies suggest that influenza vaccine may reduce future cardiovascular events in patients with cardiovascular disease.
- This is a double-blind, randomized controlled trial to test whether influenza vaccination early after admission with myocardial infarction or high-risk coronary artery disease reduces cardiovascular events.
- Influenza vaccination resulted in a lower risk of a composite of all-cause death, myocardial infarction, or stent thrombosis, and a lower risk, as well, of all-cause death and cardiovascular death at 12 months compared with placebo.

What Are the Clinical Implications?

- These findings suggest that influenza vaccination should be considered as part of in-hospital treatment after myocardial infarction.
- Despite being guideline-recommended, influenza vaccination is underused, and the findings from this study emphasize the importance of seasonal influenza vaccination in patients with cardiovascular disease.

Nonstandard Abbreviations and Acronyms

FLUCAD	Influenza Vaccination in Prevention From Acute Coronary Events in Coronary Artery Disease study
FLUVACS	FLU Vaccination Acute Coronary Syndromes and Planned Percutaneous Coronary Interventions Study
IAMI	Influenza vaccination After Myocardial Infarction trial
MI	myocardial infarction
PCI	percutaneous coronary intervention

events was described in a study of influenza epidemics from 1915 to 1929, including the 1918 to 1920 pandemic.[2] Later observational studies confirmed a temporal association.[3–7] A few clinical trials of influenza vaccine versus no vaccine or placebo in high-risk patients with cardiovascular disease observed fewer cardiovascular events with vaccine,[8–10] but a recent large, randomized trial in a high-risk cardiovascular population comparing high-dose trivalent influenza vaccine with standard-dose quadrivalent vaccine found no differences in mortality or cardiopulmonary hospitalizations.[11] Evidence from large clinical trials is required to reliably assess whether influenza vaccination is effective in preventing future cardiovascular events in patients with cardiovascular disease.[12]

In the IAMI trial (Influenza Vaccination After Myocardial Infarction), we hypothesized that influenza vaccination may reduce the combined incidence of death, myocardial infarction (MI), and stent thrombosis in patients with recent MI or high-risk coronary disease.

METHODS

The IAMI trial was a randomized, double-blind, placebo-controlled, investigator-initiated trial designed to evaluate the efficacy of influenza vaccine after MI or percutaneous coronary intervention (PCI) in high-risk patients with coronary artery disease. The trial was conducted at 30 centers in 8 countries (Sweden, Denmark, Norway, Latvia, the United Kingdom, Czech Republic, Bangladesh, and Australia) from October 2016 through February 2020. Participants were enrolled during the Northern Hemisphere influenza season from September through February, and from May through September in the Southern Hemisphere influenza season (Bangladesh and Australia).

The trial was conducted in accordance with the Declaration of Helsinki and the principles of Good Clinical Practice and was approved by the Swedish Ethical Review Agency (Dnr 2014/264) and the ethical review board and national regulatory authority of each participating site. Participants provided written informed consent. Data were collected and analyzed by the investigators. The IAMI trial is registered at https://www.clinicaltrials.gov (Unique identifier: NCT02831608) and at the European Union Drug Regulating Authorities Clinical Trials Database (number 2014-001354-42).

Project coordination, medical review, data management, and site monitoring were coordinated at Örebro University Hospital. Statistical oversight and analysis were performed by statisticians at the London School of Hygiene and Tropical Medicine. The trial was overseen by a data safety and monitoring board of independent experts that periodically reviewed data by treatment group but decided not to break the code as to which group received influenza vaccine or placebo.

Participants

Participants were eligible if they had ST-segment–elevation myocardial infarction or non–ST-segment–elevation myocardial infarction and had completed coronary angiography or PCI. The minimum age of eligibility was 18 years. Participants were excluded if they had received an influenza vaccination during the previous 12 months, intended to be vaccinated during that influenza season, or met other exclusion criteria (see Eligibility Data in the Data Supplement). Participants were not revaccinated within the trial setting and could not be re-enrolled in multiple influenza seasons. To optimize recruitment, changes were made to the enrollment criteria during the course of the trial to include patients with stable coronary artery disease if they were ≥75 years, and had at least 1 additional risk criterion as specified in the Data Supplement. Exclusion of subjects who had received influenza vaccination during the previous 12 months was changed to exclude subjects who had received influenza vaccination during the ongoing influenza season. In Bangladesh, inclusion criteria did not include coronary angiography or PCI.

Participants were allowed to obtain influenza vaccination outside the study on their own behalf. Baseline information was collected from national heart disease registries in Sweden (all sites) and Denmark (3 of 5 sites) and from electronic case report forms at other participating sites.

Trial Procedures

We randomly assigned participants in a 1:1 ratio to receive either influenza vaccine or placebo through a secure website. Randomization lists were generated with a permuted block design prepared by a data scientist not involved in the trial and stratified according to trial site (block size 6).

At each site, study nurses not otherwise involved or participating in the study prepared 0.5 mL of the trial medication out of the participants' sight and administered it as a deep subcutaneous or intramuscular injection in the deltoid region within 72 hours of coronary angiography/PCI or, in Bangladeshi centers, hospital admission. The study participants and all other study personnel were blinded to group assignment. The trial protocol and a list of investigators is provided in the Data Supplement.

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.

Outcomes

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 next of kin. If the patient or relatives could not be contacted, information was collected through review of hospital records. 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. Source documents of all primary and secondary end points were collected for adjudication by an independent event committee composed of experienced cardiologists who were blinded to the trial group assignments.

Enrolled participants were provided with a questionnaire to document local and systemic reactions to vaccination for 1 week. Serious adverse events were recorded and graded throughout the 12-month follow-up period.

Statistical Analysis

Sample size was calculated based on 3 smaller randomized studies[8–10] and demographic data from annual Swedish health registry reports.[13] The composite 12-month primary end point of all-cause death, new MI, or stent thrombosis was estimated at 10.0% for individuals randomly assigned to placebo.

An analysis of data from Swedish health registry reports on 11 761 individuals with stable coronary artery disease identified a subgroup with a 12-month risk of cardiovascular events equal to that seen in patients with ST-segment–elevation myocardial infarction and non–ST-segment–elevation myocardial infarction. In individuals with stable coronary artery disease ≥75 years of age with at least 1 additional risk criterion (Data Supplement), the risk for the primary composite end point was calculated to be equivalent to that of patients with MI.

We calculated that 386 events would need to occur for the study to have 80% statistical power to detect a 25% reduction in the primary end point in the influenza vaccination group, corresponding to a hazard ratio (HR) of 0.75 with 2-sided α=0.05, requiring 2186 participants per group. We used a log-rank test stratified by center to compare the time from randomization to the first occurrence of the primary end point. Cumulative incidence of the primary end point at 12 months was estimated by the Kaplan-Meier method, and a Cox proportional-hazards model stratified by center was used to estimate the HR and 95% CI. The same approach was used for secondary end points. We prespecified a fixed-sequence hierarchical testing approach for the 4 key secondary end points to control the type 1 error rate: all-cause death, cardiovascular death, MI, and stent thrombosis. Other secondary end points were considered exploratory. Potential interactions between study treatment and 8 prespecified subgroups were evaluated using a Cox proportional-hazards model. All analyses were performed on a modified intention-to-treat population comprising all patients who underwent randomization and received the study treatment. Patients who withdrew consent after receiving the study treatment were censored at the date of withdrawal of consent. Patients who were lost to follow-up at 12 months were censored on the day of randomization.

We performed an exploratory meta-analysis for the key secondary end point of cardiovascular death at 1 year, combining our results with those from published randomized clinical trials that had investigated the effect of influenza vaccination in patients with cardiovascular disease. Estimates of the log HR and its standard error were obtained from the reported HRs and 95% CIs, and a pooled estimate was obtained using a fixed-effect model with weights calculated using the inverse variance method.

All analyses were performed using Stata version 16.1.

Patient and Public Involvement

No patients were involved in the design of the study, nor were any patients involved in the implementation, recruitment, or interpretation of the results.

Data Sharing

Requests for data collected for the study can be made to the corresponding author and will be considered by the steering group on an individual basis. A contract should be signed.

RESULTS

Because of the coronavirus disease 2019 (COVID-19) pandemic, the data safety and monitoring board recommended on April 7, 2020, that it would not be feasible for the trial to continue recruitment, because the transmission of influenza was expected to decrease, and COVID-19–related deaths were deemed likely to become common in both arms of the trial, making results difficult to interpret.

From October 1, 2016, to March 1, 2020, 6696 patients were screened, of whom 2571 provided written

informed consent and underwent randomization; 2532 received influenza vaccination or placebo and were included in the modified intention-to-treat analysis (Figure 1, Table II in the Data Supplement). The baseline characteristics of the participants were well balanced between the trial groups (Table 1). The mean (±SD) age of the participants was 59.9±11.2 years, with 462 (18.2%) women, 870 (35.5%) current smokers, and 528 (21.1%) participants with diabetes. A total of 1348 (54.5%) patients were admitted with ST-segment–elevation myocardial infarction, 1119 (45.2%) with non–ST-segment–elevation myocardial infarction, and 8 (0.3%) with stable coronary artery disease. A total of 1868 participants (74.3%) were treated with PCI, and 587 (23.4%) received medical treatment only (Table III in the Data Supplement). Left ventricular ejection fraction at discharge, assessed by echocardiography, was normal in 60.5% of participants, slightly reduced in 27.5%, moderately reduced in 9.9%, and severely reduced in 2.2%. Medication at discharge reflected current clinical practice (Table III in the Data Supplement).

The primary composite end point occurred in 67 participants (5.3%) assigned to influenza vaccine and 91 participants (7.2%) assigned to placebo (HR, 0.72 [95% CI, 0.52–0.99]; *P*=0.040; Table 2, Figure 2). With respect to key secondary end points, the rates of all-cause death were 2.9% in the influenza vaccine group and 4.9% in the placebo group (HR, 0.59 [95% CI, 0.39–0.89]; *P*=0.010). Rates of cardiovascular death were 2.7% and 4.5%, respectively (HR, 0.59 [95% CI, 0.39–0.90]; *P*=0.014), and rates of MI were 2.0% and 2.4%, respectively (HR, 0.86 [95% CI, 0.50–1.46]; *P*=0.57). Causes of death were mainly cardiovascular (Table IV in the Data Supplement). None of the 8 patients in the stable coronary artery disease group experienced an event. Across all subgroups, the findings were consistent with the primary composite end point result (Figure 3). Although country was not part of the prespecified subgroups, we also tested if the treatment effect differed by country, but there was no evidence of this (interaction *P*=0.75).

Serious adverse events were rare and similar in type and incidence in the influenza vaccine and placebo groups (Table V in the Data Supplement). Solicited systemic reactions within the 7 days after injection were reported at a similar incidence in the 2 groups, whereas injection site reactions such as pain, redness, swelling, and hardening were reported significantly more often in participants assigned to influenza vaccine (Table VI in the Data Supplement). In both groups, ≈1 in 7 participants reported receiving influenza vaccine (Table VI in the Data Supplement).

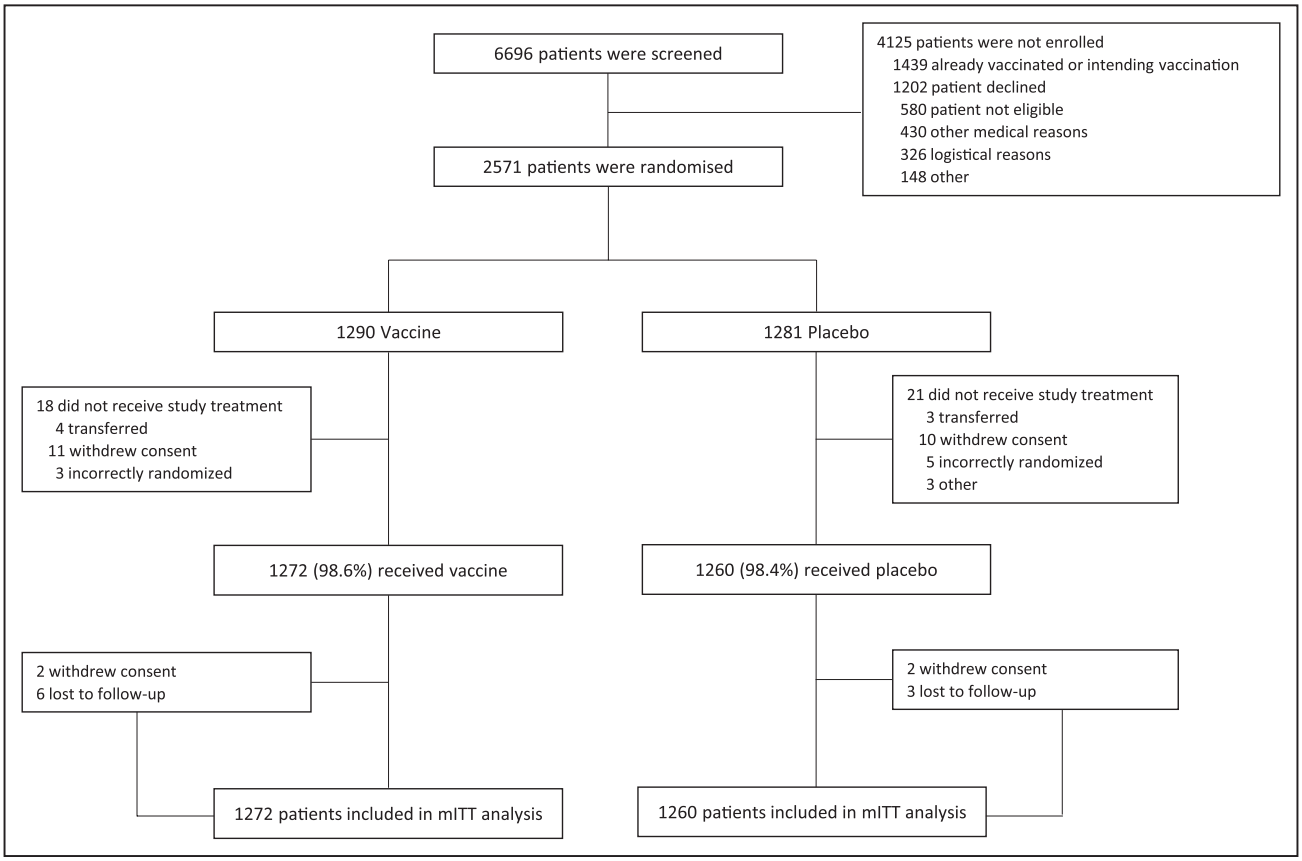

Figure 1. Allocation, follow-up, and analysis of trial participants.
Participants who withdrew consent after receiving the study medication were censored at the day of withdrawal of consent; participants who were lost to follow-up were censored at 0.5 days follow-up. mITT indicates the modified intention to treat population, all randomly assigned participants who received the study treatment.

Table 1. Baseline Characteristics of the Patients According to Randomization

Baseline characteristics	Vaccine (n=1272)	Placebo (n=1260)
Age, y	60.1 (±11.0)	59.6 (±11.4)
Male sex, n (%)	1036 (81.4)	1034 (82.1)
ST-segment–elevation myocardial infarction, n (%)	665/1239 (53.7)	683/1236 (55.3)
Non–ST-segment–elevation myocardial infarction, n (%)	568/1239 (45.8)	551/1236 (44.6)
Stable coronary artery disease, n (%)	6/1239 (0.5)	2/1236 (0.2)
Body mass index, kg/m^2	27.5 (±5.0)	27.4 (±5.1)
Diabetes, n (%)	281/1253 (22.4)	247/1254 (19.7)
Smoking status, n (%)		
Never smoked	463/1232 (37.6)	461/1222 (37.7)
Former smoker	332/1232 (26.9)	328/1222 (26.8)
Current smoker	437/1232 (35.5)	433/1222 (35.4)
Hyperlipidemia, n (%)	427/1257 (34.0)	409/1249 (32.7)
Hypertension, n (%)	650/1251 (52.0)	595/1251 (47.6)
Previous myocardial infarction, n (%)	191/1253 (15.2)	172/1249 (13.8)
Previous percutaneous coronary intervention, n (%)	138/1257 (11.0)	129/1257 (10.3)
Previous coronary artery bypass graft, n (%)	28/1258 (2.2)	37/1257 (2.9)
Killip class ≥2, n (%)	50/1157 (4.3)	45/1155 (3.9)
Number of diseased vessels, n (%)		
Normal	33/1062 (3.1)	27/1050 (2.6)
1-vessel disease	546/1062 (51.4)	590/1050 (56.2)
2-vessel disease	268/1062 (25.2)	228/1050 (21.7)
3-vessel disease	148/1062 (13.9)	148/1050 (14.1)
Left main disease	67/1062 (6.3)	57/1050 (5.4)

Values indicate mean (±SD) or frequency/total (%); percentages are calculated from all nonmissing values; body mass index data were missing for 65 and 59 patients in the vaccine and placebo groups, respectively.

About 6% of participants reported contracting acute respiratory illness during the 12-month follow-up period (Table VI in the Data Supplement).

We searched PubMed, up to June 10, 2021, for published randomized clinical trials assessing the effect of influenza vaccination among patients with coronary artery disease. The search terms were as follows: ("coronary artery disease" or "ischemic heart disease" or "myocardial infarction") AND ("influenza vaccination" or "influenza immunization") AND ("clinical trial" or "randomized"). We identified 3 other trials with 1-year follow-up data that have compared influenza vaccine with no vaccine or placebo in high-risk patients with cardiovascular disease: the FLUVACS trial (FLU Vaccination Acute Coronary Syndromes and Planned Percutaneous Coronary Interventions Study; 35 cardiovascular deaths in 301 patients)[8]; the FLUCAD trial (Influenza Vaccination in Prevention From Acute Coronary Events in Coronary Artery Disease study; 4 cardiovascular deaths in 658 patients)[9]; and the study by Phrommintikul et al[10] (17 cardiovascular deaths in 439 patients). The pooled estimate of cardiovascular death of the HR from the fixed-effect meta-analysis of all 4 trials was 0.51 (95% CI, 0.36–0.71); P=0.0001. There was no evidence of between-study heterogeneity (P=0.48, I^2=9.7%) (Figure I in the Data Supplement). A random-effects model produced almost identical results (HR, 0.50 [95% CI, 0.35–0.73]; P=0.0003).

DISCUSSION

Among participants with MI or high-risk coronary heart disease, influenza vaccine administered within 72 hours of an invasive coronary procedure or hospitalization resulted in a lower risk at 12 months of a composite primary outcome of all-cause death, MI, or stent thrombosis, and a lower risk of all-cause death and of cardiovascular death compared with placebo, as well. The results were consistent across subgroups and in agreement with a recent meta-analysis of randomized trials and observational studies comprising almost 240 000 patients with cardiovascular disease with a median follow-up of 19.5 months reporting influenza vaccine associated with reduced risk of all-cause and cardiovascular mortality but not with MI compared with controls.[14]

In this study, participants assigned to influenza vaccine reported more injection site reactions than participants assigned to placebo, but there were no differences between groups in self-reported systemic reactions or in investigator-reported adverse or serious adverse events, confirming earlier findings that influenza vaccine can be safely administered after a cardiovascular event.[8,15]

The greatest positive effect of influenza vaccine in patients with cardiovascular disease may be seen in the highest-risk subjects with recent acute coronary syndrome.[16] This observation seems supported by our findings and the findings of the FLUVACS study (200 patients with MI and 101 for whom PCI was scheduled)[8] where the primary end point of cardiovascular death at 1 year was significantly lower among patients assigned influenza vaccination and by the study by Phrommintikul et al[10] (439 patients with acute coronary syndrome) where the primary end point of major cardiovascular events was lower among patients assigned influenza vaccination. Conversely, the FLUCAD study of 658 mostly stable patients with coronary artery disease randomly assigned to influenza vaccination or placebo revealed no difference in the composite primary end point of cardiovascular death, MI, and coronary revascularization after 1 year.[9]

The circulating strains of influenza varied over the study years, and included A(H3N2), A(H1N1)pdm09, and B. In the 2 seasons when influenza vaccine most favorably impacted outcome (2017–2018 and 2019–2020; Figure 3) the corresponding estimated vaccine effectiveness was also good, up to 60%,[17,18] whereas vaccine effectiveness was poorer in the other 2 study

Table 2. Primary, Key Secondary, and Other Secondary End Points

End points	Vaccine (n=1272)	Placebo (n=1260)	Hazard ratio (95% CI)	*P* value
Primary end point, n (%)				
All-cause death, myocardial infarction, stent thrombosis	67 (5.)	91 (7.2)	0.72 (0.52–0.99)	0.040
Key secondary end points, n (%)				
All-cause death	37 (2.9)	61 (4.9)	0.59 (0.39–0.89)	0.010
Cardiovascular death	34 (2.7)	56 (4.5)	0.59 (0.39–0.90)	0.014
Myocardial infarction	25 (2.0)	29 (2.4)	0.86 (0.50–1.46)	0.57
Stent thrombosis	6 (0.5)	3 (0.2)	1.94 (0.48–7.76)	0.34
Other secondary end points, n (%)				
Cardiovascular death, myocardial infarction, stent thrombosis	64 (5.1)	86 (6.9)	0.73 (0.53–1.01)	0.064
Stroke, including transient ischemic attack	6 (0.5)	8 (0.7)	0.72 (0.25–2.08)	0.74
Hospitalization for heart failure	29 (2.3)	16 (1.3)	1.77 (0.96–3.27)	0.062
Noncardiovascular death	3 (0.2)	5 (0.4)	0.57 (0.14–2.40)	0.27
Unplanned revascularization	87/1205 (7.3)	76/1190 (6.5)	1.13 (0.83–1.54)	0.42
Hospitalization for arrhythmia	3/1263 (0.2)	7/1253 (0.6)	0.43 (0.11–1.64)	0.20

Percentages are Kaplan-Meier cumulative percentage at 1 y. *P* value is from the log-rank test; hazard ratio and 95% CI are from Cox proportional-hazards model adjusting for center; unplanned revascularization and hospitalization for arrhythmia are site-reported events only.

seasons (2016–2017 and 2018–2019).[18,20] Time-to-event curves (Figure 2) in this study began to separate early postinjection and stabilized at ≈3 months, indicative of a therapeutic effect during the vulnerable early phase post-MI characterized by a high level of inflammation.[21] Influenza vaccination results in early immune

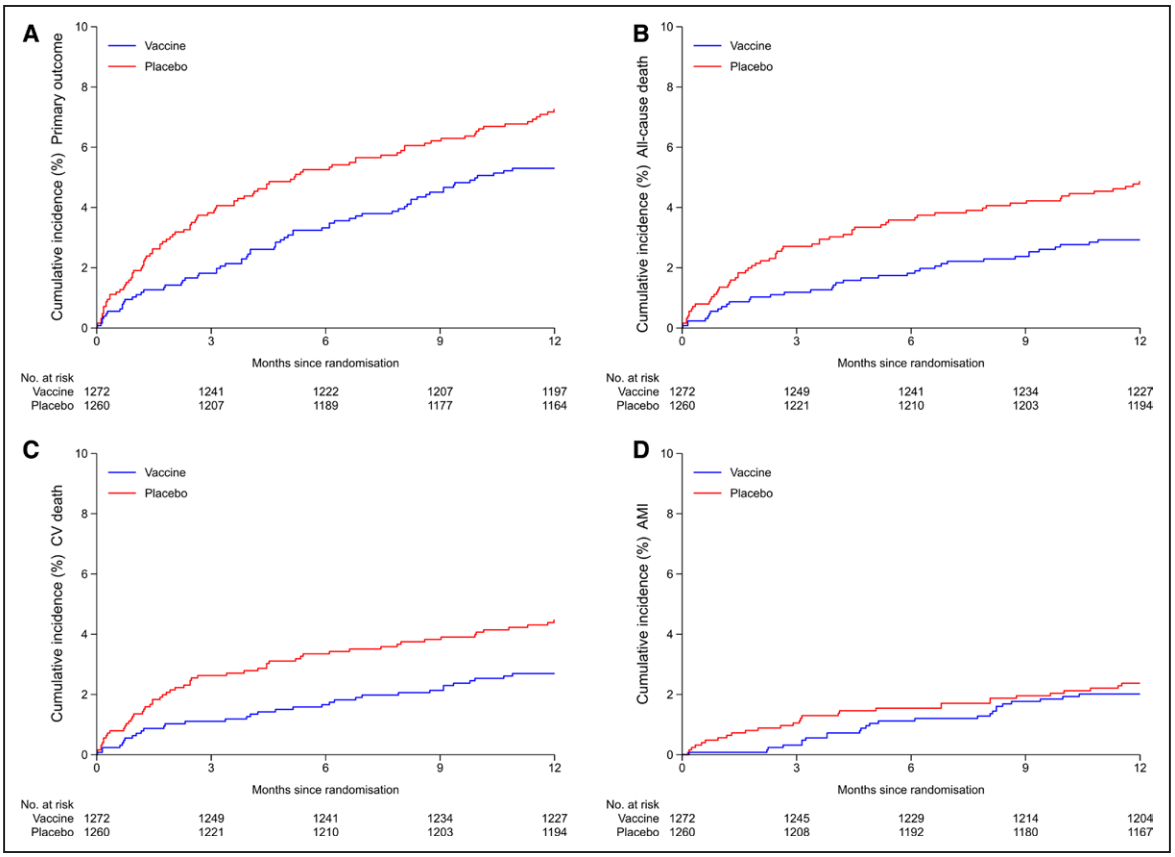

Figure 2. Kaplan-Meier event curves of the influenza vaccine and placebo groups for the primary composite end point of all-cause death, myocardial infarction, or stent thrombosis in a time-to-event analysis (A), for all-cause death (B), for cardiovascular death (C), and for myocardial infarction (D).
AMI indicates acute myocardial infarction; and CV, cardiovascular.

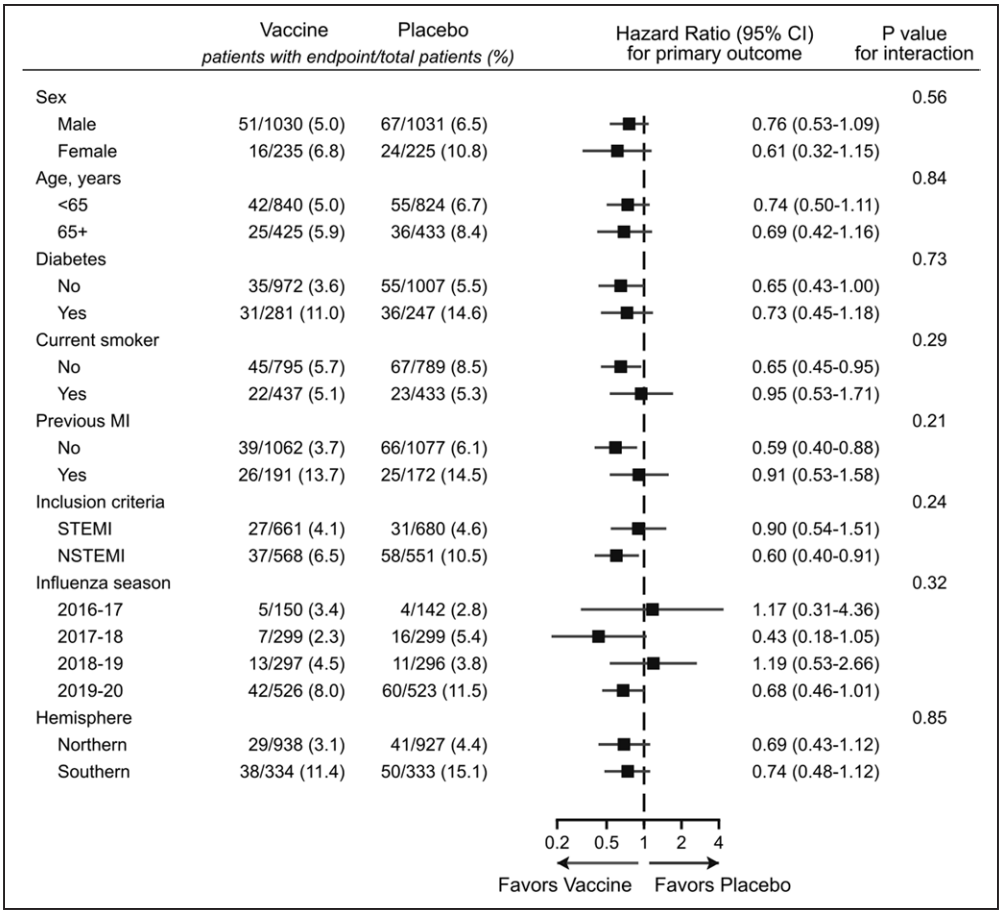

Figure 3. Hazard ratios for the primary composite end point of all-cause death, myocardial infarction, or stent thrombosis within 12 months according to predefined subgroups.

Hazard ratios (black squares) and 95% CIs (horizontal lines) are shown. MI indicates myocardial infarction; NSTEMI, non–ST-segment–elevation myocardial infarction; and STEMI, ST-segment–elevation myocardial infarction.

activation with strong upregulation of genes involved in interferon signaling and antigen presentation pathways[22] along with lowering of proinflammatory cytokines[23] and may exert an anti-inflammatory and plaque-stabilizing effect.[24] Another explanation for our findings is that influenza infection may trigger an acute cardiovascular event,[3] and patients experiencing a MI are at the highest risk of a new cardiovascular event in the initial ensuing months,[25] a period where preventing influenza could be of particular importance.

Because influenza vaccination carries a Class I, Level of Evidence B recommendation in both American and European secondary prevention cardiovascular guidelines,[26,27] it could be considered controversial to conduct a randomized clinical trial in which half of the patients received placebo. However, current guidelines are based mostly on evidence from observational studies, timing of influenza vaccination following an acute cardiovascular event is unknown, and influenza immunization rates remain low.[28] In the IAMI study only patients not routinely receiving yearly influenza vaccination and not planning to be vaccinated during the current influenza season could be enrolled. Also, participants were allowed to obtain influenza vaccination after study enrollment on their own behalf. The crossover rate in the placebo arm was 13.2%. If anything, this would have biased the results toward null. The findings of the IAMI study indicate that in-hospital vaccination after MI during the influenza season is safe and offers protection equivalent to standard therapies such as statins and angiotensin-converting enzyme inhibitors.[29] In-hospital influenza vaccination given routinely following MI will likely also lead to higher patient treatment compliance.[30]

This trial has several limitations. First, in part because the trial was stopped early because of the COVID-19 pandemic, the power to detect differences in the primary end point was reduced. Results of analyses of clinical trials ended early tend to exaggerate the effects of a treatment.[31] Second, participants enrolled in Bangladesh did not routinely undergo invasive investigation and treatment, thus precluding assessment of stent thrombosis, which was one of the 3 components of the primary end point. Third, trivalent vaccine was used in the first study season and quadrivalent vaccine was used in the following seasons. Fourth, only 8 patients with high-risk stable coronary artery disease were enrolled. Last, we did not

evaluate the effect of influenza vaccination outside of influenza seasons.

In participants with MI or high-risk coronary disease, in-hospital influenza vaccination resulted in a lower risk of a composite of all-cause death, MI, or stent thrombosis; lower risk of all-cause death; and lower risk of cardiovascular death at 12 months compared with placebo. In addition, our exploratory meta-analysis, for this trial plus 3 previous trials,[8–10] demonstrated a reduction by half of cardiovascular death at 1 year in patients assigned to influenza vaccination. Overall, these findings suggest that influenza vaccination should be considered as part of in-hospital treatment after MI.

ARTICLE INFORMATION

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Affiliations

Örebro University, Faculty of Health, Department of Cardiology, Sweden (O.F., F.C.). Department of Cardiology, Skane University Hospital, Clinical Sciences, Lund University, Sweden (M.G., D.E., A.M.). International Centre for Diarrhoeal Disease Research, Bangladesh, Dhaka (Z.A.). Department of Cardiology, Aarhus University Hospital, Denmark (E.H.C., L.J.). The Kirby Institute, UNSW Medicine, University of New South Wales, Sydney, Australia (C.R.M.). British Heart Foundation Glasgow Cardiovascular Research Centre, Institute of Cardiovascular and Medical Sciences, University of Glasgow, United Kingdom, and West of Scotland Heart and Lung Centre, Golden Jubilee National Hospital, Clydebank, Glasgow, United Kingdom (K.G.O.). Cardiocenter, Third Faculty of Medicine, Charles University, and University Hospital Kralovske Vinohrady, Prague, Czech Republic (Z.M.). Pauls Stradins Clinical University Hospital, University of Latvia, Riga (A.E.). LHL-sykehuset Gardermoen, Oslo, Norway (R.M.). International clinical research center, St. Anne University Hospital and Masaryk University, Brno, Czech Republic (O.H.). Rigshospitalet, University of Copenhagen, Denmark (T.E.). Department of Cardiology, Odense University Hospital, Denmark (L.O.J., C.O.F.). Department of Cardiology, Aalborg University Hospital, and Department of Clinical Medicine, Aalborg University, Denmark (S.E.J.). Sahlgrenska University Hospital and Institute of Medicine, Department of molecular and clinical medicine, Gothenburg University, Sweden (O.A.). Västmanlands sjukhus Västerås, Sweden (A.K.). Department of Cardiology, Jönköping, Region Jönköping County, and Department of Health, Medicine and Caring, Linköping University, Sweden (J.L.). Cardiology, Heart Centre, Department of Public Health and Clinical Medicine, Umeå University, Sweden (J.N.). Division of Cardiovascular Medicine, Department of Clinical Sciences, Karolinska Institutet, Danderyd University Hospital, Stockholm, Sweden (J. Persson). Department of Cardiology, Karlstad Central Hospital, Sweden (P.S.). National Institute of Cardiovascular Diseases, Sher-e-Bangla Nagar, Dhaka, Bangladesh (A.K.K.M.I., A.R.). National Heart Foundation Hospital and Research Institute, Dhaka, Bangladesh (F.M., S.C.). Department of Medical Statistics, London School of Hygiene and Tropical Medicine, United Kingdom (T.C., S.J.P.). Cardiology Unit, Department of Medicine Solna, Karolinska Institutet and Karolinska University Hospital, Stockholm, Sweden (J. Pernow).

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Supplemental Materials

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Expanded Methods
Data Supplement Tables I–VI
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Protocols with Summary of Changes
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