

Influenza Vaccination after Myocardial Infarction: A Randomized, Double-Blind, Placebo-Controlled, Multicenter Trial

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Abstract

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 endpoint was the composite of all-cause death, MI, or stent thrombosis at 12 months. A hierarchical testing strategy was used for the key secondary endpoints: all-cause death, cardiovascular death, MI, and stent thrombosis.

Results: Due to the Covid-19 pandemic, the data safety and monitoring board decided 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 eight countries; 1290 assigned to influenza vaccine and 1281 to placebo. 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% confidence interval, 0.52 to 0.99; $P=0.040$). Rates of all-cause death were 2.9% and 4.9% (hazard ratio, 0.59; 0.39 to 0.89; $P=0.010$), of cardiovascular death 2.7% and 4.5%, (hazard ratio, 0.59; 0.39 to 0.90; $P=0.014$), and of MI 2.0% and 2.4% (hazard ratio, 0.86; 0.50 to 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, as well as a lower risk of all-cause death and cardiovascular death at 12 months compared with placebo.

Clinical Trial Registration: URL: <http://www.clinicaltrials.gov> Unique identifier: NCT02831608.

Key Words: influenza vaccination; myocardial infarction; randomized clinical trial

Non-standard 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 study
MI	Myocardial infarction
PCI	Percutaneous coronary intervention
STEMI	ST-elevation myocardial infarction

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, as well as a lower risk 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 underutilized and the findings from this study emphasize the importance of seasonal influenza vaccination in patients with cardiovascular disease.

Introduction

Inflammation plays a central role in atherosclerotic progression from initiation to rupture of atherosclerotic plaques. While 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 events was described in a study of influenza epidemics from 1915 to 1929, including the 1918–1920 pandemic.² Later observational studies have confirmed a temporal association.^{3–7} A few clinical trials of influenza vaccine vs. 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 hospitalisations.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 Influenza vaccination After Myocardial Infarction (IAMI) trial, 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 efficacy of influenza vaccine following 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 UK, 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. Written informed consent was provided by the participants. Data were collected and analyzed by the investigators. The IAMI trial is registered at ClinicalTrials.gov (number 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 & Tropical Medicine. The trial was overseen by a data safety and monitoring board of independent experts which 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-elevation myocardial infarction (STEMI) or non-STEMI 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 prior 12 months, intended to be vaccinated during that influenza season, or met other exclusion criteria (supplementary file p 7). 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 or older, and had at least one additional risk criterion as specified in the supplementary file. Exclusion of subjects who had received influenza vaccination during the prior 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 of 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 web-site. 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 supplementary file.

Influenza vaccine content was consistent with WHO 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 manuscript. Placebo was sterile 0.9% normal saline solution.

Outcomes

The primary endpoint was the composite of all-cause death, MI, or stent thrombosis at 12 months post-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 three components of the primary composite endpoint plus cardiovascular death, all at 12 months, were considered key secondary efficacy endpoints. Secondary exploratory endpoints included unplanned revascularization; stroke or transient ischemic attack; the composite of cardiovascular death, MI, or stent thrombosis; and hospitalization for heart failure or hospitalization for arrhythmia. Source documents of all primary and secondary endpoints 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 three smaller randomized studies⁸⁻¹⁰ and demographic data from annual Swedish health registry reports (accessible at <http://www.ucr.uu.se/swedeheart/>).

The composite 12-month primary endpoint of all-cause death, new MI, or stent thrombosis was estimated at 10.0% for individuals randomized to placebo.

An analysis of data from Swedish health registry reports on 11761 individuals with stable coronary artery disease identified a subgroup with a 12-month risk of cardiovascular events equal to that seen in patients with STEMI and non-STEMI. In individuals with stable coronary artery disease ≥ 75 years of age with at least one additional risk criterion (Data Supplement), the risk for the primary composite endpoint 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 endpoint in the influenza vaccination group, corresponding to a hazard ratio (HR) of 0.75 with two-sided $\alpha = 0.05$, 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 endpoint. Cumulative incidence of the primary endpoint 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% confidence interval (CI). The same approach was used for secondary endpoints. We prespecified a fixed sequence hierarchical testing approach for the four key secondary endpoints to control the type-1 error rate: all-cause death, cardiovascular death, MI, stent thrombosis. Other secondary endpoints were considered exploratory. Potential interactions between study treatment and eight 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 endpoint of cardiovascular death at one year, combining our results with those from published randomized clinical trials which 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 (College Station, Texas).

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

Due to the coronavirus disease 2019 pandemic, the data safety and monitoring board decided on April 7, 2020 that it would not be feasible for the trial to continue recruitment, since 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 (\pm standard deviation [SD]) age of the participants was 59.9 ± 11.2 years, with 462 (18.2%) female, 870 (35.5%) current smokers, and 528 (21.1%) with diabetes. A total of 1348 (54.5%) were admitted with STEMI, 1119 (45.2%) with non-STEMI and eight (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 endpoint 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 to 0.99; $P=0.040$) (Table 2, Figure 2). With respect to key secondary endpoints, 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 to 0.89], $P=0.010$). Rates of cardiovascular death were 2.7% and 4.5%, respectively (HR 0.59 [95% CI 0.39 to 0.90], $P=0.014$), and of MI were 2.0% and 2.4%, respectively (HR 0.86 [95% CI 0.50 to 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 endpoint result (Figure 3). Although 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 of similar type and incidence in the influenza vaccine and placebo groups (Table V in the Data Supplement). Solicited systemic reactions within the seven days post-injection were reported at a similar incidence in the two groups, while injection site reactions like 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, about one in seven participants reported receiving influenza vaccine (Table VI in the Data Supplement). 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 (“coronary artery disease” or “ischemic heart disease” or “myocardial infarction”) AND (“influenza vaccination” or “influenza immunization”) AND (“clinical trial” or “randomized”). We identified three 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 FLU Vaccination Acute Coronary Syndromes and Planned Percutaneous Coronary Interventions Study (FLUVACS, 35 cardiovascular deaths in 301 patients);⁸ the Influenza Vaccination in Prevention From Acute Coronary Events in Coronary Artery Disease study (FLUCAD, 4 cardiovascular deaths in 658 patients)⁹ and Phrommintikul, A. et al. (17 cardiovascular deaths in 439 patients).¹⁰ The pooled estimate of cardiovascular death of the HR from the fixed-effect meta-analysis of all four trials was 0.51; 95% CI, 0.36 to 0.71; P=0.0001. There was no evidence of between study heterogeneity (P=0.48, I-squared=9.7%) (Figure I in the Data Supplement). A random-effects model produced almost identical results (HR=0.50; 95% CI 0.35 to 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, as well as a lower risk of all-cause death and of cardiovascular death compared with placebo. 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.¹³

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.^{8,14}

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.¹⁵ 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 endpoint of cardiovascular death at 1 year was significantly lower among patients assigned influenza vaccination and by the study by Phrommintikul, A. et al. (439 patients with acute coronary syndrome)¹⁰ where the primary endpoint of major cardiovascular events was lower among patients assigned influenza vaccination. Conversely, the FLUCAD study of 658 mostly stable patients with coronary artery

disease randomized to influenza vaccination or placebo revealed no difference in the composite primary endpoint 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 two seasons when influenza vaccine most favorably impacted outcome (2017-18 and 2019-20, Figure 3) the corresponding estimated vaccine effectiveness was also good, up to 60%,^{16, 17} while vaccine effectiveness was poorer in the other two study seasons (2016-17 and 2018-19).^{18, 19} Time-to-event curves (Figure 2) in this study began to separate early post-injection and stabilized at around three months, indicative of a therapeutic effect during the vulnerable early phase post-MI characterized by a high level of inflammation.²⁰ Influenza vaccination results in early immune activation with strong upregulation of genes involved in interferon signaling and antigen presentation pathways²¹ along with lowering of pro-inflammatory cytokines²² and may exert an anti-inflammatory and plaque stabilizing effect.²³ Another explanation to our findings is that influenza infection may trigger an acute cardiovascular event,³ and patients suffering MI are at the highest risk of a new cardiovascular event in the initial ensuing months,²⁴ a time period where preventing influenza could be of particular importance.

Since influenza vaccination carries a class I, level of Evidence B recommendation in both American and European secondary prevention cardiovascular guidelines,^{25, 26} 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.²⁷ 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 enrolment on their own behalf. The cross over rate in the placebo arm was 13.2%. If anything, this would have biased the results towards 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 like statins and angiotensin-converting enzyme inhibitors.²⁸ In-hospital influenza vaccination as routine following MI will likely also lead to higher patient treatment compliance.²⁹

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 endpoint was reduced. Results of analyses of clinical trials ended early tend to exaggerate the effects of a treatment.³⁰ Second, participants enrolled in Bangladesh did not routinely undergo invasive investigation and treatment, thus precluding assessment of stent thrombosis, which was one of the three components of the primary endpoint. Third, trivalent vaccine was used in the first study season and quadrivalent in the following seasons. Fourth, only eight patients with high-risk stable coronary artery disease were enrolled. Lastly, 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 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 three previous trials,⁸⁻¹⁰ demonstrated a reduction by half of cardiovascular death at one 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.

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Contributors

OF conceived the study, wrote the first draft of the study protocol, and wrote the first draft of the manuscript. All authors participated in patient recruitment and data collection. TC, SP, DE, EHC, JP, MG, CRM, and OF analysed the data. All authors vouch for the data and the analysis, contributed to writing the paper, and participated in the decision to publish the paper. All authors approved the final version of the manuscript to be submitted. OF is guarantor. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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and implementation of this study, all study analyses, the drafting and editing of the paper, and its final content.

Disclosures

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Ethical approval

This trial was approved by the ethical review board and national regulatory authority of each participating site.

The lead author (OF) affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Dissemination to participants and related patient and public communities

The results will be disseminated to study participants upon request and to the general public through press release, social media and conference presentations.

Supplemental Materials

Study Organization and Investigators

Expanded Methods

Supplemental Tables I-VI

Supplemental Figure I

Protocols with Summary of Changes

Statistical Analysis Plan

References

1. Libby P, Loscalzo J, Ridker PM, Farkouh ME, Hsue PY, Fuster V, Hasan AA, Amar S. Inflammation, Immunity, and Infection in Atherothrombosis: JACC Review Topic of the Week. *J Am Coll Cardiol*. 2018; 72: 2071-2081.
2. Collins SD. Excess mortality from causes other than influenza and pneumonia during influenza epidemic. *Public Health Rep*. 1932; 47: 2159-2179.
3. Kwong JC, Schwartz KL, Campitelli MA, Chung H, Crowcroft NS, Karnauchow T, Katz K, Ko DT, McGeer AJ, McNally D, et al. Acute Myocardial Infarction after Laboratory-Confirmed Influenza Infection. *N Engl J Med*. 2018; 378: 345-353.
4. Warren-Gash C, Hayward AC, Hemingway H, Denaxas S, Thomas SL, Timmis AD, Whitaker H, Smeeth L. Influenza infection and risk of acute myocardial infarction in England and Wales: a CALIBER self-controlled case series study. *J Infect Dis*. 2012; 206: 1652-1659.
5. Macintyre CR, Heywood AE, Kovoov P, Ridda I, Seale H, Tan T, Gao Z, Katelaris AL, Siu HW, Lo V, et al. Ischaemic heart disease, influenza and influenza vaccination: a prospective case control study. *Heart*. 2013; 99: 1843-1848.
6. Mohammad MA, Tham J, Koul S, Rylance R, Bergh C, Erlinge D, Frobert O. Association of acute myocardial infarction with influenza: A nationwide observational study. *PLoS One*. 2020; 15: e0236866.
7. Gwini SM, Coupland CA, Siriwardena AN. The effect of influenza vaccination on risk of acute myocardial infarction: self-controlled case-series study. *Vaccine*. 2011; 29: 1145-1149.
8. Gurfinkel EP, Leon dIF, Mendiz O, Mautner B. Flu vaccination in acute coronary syndromes and planned percutaneous coronary interventions (FLUVACS) Study. *Eur Heart J*. 2004; 25: 25-31.
9. Ciszewski A, Bilinska ZT, Brydak LB, Kepka C, Kruk M, Romanowska M, Ksiezzycka E, Przyłuski J, Piotrowski W, Maczynska R, et al. Influenza vaccination in secondary prevention from coronary ischaemic events in coronary artery disease: FLUCAD study. *Eur Heart J*. 2008; 29: 1350-1358.

10. Phrommintikul A, Kuanprasert S, Wongcharoen W, Kanjanavanit R, Chaiwarith R, Sukonthasarn A. Influenza vaccination reduces cardiovascular events in patients with acute coronary syndrome. *Eur Heart J*. 2011; 32: 1730-1735.
11. Vardeny O, Kim K, Udell JA, Joseph J, Desai AS, Farkouh ME, Hegde SM, Hernandez AF, McGeer A, Talbot HK, et al. Effect of High-Dose Trivalent vs Standard-Dose Quadrivalent Influenza Vaccine on Mortality or Cardiopulmonary Hospitalization in Patients With High-risk Cardiovascular Disease: A Randomized Clinical Trial. *JAMA*. 2021; 325: 39-49.
12. Clar C, Oseni Z, Flowers N, Keshtkar-Jahromi M, Rees K. Influenza vaccines for preventing cardiovascular disease. *Cochrane Database Syst Rev*. 2015; 5: CD005050.
13. Yedlapati SH, Khan SU, Talluri S, Lone AN, Khan MZ, Khan MS, Navar AM, Gulati M, Johnson H, Baum S, et al. Effects of Influenza Vaccine on Mortality and Cardiovascular Outcomes in Patients With Cardiovascular Disease: A Systematic Review and Meta-Analysis. *J Am Heart Assoc*. 2021; 10: e019636.
14. Smeeth L, Thomas SL, Hall AJ, Hubbard R, Farrington P, Vallance P. Risk of myocardial infarction and stroke after acute infection or vaccination. *N Engl J Med*. 2004; 351: 2611-2618.
15. Udell JA, Zawi R, Bhatt DL, Keshtkar-Jahromi M, Gaughran F, Phrommintikul A, Ciszewski A, Vakili H, Hoffman EB, Farkouh ME, et al. Association between influenza vaccination and cardiovascular outcomes in high-risk patients: a meta-analysis. *JAMA*. 2013; 310: 1711-1720.
16. Rondy M, Kissling E, Emborg HD, Gherasim A, Pebody R, Trebbien R, Pozo F, Larrauri A, McMenamin J, Valenciano M, et al. Interim 2017/18 influenza seasonal vaccine effectiveness: combined results from five European studies. *Euro Surveill*. 2018; 23.
17. Rose A, Kissling E, Emborg HD, Larrauri A, McMenamin J, Pozo F, Trebbien R, Mazagatos C, Whitaker H, Valenciano M, et al. Interim 2019/20 influenza vaccine effectiveness: six European studies, September 2019 to January 2020. *Euro Surveill*. 2020; 25.
18. Sullivan SG, Chilver MB, Carville KS, Deng YM, Grant KA, Higgins G, Komadina N, Leung VK, Minney-Smith CA, Teng D, et al. Low interim influenza vaccine effectiveness, Australia, 1 May to 24 September 2017. *Euro Surveill*. 2017; 22.
19. Kissling E, Rose A, Emborg HD, Gherasim A, Pebody R, Pozo F, Trebbien R, Mazagatos C, Whitaker H, Valenciano M, et al. Interim 2018/19 influenza vaccine effectiveness: six European studies, October 2018 to January 2019. *Euro Surveill*. 2019; 24.
20. Tobin SW, Alibhai FJ, Weisel RD, Li RK. Considering Cause and Effect of Immune Cell Aging on Cardiac Repair after Myocardial Infarction. *Cells*. 2020; 9.
21. Bucacas KL, Franco LM, Shaw CA, Bray MS, Wells JM, Nino D, Arden N, Quarles JM, Couch RB, Belmont JW. Early patterns of gene expression correlate with the humoral immune response to influenza vaccination in humans. *J Infect Dis*. 2011; 203: 921-929.
22. Atoui R, F FE, Saroka K, Mireau J, McElhaney JE, Hare G. Influenza Vaccination Blunts the Inflammatory Response in Patients Undergoing Cardiopulmonary Bypass. *Ann Thorac Surg*. 2020.
23. Bermudez-Fajardo A, Oviedo-Orta E. Influenza vaccination promotes stable atherosclerotic plaques in apoE knockout mice. *Atherosclerosis*. 2011; 217: 97-105.
24. Fokkema ML, James SK, Albertsson P, Akerblom A, Calais F, Eriksson P, Jensen J, Nilsson T, de Smet BJ, Sjogren I, et al. Population trends in percutaneous coronary intervention: 20-year results from the SCAAR (Swedish Coronary Angiography and Angioplasty Registry). *J Am Coll Cardiol*. 2013; 61: 1222-1230.

25. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, Prescott E, Storey RF, Deaton C, Cuisset T, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J*. 2020; 41: 407-477.
26. Davis MM, Taubert K, Benin AL, Brown DW, Mensah GA, Baddour LM, Dunbar S, Krumholz HM. Influenza vaccination as secondary prevention for cardiovascular disease: a science advisory from the American Heart Association/American College of Cardiology. *J Am Coll Cardiol*. 2006; 48: 1498-1502.
27. O'Halloran AC, Lu PJ, Williams WW, Bridges CB, Singleton JA. Influenza Vaccination Coverage Among People With High-Risk Conditions in the U.S. *Am J Prev Med*. 2016; 50: e15-e26.
28. Du L, Cheng Z, Zhang Y, Li Y, Mei D. The impact of medication adherence on clinical outcomes of coronary artery disease: A meta-analysis. *Eur J Prev Cardiol*. 2017; 24: 962-970.
29. Muhlestein JB, Horne BD, Bair TL, Li Q, Madsen TE, Pearson RR, Anderson JL. Usefulness of in-hospital prescription of statin agents after angiographic diagnosis of coronary artery disease in improving continued compliance and reduced mortality. *Am J Cardiol*. 2001; 87: 257-261.
30. Pocock SJ. When to stop a clinical trial. *BMJ*. 1992; 305: 235-240.



Circulation

Table 1. Baseline Characteristics of the Patients According to Randomization

	Vaccine	Placebo
	(N=1272)	(N=1260)
Age, yr	60.1 (±11.0)	59.6 (±11.4)
Male sex – no. (%)	1036 (81.4)	1034 (82.1)
ST-segment elevation MI – no. (%)	665/1239 (53.7)	683/1236 (55.3)
Non-ST-segment elevation MI – no. (%)	568/1239 (45.8)	551/1236 (44.6)
Stable coronary artery disease – no. (%)	6/1239 (0.5)	2/1236 (0.2)
Body-mass index, kg/m ²	27.5 (±5.0)	27.4 (±5.1)
Diabetes – no. (%)	281/1253 (22.4)	247/1254 (19.7)
Smoking status – no. (%)		
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 – no. (%)	427/1257 (34.0)	409/1249 (32.7)
Hypertension – no. (%)	650/1251 (52.0)	595/1251 (47.6)
Previous MI – no. (%)	191/1253 (15.2)	172/1249 (13.8)
Previous PCI – no. (%)	138/1257 (11.0)	129/1257 (10.3)
Previous CABG – no. (%)	28/1258 (2.2)	37/1257 (2.9)
Killip class ≥2 – no. (%)	50/1157 (4.3)	45/1155 (3.9)
Number of diseased vessels – no. (%)		
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)

Numbers in table are mean (± standard deviation) or frequency/total (percentage); percentages are calculated out of all non-missing values; body-mass index was missing for 65 and 59 patients in the vaccine and placebo groups respectively.

Table 2. Primary, Key Secondary and other Secondary Endpoints

	Vaccine (N=1272)	Placebo (N=1260)	Hazard Ratio (95% CI)	P-value
Primary Endpoint, no (%)				
All-cause death, myocardial infarction, stent thrombosis	67 (5.)	91 (7.2)	0.72 (0.52-0.99)	0.040
Key Secondary Endpoints, no.(%)				
All-cause death	37 (2.9)	61 (4.9)	0.59 (0.39-0.89)	0.010
CV 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 Endpoints, no.(%)				
CV death, myocardial infarction, stent thrombosis	64 (5.1)	86 (6.9)	0.73 (0.53-1.01)	0.064
Stroke, including TIA	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
Non-CV 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 year; CV=cardiovascular; TIA=transient ischemic attack; p-value from log-rank test; hazard ratio and 95% confidence interval from Cox PH model adjusting for center; unplanned revascularization and hospitalization for arrhythmia are site reported events only.

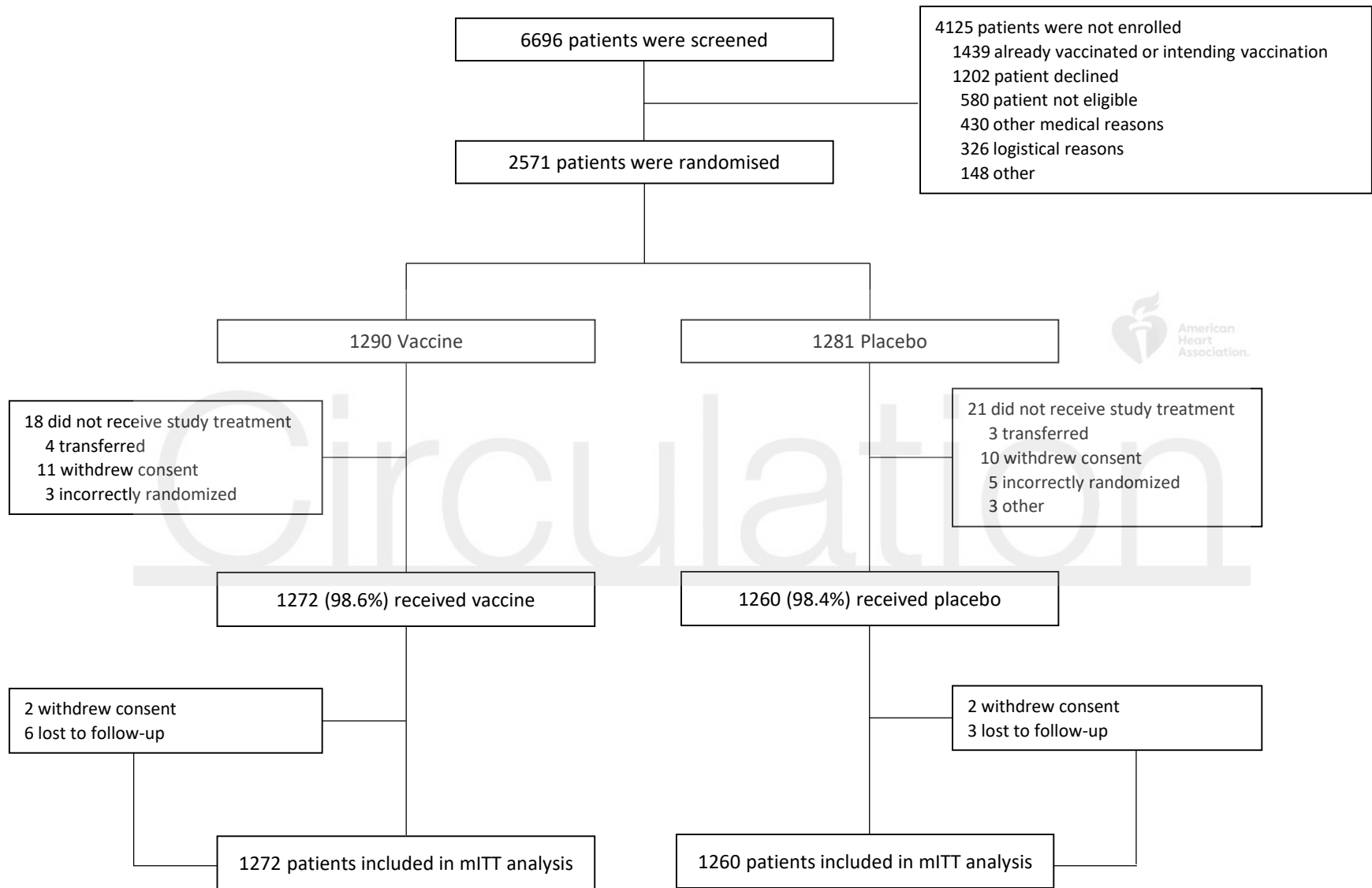
Figure Legends

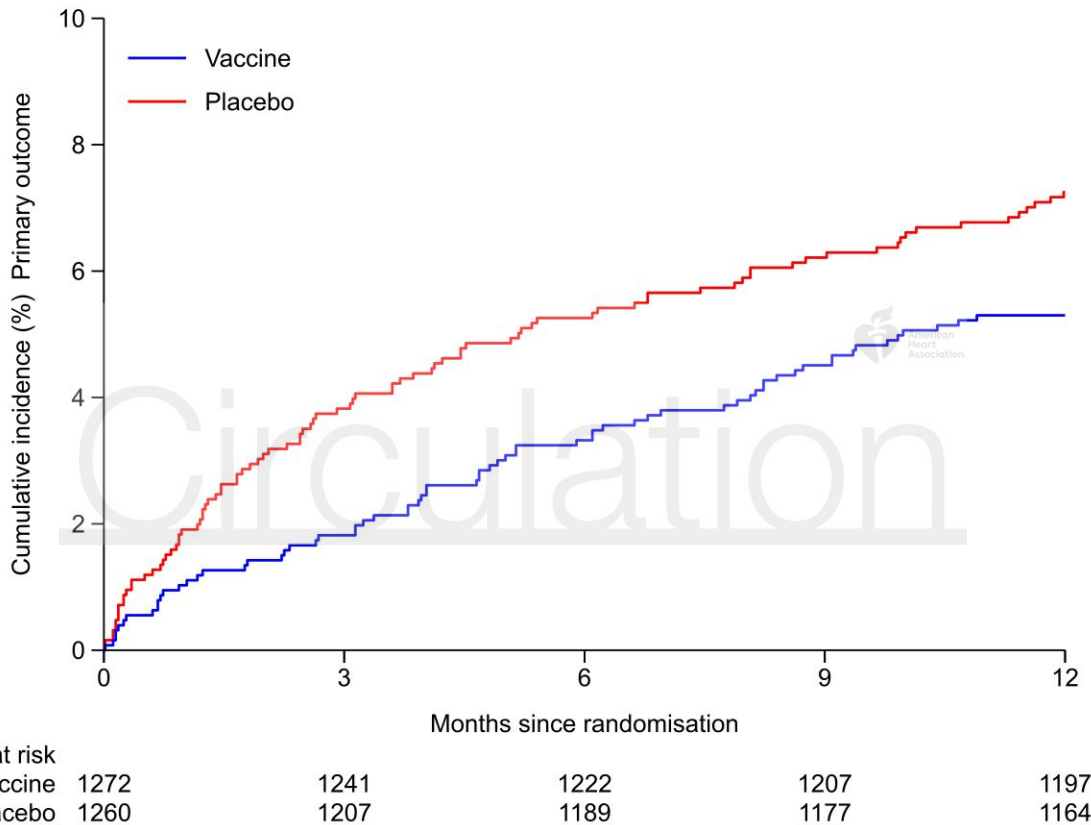
Figure 1. Allocation, follow-up, and analysis of trial participants. Participants who withdrew consent after receiving the study medication were censored at the day of withdrawal of consent; participants who were lost to follow-up were censored at 0.5 days follow-up; mITT modified intention to treat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

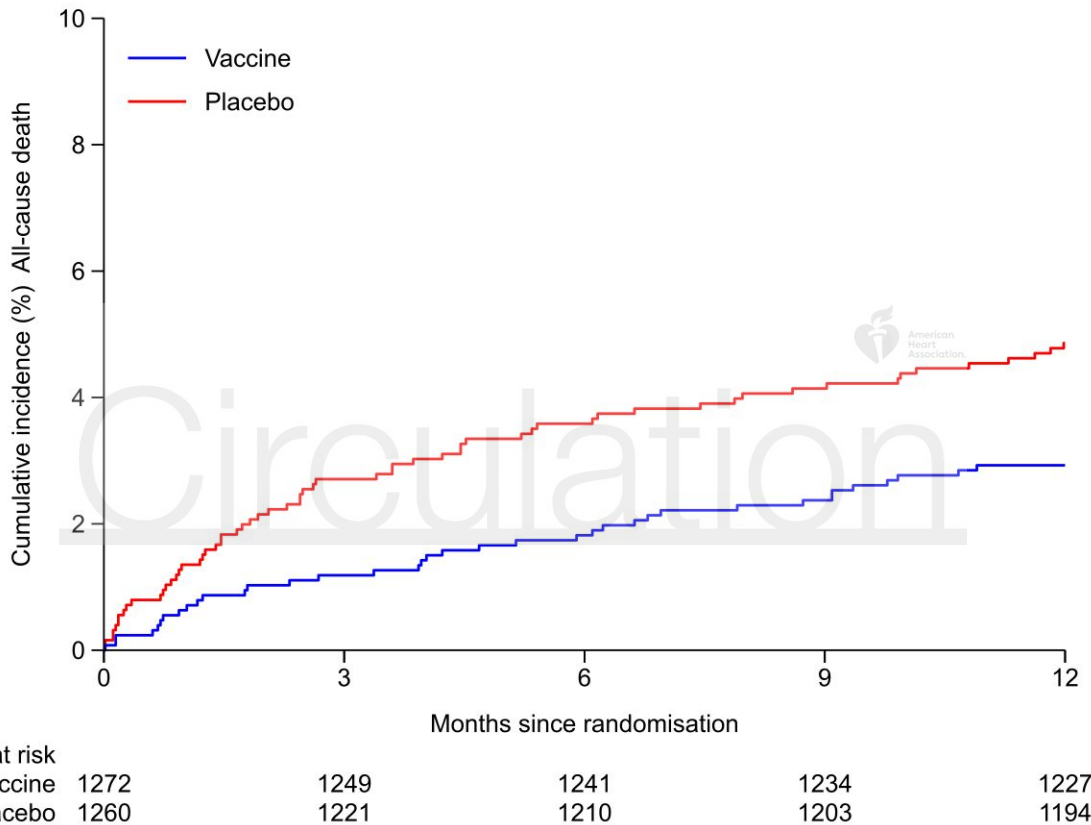
Figure 2. Kaplan-Meier event curves of the influenza vaccine and placebo groups for the primary composite endpoint of all-cause death, myocardial infarction, or stent thrombosis in a time-to-event analysis (A); for all-cause death (B); for cardiovascular death (C); and for myocardial infarction (D).

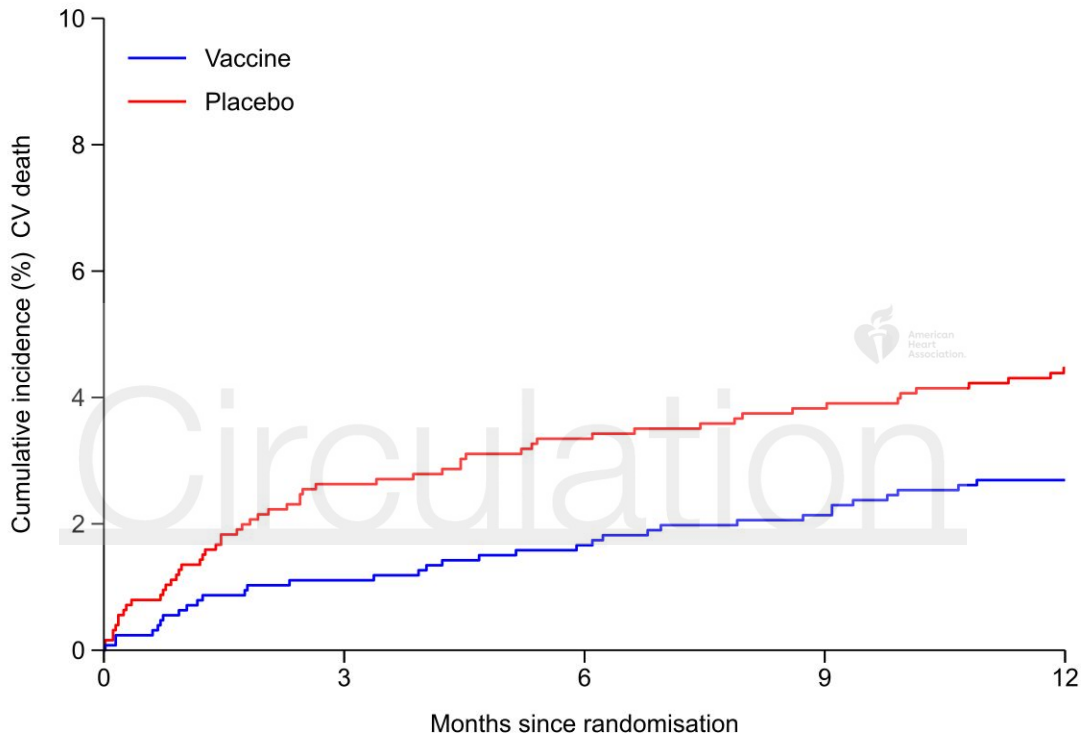


Figure 3. Hazard ratios for the primary composite endpoint of all-cause death, myocardial infarction, or stent thrombosis within 12 months according to predefined subgroups. Hazard ratios (black squares) and 95% confidence intervals (horizontal lines) are shown. MI = myocardial infarction, NSTEMI = non-ST-elevation myocardial infarction, and STEMI = ST-elevation myocardial infarction.

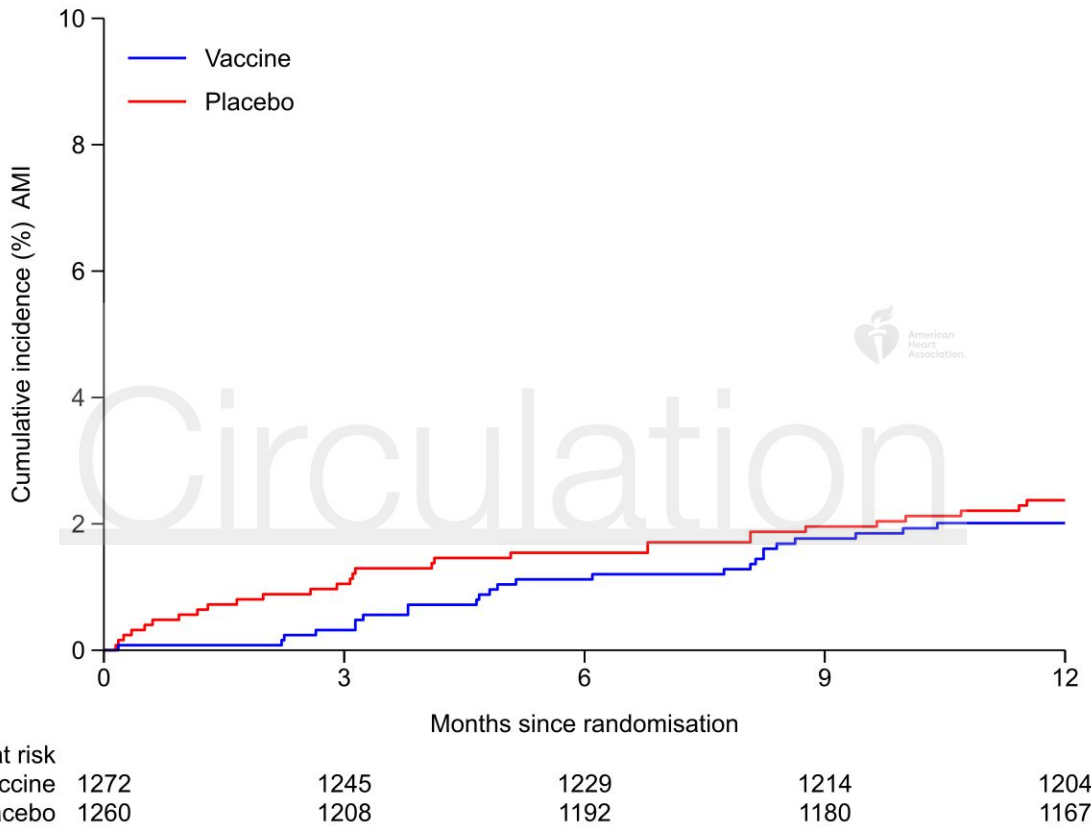








No. at risk					
Vaccine	1272	1249	1241	1234	1227
Placebo	1260	1221	1210	1203	1194



Vaccine
patients with endpoint/total patients (%)

Placebo

Hazard Ratio (95% CI)
for primary outcome

P value
for interaction

Sex

0.56

Male	51/1030 (5.0)	67/1031 (6.5)		0.76 (0.53-1.09)
Female	16/235 (6.8)	24/225 (10.8)		0.61 (0.32-1.15)

Age, years

0.84

<65	42/840 (5.0)	55/824 (6.7)		0.74 (0.50-1.11)
65+	25/425 (5.9)	36/433 (8.4)		0.69 (0.42-1.16)

Diabetes

0.73

No	35/972 (3.6)	55/1007 (5.5)		0.65 (0.43-1.00)
Yes	31/281 (11.0)	36/247 (14.6)		0.73 (0.45-1.18)

Current smoker

0.29

No	45/795 (5.7)	67/789 (8.5)		0.65 (0.45-0.95)
Yes	22/437 (5.1)	23/433 (5.3)		0.95 (0.53-1.71)

Previous MI

0.21

No	39/1062 (3.7)	66/1077 (6.1)		0.59 (0.40-0.88)
Yes	26/191 (13.7)	25/172 (14.5)		0.91 (0.53-1.58)

Inclusion criteria

0.24

STEMI	27/661 (4.1)	31/680 (4.6)		0.90 (0.54-1.51)
NSTEMI	37/568 (6.5)	58/551 (10.5)		0.60 (0.40-0.91)

Influenza season

0.32

2016-17	5/150 (3.4)	4/142 (2.8)		1.17 (0.31-4.36)
2017-18	7/299 (2.3)	16/299 (5.4)		0.43 (0.18-1.05)
2018-19	13/297 (4.5)	11/296 (3.8)		1.19 (0.53-2.66)
2019-20	42/526 (8.0)	60/523 (11.5)		0.68 (0.46-1.01)

Hemisphere

0.85

Northern	29/938 (3.1)	41/927 (4.4)		0.69 (0.43-1.12)
Southern	38/334 (11.4)	50/333 (15.1)		0.74 (0.48-1.12)

0.2 0.5 1 2 4

Favors Vaccine Favors Placebo