Occurrence of cardiovascular events in patients with coronary artery disease receiving the influenza vaccine

Dilpreet Bal

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Abstract

Background: Cardiovascular disease is the leading cause of death worldwide with coronary artery disease (CAD) making up a majority of those deaths. Coronary artery diseases are atherosclerotic or thrombotic in nature leading to a disparity of blood in the coronary arteries and subsequent infarction of heart muscle. Influenza has been established as a pro-inflammatory agent that has been implicated in increased death rates from cardiovascular disease. With the establishment of this causal relationship, several trials were run to assess the effect of the influenza vaccine on major cardiovascular risk factors, myocardial infarctions (MI), and strokes. This review focuses on the effect of the influenza vaccine on major adverse cardiovascular events (MACE) in patients with CAD.

Methods: An exhaustive search of available medical literature was performed using Medline-Ovid, Medline-Pubmed, CINAHL and Web of science using the following keywords: influenza vaccine, heart diseases, cardiovascular events, acute coronary syndrome, myocardial infarction, stroke, and angina pectoris. Relevant studies were assessed for quality using GRADE.

Results: A 164 studies were reviewed for relevancy. Three studies met the inclusion criteria and were included in this systematic review. All three of these randomized controlled trials (RCT) demonstrate a decrease in major adverse cardiovascular events (MACE) in patients with CAD or acute coronary syndrome (ACS) with the administration of the influenza vaccine: adjusted HR 0.67 (0.51-0.86), HR 0.54 (0.24-1.21), and RR 0.51 (0.30-0.86) respectively.

Conclusion: The influenza vaccine has shown a decrease in cardiovascular death, MI, unstable angina, hospitalization, and ischemia in patients with already existing heart problems. This decrease in MACE has been demonstrated for up to a year in all three studies with a two year follow up study showing a similar result. The high quality of evidence presented from these studies, the low side effect profile of the influenza vaccine as well as its low cost lead to a strong recommendation for the use of influenza vaccine in secondary prevention of cardiovascular events in patients with CAD.

Keywords: Influenza vaccine, heart diseases, cardiovascular events, acute coronary syndrome, myocardial infarction, stroke, angina pectoris

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Degree Name
Master of Science in Physician Assistant Studies

First Advisor
Saje Davis-Risen, MS, PA-C

Second Advisor
Annjanette Sommers, PA-C, MS

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Keywords
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Occurrence of cardiovascular events in patients with coronary artery disease receiving the influenza vaccine

Dilpreet Bal

A Clinical Graduate Project Submitted to the Faculty of the

School of Physician Assistant Studies

Pacific University

Hillsboro, OR

For the Masters of Science Degree, August 8th 2015

Faculty Advisor: Saje Davis Risen, PA-C

Clinical Graduate Project Coordinator: Annjanette Sommers, PA-C, MS
Biography

Dilpreet Bal is a native of Nevada. She received a Bachelor of Science, cum laude, from the University of Reno, Nevada in the summer of 2012. While in school, she worked as a research assistant in a pseudoscorpian biology lab under the supervision of the head of the biology department. She spent the year after graduation continuing a job as a medical scribe and lab technician at a small clinic for the underserved in Reno. After a year and half of clinical work, she was accepted to PA school at Pacific. She is interested in pursuing a career in Cardiology and Family Medicine.
Abstract

**Background:** Cardiovascular disease is the leading cause of death worldwide with coronary artery disease (CAD) making up a majority of those deaths. Coronary artery diseases are atherosclerotic or thrombotic in nature leading to a disparity of blood in the coronary arteries and subsequent infarction of heart muscle. Influenza has been established as a pro-inflammatory agent that has been implicated in increased death rates from cardiovascular disease. With the establishment of this causal relationship, several trials were run to assess the effect of the influenza vaccine on major cardiovascular risk factors, myocardial infarctions (MI), and strokes. This review focuses on the effect of the influenza vaccine on major adverse cardiovascular events (MACE) in patients with CAD.

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**Conclusion:** The influenza vaccine has shown a decrease in cardiovascular death, MI, unstable angina, hospitalization, and ischemia in patients with already existing heart problems. This decrease in MACE has been demonstrated for up to a year in all three studies with a two year follow up study showing a similar result. The high quality of evidence presented from these studies, the low side effect profile of the influenza vaccine as well as its low cost lead to a strong recommendation for the use of influenza vaccine in secondary prevention of cardiovascular events in patients with CAD.

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Table I: GRADE Quality of Assessment and Summary of Findings

List of Abbreviations

ACE-I  ACE Inhibitors
ACS   Acute Coronary Syndrome
CAD   Coronary Artery Disease
GRADE  Grading of Recommendations, Assessment, Development and Evaluations
MACE  Major Adverse Cardiovascular Events
MI   Myocardial Infarction
NSTEMI Non-ST segment elevation MI
PCI   Percutaneous Coronary Intervention
PROBE Prospective Randomized Open with Blinded Endpoint
RCT   Randomized Controlled Trial
STEMI ST segment elevation MI
URI   Upper Respiratory Infection
Occurrence of Cardiovascular Events in Patients with Coronary Artery Disease Receiving the Influenza Vaccine

BACKGROUND

Cardiovascular diseases are responsible for 17.3 million deaths globally with 42% of those deaths being attributed to coronary heart diseases.\(^1\) Atherosclerosis is most commonly implicated in coronary artery disease, progression of which can lead to thrombotic or embolic events such as myocardial infarctions (MIs) or strokes. Atherosclerosis itself is a chronic inflammatory disease of the arteries with pro-inflammatory properties.\(^2,3\) Inflammation of the intima of arteries leads to initial formation of plaque. Continued inflammation leads to the progression and rupture of said atherosclerotic lesions causing thrombosis of the involved arteries.\(^3\)

Studies have suggested that infections play a role in the atherosclerotic process as well. Acute infection in particular has been implicated in abrupt and severe inflammatory changes in atherosclerotic plaque which may lead to destabilization and rupture causing acute coronary syndrome (ACS) over a few days to weeks.\(^3,4\) Increasing incidences of MIs and strokes in the winter coinciding with upper respiratory tract infections (URIs)\(^5\) led to the study of the role of influenza infection in the development of atherosclerosis and the triggering of it’s complications. These studies revealed that influenza infection increases inflammation, smooth muscle cell proliferation and fibrin deposition in the arterial intima,\(^6\) confirming that influenza infection is both pro-inflammatory and prothrombotic.\(^7\) Another study affirms the increase in atherosclerosis with influenza infection and also denotes that more cardiovascular deaths are seen during influenza epidemics\(^8\) and risks of both MI and stroke are increased after an acute influenza
infection. A subsequent study also shows that 19% of people suffering from an acute MI recalled having a URI in the past two weeks.

Conversely, studies of patients with acute infections treated with antibiotics suggests a strong involvement of the immune system in the development of atherosclerosis, namely due to the immunosuppression of B lymphocytes. Vaccinations are known to cause a rapid humoral response with activation and immediate migration of B lymphocytes to the site of the induced stimulus. The influenza vaccination in particular has been shown to create an immediate and significant immune response with viral antibodies found in the periphery for up to a week, which presumably is what deters atherosclerosis.

With the positive causal association between influenza infection and ACS, and the negative causal association between the influenza vaccination and atherosclerosis, the effect of influenza vaccination on ACS was studied. Several case control studies demonstrated that the influenza vaccine reduces risk of recurrent MI, primary cardiac arrest and all cause specific mortality. Several randomized controlled trials (RCTs) have also looked at the effect of influenza vaccine on patients with established heart disease but no guidelines or recommendations exist for or against the use of influenza vaccine in this population. This systemic review looks to see if cardiovascular events in patients with CAD can be decreased with the use of influenza vaccine and whether a recommendation for the use of this vaccine can be made.

METHODS

An exhaustive search of available medical literature was performed using Medline-Ovid, Medline-Pubmed, CINAHL, and Web of science with the following keywords: influenza
vaccine, heart diseases, cardiovascular events, acute coronary syndrome, myocardial infarction, stroke, and angina pectoris. The search was narrowed to use English language articles and human trials only. Studies to be considered for inclusion were required to use the influenza vaccine in patients with CAD or ACS, a subclass of CAD, and look at incidence of cardiovascular outcomes post vaccination. Bibliographies of relevant studies were looked at for further sources. Relevant articles were assessed for quality using Grading of Recommendations, Assessment, Development and Education (GRADE).24

RESULTS

A total of 164 studies were reviewed for relevancy. Four studies that focused primarily on the effects of influenza vaccine on patients with some form of CAD or ACS were considered for inclusion. One study13 was excluded on account of being a case control study leaving three RCTs17-19 for inclusion in this systematic review. Two follow up studies20-21 of the FLUVACS study19 were found and used as supplements. No additional studies were found by searching the references of the included studies. See Table I.

Phrommintikul et al

This prospective randomized open with blinded endpoint (PROBE) study17 investigated the effect of influenza vaccination on cardiovascular events in patients with acute coronary syndrome. This study enrolled 439 patients all of whom had been admitted due to ACS sometime within the past 8 weeks and randomly allocated them to receive either the inactivated influenza vaccine in the vaccine group or no treatment in the control group. The primary endpoint being looked at was combined major adverse cardiovascular events (MACE) including: death, hospitalization from ACS, hospitalization from heart failure, and hospitalization from stroke. The
secondary endpoint being studied was cardiovascular death. Both endpoints were verified by cardiologists who were unaware of patient group allocation.17

Eligibility criteria for patients were admission due to ACS within the past 8 weeks, age greater than 50 years, and agreement to participation. Patients were excluded if they had a serum creatinine level > 2.5mg/dL, significant liver disease, a hemoglobin level < 10g/dL, cancer, a life expectancy < 1 year, or contradictions to the influenza vaccine. The 439 eligible patients were randomly assigned to either the vaccine group or control group using a computer generated block randomization size of 4. A single dose intramuscular injection of 0.5ml of split, inactivated influenza vaccine was given to patients in the vaccine group. All patients were given the standard ACS treatment, including coronary revascularization, according to their primary cardiologists.17

Both treatment and control groups were balanced at all baseline characteristics. There were 221 patients randomized to the vaccine group and 218 patients randomized to the control group. About one third of the patients had STEMI (ST segment elevation MI), of which 75% received reperfusion therapy. Out of the patients with NSTEMI (non-ST segment elevation MI), 33.3% underwent revascularization during admission and 15.7% underwent revascularization after admission, whereas 48.9% did not undergo any revascularization. Majority of the patients received standard medications including aspirin, beta blockers, and statins. Patients in the vaccine group received ACE inhibitors (ACE-I) more frequently than the control group. Intention to treat analysis was performed. Both groups had one loss to follow and no cross overs during the trial. The median time for follow up was 360 days for each group.17

Administration of the influenza vaccine resulted in decreased rates of MACE (9.5% vs 19.3%, HR 0.70, CI 0.57-0.86, p = 0.004, NNT = 10) and hospitalization for ACS (4.5% vs 10.6%, unadjusted HR 0.73, CI 0.55-0.91, p = 0.032). There wasn’t a significant difference in the
rate of hospitalization for heart failure (1.8 vs 4.6%, unadjusted RR 0.9, CI 0.49-1.01, p = 0.111),
total mortality (2.7 vs 5.5%, unadjusted HR 0.73, CI 0.50-1.03, p = 0.156) or incidence of
cardiovascular death (2.3% vs 5.5%, unadjusted HR 0.39, CI 0.14-1.12, p = 0.088). The rates of
MACE when adjusted for age, sex, serum creatinine, ACE-I, and coronary revascularization
continued to be significantly lower for the vaccine group as compared to the control group
(adjusted HR 0.67, CI 0.51-0.86, p = 0.005).17

The limitations of this study, as described by the authors are as follows: the open label
design of the study may have compromised the validity of study by crossing over of patients
from the control group to vaccination group, or by bias of the physicians towards more invasive
treatment strategies for the control group. However, no crossing over occurred in this trial and
the treatment strategies for ACS were planned before patient recruitment into this study. In
addition, there was no active survey for influenza infection.17

Ultimately the authors recommend the use of the influenza vaccine as a secondary
prevention in patients with ACS as it reduced the rates of MACE in these patients.17

**FLUCAD Study**

In this randomized, double blind, placebo controlled study,18 the authors evaluated the
effect of influenza vaccination on the coronary events in patients with confirmed CAD. This
study enrolled 658 optimally treated CAD patients who were randomized to receive either the
influenza vaccine or placebo vaccine. The randomization sequence was computer generated by
an independent statistician. The syringes for vaccine and placebo were identical and labelled
with randomization numbers according to a code and delivered to the trial site. The study nurses
and all study personnel were blinded till the database was closed. The primary endpoint studied
was 12 month cardiovascular death. The two secondary endpoints studied were MACE
(composite of cardiovascular death, acute MI, or coronary revascularization) and coronary ischemic events (MACE or hospitalization for myocardial ischemia), both assessed at 12 month periods.\textsuperscript{18}

The eligibility criteria for patients included age of 30-80 years and CAD confirmed by angiography with at least 50% stenosis of at least one large coronary artery. Patients with congestive heart failure, stage III or IV, planned cardiovascular surgery within 6 months, renal failure, neoplasm, psycho-organic disorders, factors impeding follow up, or any contraindications to vaccination were excluded. Patients in the vaccination group received a single intramuscular inactivated subunit influenza vaccine containing 0.5 ml dose hemagglutinin containing three strains of viral antigens or a placebo vaccine containing all of the components except for viral antigens. Patients hospitalized for percutaneous coronary interventions (PCIs) were vaccinated before the scheduled procedure while other patients were vaccinated at outpatient visits to cardiologists.\textsuperscript{18}

The baseline characteristics of both vaccine and controls groups were similar. Of the 658 total, 325 patients were randomized to the vaccine group and 333 patients were randomized to the placebo group. There were 157 patients who had primary PCI with ACS or unstable angina, 131 patients had elective PCI with stable angina, and 370 outpatients had stable angina and confirmed CAD by angiography. Most of the patients received aspirin, statins, ACE-I and beta blockers. Median follow up for the patients was 298 days with no losses to follow up and no cross overs.\textsuperscript{18}

The primary endpoint, cardiovascular death, occurred in two patients in each group. The estimated 12-month cumulative cardiovascular death rate was similar in both group as well (0.63\% vs 0.76\% in the placebo group, unadjusted HR 1.06, CI 0.15-7.56, p = 0.95). Two
patients died of non-cardiovascular causes in each group as well leading to an overall mortality of three patients in each group. MACE occurred less frequently in the vaccine group (3.00% vs 5.87%, HR 0.54, CI 0.24-1.21, p = 0.13, NNT 35) as did coronary ischemic events (6.02% vs 9.97%, HR 0.54, CI 0.29-0.99, p = 0.047).\textsuperscript{18}

The demographic, clinical, biochemical and angiographic data from this trial was also used to search for predictors of coronary ischemic events. Univariate analysis of seven factors, namely gender, influenza vaccination, history of heart failure, primary PCI for ACS, elective PCI for stable angina, and two nitrates was conducted revealing association with coronary ischemic events. Influenza vaccination was found to be a negative predictor associated with significant reduction of the risk of coronary ischemic events. Multivariate analysis also predicted that lack of influenza vaccination is as an independent predictors of coronary ischemic events (HR 0.38, CI 0.19-0.78, p = 0.0086).\textsuperscript{18}

The authors of this study listed three limitations in their opinion. Firstly, there are a small number of cardiac events due to small sample size. The authors estimate that a sample size of 2240 patients is needed to estimate optimal amounts of MACE events. Secondly the effect of the flu vaccination on restenosis is not known as routine angiography was not planned in this study. Lastly, there may have been a patient selection bias but PCI patients were recruited after successful angioplasty and congestive heart failure patients were excluded from this study thus there is a low risk of bias.\textsuperscript{18}

In conclusion, the authors state that the influenza vaccination in addition to optimal medical treatment, improves the clinical course of CAD, reducing the frequency of MACE, coronary ischemic events and myocardial ischemia.\textsuperscript{18}
FLUVACS study

This study is a randomized, prospective, multicenter, single-blind, parallel group, controlled pilot study\(^\text{19}\) consisting of two different cohorts of patients: a clinical group including those patients with STEMI or NSTEMI occurring within the previous 72 hours and an intervention group of patients undergoing angioplasty/stenting. A total of 305 patients were enrolled, 204 in the clinical group and 101 in the intervention group, from six care units in Argentina. The primary outcome examined was cardiovascular death. The secondary outcome was the composite of cardiovascular death, nonfatal MI and severe recurrent ischemia in a six month follow up.\(^\text{19}\)

The inclusion criteria consisted of patients over 21 years of age with an episode of angina at rest lasting at least 20 minutes and having occurred in the previous 72 hours. Definitive evidence of underlying heart ischemia was obtained using ECG changes and cardiac enzymes. Patients with evidence of hepatic or renal failure, congestive heart failure, terminal disease, contradictions to follow up, the vaccination or prior vaccination were excluded from the study. The clinical group was divided into two groups of a 100 patients each: group A received a single intramuscular vaccination of 0.5 mL of two different viral antigens while group B served as a control. The intervention group was divided into two groups as well: a group of 51 patients who received the influenza vaccination and 50 patients who served as control. A total of 151 patients were in the vaccination group and a 150 in the control. The two groups in both the intervention and clinical group were similar at baseline.\(^\text{19}\)

The primary outcome of cardiovascular death occurred in 2\% of the vaccine group as compared to 8\% of the control group (RR 0.25, CI 0.07-0.86, p = 0.01, NNT 17). The triple composite end point consisting of cardiovascular death, nonfatal MI or severe ischemia occurred
in 11% of vaccine group as compared to 23% in the control group (RR 0.51, CI 0.30-0.86, p = 0.009, NNT 8). No patients were lost to follow up and intention to treat analysis was performed. The only limitation of this study per the authors was the inability to confirm further influenza infection in the population studied particularly in the control group as serological analysis was no performed.\(^\text{19}\)

The conclusion of this pilot study of 301 patients was that vaccination was associated with a significant reduction of subsequent ischemia events in the clinical group.\(^\text{19}\)

**DISCUSSION**

Atherosclerosis is a chronic inflammatory condition of arterial intima\(^\text{2,3}\) which under the stress of an acute infection destabilizes and ruptures leading to ACS.\(^\text{3,4}\) Acute influenza infection is known to accelerate atherosclerosis and precipitate the occurrence of ACS.\(^\text{5,7,8}\) And the influenza vaccination has been shown to decrease recurrent MI, primary cardiac arrest, and all-cause mortality.\(^\text{4,14,15}\) There are however no clear guidelines nor systematic review for the use of influenza vaccine to decrease cardiovascular events in patients with existing heart disease.

This systemic review used three studies\(^\text{17-19}\) that look specifically at the use of influenza vaccine to decrease cardiovascular events, namely MACEs, in patients with CAD or ACS. Phrommintikul et al\(^\text{17}\) showed a significant decrease in MACE in ACS patients receiving the Influenza vaccine (HR 0.70, CI 0.57-0.86, p = 0.004, NNT = 10). This decrease remained with the adjustment for variables as well as subgroup analysis (adjusted HR 0.67, CI 0.51-0.86, p = 0.005). The FLUCAD study,\(^\text{18}\) the only placebo controlled RCT, found that influenza vaccination led to a decrease in MACE (HR 0.54, CI 0.24-1.21, p = 0.13), namely coronary ischemia events (HR 0.54, CI 0.29-0.99, p = 0.047), as well as a better MACE free survival in vaccinated patients versus control. In the FLUVACS study,\(^\text{19}\) vaccination showed a significant reduction in
subsequent ischemic events (RR 0.25, CI 0.07-0.86, p = 0.01) and the triple composite endpoint (RR 0.51, CI 0.30-0.86, p = 0.009) in the clinical cohort within six months. The two follow up studies of the FLUVACS pilot study found a similar decrease in triple composite endpoint at one year\textsuperscript{20} (HR 0.59, CI 0.4-0.86, p = 0.004) and at two years\textsuperscript{21} (HR 0.36, CI 0.12-1.09, p = 0.05) as well. In addition to decreasing MACE, influenza vaccination was also proven to be a negative predictor of risk of coronary ischemic events by both univariate and multivariate analysis in the FLUCAD study (HR 0.38, CI 0.19-0.78, p = 0.0086).\textsuperscript{19} This results in an overall high quality of evidence and a strong recommendation is made in vaccinating against influenza in patients with CAD.

As far as cardiovascular death is concerned, the three studies do not share a complete consensus. Only the FLUVACS study\textsuperscript{19} documents a decrease in cardiovascular mortality with the use of vaccination in CAD patients at 6 months, 1 year and 2 years.\textsuperscript{19-21} The study by Phrommintikul et al\textsuperscript{17} and the FLUCAD study\textsuperscript{18} find no significant difference in cardiovascular death or all-cause mortality between the control and vaccination groups; however, the results were trending towards significance and may have achieved significance given enough time. Though the reason for this discrepancy in the results between studies is not known, it can be assumed that the low event rate may have played a role.

While all three studies have demonstrated the influenza vaccine to be affective in decreasing MACE, they do have some limitations (See table I). Two of the studies, Phrommintikul et al\textsuperscript{17} and the FLUVACs study\textsuperscript{18} are not placebo controlled. Though there no cross overs in either study, there was still a possibility of bias. Patients in the control group knew they were control by virtue of not getting a vaccine or placebo.
Another limitation of these studies is the small sample sizes. Though the FLUVACs study\textsuperscript{19} has the smallest population size, it is the FLUCAD study\textsuperscript{18} that states they may be underpowered to detect a statistical difference in mortality and MACE rates. The optimal sample size calculated by this study was 2240, a feat none of the three studies have accomplished.

Despite these limitations, influenza vaccination remains safe for use in CAD patients\textsuperscript{22} as it maintains very low side effect profile.\textsuperscript{17-19} Not only does the influenza vaccination benefit patients by decreasing their chances of getting influenza, it also decreases the prothrombotic events related to influenza.\textsuperscript{7} In addition the influenza vaccine remains a cheap and easily available intervention for secondary prevention in CAD patients. Further studies are still needed to fully assess the effect of the influenza vaccine. Firstly, a larger scale or longer duration double blinded, placebo controlled trial is needed to obtain statistical significance in mortality and MACE rates. Secondly, a study on restenosis after administration of influenza vaccination is needed to fully determine the anti-inflammatory properties of the influenza vaccine. Lastly, a study on the cardiovascular effects of contracting influenza post influenza vaccination is needed to further understand the inflammatory properties of acute infections and the anti-inflammatory properties of the influenza vaccination.

CONCLUSION

The influenza vaccine has been demonstrated to be a safe and cost effective method of decreasing major adverse cardiovascular events in patients with coronary artery disease and acute coronary syndrome. Specifically, the influenza vaccine has shown a decrease in the occurrence of ischemia, angina, and myocardial infarction in patients who are being optimally treated for their underlying heart disease. No benefits have been seen in terms of cardiovascular death or all-cause mortality although a benefit may be demonstrated with larger studies. The
overall combined quality of the articles reviewed was high in the GRADE criteria. Based on these results, a strong recommendation can be made for the use of influenza vaccinations as a secondary prevention in patients with coronary artery disease. Further research with larger population sizes and post vaccination angiography is needed to fully understand the impact of influenza vaccination in these patients as well to understand the mechanism by which influenza vaccine decreases atherosclerosis. The role of the humoral immunity and B lymphocytes needs further study as well.
REFERENCES


Table I: GRADE Quality of Assessment and Summary of Findings

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\(^{a}\) No placebo for control group hence only single blinded  
\(^{b}\) Sample number of cardiac events due to small sample size; optimal estimated sample size should be 2240, study sample size was 658  
\(^{c}\) RR < 0.5, RR = 0.25