Influenza and Coronary Artery Disease: Exploring a Clinical Association With Myocardial Infarction and Analyzing the Utility of Vaccination in Prevention of Myocardial Infarction

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Both coronary artery disease and influenza outbreaks contribute significantly to worldwide morbidity and mortality. An increasing number of epidemiologic studies have concluded that a temporal association exists between acute viral illnesses and myocardial infarction. Viral illnesses such as influenza can cause or exacerbate coronary atherosclerosis by activating inflammatory pathways. Data from a large case-controlled trial and two randomized controlled trials suggest that influenza vaccination in patients with coronary artery disease may lead to a decrease in incidence, morbidity, and mortality from acute myocardial infarction. A meta-analysis of the two randomized controlled trials for cardiovascular death demonstrated a pooled relative risk of 0.39 (95% confidence interval, 0.20-0.77) for patients who received the influenza vaccine compared with placebo.

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KEY WORDS

Coronary artery disease • Myocardial infarction • Inflammation • Influenza vaccine

There are over 16 million Americans living with coronary artery disease (CAD), and in 2008 over 800,000 died of heart disease.[1] Given such a high prevalence of disease, it is important to continue to identify modifiable risk factors for primary and secondary prevention. In the past two decades, much work has been done at both the clinical and laboratory level to understand the relationship between inflammation and myocardial infarction (MI). In particular, inflammation caused by infectious agents such as Chlamydia species, herpesviridae, mycoplasma, and influenza has been linked to acute coronary syndromes.[2]

In 2010, influenza was responsible for 226,000 hospitalizations in the United States, resulting

in 36,000 deaths. This burden appears to be similar across temperate climates resulting in deaths and hospitalizations throughout the world. Unlike other infectious agents linked to acute coronary syndromes, influenza A virus is easily preventable with an annual vaccine generally considered 70% to 90% effective.[3] Despite this, the Centers for Disease Control and Prevention (CDC) reported that in 2011-2012, among adults over the age of 65, only 67% were vaccinated.[4] The CDC has reported that the influenza season has reached epidemic status in certain regions. The most likely affected are those over the age of 65 with cardiovascular comorbidities.

At a time when health care resources are increasingly focused on prevention, whether for heart disease or vaccine-preventable infections, it is critical to understand any potential relationship between influenza and coronary disease. This article reviews the growing body of literature investigating the link between influenza infection and atherosclerosis and assessing the efficacy of influenza vaccination in preventing MI.

Articles for this review were searched using PubMed up to December 2012 and EmBase from 1980 through December 2012. MeSH terms in PubMed used were *influenza*, *influenza vaccine*, *myocardial infarction*, *acute coronary syndrome*, and *atherogenesis*. Keyword searches relevant to section headings were also performed in both databases. No language limits were placed. Original articles, meta-analyses, and review articles were selected based on their relevance to particular sections. Case reports, clinical guidelines, and editorials were excluded. Epidemiology statistics publically available through internationally recognized institutions (eg, CDC and the World Health Organization) were also used.

The Link Between Inflammation and Coronary Atherosclerosis

The relationship between inflammation and coronary atherosclerosis is well described and many large prospective trials have reinforced this theory.[5-8] This association has been best described in animal models but human studies have corroborated this relationship. Endothelial dysfunction is typically thought to be precipitated by vascular injury. The inflammatory cascade includes platelet activation, induction of procoagulants and smooth muscle growth factors, and leukocyte migration.[5] Numerous infectious agents such as cytomegalovirus (CMV), influenza viruses, and herpesviruses studied in animal models have been shown to induce endothelial inflammation. For example, CMV has been associated with reducing the anticoagulant properties of endothelium by inhibiting plasminogen activator.[9] CMV is also thought to inhibit p53 and induce hyperproliferation of cells. A study by Minick and colleagues[10] showed that patients who underwent cardiac surgery had higher titers of CMV compared with matched control subjects (70% vs 43%). A history of prior CMV infection alone has been linked with atherosclerosis. In one study of patients undergoing coronary atherectomy, CMV immunoglobulin titers were significantly higher in patients who had greater luminal reduction at 6-month follow-up.[11] Other mechanisms include inducing smooth muscle dysfunction. A study by Nachtigal and colleagues[12] showed that rabbit vascular smooth muscle, when infected with herpes simplex 2 virus, was transformed into having rampant monoclonal expansion of smooth muscle.

There are also specific mechanisms proposed by which influenza can increase the risk of developing CAD. A study by Van Lenten and associates[13] described the differential lipid metabolism in mice infected with influenza A virus. They found that high-density lipoproteins lost their ability to inhibit oxidization of low-density lipoprotein (LDL) and were unable to inhibit LDL-induced chemotaxis of monocytes. Furthermore, knockout mice that have apolipoprotein E (Apo E) deficiency have been used as a model for studying atherosclerosis. In one study, apo E -/- mice and apo E+ mice were infected with influenza A virus and their aortas were harvested at days 3, 5, and 10. The Apo E -/- mice had markedly increased smooth muscle proliferation, macrophages, and CD3+ lymphocytes, suggesting that influenza infection can exacerbate preexisting atherosclerosis.[14] Cases of severe viral sepsis may also induce generalized microcirculatory dysfunction mediated through a host of cellular mediators and biomarkers. This can lead to cardiorenal syndrome type 5, circulatory collapse, and death.[15] Figure 1 is a simplified schematic of the proposed mechanism of atherosclerosis caused by influenza infection.

Numerous infectious agents such as cytomegalovirus, influenza viruses, and herpes viruses studied in animal models have been shown to induce endothelial inflammation.

It has also been widely reported that infectious agents can be found directly within the atheromatous vasculature of both animal models and humans.[16-19] In large part, however, these studies used antigens

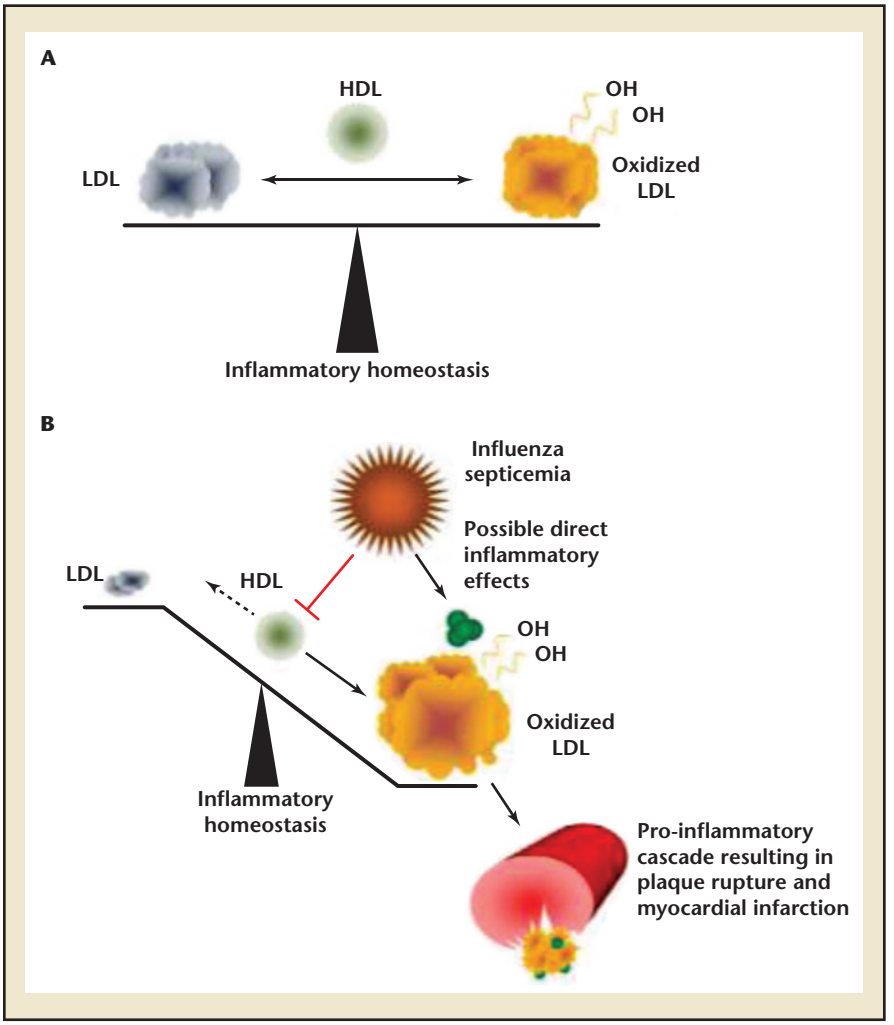

Figure 1. Proposed mechanism of endothelial dysfunction in influenza septicemia. **(A)** The balance of proinflammatory low-density lipoprotein (LDL) oxidation is, in part, regulated by high-density lipoproteins (HDL). **(B)** In influenza septicemia, the antioxidant properties of HDL are disrupted, increasing the homeostatic burden of oxidized LDL. Direct endothelial inflammatory effects of the influenza virus have also been demonstrated in an apolipoprotein E knockout mouse model. The proinflammatory state results in endothelial damage, plaque rupture, and myocardial infarction.

specific to infectious agents rather than more direct methods to identify the presence of infection.

In addition to atherogenesis, many studies have established at least a circumstantial link between MI and high titers of Chlamydia immunoglobulin A.[20] Despite this association, prophylactic treatment with macrolide therapy has not been effective for the secondary prevention of MI. A meta-analysis by Etminan and associates[21] that included nine randomized controlled trials (RCTs) showed no benefit. A small study by Gurevich and colleagues[22] used hemagglutinin proteins from influenza A (H1N1) and influenza A (H3N2) and performed DNA polymerase chain reaction to detect viral DNA from the aorta of patients undergoing coronary artery bypass surgery. Gurevich[23] also tested serum immunoglobulin levels against influenza A in patients with CAD and found a statistically significant relationship between the two.

Temporal Association Between MI and Influenza

There are multiple links between CAD and the influenza epidemics that surface each year in temperate climates.[24] The National Registry of Myocardial Infarction has reported seasonal variation in MI. There were 53% more cases of acute MI in the winter months than in the summer months. This pattern was consistent and irrespective of age and sex.[25] Influenza follows a similar seasonal pattern. The population-based study by Monto and Ullman[24] showed that patients were 1.5 to 1.6 times more likely to have upper respiratory tract infections in the winter months. Also, of all upper respiratory tract infections, up to 25% of those were due to influenza.[24]

A relationship between influenza and MI is reinforced, although not confirmed, by observational studies exploring the incidence of MI following infection.[26-29] In a landmark case series, Smeeth and colleagues[26] examined over 20,000 patients who had MI. The incidence ratio of having an MI within the first 3 days after infection was 4.95 (95% confidence interval [CI], 4.43-5.53).[26] Similar results were shown for patients who had stroke. It is also noteworthy that patients in this study who received the influenza vaccine had no statistically significant risk of infarction or stroke.[26]

A relationship between influenza and MI is reinforced, although not confirmed, by observational studies exploring the incidence of MI following infection.

A paper by Madjid and coworkers[30] evaluated almost 12,000 patients that died of MI in St. Petersburg, Russia, during an 8-year period. In every year of the study period, the peak acute MI coincided with an influenza epidemic. The odds for an acute MI increased by 1.30 (95%

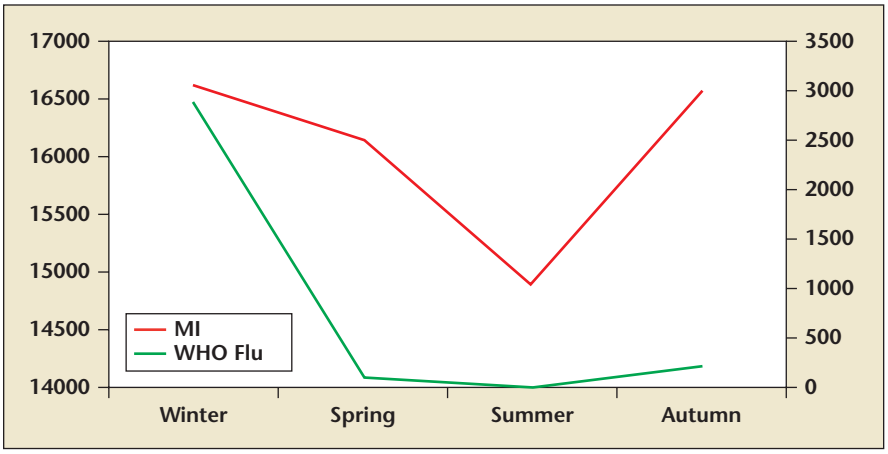

Figure 2. Seasonal incidence of myocardial infarction (MI) and influenza virus infection. Superimposition of seasonal incidence of MI with World Health Organization (WHO) Influenza (Flu) data from Italy from 1998 to 2006. There is an increased incidence of both MI and influenza in the winter, with declining incidence in warmer months and subsequent increase through autumn. Data from Manfredini R et al[31] and World Health Organization.[32]

CI, 1.08-1.56).[30] Manfredini and coworkers performed a retrospective analysis of admissions for acute MI in the Emilia-Romagna region of Italy between 1998 and 2006.[31] Comparison of temporal variation of admission can be plotted against World Health Organization influenza reporting data from Italy over the same time period (Figure 2).[32] Although influenza reporting is quite variable, there are similarities between the two trends.

Peak acute MI and peak influenza periods can be influenced by the same ecologic factors, in particular, weather. A unique ecologic paper by Warren-Gash and colleagues[33] addressed this question. In a time series study, patients who had acute MI in two separate climates were examined: Hong Kong, which has very mild temperatures, and the United Kingdom, which has temperate climates (both areas have known influenza epidemics). The study found that irrespective of the climate and temperature, there was a strong association between influenza outbreaks and acute MI. In a subgroup analysis, the strongest association was in the elderly population.[34] Such ecologic studies, however, have many confounding factors. For example, in times of influenza epidemics, there can also be a concomitant rise in other respiratory pathogens, namely, respiratory syncytial virus. Also in this study, the minor temperature changes in each region were not studied. Even though subtropical climates such as Hong Kong may not have average temperatures as low as in the United Kingdom, relative temperature decreases during the time of influenza outbreaks may have occurred, which could have independently led to increased incidence of acute MI.

Effectiveness of Influenza Vaccine in Preventing MI

Although true causality between influenza and MI may be difficult to confirm, a more practical question is whether vaccination against influenza would lead to a decrease in the incidence, morbidity, and mortality of acute MI. There have been several population-based retrospective studies looking at vaccination and heart disease. Siriwardena and associates[34] conducted a large case-control retrospective study in which 16,012 patients diagnosed with MI and 62,694 case-matched control subjects were analyzed for MI within 1 year. There was a 19% reduction in MI in patients who received influenza vaccine.

Conversely, there have been several population-based cohort studies that have found no association between influenza vaccination and cardiovascular outcomes.[35,36] A study by Jackson and coworkers[35] looked at 1378 patients who were part of the Group Health Cooperative. All patients were survivors of MI between 1992 and 1996. There were 127 fatal and nonfatal cardiac events and no seasonal variation was evident. Adjusting for age, there was no decreased risk of recurrent infarction or death with influenza vaccination. A Cox multivariate analysis using 11 variables (such as vaccination, chronic obstructive pulmonary disease, age, diabetes, hypertension, statin use) failed to show any significant association of influenza vaccination. The strength of this study was that, unlike many population-based studies, the administration of the influenza vaccine was well documented. It can be noted however, that the median age of the cohorts was 64 years. This is lower than the median age in similar studies that had positive results, which may favor fewer cardiovascular events with or without vaccination.[35]

The Flu Vaccination in Acute Coronary Syndromes and Planned Percutaneous Coronary Interventions (FLUVACS) trial is a nonblinded RCT in which 200 patients with an acute MI and 101 patients undergoing planned percutaneous coronary intervention (PCI) for known CAD were randomized for the influenza vaccine. The primary outcome of cardiovascular death occurred in 2% of the group randomized to vaccination versus 8% in the control group ($P < .01$). Secondary outcomes of death, reinfarction, and rehospitalization for ischemia

were 11% versus 23% in favor of the vaccination group ($P < .009$). At 1-year follow-up, the benefit of vaccination remained significant but only in those patients who had MI. Patients that had planned PCI showed no significant difference in outcomes at 1 year between those who were vaccinated and control subjects. This was possibly due to a small effect size, as patients without MI have a dramatically lower 1-year morbidity and mortality. This study was underpowered to capture this difference.[37,38]

In 2008, the Influenza Vaccination in Prevention From Acute Coronary Events in Coronary Artery Disease (FLUCAD) trial was the first double-blind RCT looking at the effectiveness of the influenza vaccine. In total, 658 patients with treated CAD were randomized in a 1:1 fashion; 325 patients received the vaccine and 333 received placebo. At 12-month follow-up, the mortality event rate was 0.63% in the vaccinated group and 0.76% in the control group ($P = .95$). The secondary endpoint of major adverse cardiac events (MACE) occurred in 3% of the experimental arm and 5.87% of the placebo arm ($P = .13$). A subsequent analysis in which hospitalization for myocardial ischemia was added to MACE showed an event rate of 6.02% versus 9.97% in the experimental and control groups, respectively ($P = .047$). The authors recognized that the study was likely underpowered and offered this as a reason that there was not a similar benefit to vaccination as seen in the FLUVACS trial. Also, the baseline characteristics of the patients in this trial showed that > 90% were on statins, β-blockers, aspirin, and angiotensin-converting enzyme inhibitors, perhaps dampening the event rates in both groups.[39] No major adverse events related to vaccination were observed in either prospective study.

A meta-analysis of these two trials pooled data from the total of 476 vaccinated and 483 unvaccinated patients. In the fixed-effects model analysis, cardiovascular death occurred in 11 (2.3%) patients in the vaccinated group and 28 (6.2%) patients in the placebo group (relative risk 0.39; 95% CI, 0.20-0.77). In the random-effects model, which took into account the heterogeneity between the two trials, influenza vaccination had a smaller effect. Neither model showed vaccination effective for decreasing acute MI specifically.[40] The many confounding variables associated with influenza and CAD such as age, treatment variation, comorbidities, medications, and coinfections further limit the results of these RCTs. Recently, a paper by Phrommintikul and associates[41] presented a randomized double-blind study of patients who had acute coronary syndromes within 8 weeks and were randomized to the influenza vaccine or no treatment. The primary endpoint of MACE was significantly decreased in the vaccinated group at 12 months ($P = .004$). Of note, the cardiovascular mortality did not differ between patient groups.

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A large, randomized prospective trial of 31,546 patients looking at telmisartan in patients with vascular disease also studied the benefit of influenza vaccination during four influenza and non-influenza seasons between 2002 and 2007. Unlike the other two RCTs, this was a comparatively large trial encompassing over 40 countries. Influenza vaccination was associated with significantly lower risk of cardiovascular death in three of the four seasons. The only season it was not significantly associated with lower death was in 2003, when there was an incomplete match between the vaccine and the circulating strain, perhaps strengthening the argument that there is a clear benefit of influenza vaccine in preventing cardiovascular disease.[42]

The population whose risk profiles for MI and influenza overlaps the most is the elderly.[43-45] A population cohort study in Hong Kong recruited patients over age 65 with chronic illnesses including diabetes, stroke, and MI. This study looked at pneumococcal vaccination in tandem with the influenza vaccine. Those who received both vaccines had significantly fewer deaths, pneumonia, ischemic stroke, and MI when compared with an unvaccinated cohort. In those patients who received the influenza vaccine alone, when compared with the unvaccinated group, there were no significant differences in the rates of MI, ischemic heart disease, or stroke.[44] Table 1 is a summary of major trials of influenza vaccination for the prevention of MI.

A limitation of most of these studies is the relative efficacy of influenza vaccination. Efficacy is rarely reported and may be variable depending on the match between the influenza strains predicted by the World Health Organization and the predominant circulating strains in a given season, the age and relative health of the population being vaccinated, and the vaccine manufacturer.[46,47] Side effects related to inactivated influenza vaccination

TABLE 1

Summary of Studies Investigating the Effectiveness of Influenza Vaccination on the Prevention of Myocardial Infarction

Study	Study Type	N	Primary Outcome	OR/HR, 95% CI of Primary Outcome	*P* Value	Comments
Gurfinkel EP et al[37]	Randomized control	200	Cardiovascular death	HR 0.34; 95% CI, 0.17-0.71	.02	Secondary endpoint of death, nonfatal MI, or severe ischemia (RR 0.51; 95% CI, 0.30-0.86; $P = .009$)
Heffelfinger JD et al[36]	Case controlled	750	MI	OR 0.97; 95% CI, 0.75-1.27	.95	
Ciszewski C et al[39]	Randomized control	658	Cardiovascular death	HR 1.06; 95% CI, 0.15-7.56	.95	Secondary endpoint #1: MACE (RR 48%; $P = .13$) Secondary endpoint #2: MACE plus hospitalization for myocardial ischemia (RR 40%; $P = .047$)
Warren-Gash C et al[40]	Meta-analysis	959	Cardiovascular death	RR 0.39; 95% CI, 0.2-0.77	—	Minimal estimated protective effect
Hung IF et al[44]	Cohort	36,636	Acute MI	HR 0.52; 95% CI, 0.38-0.71	$< .001$	
Siriwardena AN et al[34]	Case controlled	78,706	Acute MI	OR 0.81; 95% CI, 0.77-0.85	$< .001$	
Phrommintikul A et al[41]	Randomized control	439	Death, hospitalization from ACS, hospitalization from heart failure, hospitalization from stroke	HR 0.70; 95% CI, 0.57-0.86	.004	Primary endpoint was MACE; however, there was no significant decrease in cardiovascular deaths between the control and vaccine group
Johnstone J et al[42]	Retrospective	31,546	Death from cardiovascular cause, stroke, MI	OR 0.81; 95% CI, 0.61-1.09	0.16	In years where influenza vaccine completely matched influenza strain 2004-2005: (OR 0.62; 95% CI, 0.50-0.77; $P < .001$) 2005-2006: (OR 0.69; 95% CI, 0.50-0.77; $P = .009$ 2006-2007: (OR 0.52; 95% CI, 0.42-0.65; $P < .0001$)

The three largest studies to date have been retrospective studies (Heffelfinger JD et al,[36] Siriwardena AN et al,[34] and Johnstone J et al.[42]). Only two randomized controlled studies dedicated to studying the effects of influenza vaccine have been performed (Gurfinkel EP et al.[37] and Ciszewski A et al.[39]). The primary endpoints were not met in either trial. A meta-analysis by Warren-Gash C et al.[40] pooled data from the two randomized controlled trials and showed a significant risk reduction of cardiovascular death with vaccination although a random effects model was never applied despite significant heterogeneity between groups.
ACS, acute coronary syndromes; CI, confidence interval; HR, hazard ratio; MACE, major adverse cardiac event; MI, myocardial infarction; OR, odds ratio; RR, relative risk.

are typically mild, even in high-risk patients. The only major adverse event attributable to vaccination is severe anaphylaxis, usually secondary to inactive vaccine components.

Conclusions

The hypothesis that there is a causal relationship between infection with influenza virus and MI is best supported by ecologic and epidemiologic data. On the molecular level, the evidence has been less robust. There is good evidence of the atherogenic effects of inflammation and infection but these are

not specific to influenza infection in patients with MI. If there is a causal link between influenza and MI, then the administration of the influenza vaccine should decrease the incidence of MI. To date, the evidence is largely based on population cohort studies but the data from these studies do support improved cardiovascular outcomes from administration of the vaccine. The two large prospective trials, FLUVACS and FLUCAD, have both shown a protective benefit of vaccination to some degree. In response to this mounting evidence, and given the vaccine's low side-effect profile, the American College of Cardiology and European Society of Cardiology guidelines now recommend administering annual influenza vaccination to promote secondary prevention of cardiovascular events. This recommendation is identified as Class I, Level B. However, there remains a need for larger randomized placebo-controlled trials with adequate power to establish good primary and secondary endpoints to clarify the benefit of vaccination in preventing MI. ■

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MAIN POINTS

- Given the high prevalence of coronary artery disease, it is important to identify modifiable risk factors for primary and secondary prevention. In the past 2 decades, much work has been done at both the clinical and laboratory level to understand the relationship between inflammation and myocardial infarction (MI).
- The relationship between inflammation and coronary atherosclerosis is well known. Numerous infectious agents such as cytomegalovirus, influenza viruses, and herpes viruses studied in animal models have been shown to induce endothelial inflammation.
- Although causality between influenza and MI may be difficult to confirm, of interest is whether vaccination against influenza would lead to a decrease in the incidence, morbidity, and mortality of acute MI.
- The American College of Cardiology and European Society of Cardiology guidelines now recommend administering annual influenza vaccination to promote secondary prevention of cardiovascular events.

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