Myocardial infarction vaccine? Evidence supporting the influenza vaccine for secondary prevention

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This editorial refers to ‘Influenza vaccination reduces cardiovascular events in patients with acute coronary syndrome’, by A. Phrommintikul et al., on page 1730

Coronary heart disease (CHD) is one of the leading causes of morbidity and mortality worldwide. Both primary and secondary prevention strategies thus far substantially reduce the risk of acute cardiovascular events, but still a substantial number of patients have outcomes. As a result, there has been a call for newer avenues for risk reduction.

The complex interplay between infection and atherosclerosis has been under scientific scrutiny for years. Many organisms have been implicated, including herpesviruses, Chlamydia pneumoniae, Mycoplasma pneumoniae, periodontal pathogens, and many others.¹ There was much excitement regarding C. pneumoniae given its association with CHD and animal models suggesting a direct involvement in the pathogenesis of atherosclerosis, but trials using suppressive antibiotic therapy failed to show a reduction in clinical events.²,³ Although the evidence for chronic infections of intracellular pathogens and atherosclerosis exists, it was speculated that infection in CHD had begun the process of atherosclerosis decades before, thereby limiting the ability to employ antibiotic treatment so late in the evolution of CHD. However, the paradigm of inflammation significantly contributing to atherosclerosis and triggering acute cardiovascular events is firmly established, and as such there has been a continued interest in the role of infection as a contributor to this inflammatory response.

Of acute infectious organisms, the influence of the influenza virus has been closely examined since it is one of the most severe respiratory viral pathogens and essentially the only one with effective prophylaxis and available treatment. Influenza virus has been associated with 36 000 deaths and 226 000 hospitalizations annually in the USA.⁴ The study of Phrommintikul et al. further examines the effect of influenza vaccination on secondary prevention.⁵ In this study, patients with recent acute coronary syndromes given the influenza vaccine had an absolute risk reduction of nearly 10% of major cardiovascular events over a 12 month follow-up period. Notably, more patients in the vaccine group received angiotensin-converting enzyme inhibitors (ACEIs) and they also had slightly lower serum creatinine levels. However, adjustment for ACEIs and serum creatinine suggested that there was still a lower incidence of the primary outcome and hospitalization for acute coronary syndromes in patients receiving the influenza vaccine. Also there was no difference in cardiovascular death with influenza immunization.

The first randomized controlled trial to examine the role of the influenza vaccine in patients for secondary prevention was the FLUVACS study.⁶ Although FLUVACS had only 301 patients, less than the size of this trial, it is the only randomized controlled trial based on the recommendations of the European Society of Cardiology, American College of Cardiology, and American Heart Association to vaccinate patients with cardiovascular disease.⁷,⁸ The FLUVACS trial included a combination of patients with recent myocardial infarctions and patients with elective percutaneous coronary intervention without recent or prior acute coronary syndromes as well as previous revascularization. There was no observed benefit in those who underwent elective revascularization, but 200 patients in the myocardial infarction arm were less likely to suffer cardiovascular death or recurrent ischaemic events with the influenza vaccine at 1 year.⁶ Concurrently, there was much concern about the acute inflammatory response elicited by vaccination soon after cardiovascular events. Fears were largely allayed with a cohort study of nearly 40 000 patients who had no increased short-term risk of acute myocardial infarction or stroke after immunization for influenza, pneumococcus, or tetanus.⁹ Notably, preceding systemic respiratory illnesses were noted to correlate with an increased risk of cardiovascular events in this cohort.⁹ With the aforementioned data and other large cohort

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studies, the practice guidelines currently recommend the administration of the influenza vaccine to patients with cardiovascular disease with a level IIB recommendation.\textsuperscript{7,8}

More recently, the Polish FLUCAD study evaluated the effects of the influenza vaccine on 658 patients with stable CHD.\textsuperscript{10} There was no difference in cardiovascular death in this study, but the pre-specified secondary outcome of a coronary ischaemic event was slightly lower in those receiving the influenza vaccine. A pooled analysis of FLUCAD and FLUVCAS suggested a reduction in cardiovascular death, but the heterogeneity, small sample size, and small event rate have led a recent Cochrane Review to conclude that the two studies do not provide enough data to evaluate the effects of influenza immunization on CHD sufficiently.\textsuperscript{11} Although the study by Phrommintikul \textit{et al.}\textsuperscript{5} is a small randomized controlled trial, it provides us with some additional insight into this relationship. From the presented studies, patients with recent cardiovascular events may derive the greatest benefit from immunization (Figure 1).

The relationship between influenza and acute coronary syndromes is still not clear despite various epidemiological observations regarding the correlation. Although a systemic inflammatory response associated with infections could potentially lead to plaque rupture, the higher heart rate and fever from the illness would be expected to lead to higher incidences of ‘demand ischaemia’ without atherothrombosis and plaque rupture. However, in a compelling autopsy study of nearly 35,000 patients succumbing to respiratory illnesses, there was an increase in coronary deaths during influenza epidemics.\textsuperscript{12} This observation along with the interesting trials suggests that we may need to re-frame our current clinical management of non-ST-elevation myocardial infarctions and unstable angina in the setting of severe systemic illnesses. Further studies to risk stratify this subset of patients who may benefit from aspirin, statins, \(\beta\)-blockers, anticoagulation, and even revascularization for their initially non-coronary presentation are warranted. The complexities of attempting to identify patients at risk for plaque rupture is further confounded by added physiological stressors of an infectious illness.

Part of the intrigue of this study is the persistent relationship of influenza with acute coronary syndromes, although studies of other pathogens thus far have been less fruitful. There are even observational data with the use of oseltamivir in patients with underlying cardiovascular disease infected with influenza associated with a reduction in recurrent cardiovascular events.\textsuperscript{13} This lends the question of whether there is a causative role and the mechanisms that may exist. Atherosclerotic mice inoculated with influenza had a significant infiltration of inflammatory and smooth muscle cells as well as evidence of platelet aggregation and thrombus formation in areas of atherosclerotic plaque without evidence of a panarteritis.\textsuperscript{14} Interestingly, this was not evident in wild-type mice, consistent with the randomized trials suggesting that patients at higher risk, with recent acute myocardial infarctions, may obtain more benefit from preventing against influenza. Furthermore, after inoculation with influenza and in the absence of viraemia, atherosclerotic mice were found to have more viral antigens in coronary atheroma, but this effect was not evident in their wild-type counterparts after inoculation.\textsuperscript{15} Viral antigens were not seen in the spleen, liver, or lymph nodes. Additionally, this vascular tropism was not seen with respiratory syncytial virus (RSV) infection. Influenza infection in mice has also demonstrated an impairment of the ability of HDL cholesterol to protect against oxidation of LDL cholesterol.\textsuperscript{16}

Although mouse models, observational studies, and randomized trials have largely been promising, larger studies need to be performed before we can draw further conclusions. Influenza has been an ideal target given the ability to vaccinate and treat. However, influenza may not be the only acute respiratory pathogen that might be associated with cardiovascular events. Streptococcus pneumoniae, another respiratory microbe with a vaccine and treatment, may also be another target for further investigation. In the absence of infection, hypercholesterolaemic mice immunized to \textit{S. pneumoniae} had a reduction in the extent of

\begin{figure}[h]
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\includegraphics[width=\textwidth]{figure1.png}
\caption{The effect of the influenza vaccine on major cardiovascular events in patients with CHD according to the current randomized controlled trials.}
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Conflict of interest: none declared.

References