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Influenza vaccine as a coronary intervention for prevention of myocardial infarction

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ABSTRACT

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality globally. Influenza is one of the leading infectious causes of morbidity and mortality globally, and evidence is accumulating that it can precipitate acute myocardial infarction (AMI). This is thought to be due to a range of factors including inflammatory release of cytokines, disruption of atherosclerotic plaques and thrombogenesis, which may acutely occlude a coronary artery. There is a large body of observational and clinical trial evidence that shows that influenza vaccine protects against AMI. Estimates of the efficacy of influenza vaccine in preventing AMI range from 15% to 45%. This is a similar range of efficacy compared with the accepted routine coronary prevention measures such as smoking cessation (32–43%), statins (19–30%) and antihypertensive therapy (17–25%). Influenza vaccine should be considered as an integral part of CVD management and prevention. While it is recommended in many guidelines for patients with CVD, rates of vaccination in risk groups aged <65 years are very low, in the range of 30%. The incorporation of vaccination into routine CVD prevention in patient care requires a clinical practice paradigm change.

In 2008, cardiovascular disease (CVD) overtook communicable diseases for the first time to become the leading cause of mortality in the world, now causing approximately 13% of all deaths globally.[1] Given the high global burden of coronary heart disease (CHD), prevention through identifying and mitigating risk factors is a priority. Cigarette smoking, elevated serum cholesterol levels and high blood pressure are major risk factors for developing CHD and significant predictors of death, and are therefore accepted targets for preventive strategies.[2] When considering attributable deaths, raised blood pressure is categorised as the leading risk factor followed by tobacco use while high serum cholesterol is ranked sixth.[3] Behavioural interventions such as smoking cessation, dietary and lifestyle changes, use of statins and antihypertensive drugs are accepted public health strategies for reducing the burden of CHD.[4] Could influenza vaccine be an additional strategy to reduce CHD burden?

INFLUENZA AS A TRIGGER FOR ACUTE MYOCARDIAL INFARCTION

While many infections have been studied for their role in triggering vascular events, the most consistent evidence is for influenza.[5] There is compelling evidence for the association between influenza infection and acute myocardial infarction (AMI). There is a peak of both influenza and cardiac deaths in winter.[5 6] Influenza epidemics are associated with increased hospitalisation rates for AMI and other cardiovascular-related conditions.[7 8] A number of studies have shown a strong association between influenza and AMI.[5 9–11] There is a wealth of retrospective and prospective[5] studies showing a temporal relationship, with influenza respiratory illnesses preceding AMI by a variable time, with the strongest association occurring in the first three days, but lasting up to 1 year.[12]

Atherosclerosis is an inflammatory response culminating in a plaque comprised of a core rich in lipids, pro-inflammatory cells and cytokines, and a fibrous cap. It is thought that influenza acts by many mechanisms, including inflammatory release of cytokines that causes a pro-thrombotic state, local disruption of coronary plaques, as well as physiological effects such as hypoxia and tachycardia, to cause acute obstruction of coronary arteries that may be otherwise subcritically stenosed.[13] Other mechanisms include sympathetic activation with subsequent effects on vascular tone with vasoconstriction; thrombogenesis through the non-specific pro-coagulant and thrombophilic effects of inflammation; epithelial dysfunction; and inadequate coronary artery blood flow through increased metabolic demand with fever and tachycardia, reduced oxygen saturation and hypotension with secondary vasoconstriction.[14] Further, influenza has been shown to produce direct effects on the heart. Histopathological and molecular studies on influenza-infected mice have shown that the virus can be isolated from heart tissue and that its presence leads to local inflammatory changes.[15] The multiple mechanisms by which influenza may precipitate AMI are shown in figure 1.

INFLUENZA VACCINE FOR SECONDARY CORONARY PREVENTION

Evidence is accumulating about the effectiveness of influenza vaccination in coronary disease prevention. Observational studies have shown the protective effectiveness of influenza vaccine against AMI is between 19% and 45%.[9 16 17] A meta-analysis of case–control studies showed that influenza vaccine has a summary vaccine effectiveness of 29% against AMI.[18] In a meta-analysis of randomised controlled trials (RCTs), influenza vaccine was protective against the outcome of AMI but the pooled estimate was not statistically significant (relative risk (RR) 0.85, 95% CI 0.44 to 1.64).[5] However, each RCT showed efficacy of influenza vaccine against composite coronary morbidity and mortality outcomes.[19 20] Another RCT found that influenza vaccine reduced major cardiovascular events by 10% in patients with acute coronary syndromes during a 12-month follow-up period.[21]

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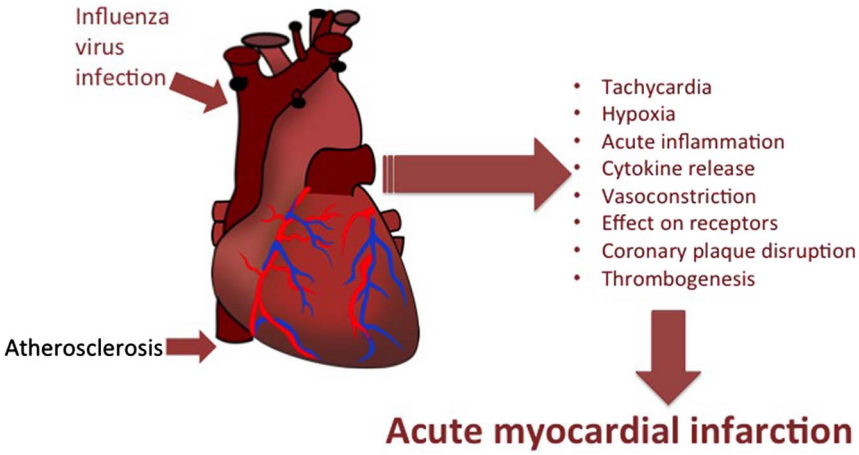

Figure 1 Mechanisms by which influenza infection may precipitate acute myocardial infarction.

If influenza vaccine protects against AMI, the mechanism is through preventing influenza, thereby preventing the possibility of AMI triggered by the mechanisms discussed above. An additional putative molecular mechanism for the protective effect of vaccination is that vaccine-induced antibody cross-reacts with a human bradykinin receptor.[22] It is postulated that this interaction could lead to increased levels of nitric oxide, which increases the efficiency of myocardial oxygen use, as well as leading to increased blood flow through vasodilation and possible angiogenesis.

SMOKING CESSATION FOR SECONDARY PREVENTION

A significant body of evidence exists supporting that smoking cessation is effective in the secondary prevention of AMI and reduces AMI mortality rates.[4 23–25] The OASIS 5 study revealed that adherence to smoking cessation interventions among recent quitters within 6 months of an index AMI was associated with a 43% RR reduction for recurrent myocardial infarction.[4] The survival and ventricular enlargement (SAVE) trial found that smoking cessation among people who had left ventricular systolic dysfunction secondary to AMI was associated with a 32% reduction in risk of death/recurrent myocardial infarction during a median follow-up period of 42 months.[26] Pooled estimates from one systematic review revealed that people with established CHD who quit smoking had a 32% and 36% risk reduction in non-fatal myocardial infarction and all-cause mortality, respectively.[24]

ANTIHYPERTENSIVE MEDICATION FOR SECONDARY PREVENTION

Individual RCTs have established the efficacy of antihypertensive medications in secondary prevention of AMI to be approximately 20–25% despite the differences in the study populations in terms of presence or absence of left ventricular dysfunction or heart failure.[26–29] In addition, a systematic review focusing on specific antihypertensive agents showed that the use of long-term β-blockers reduces the risk of reinfarction by approximately 25%.[30] In their meta-analysis, Pepine *et al*[31] demonstrated that verapamil reduced the incidence of non-fatal reinfarction by 21% among patients with CVDs. In patients with preserved left ventricular function, ACE inhibitors have been shown to be effective in the secondary prevention of both fatal and non-fatal myocardial infarction by 17.3%.[32] The role of calcium antagonists in secondary prevention has been controversial, with some studies showing calcium antagonists to be more harmful than beneficial, particularly in increasing the risk of AMI among hypertensive patients.[33 34] It has been argued however that individual calcium antagonists should be taken into consideration while analysing their efficacy.[31]

STATINS FOR SECONDARY PREVENTION

Several studies have investigated the impact of statins in the secondary prevention of coronary heart diseases. RCTs involving patients from a range of age groups, different cholesterol levels, C reactive protein levels with/without a history of angina or previous myocardial infarction have revealed statin efficacy ranging from 19% to 30%.[35–37]

Afilalo *et al*[38] conducted a meta-analysis that showed that statins reduced the risk of reinfarction by 26%. These findings are similar to other meta-analyses done by Cholesterol Treatment Trialists Collaborators, Sheng *et al* and Gould *et al*,[39–41] who reported 23%, 28% and 29.5% RR reduction of myocardial infarction, respectively. When comparing the efficacy of statins by gender, the overall risk reduction of major coronary events was found to be similar among men and women (approximately 30%).[42] When assessing the efficacy of intensive (high dose) versus less intensive statin therapies (low dose), a meta-analysis of RCTs established that more intensive statin therapy was associated with a further 17% RR reduction of myocardial infarction compared with the latter.[43]

DOES INFLUENZA VACCINE HAVE A PLACE IN ROUTINE CORONARY PREVENTION?

Despite the large body of evidence supporting a role for influenza vaccine in coronary prevention, rates of influenza vaccination in patients with heart diseases are low,[44] and vaccination is not a priority among physicians. A significant proportion of healthcare budgets is spent on the acute treatment of AMI and the long-term management of CHD. Costs per year of life saved range from US$4350 for smoking cessation programmes to US $142–760 for statin use in under 65 year olds.[45 46] Further gains in prevention of CHD would therefore likely be cost-effective, especially if using a low-cost strategy such as influenza vaccination. Influenza vaccination is a relatively cheap, safe and evidence-based public health measure that is underused in at-risk populations currently. Influenza vaccination has been shown to be cost-effective in preventing influenza-like illnesses and hospitalisation for pneumonia and influenza, without any consideration of its efficacy in the prevention of AMI.[47] It is therefore likely that influenza vaccine could be highly cost-effective in the prevention of AMI particularly for high-risk

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Table 1 Efficacy of accepted coronary interventions and influenza vaccine in the prevention of myocardial infarction

Coronary intervention	Prevention	Intervention efficacy/effectiveness against acute myocardial infarction (%)
Smoking cessation[4 23–25]	Secondary	32–43
Statins[38]	Secondary	19–30
Antihypertensive drugs[26–29 32]	Secondary	17–25
Influenza vaccine[5 9 18]	Secondary	15–45

people. Table 1 summarises the range of efficacy of accepted coronary interventions compared with influenza vaccination and highlights the potential gains of including vaccination in routine prevention of CHD.

A well-powered RCT of influenza vaccine in AMI prevention would add to the available evidence.[48] However, there is already compelling evidence that influenza vaccine should be considered as an integral part of CHD management and prevention. While it is recommended in many guidelines for patients with coronary artery disease, rates of vaccination in risk groups aged <65 years are low.[49] In addition, this recommendation is seen as one that aims to prevent influenza, rather than to reduce the risk of AMI. A paradigm change may be required to encourage clinicians to see influenza vaccine as a cheap, safe and effective additional prevention strategy for patients with CHD.

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