The link between influenza and myocardial infarction: vaccination protects

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The association between influenza and cardiovascular disease has been known since the influenza pandemics of the early years of the last century. This association is more consistent and more lasting in the case of particularly severe infections. Several pathogens, including influenza viruses, can modulate the inflammatory response and influence the biology of atherosclerotic plaque to rupture it and cause a Type 1 myocardial infarction. Clinically relevant viral infections can also exacerbate pre-existing cardiovascular disease and contribute to the development of a Type 2 myocardial infarction through an increase in the metabolic demands of the myocardial tissue for fever and tachycardia and the possible induction of hypoxaemia. Evidence of a relevant protective efficacy of influenza vaccination provides further robust and convincing support for a causal link between influenza and myocardial infarction. Consistent cardiovascular protection linked to influenza vaccination has also been demonstrated in patients with recent myocardial infarction to suggest the possibility that this procedure may become an integral part of in-hospital management of acute coronary syndromes. Despite the solidity of these evidences, acknowledged by the guidelines that recommend influenza vaccination in patients at increased cardiovascular risk, still today an unacceptably high proportion of patients at high cardiovascular risk do not receive flu vaccination. Despite some potential limitations of the current flu vaccination, its advantages in terms of reducing cardiovascular events and related mortality are still such as to justify its wide use, especially, but not limited to, in patients with high cardiovascular risk.

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Pathophysiological mechanisms underlying the relationship between influenza and myocardial infarction

The association between acute infections and increased risk of myocardial infarction has been documented for various pathogens, both viruses and bacteria, and for a variety of infection sites. This association is more consistent and more lasting in the case of particularly severe infections. Such evidence suggests that both the infectious agent and the host response may have a significant pathophysiological role (Figure 1). In this regard, the central role that inflammation plays in the development and progression of atherosclerotic disease should be considered first. Although the pathogenesis of the inflammatory process is multifactorial, various pathogens, including influenza viruses, can modulate the inflammatory response and influence the biology of the atherosclerotic plaque up to inducing its rupture and causing a Type 1 myocardial infarction. During an infectious process, inflammatory cytokines are released into the circulation, such as interleukins 1, 6 and 8 and tumour necrosis factor α, which are able to activate inflammatory cells within the atherosclerotic plaque. Experimental and autopsy studies have shown that, after an infectious stimulus, the inflammatory activity in the atherosclerotic plaque significantly increases with the production of metalloproteinases, peptidases and reactive oxygen species that can lead to destabilization of the plaque. The pro-thrombotic and procoagulant status associated with acute infections further increases the risk of coronary thrombosis at the site of plaque rupture. In the course of infection with influenza viruses and other respiratory viruses, an increased expression of genes associated with platelet activation and the risk of myocardial infarction has also been described. Influenza viruses also seem to have a particular tropism for vascular structures, as suggested in experimental models of atherosclerosis accelerated by their specific localization in the fibrolipidic plaques even in the absence of apparent viremia. This localization is associated with a pronounced local inflammatory response with macrophage infiltration and release of inflammatory cytokines into the circulation. This state of increased systemic and plaque inflammatory activity, hypercoagulability and endothelial and platelet dysfunction/activation tends to persist even after the clinical resolution of the acute infection.

Clinically relevant viral infections may also exacerbate pre-existing cardiovascular disease and contribute to the development of Type 2 myocardial infarction through increased metabolic demands of myocardial tissue for fever and tachycardia and the eventual induction of hypoxaemia. The increase in heart rate that accompanies febrile states, however, reduces the diastolic time and consequently the coronary perfusion that occurs mostly during this phase of the cardiac cycle. In the elderly, the perfusion deficit may be further exacerbated by the presence of coronary stenosis or even by toxin-mediated vasoconstriction. Mismatch ischaemia, which physio-pathologically underlies Type 2 myocardial infarction, however, explains only a modest proportion of heart attacks that occur in the period immediately following an infectious process, while it has no significant pathophysiological role in events that occur later.

Experimental models also suggest the possibility of direct cardiovascular damage from influenza viruses. In experimental models of animals infected with the influenza virus, phenomena of cell destruction more than inflammation were described at the level of myocardial tissue, and similar lesions were also observed in some patients who died of influenza. These foci of damaged myocardial tissue do not involve the coronary arteries but can exacerbate myocardial damage on an acute ischaemic basis and can contribute to the onset of arrhythmias and the onset or worsening of heart failure.

Benefits of flu vaccination

Evidence of a relevant protective efficacy of influenza vaccination provides further robust and convincing support for a causal link between influenza and myocardial infarction. A meta-analysis that included 4 randomized trials and 12 observational studies for a total of about 240,000 patients with cardiovascular disease showed that influenza vaccination is associated with a 28% reduction in the relative risk of all-cause mortality and 18% relative risk of cardiovascular mortality and concomitant with a 13% reduction in major cardiovascular events over a median follow-up of 20 months. Quite recently, the Influenza Vaccination After Myocardial Infarction (IAMI) trial has provided an interesting perspective on the possible use of influenza vaccination as an integral part of the in-hospital treatment of patients with myocardial infarction. The double-blind, randomized controlled study evaluated the protective efficacy of influenza vaccination vs. placebo in reducing major cardiovascular events in a cohort of 2571 patients, in almost all cases with myocardial infarction (only 0.3% with a stable coronary heart disease at high-risk), over a 12-month period.

Influenza vaccination within 72 h of hospitalization for myocardial infarction or invasive coronary procedure resulted in a 28% reduction in the risk of primary outcome (hazard ratio 0.72, 95% CI: 0.52–0.99, P = 0.040), a combined outcome of all-cause mortality, myocardial infarction or stent thrombosis, and a 41% reduction in all-cause mortality (hazard ratio 0.59, 95% CI: 0.39–0.89, P = 0.010) and cardiovascular mortality (hazard ratio 0.59, 95% CI: 0.39–0.90, P = 0.014). The study also showed a trend towards a reduction in myocardial infarction (hazard ratio 0.86, 95% CI: 0.50–1.46, P = 0.57), which did not reach statistical significance probably due to the small number of events that did not ensure adequate statistical power. Influenza vaccination was not associated with any increase in serious adverse events, confirming the possibility of safely administering influenza vaccination in the immediate post-infarction period. The 41% reduction in both all-cause and cardiovascular mortality certainly appears to be of considerable significance if we consider that it has been observed in patients in any
case treated with standard therapies in secondary prevention, therapies whose impact is well known, reducing the risk of recurrence of heart attack by 20–25%.  

Patients enrolled in the IAMI study, in fact, at the time of discharge had received aspirin prescription in 98% of cases, P2Y12 inhibitors in 97% of cases, angiotensin converting enzyme inhibitors or angiotensin II AT1 receptor inhibitors in 70% of cases, beta-blockers in 78% of cases and statins in 98% of cases.  

The mechanisms underlying such an important protective effect of vaccination are probably multifactorial. Certainly, the fact of preventing the flu syndrome is of considerable importance in terms of cardiovascular prevention as it prevents the haemodynamic and metabolic stress associated with viral infections that present a more demanding course. Vaccination could also favour a stabilization of atherosclerotic plaque by interacting with the immune system and inflammatory mechanisms. Indeed, the analysis of the Kaplan-Meier curves shows an early separation between the two treatment arms in favour of vaccination and a stabilization of the trend around the third month. This study, albeit of unquestionable value, could raise ethical perplexities as the possibility of randomization to placebo is not in line with the guidelines, both American and European, which recommend Class I influenza vaccination with a level of evidence B.  

Indeed, the IAMI study only enrolled patients who had not received the annual flu vaccination and did not plan to undergo such vaccination during the flu season during which they were recruited into the study. Moreover, all participants had the opportunity to undergo vaccination of their own choice after enrolment even in the case of assignment to the placebo arm, but only in 13% of cases was this opportunity exploited. Moreover, this transition of patients from the placebo arm to the active treatment may have weakened, certainly not amplified, the positive results observed. The main limitation of the study is its premature interruption due to the spread of the COVID pandemic with consequent reduction in the ability of the study to better define the real differences in the primary outcome. The early termination of a study, in fact, often tends to amplify the benefits of the treatment.  

Nonetheless, the evidence from the IAMI study is adequately robust to further bolster the prevention message of current guidelines recommending influenza vaccination in patients most at risk of cardiovascular events. The authors combined the results of the IAMI trial with those of three other studies with similar design, highlighting a reduction in cardiovascular mortality of 49% (overall hazard ratio 0.51, 95% CI: 0.36–0.71, \( P = 0.0001 \)). Further confirmation of the cardiovascular protective efficacy of the influenza vaccine derives from a recent and larger meta-analysis that included 6 randomized controlled trials, of which 3 of high quality, for a total of 9001 patients (mean age 65.5 years, 42.5% women, 52.3% with a history of cardiovascular disease). The composite outcome frequency of major cardiovascular events and cardiovascular mortality at 1 year of follow-up was 3.6% in vaccinated patients and 5.45% in patients who received placebo [risk ratio 0.66, 95% confidence interval (CI): 0.53–0.83, \( I^2 = 19\% \), \( P < 0.001 \) with an absolute relative risk reduction of 1.8% (95% CI: 0.9–2.7%, \( P < 0.001 \)) and a number of patients to be treated necessary to prevent 1 cardiovascular event equal to 56 (95% CI: 38–107 patients).  

The protective efficacy of influenza vaccination was particularly evident in 3313 patients with recent acute coronary syndrome (6.5% of events in vaccinated patients vs. 11%
of events in the control group; risk ratio 0.55, 95% CI: 0.41-0.75, $I^2 = 33\%$, $P < 0.001$) with an absolute relative risk reduction of 4.5% (95% CI: 2.6-6.4%, $P < 0.001$) and a number of patients to be treated necessary to prevent 1 equal cardiovascular event at 23 (95% CI: 16-39 patients). In these patients with recent acute coronary syndrome, a significant reduction in mortality from cardiovascular causes was also observed in the vaccinated subjects compared with the control group (2.6 vs. 5.4%; risk ratio 0.44, 95% CI: 0.23-0.85, $I^2 = 43\%$, $P = 0.01$) with an absolute relative risk reduction of 2.8% and a number of patients needed to treat to prevent 1 cardiovascular event equal to 36 (95% CI: 15-100 patients). This reduction in the risk of cardiovascular events and death from cardiovascular causes is similar, if not greater, to that observed during treatment with the reference drugs recommended by the guidelines for this type of patient. Regarding the type of vaccine to be used preferentially, the Influenza Vaccine to Effectively Stop Cardio Thoracic Events and Decompensated Heart Failure study did not show differences in the efficacy between high-dose trivalent vaccine and standard-dose quadrivalent vaccine in patients recently hospitalized for heart failure or myocardial infarction.

**Guideline recommendations**

To mitigate the potentially damaging impact of influenza on atherosclerotic disease, as early as 2006, the American Heart Association/American College of Cardiology guidelines recommended influenza vaccination with the utmost strength and level of evidence B for patients with overt coronary disease. A similar recommendation (Class I, Level B) has been proposed by the guidelines for the management of chronic coronary syndrome, especially for elderly patients. Quite recently, the Centers for Disease Control and Prevention has reiterated the opportunity of annual influenza vaccination for all adults, especially for individuals at a higher risk of a severe course of influenza or with relevant comorbidities such as coronary heart disease, heart failure or chronic obstructive pulmonary disease. However, these recommendations have not yet found an adequately broad acceptance by the scientific community. The analysis of the Get With The Guidelines—Heart Failure registry, associated with the annual survey by the American Hospital Association, showed that in the period 2012-17, on average one out of three patients hospitalized for heart failure had received an influenza or pneumococcal vaccination, with no evidence of any trend of improvement over the 5-year study duration. Similarly, a US survey conducted in the period 2016-19 showed that only 50% of patients with atherosclerotic disease had received the flu vaccination, underlining the importance of socio-economic factors as the main determinants of the scarce diffusion of this preventive approach.

**Conclusions**

Influenza continues to be a major public health problem even during the COVID pandemic, which is why it is desirable that the use of respiratory virus vaccines in combination with influenza can be achieved by resorting to production platforms that can ensure wide availability of even more effective vaccines. Patients with cardiovascular diseases, in fact, may present an immune response to vaccination that is variously deficient due to immunosenescence phenomena and a chronic inflammatory state linked to age. Despite these potential limitations of the current flu vaccination, its advantages in terms of reducing cardiovascular events and related mortality are still such as to justify its widespread use, especially, but not limited to, to patients with a high cardiovascular risk.

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