

Influenza and Pneumococcal Vaccination in Coronary Artery Disease

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Prolonging lives of patients is the ultimate aim of physicians. Patients with coronary artery disease now benefit from a variety of medicines, including antiplatelets, statins, renin-angiotensin system inhibitors, and others, which are proven to reduce the risk of cardiovascular death in such patients¹⁾. Nonetheless, communicable diseases, such as influenza, pneumococcal pneumonia, and more recently COVID-19, cause risks of deaths in patients with cardiovascular diseases²⁾. Based on the evidence that influenza vaccination reduces the risk of cardiovascular disease³⁾ and that lack of pneumococcal vaccination was associated with a higher independent risk of heart failure and mortality among octogenarians⁴⁾, the Japanese Circulation Society 2018 guideline on diagnosis and treatment of acute coronary syndrome recommends influenza vaccination in patients with a history of myocardial infarction within one year, and pneumococcal vaccination in elderly patients and high-risk patients⁵⁾. It is shown that simultaneous vaccination, compared to sequential administration, is a safe and effective procedure among the elderly in Japan⁶⁾; however, the safety and efficacy of simultaneous vaccination among Japanese patients with coronary artery disease were unknown.

In this issue of the Journal of Atherosclerosis and Thrombosis, Shimada *et al.*⁷⁾ reported a clinical trial that tested the safety and efficacy of a simultaneous vaccination with a trivalent influenza vaccine and pneumococcal polysaccharide vaccine (PPSV23) in Japanese patients with coronary artery disease. Although data regarding the efficacy were limited by the number of subjects and a short study period, this study showed that simultaneous vaccination could be done safely, without serious adverse events and with

minor local reactions. Since the Japanese Ministry of Health, Labour and Welfare started the routine PPSV23 vaccination every 5 years for the elderly in 2014 that is still underrecognized, annual influenza vaccination may provide good opportunities to both receive vaccines safely and protect such patients from respiratory infections and cardiovascular events (**Fig. 1**). Further impacts of this study are discussed from two perspectives.

First, the simultaneous vaccination benefits patients by enhancing efficacy regarding protection from respiratory infections. A review of clinical studies of simultaneous use of PPV23 with seasonal influenza vaccines⁸⁾ pointed out that there are additive effects of the two vaccines; patients who received both vaccines gained greater risk reductions of hospitalization for pneumonia or death. On the other hand, a well-designed randomized trial comparing simultaneous versus sequential administration of a PPSV23 and an influenza vaccine conducted in Japan showed a noninferiority of simultaneous vaccination regarding immunogenicity⁶⁾. Although an additive effect of simultaneous vaccination on the prevention of respiratory infections still remains to be elucidated, one can expect noninferior protection against each infection by simultaneous vaccination in Japanese patients with coronary artery disease.

Second, the mechanisms by which vaccination prevents cardiovascular events gather growing interests from scientists. For instance, acute influenza infection may be associated with coronary plaque ruptures, heart failure from fluid overload, myocarditis, and arrhythmia, which are preventable by vaccination³⁾. However, cardioprotective effects of influenza vaccination are observed beyond influenza season, which suggest a possibility that influenza vaccination possesses direct cardiovascular protective effects. One study by Veljkovic *et al.*⁹⁾ employed an informational

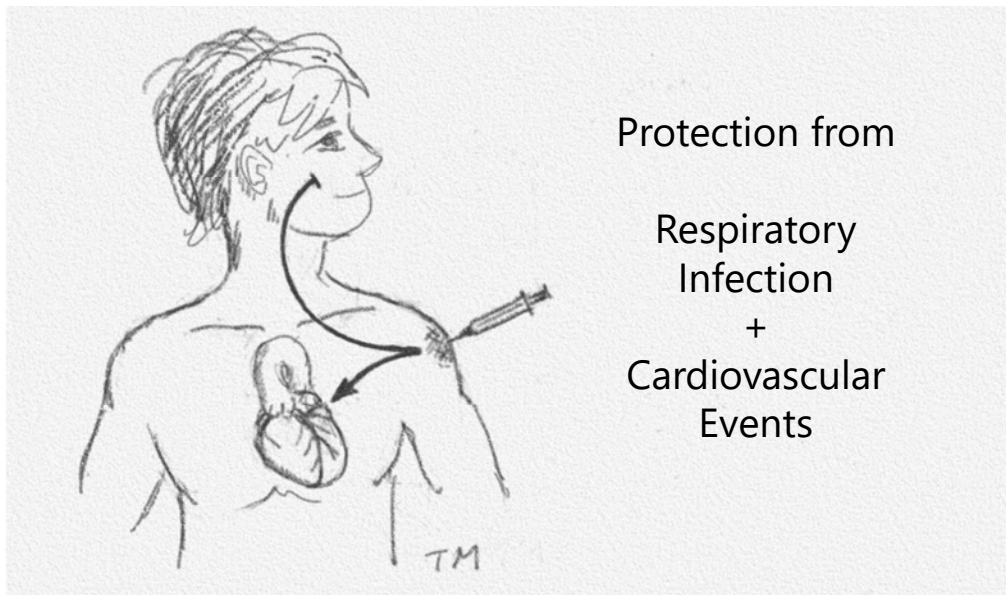


Fig. 1.

Vaccination of influenza and PPSV23 in patients with coronary artery disease provides protection from cardiovascular events by prevention of respiratory infection and potential direct mechanisms of cardiovascular protection.

spectrum method (ISM) to analyze potential host targets of antibodies that are elicited by influenza vaccination. Although functional evidence is lacking, ISM identified bradykinin B2 receptor as a candidate among host proteins that may cross-react with influenza hemagglutinin HA1. Bradykinin B2 receptor, stimulated by agonistic antibody, may activate an endothelial nitric oxide synthase system, which may exert vasoprotective and cardioprotective effects during the development of cardiovascular disease⁹. Shimada *et al.*⁷ experimentally found that the levels of antioxidantized LDL antibody decreased from baseline, to 4- and 12-week vaccinations with either influenza plus PPSV23 or influenza alone. Since several conflicting results are published regarding the effects of influenza or pneumococcal vaccination on the levels of the antioxidantized LDL antibody, further study is needed to clarify a potentially anti-inflammatory mechanism by which vaccination protects patients from atherosclerotic cardiovascular disease⁷.

In conclusion, simultaneous vaccination of influenza and PPSV23, based on its safety, greatly benefits patients with coronary artery disease by protection from respiratory infections and cardiovascular events. Further studies are needed to clarify the direct vasculoprotective and cardioprotective mechanisms exerted by vaccination.

Disclosures

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