



Review

Cardioprotective effect of influenza and pneumococcal vaccination in patients with cardiovascular diseases



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ABSTRACT

Due to the wide interaction between the respiratory and the circulatory systems, influenza and pneumococcal vaccinations are recommended in the prevention and treatment of cardiovascular diseases. The review summarizes the results of recent studies and meta-analyses demonstrating that in this group of high-risk patients both vaccinations have potentially beneficial properties. However, in the era of Evidence Base Medicine, there is still a lack of randomized prospective clinical trials, especially those evaluating the effect of pneumococcal vaccination. As the burden of cardiovascular diseases represents various pathologies, it is important to point that the beneficial effect of vaccination is more pronounced in the atherosclerotic etiology, especially in patients after recent coronary events. This information contributes significantly to the appreciation of the role of the adaptive and innate immunity in atherosclerosis, which is now considered as immuno-inflammatory process driven by LDL-cholesterol intimal infiltration and macrophages activation. The mechanism of the cardioprotective effect of vaccination may not only be associated with the elimination of infections and their complications, but also related to the modification of the immuno-inflammatory model of atherosclerosis.

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1. Introduction

There is a wide interaction between cardiovascular and respiratory pathologies. The recent Guidelines on Prevention of Cardiovascular Diseases of the European Society of Cardiology

(ESC) recommend influenza vaccination in the prevention and treatment of the whole spectrum of cardiovascular diseases (CVD). The power of recommendation (class IIb/level C – “action may be considered”) is not strong and based on experts’ opinions, small randomized and retrospective studies [1]. Some other ESC Guidelines declared stronger recommendation (Class I – “action is indicated”) for influenza and interestingly also for pneumococcal vaccination in specific subsets of CVD (Table 1).

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Table 1

Recommendations for influenza and pneumococcal vaccination in the current guidelines of the European Society of Cardiology.

Type of guidelines	Year of publication	Recommended vaccination	Power of recommendation
Prevention of Cardiovascular Diseases	2016	Influenza	Class IIb/Level C
Acute and Chronic Heart Failure – prevention and treatment	2016	Influenza and pneumococcal vacc.	According to local guidelines
Pulmonary Hypertension	2015	Influenza and pneumococcal vacc.	Class I/Level C
Stable Coronary Artery Disease	2013	Influenza vacc.	Class I/Level C

Respiratory infection is a leading cause of hospitalization among patients with heart failure (HF) and is associated with increased in-hospital mortality rates [2]. Epidemiological data confirmed a link between pneumococcal and influenza infections and cardiovascular events. Corrales-Medina et al. found a 4-fold higher risk of a myocardial infarction, cardiovascular death or cardiac hospitalization in 30 days after pneumonia, which declines progressively, but remains 1.5-fold higher for up to 10 years [3]. Smeeth et al. in another study reported significantly higher rate of myocardial infarction during a 90-day period after acute lower respiratory tract infection [4]. Numerous studies have shown that influenza vaccinations reduce mortality, hospitalization, acute coronary syndromes (ACS) in patients with coronary heart disease (CHD) and/or HF [5–7]. Recent years have provided us with interesting results of new clinical studies and meta-analyses as well as data about possible mechanisms of the cardioprotective effect of vaccinations. However, the efficacy of pneumococcal vaccination remains not well established, as there have been no randomized clinical trials (RCT) in this field and many studies had negative results [8–10].

2. Influenza vaccination

2.1. Recent contribution

The results and findings of several new randomized clinical trials (RCT) confirmed previous data about beneficial effects of influenza vaccination on the clinical course of CHD [5,6] (Table 2). The number of patients observed in randomized trials increased significantly thus enabling the effect of vaccination on mortality to be

evaluated. Clar et al. in a meta-analysis of more than 12 thousand patients from 8 RCTs found a significant reduction in cardiovascular mortality among patients vaccinated against influenza: RR 0.45 (95%CI 0.26–0.76), $p = .003$ [7].

Heart failure is a growing epidemiological problem of populations in developed countries. The overlap between pulmonary congestion, respiratory infection and decompensation of chronic HF is evident and intuitive for clinicians. The guidelines for the prevention and treatment of acute and chronic HF recommend both influenza and pneumococcal vaccination invariably and for the longest period [11]. Recently, Mohseni et al. published an elegant self-controlled study on a large population with HF and found that during a year after a patient was vaccinated against influenza, the risk for hospitalization due to CVD was significantly lower than in a year a p. was not vaccinated: IRR 0.73 (0.71–0.76) [12] (Table 2).

The *post hoc* analysis of the PARADIGM-HF Trial, which recently introduced neprilysin inhibitor to HF treatment, also confirmed that influenza vaccination was associated with a lower risk for all-cause mortality: HR 0.81 (0.67–0.97), $p = .015$ [13] This study gives us also information about the real rate of vaccination against influenza among HF patients across the world. It varies significantly being nearly 80% in Holland and Great Britain through 10–30% in such countries as Slovakia, Brasil and Korea to less than 2% in China, Russia and Bulgaria.

2.2. Lack of evidence and study direction

The burden of CVD and particularly HF represents a large number of various pathologies and it remains unclear how etiology,

Table 2

Significant studies evaluating the effect of influenza and pneumococcal vaccination on the course of cardiovascular diseases published in recent years. Abbreviations: CHD - coronary heart disease, HF - heart failure, LVEF - left ventricle ejection fraction, ACS - acute coronary syndrome.

Publication	Methods and study group	Results
Phrommintikul A et al. Eur Heart J 2011;32 (14):1730–5	Prospective randomized clinical trial.439 CHD p. (32% p. with HF)	Influenza vaccination: Reduction of Coronary Events: 9.5% vs 19.3%, RR 0.70, 95%CI 0.57–0.86
Clar et al. Cochrane Database 2015; Issue 5. Art.No: CD005050	Meta-analysis of randomized clinical trials. 12,029p. with CHD	Influenza vaccination: Reduction of cardiovascular mortality: RR 0.45, 95%CI 0.26–0.76
Vardeny O et al. JACC Heart Fail 2016;4:152–8	Post-hoc PARADIGM_HF Trial 8099p with LVEF ≤ 40%	Influenza vaccination: Reduction of all-cause mortality: HR 0.81;95%CI: 0.67–0.97
Mohseni H et al. Eur Heart J 2017;38:326–33	Self-controlled 59,202p with HF	Influenza vaccination: Reduction of cardiovascular hospitalization: HR 0.73, 95%CI: 0.71–0.76 Reduction of hospitalization due to respiratory infection: HR 0.83; 95% CI: 0.77–0.90
Wu W-C et al. Am Heart J 2014;168:713–20	Retrospective study 107,045p with LVEF ≤ 40%	Pneumococcal vaccination: Reduction of one-year mortality: AOR 0.77, 95%CI:0.62–0.96 Influenza vaccination: Reduction of 30-day mortality: AOR 0.51, 95%CI: 0.51–0.77 and one-year mortality: AOR 0.75, 95% CI: 0.58–0.96
Lamontagne F et al. CMAJ 2008;179(8):773–7	Case-control 4995 p with high cardiovascular risk	Pneumococcal vaccination: Reduction of ACS incidence: OR 0.53, 95%CI: 0.40–0.70
Ren S I et al. Open Heart 2015;2:e000247	Meta-analysis of observational studies 230,426p with ACS	Pneumococcal vaccination: Reduction of ACS incidence in p ≥ 65 years old: OR 0.83, 95%CI: 0.71–0.97
Siriwardena AN et al. CMAJ 2010;182(15): 1617–23	Case-control 16012 p with first Myocardial Infarction	Influenza vaccination: Reduction of Myocardial Infarction: OR 0.81, 95%CI 0.77–0.83 Pneumococcal vaccination: negative result No effect on Myocardial Infarction: OR 0.96, 95%CI 0.91–1.02
Ochoa-Gondar O et al. Vaccine 2014;32:252–7	Prospective cohort study, 27,204p, age > 60 years	Pneumococcal vaccination: negative study No effect on all-cause death: HR:0.97, 95%CI: 0.89–1.05 and no effect on risk of Myocardial Infarction HR:0.95, 95%CI: 0.76–1.18

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