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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.

Contents

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 morality 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
Phromminticul 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 $\leq$ 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 $\leq$ 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 $\geq$ 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

functional or demographic status modify the effect of influenza vaccination. Data analysis from different studies shows that the beneficial effect of influenza vaccination is more pronounced in the atherosclerotic etiology, especially after recent ACS or coronary intervention [5,14]. Most HF studies have been focused on patients with reduced left ventricular ejection fraction (EF). As now the population of patients with HF and preserved left ventricular function is observed to increase abruptly, there is a large gap in data concerning this group of patients. Another problem defined in recent years is that HF is often accompanied by a depressed immune response. Vardeny et al. suggest that upregulation of the sympathetic nervous system in HF, via modulation of beta2 adrenergic receptors decreases the antibody immune response [15]. Thus a high-dose influenza vaccination in HF has been proposed and remains under clinical and immunological evaluation [16]. Interestingly, Sribhutorn et al. found that beta-blockers, which reduce the sympathetic upregulation in HF, significantly improve the effect of influenza vaccination in HF [17].

Respiratory infections have important seasonal variations in many countries. Thus the beneficial effect of vaccination may be different in different years, may depend on the time of vaccination and may be limited only to the epidemic season. Siriwarenda et al. noticed that early vaccination (September – mid-November in the northern hemisphere) protected against acute myocardial infarction significantly better than later vaccination (after mid-November) (OR 0.90, 95% CI 0.82–1.00, p = .42), and that repeated vaccination (consecutive 5 seasons) protected better than vaccination only during the current season [8]. The duration of the protective effect of influenza vaccination against cardiovascular events remains a subject of controversy. In many studies, it is up to 12 months long and extends the influenza epidemiological season [6,8,14]. In other studies it is restricted to the epidemiological season [18]. The hypothetic pleiotropic effect of vaccination is discussed in section “The specific mechanism”.

Another problem, still unresolved, is a theoretically possible difference between countries with vs those without seasonal variations of influenza or pneumococcal infections. In their study from Thailand, Phrommintikul et al. reported a significant reduction in MACE (HR 0.70:0.57–0.86, p = .004) and no effect on mortality, in patients after recent ACS vaccinated against influenza [6]. In this study, as in other countries from tropical regions, patients were vaccinated along the whole year and the authors failed to mention any differences in the number of events between the rainy and dry seasons.

3. Pneumococcal vaccination

3.1. Recent contribution

Streptococcus pneumoniae (Str.pneumoniae) is a leading cause of community-acquired pneumonia and hospitalization due to respiratory infections [19]. Many epidemiological studies have shown a 2–8-fold increase of ACS, HF and of the incidence of arrhythmia in a short-term period after pneumonia [3,19]. Some studies have also shown a long-term, up to 10 years, increased risk for cardiovascular events after pneumonia and postulated pneumonia to be considered a new independent cardiovascular risk factor [10].

It is important to mention that there have been no prospective RCTs evaluating the effect of pneumococcal vaccination on clinical course of cardiovascular diseases and many studies have had negative results [8,21]. The recommendations for pneumococcal vaccination in patients with CVD are based on consensus of experts’ opinion and retrospective epidemiological studies [3,10]. Recently Wu et al., in a large study of 1,07,045 patients with HF, reported that pneumococcal vaccination was associated with a significant reduction of one-year mortality: AOR 0.77, 95%CI:0.62–0.96 [20]. However Siriwarenda et al. and Ochoa-Gondar et al. in their large negative studies found no effect of pneumococcal vaccination on the mortality and on the risk for myocardial infarction [8,9]. As protective antibodies titers after pneumococcal vaccination are present for several years, guidelines recommend revaccination each 5 years. In studies with positive results beneficial effect of vaccination begins in second year after vaccination and is driven be the older population [10,16,20] .

3.2. Lack of evidence and study direction

Since the importance of Evidence Base Medicine is constantly growing, the lack of RCTs evaluating the effect of pneumococcal vaccination on the course of CVD creates an important problem, as some studies yield negative or conflicting results [8–10]. Experts agree that there is a need for large prospective RCTs evaluating the effect of pneumococcal vaccination in p. with established CVD (secondary prevention) and in patients with cardiovascular risk factors (primary prevention). Patients in such studies should represent a large spectrum of CVDs, particularly: ischemic vs nonischemic etiology, arrhythmias, p. with preserved vs reduced EF. As the previous studies were usually focused on older population, special attention should be paid to the results of future studies on population under 65 years of age. There is a shortage of information about the effect of vaccination between countries with seasonal and those without seasonal variations of pneumonia. Such a difference may be influenced by different geographical serotype distributions, or also differences in vaccine uptake and surveillance systems [21].

4. The mechanism of a possible cardioprotective effect of influenza and pneumococcal vaccination on the heart and the cardiovascular system

There are two possible mechanisms of a protective effect of influenza and pneumococcal vaccination on the heart and on the course of CVD (Fig. 1).

The unspecific mechanism considers influenza and pneumococcal pneumonia as two most common worldwide acute infections associated with a sudden onset of fever, tachycardia, dehydration, hypoxemia, endothelial dysfunction, hypercoagulation and bolus secretion of pro-inflammatory mediators. Such a stress may be devastating for patients with chronic HF or angina on optimal pharmacological treatment as well as for asymptomatic individuals with depressed left ventricular function or severe coronary stenosis. In such patients acute infection frequently causes acute heart failure, pulmonary edema or destabilization of angina with ACS or sudden cardiac death [5,10,12]. The unspecific mechanism was recently strongly supported by the inflammatory theory of atherosclerosis and the theory of thin-cap fibroatheroma rupture as a cause of ACS [22,23]. Atherosclerosis is no longer considered a degenerative disease, but as an inflammatory process of the arterial wall driven by LDL-cholesterol intimal infiltration and macrophages activation. It is a chronic process with stable periods, as well as intervals of acute destabilization, formation of vulnerable plaque leading to ACS. The results and findings of these studies have made CRP and other mediators of inflammation become novel cardiovascular risk factors better reflecting mid- and short-term risks for myocardial infarction than the cholesterol level does [24]. Pro-inflammatory cytokines released during the atherosclerotic process have several different cardiac and vascular effects. They cause leukocytes migration and differentiation (CRP), depressed NO secretion (sphingomyelinase), direct depression of contractility (TNF- , interleukin-1), rupture of unstable plaque and cardiac remodeling (metalloproteinases) [24]. The unspecific

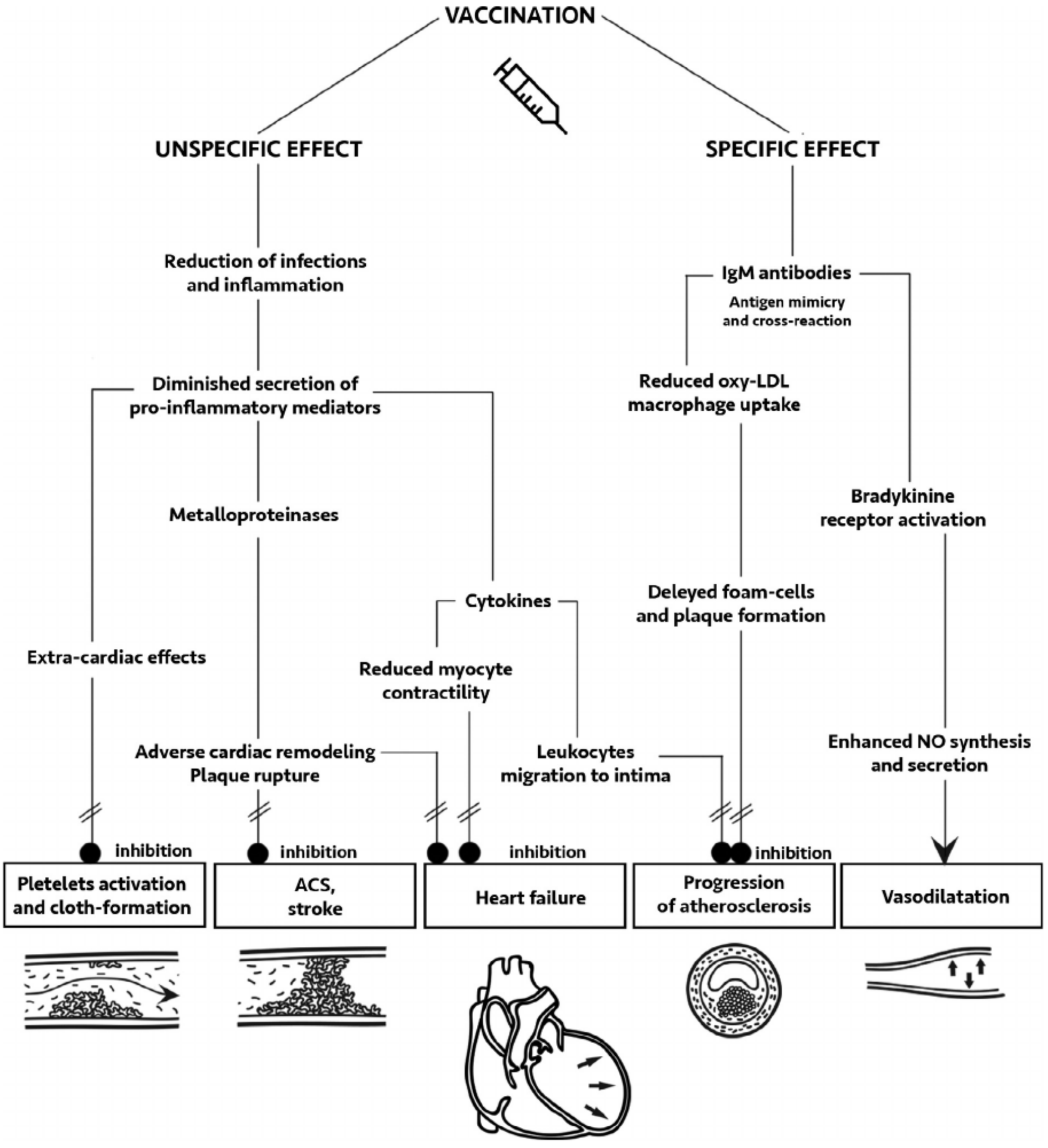

Fig. 1. Proposed cardioprotective mechanism of influenza and pneumococcal vaccination.

protective effect of vaccination is then associated with the elimination of most common infections which may destabilize the chronic atherosclerotic inflammation of the arterial wall by sudden activation of an inflammatory cascade. Several studies have also reported an increased risk for cardiovascular complications after urinary, gastrointestinal and peridental infections. A good resume of the unspecific mechanism is an interesting concept of a cumulative "infectious burden" as a risk factor of cardiovascular events [25].

The specific mechanism assumes particular immunogenic properties of the influenza virus and *Str. pneumoniae*. Most studies on influenza vaccination in patients with CHD have surprisingly found that the protective effect of vaccination was not restricted to flu season. The number of cardiac events in vaccinated patients was also reduced in summer months and extended to the next vaccination time covering a period generally free from virus circulation [5,6,12]. In order to explain this pleiotropic effect Madjid and Naghavi proposed an "antigen mimicry" between influenza virus and the antigens of atherosclerotic plaque [26]. Other authors found correlations between titers of antibodies against influenza hemagglutinin A and antibodies to oxidized LDL-lipoproteins in p. with rapid progression of atherosclerosis and suggested that this autoimmune "cross-reaction" was a link between influenza and atherosclerosis [27]. Some experts have serious doubts about the pleiotropic effect of vaccination and suggest that an extension of the beneficial effect of influenza vaccination may be related to the "healthy user" effect or biased methodology.

Str. pneumoniae is also a potent antigen which may interact with the immuno-inflammatory mechanism of atherosclerosis. Binder et al. reported in an animal model a 40% reduction of atherosclerotic plaque after pneumococcal vaccination [28]. Lamontage et al. found in a clinical case-control study that vaccination against pneumococcal pneumonia significantly reduced the

risk for ACS development (OR 0.53, 95%CI: 0.40–0.70) [29]. The authors proposed "antigen mimicry" between oxidized LDL and *Str. Pneumoniae* as an explanation of the phenomenon observed. According to the authors, IgM antibodies against *Str. pneumoniae* arisen after vaccination recognized also oxidized LDL and reduced their uptake by macrophages, which decelerated plaque formation and progression. Despite several years having elapsed since their publication, these results were not confirmed by other authors, however they contribute to the appreciation of the role of the adaptive and innate immunity in atherosclerosis.

5. The "healthy user effect

The majority of data on influenza vaccination, and practically all data on the influence of pneumococcal vaccination on the clinical course of CVD derive not from RCTs but from retrospective and epidemiological studies. Many experts emphasize the substantial difference between vaccinated and unvaccinated population of these studies. Vaccinated persons, so called "healthy-users" represent health-promoting behavior which affects not only vaccination but also physical activity, nutrition, personal care, frequent medical contacts and thousands of daily unconscious decisions that may not be eliminated even by sophisticated propensity statistical methods. In such a situation the results of published studies should be treated with caution and special attention to the methodology and potential biased evaluation.

6. Closing remarks

For scientists, the large area is still unrecognized and many questions remain unanswered. Yet, as clinicians, we should rely on the majority of published results and guidelines that shows beneficial effects of influenza vaccination on patients with CVD. The efficacy of pneumococcal vaccination remains not well proved as many studies had negative results and there were no RCTs in this field. However, a higher rate of cardiovascular mortality and morbidity following pneumococcal pneumonia is well documented and consistent with clinical experience and expert opinions [3,8]. Vaccination is a low-cost potentially lifesaving procedure. We can expect that due to increasing antibiotic-resistance and aging of the population the role of vaccination will grow rapidly and should become a first line of prevention of avoidable infections and their cardiovascular complications. For many countries seeking the reduction of health-care costs, influenza and pneumococcal vaccinations in high risk patients remain a missed opportunity. The results observed in the countries and organizations that reached in p. with heart failure a vaccination rate of nearly 80% for influenza (Holland, Great Britain) and nearly 90% for pneumococcal pneumonia (US Veterans Health Administration) point that successful models are available and waiting for implementation.

Conflict of interest

I declare no conflict of interest.

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