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Beneficial Effects of Vaccination on Cardiovascular Events: Myocardial Infarction, Stroke, Heart Failure

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Coronary artery disease · Heart failure · Myocardial infarction · Stroke · Vaccination

Abstract
Influenza and pneumococcal infections have been suggested to be potential risk factors for causing adverse cardiovascular events, especially in high-risk patients. Vaccination against respiratory infections in patients with established cardiovascular disease (CVD) could serve as a potential cost-effective intervention to improve their clinical outcomes and cardiac societies have encouraged it. Previous studies have shown that influenza vaccination reduce mortality, acute coronary syndromes and hospitalization in patients with coronary heart disease (CHD) and/or heart failure (HF). However, there is a paucity of randomized prospective clinical trials in the field of the pneumococcal vaccination, and additional higher-quality evidence is needed. Furthermore, questions around the role of vaccination in the primary prevention of CVD, the optimal dose and timing are largely unanswered. The pathophysiologic mechanism in which vaccination provides cardiovascular protection may be related to the modification of the immune-inflammatory model of atherogenesis. The present review summarizes the current evidence and understanding for vaccination against influenza and *streptococcus pneumoniae* in CHD, HF and stroke and highlights its beneficial effect in the reduction of adverse cardiovascular events.

Introduction

Cardiovascular disease (CVD) is among the leading causes of morbidity and mortality worldwide, especially among the elderly population [1]. In addition to conventional culprits, such as smoking, obesity, hypertension, diabetes and dyslipidaemia, influenza and pneumococcal infections have been suggested to be potential risk factors [2–4]. CVD is more common in the winter and during influenza epidemics, which could partially be explained by temperature-induced vascular damage [5]. However, mounting evidence suggests that influenza itself could trigger adverse CV events, further adding to the infection – associated morbidity and mortality.

The mechanisms by which influenza increases the risk of CV events may be related to pro-inflammatory media-

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tors, sympathetic stimulation and the activation of the coagulation cascade that may trigger rupture of vulnerable atherosclerotic plaques. Contributing factors may include the higher metabolic demand due to adrenergic surge and hyperdynamic CV response as well as potential compromise of oxygenation due to pulmonary infection. Moreover, influenza has been shown to cause myocardial dysfunction directly, possibly through increases in pro-inflammatory cytokines 23 [6, 7].

Influenza vaccination is a well-established strategy to reduce influenza-related illness [8, 9]. Scarce evidence has been available to establish whether influenza vaccination has a role to play in the primary prevention of CVD; nevertheless, the potential benefit in high-risk CV populations is reflected in current recommendations. According to the World Health Organization, influenza vaccination aims primarily at protecting vulnerable high-risk groups, including those of older age or with certain chronic conditions, against severe influenza-associated disease and death [10]. Both the American Heart Association/American College of Cardiology and the European Society of Cardiology recommend the influenza vaccine annually for individuals with established CVD [11–13]. The efficacy of pneumococcal vaccination has not been well established, mainly due to the lack of prospective randomized clinical trials (RCTs) and the negative results of many studies in this field [14–15]. The recommendations for pneumococcal vaccination in patients with CVD are based on the consensus of experts' opinion and retrospective epidemiological studies. A summary of major findings of randomized control trials and meta-analyses evaluating the effect of respiratory vaccination on CV disease is listed in Tables 1 and 2 respectively.

Table 1. RCTs evaluating the effect of influenza on CVD

Publication	Study design	Study group/subjects, *n*	Control group/ follow-up	Vaccination type	Results
Gurfinkel et al. [35], Eur Heart J 2004;25: 25–31 (FLUVACS)	Prospective RCT	Inpatients MI within the first 72 h and planned PCI/200 and 101	No vaccination/ 12 months	Influenza	Vaccine group vs. control group: reduction of the primary endpoint (CV death; 6 vs. 17%, RR 0.34 [95% CI 0.17–0.71], $p = 0.002$)
Ciszewski et al. [36], Eur Heart J 2008;29: 1350–1358 (FLUCAD)	Prospective RCT	Outpatients CAD/658	Placebo/298 days	Influenza	Vaccine group vs. control group: No difference in the primary endpoint (CV death; 0.63 vs. 0.76%, HR 1.06 [95% CI 0.15–7.56], $p = 0.95$);reduction of coronary ischaemic event (MACE or hospitalization for myocardial ischaemia; 6.02 vs. 9.97%, HR 0.54 [95% CI 0.29–0.99], $p = 0.047$)
Phrommintikul et al. [37], Eur Heart J 2011;32:1730–1735	Prospective RCT	Inpatients ACS within 8 weeks/439	No vaccination/ 12 months	Influenza	Vaccine group vs. control group: reduction of the primary endpoint (combined MACE, including death and hospitalizations from ACS, HF and stroke; 9.5 vs. 19.3%, unadjusted HR 0.70 [95% CI 0.57–0.86], $p = 0.004$); No significant difference in the incidence of CV death (2.3 vs. 5.5%, unadjusted HR 0.39 [95% CI 0.14–1.12], $p = 0.088$)
Vardeny et al. [50], JACC Heart Fail 2016;4:152–158	Post-hoc PARADIGM – HF trial	Symptomatic HF, LVEF ≤40%/8,099	No vaccination (1,769 vaccinated vs. 6,630 non-vaccinated pts)/12 months	Influenza	Influenza vaccination: Reduction of all-cause mortality (HR 0.81 [95% CI 0.67–0.97], $p = 0.015$)

CVD, cardiovascular disease; RCT, randomized clinical trial; MI, myocardial infarction; PCI, percutaneous coronary angioplasty; CV, cardiovascular; CAD, coronary artery disease; MACE, major cardiovascular events; ACS, acute coronary syndrome; HF, heart failure.

Coronary Heart Disease

Atherosclerosis is considered not only a disorder of lipid accumulation in the arterial wall but mainly an immune-mediated inflammatory disease, with both the innate and adaptive immune systems responding to various endogenous and exogenous antigens [16–18]. It is a chronic process with periods of acute destabilization and formation of vulnerable plaques leading to acute coronary syndrome (ACS). Over the last years, our understanding of the pathophysiology of ACS has changed from plaque rupture to the novel definitions of plaque erosion and "calcified nodule," a rare type of coronary thrombosis related to disruptive nodular calcifications protruding into the lumen [17]). Systemic inflammation

Table 2. Meta-analyses evaluating the effect of influenza and pneumococcal vaccination on CVD

Publication	Methods	Study group/subjects, *n*	Vaccination type	Results
Udell et al. [38], JAMA 2013;310: 1711–1720	Meta-analysis of 12 RCTs	Subjects at high risk of CV disease/6,735	Influenza	Influenza vaccination: reduction of a composite of MACE (RR 0.64 [95% CI 0.48–0.86], $p = 0.003$)
Clar et al. [39], Cochrane Database Syst Rev 2015; CD005050	Meta-analysis of 8 RCTs	Subjects with or without CV disease/12,029	Influenza	CV mortality was reported by 4 secondary prevention trials – Influenza vaccination: reduction of CV mortality (RR 0.45, [95% CI 0.26–0.76], $p = 0.003$)
Tsivgoulis et al [58], J Neurol Sci 2018;386: 12–18	Meta-analysis of 12 studies (5 RCTs and 7 prospective observational studies)	Subjects with or without CV disease/543,311 (47.4% vaccinated)	Influenza in 8 studies Pneumococcal in 2 studies Both in 2 studies	Influenza vaccination: reduction of IS (RR 0.87, [95% CI 0.79–0.96] $p = 0.004$); Pneumococcal vaccination: no association (RR 1.38, [95% CI 0.60–3.16], $p = 0.45$)
Ren et al. [41], Open Heart 2015;2: e000247	Meta-analysis of 8 observational studies	ACS/230,426	Pneumococcal	Pneumococcal vaccination: reduction of ACS events in pts ≥65 years (pooled OR 0.83 [95% CI 0.71–0.97], $I^2 = 77.0\%$)

CVD, cardiovascular disease; RCT, randomized clinical trial; CV, cardiovascular; MACE, major cardiovascular; IS, ischaemic stroke; ACS, acute coronary syndrome.

in patients with autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis, gout, psoriatic arthritis, and medium and large vessel vasculitis has been linked to an increased risk of premature coronary heart disease (CHD) and stroke that associates with the degree of inflammation [19]. Even non-cardiac sarcoid affects the heart by reducing coronary flow reserve [20]. Atherosclerosis likely underlies the majority of CV events in patients with autoimmune diseases.

It has been demonstrated that after an acute myocardial infarction (MI) or stroke, atherosclerotic plaques at a distance grow faster and display higher protease activity. This phenomenon persists for several months after the acute event and is driven by an increased supply of innate immune cells [21]. Systemic inflammation leading to plaque growth and instability is also the major determinant of increased CV risk after cardiac and non-cardiac major surgery [22]. Even psychosocial stress causes chronic low-grade systemic inflammation through the crosstalk between the brain and immune system, worsens atherosclerosis and increases CV risk [23].

Infections, as a stimulus of inflammation, have long been linked to the genesis, progression and instability of atherosclerotic plaques [24]. Multiple infectious agents, including influenza, have been shown to induce local proatherosclerotic mechanisms, such as expression of adhesion molecules, production of monocyte chemoattractant protein-1, oxidation of LDL, that lead to activation of endothelium, migration of leucocytes and eventually formation of lipid core [24–27]. Infections have also been associated with increased smooth muscle cell proliferation in the vessel wall that contributes to plaque progression [24]. In an animal model of atherosclerosis, it has been shown that influenza infection promotes inflammation, smooth muscle cell proliferation, and fibrin deposition in atherosclerotic plaques, similar to unstable plaques after MI [28]. Coronary artery tone abnormalities may also be involved in the pathogenesis of CV complications, as bacterial exotoxins have been shown to provoke coronary vasoconstriction and loss in myocardial contractility in perfused rat hearts, an effect largely attributable to the generation of thromboxane [29]. In patients hospitalized for community-acquired pneumonia, increased in vivo platelet activation and serum thromboxane B2 overproduction may explain the increased incidence of MI as an early complication of pneumonia, and aspirin 100 mg/day seems insufficient to mitigate thromboxane biosynthesis [30].

Systemic factors as fever, dehydration, tachycardia, increased cardiac metabolic demands, hypoxemia and de-

creased blood pressure (i.e., in severe sepsis) may contribute to the development of myocardial ischaemia by diastole shortening, impaired myocardial perfusion through stenotic coronary segments, adrenergic surge, endothelial dysfunction and hypercoagulability [7, 18].

A fourfold higher risk of MI, stroke and fatal CHD has been described in the first 30 days after pneumonia hospitalization, which declines progressively but remains elevated for up to 10 years [31]. In a self-controlled case series study (cases acted as their own control in periods when not exposed) of more than 22,000 patients, the risk for acute MI during the first 3 days after medical contact for acute respiratory infection was significantly increased (incidence ratio 4.19, 95% CI 3.18–5.53) [32]. In a case-control study of more than 11,000 cases of acute MI and an equal number of matched controls, the adjusted OR for acute MI risk in the 7 days following respiratory infection was 2.10 (95% CI 1.38–3.21), and the risk of stroke was doubled [33].

Whether influenza vaccination protects against future CV events was investigated in several nonrandomized and randomized controlled trials. A population-based case-control study, reported that after adjusting for demographic, clinical and behavioural risk factors, influenza vaccination was associated with a reduction (OR 0.51, 95% CI 0.33–0.79) in risk of out-of-hospital primary cardiac arrest [34]. The Flu Vaccination ACSs study randomized 301 patients to receive the influenza vaccine versus no vaccination in patients admitted for MI or planned percutaneous coronary intervention in Argentina during flu season [35]. The primary endpoint of CV mortality was lower in the vaccination group (2 vs. 8%, relative risk [RR] 0.25, 95% CI 0.07–0.86), and this effect was significantly evident at 1-year follow-up (6 vs. 17%, RR 0.34, 95% CI 0.17–0.71). The same was true for the composite of major CV events (MACE), defined as CV death, nonfatal MI or rehospitalization for ischaemia (11 vs. 23%, RR 0.50, 95% CI 0.29–0.85 at 6 months and 22 vs. 37%, RR 0.59, 95% CI 0.40–0.86 at 1-year follow-up). The greater benefit with flu vaccination was observed in patients at high risk according to the TIMI score, and those with non-ST-segment deviation MI [35]. The Influenza Vaccination in Secondary Prevention from Coronary Ischemic Events in Coronary Artery Disease (FLUCAD) trial showed a reduction in the composite of MACE or hospitalization for myocardial ischaemia (HR 0.54, 95% CI 0.29–0.99) in 658 Polish patients with known CHD but failed to show any difference in CV death (HR 1.06, 95% CI 0.15–7.56) [36].

Another randomized placebo-controlled trial of 439 post-ACS patients found that the primary endpoint of MACE, including death, hospitalization from ACSs, hospitalization from heart failure (HF), and hospitalization from stroke, occurred less frequently in the influenza vaccine group than that in the control group (9.5 vs. 19.3%, unadjusted HR 0.70 [0.57–0.86], $p = 0.004$), a result that was driven primarily by a reduction in hospitalization for ACS [37]. CV death was not significantly different between groups (2.3 vs. 5.5%, unadjusted HR 0.39 [0.14–1.12], $p = 0.088$) [37]. This finding was supported by a meta-analysis of 12 RCTs that followed 6,735 high-risk patients for a mean duration of 7.9 months [38]. In the subgroup of patients with recent (≤1 year) ACS ($n = 815$), influenza vaccine significantly reduced MACE (risk ratio 0.46, 95% CI 0.33–0.64, $I^2 = 0\%$) but not CV death (risk ratio 0.44, 95% CI 0.17–1.15, $I^2 = 38\%$), whereas there was no difference in MACE or CV death in the pre-specified subgroup of patients with stable CHD ($n = 840$) [38].

A subsequent Cohrane Collaboration meta-analysis of 12.029 patients with CHD from 8 RCTs reported a significant reduction in CV mortality among patients vaccinated against influenza (RR 0.44, 95% CI 0.26–0.76, $I^2 = 0\%$) [39]. However, there was no difference in CV death in the subgroup of patients with ACS ($n = 350$; risk ratio 0.46, 95% CI 0.04–5.20, $I^2 = 58\%$) or stable angina and elective percutaneous coronary intervention ($n = 602$; risk ratio 0.35, 95% CI 0.07–1.73, $I^2 = 0\%$) [39]. Of note, despite including the same 4 RCTs, the results of the 2 above-mentioned meta-analyses were not identical. A possible explanation could be the small sample sizes and the variable outcome reporting of the original studies [40].

In a meta-analysis of observational studies, pneumococcal vaccination was associated with a significantly lower risk of ACS events, but not stroke, in patients 65 years and older [41]. However, other studies failed to show any beneficial effect of pneumococcal vaccination on the risk for MI and that there have been no prospective RCTs evaluating the effect of pneumococcal vaccination on the clinical course of CVD [14, 15].

Heart Failure

Respiratory infection is a significant cause of decompensation and hospitalization among HF patients and is associated with increased in-hospital mortality [42]. Remarkably, 32.2% of patients admitted for pneumonia have CV events in the following 30 days and the risk of

death due to these complications is 5.5 times higher, with prior HF being a strong independent risk factor [43]. It has also been demonstrated in patients with community-acquired pneumonia that most cardiac complications were diagnosed within the first week after presentation and more than half of them were recognized in the first 24 h [44]. All the studies about cardiac complications during community-acquired pneumonia hospitalizations have clearly shown a much higher risk of HF compared with MI [45].

The benefits of influenza vaccination in secondary prevention of CHD have been previously mentioned. However, the evidence of influenza and pneumococcal vaccination in the HF population is less well proved, as most vaccination trials have either not enrolled HF patients or not assessed impact in an HF cohort sub-study.

Large epidemiological studies support influenza vaccination-induced prevention of HF hospitalization in the elderly [46, 47]. A previous observational population-based study examined the clinical impact of influenza vaccination on patients with a diagnosis of CHD and/or ischemic HF and reported an independent association of vaccination with reduced risk of heart disease-related hospitalizations only during influenza seasons [48]. A recent self-controlled case series study among 59.202 HF patients in England between 1990 and 2013 found that influenza vaccination was associated with a lower risk of hospitalization due to CV disease (incidence rate ratio [95% CI] 0.73 [0.71–0.76]), including hospitalizations for HF [49].

The post hoc analysis of the PARADIGM-HF Trial, demonstrated that influenza vaccination was associated with a lower risk for all-cause mortality (HR 0.81 [0.67–0.97], $p = 0.015$), whereas in propensity adjusted models, the composite outcome of CV death and HF hospitalization did not reach statistical significance [50]. Perhaps limited long-term follow-up could explain these findings. The post hoc analysis reported influenza vaccination rates of only 21% in the overall study cohort of over 8,000 participants and provided us with interesting data about the variation of influenza vaccination rates among HF patients across the world, being highest in the Netherlands (77.5%), Great Britain (77.2%) and Belgium (67.5%), intermediate in the United States (53%), 10–30% in countries as Slovakia, Brasil and Korea and less than 2% in China, Russia and India. Significant predictors of vaccination included older age and lower NYHA functional class [50].

With regard to the clinical outcomes of pneumococcal vaccination in HF patients, there is a paucity of high-level evidence, requiring further research.

Stroke

Increasing evidence suggests that infection is an independent risk factor for ischemic stroke (IS). Increased risk for cerebrovascular ischaemia after a recent infection has been associated with impairments in the protein C pathway and endogenous fibrinolysis [51]. In an experimental model of infected mice, influenza virus was found to trigger a cytokine cascade that aggravates ischemic brain damage and increases the risk of intracerebral haemorrhage after tissue plasminogen activator treatment [52].

A prospective case-control study involving 11 Italian stroke units indicated that early previous infections are reported in approximately 1 out of 10 patients hospitalized for acute IS [53]. Data from the South London Stroke Register, a prospective population-based stroke registry between 1995 and 2004, suggested a seasonal trend for IS with a significant increase in incidence within 2 weeks after influenza infection [54]. A case-control study demonstrated that recent respiratory tract infections were significantly associated with an increased risk of large-vessel and/or cardioembolic IS, especially in patients without vascular risk factors, as well as with a more severe neurological deficit on admission [55].

A recent retrospective, population-based case-control study suggested that influenza vaccination is associated with reduced IS and MI risks in an elderly population aged ≥65 years, including those with influenza-like illness [56]. Data from the Taiwan National Health Insurance Research Database revealed that influenza vaccination was an independent protective factor and dose-dependently reduced the risk of IS in patients with atrial fibrillation who have risk factors for IS, irrespective of age, sex, hypertension, heart disease or anticoagulant use [57]. Our recent meta-analysis of RCTs and prospective observational studies indicated that influenza vaccination may be associated with a lower risk of IS (RR 0.87, 95% CI 0.79–0.96, $p = 0.004$) [58]. This finding was not reproduced for pneumococcal vaccination or the combination of the 2 vaccines [58]. Further randomized controlled trials are needed to confirm the protective effect of influenza and pneumococcal vaccination on the risk of stroke.

Potential Cardiovascular Protective Mechanisms of Influenza and Pneumococcal Vaccination

Numerous mechanisms support a causal association between acute respiratory infection and CV events: an increase in pro-inflammatory, prothrombotic cytokines,

endothelial dysfunction, stimulation of platelet activity, increased shear force, induction of procoagulant activity and inhibition of anticoagulant mechanisms, reduction in the clotting time, increase in the expression of tissue factor, increased plasma viscosity, loss of the anti-inflammatory properties of HDL particles, increase in trafficking of macrophages into the arterial wall, release of endogenous catecholamines, tachycardia, psychological distress, dehydration, hypoxemia [6, 7, 24]. The protective effect of vaccination is associated with the prevention of respiratory infections and the associated stresses [6, 18].

Furthermore, the cardioprotective effect of vaccination may be related to the modification of the immune-inflammatory model of atherosclerosis [18]. This specific mechanism based on studies that reported a protective effect of vaccination beyond the flu season, assumes specific immunogenic properties of the influenza virus and streptococcus pneumonia. An "antigen mimicry" between the infectious agents and antigens of the atherosclerotic plaque has been proposed [7, 18]. Recently, the bradykinin 2 receptor was identified as a principal host protein that could mediate molecular processes underlying the cardioprotective effect of influenza vaccine [59]. It has been suggested that some antibodies elicited by influenza vaccines act as agonists, which activate a bradykinin 2 receptor-associated signalling pathway contributing to the protection against CVD [59]. Pneumococcal vaccination leads to the production of IgM antibodies that share binding sites with anti-oxidized LDL antibodies [60]. In murine models, this molecular mimicry may slow the macrophage uptake of oxidized LDL, a process of foam cell and plaque formation [61, 62].

Respiratory infection-induced inflammatory process may also impair inotropy [60]. The production of TNF-α and interleukin-1 beta during acute illness can independently depress myocyte contractility [63, 64]. Moreover, sustained cytokine expression can lead to adverse myocardial remodelling and excess production of tissue inhibitors of matrix metalloproteinases [60]. These mechanisms have been associated with left ventricular dilatation and increases in myocardial collagen content, contributing to the HF phenotype [60]. Infection-related changes in cardio-renal function may exaggerate fluids shift, leading to volume overload and subsequently HF manifestation or decompensation [65]. Furthermore, histological evidence of myocarditis and myocardial necrosis has been demonstrated in patients following influenza-related deaths [66]. A direct link between vaccination-related attenuation in inflammation and atherosclerosis and the HF phenotype has not been yet firmly proved, though it would be assumed to reduce the progression of ischemic cardiomyopathy [60]. Further investigation is needed to shed light to the distinct effects of vaccination in those with ischemic versus non-ischemic cardiomyopathy [60].

When considering findings from previous retrospective and epidemiological studies on influenza vaccination and CVD, special attention should be paid to potential biased evaluation because of the differences between vaccinated and unvaccinated persons in terms of health consciousness. Vaccinated persons, the so-called healthy-users, represent a population with a higher level of education and a health-promoting behaviour, which apart from vaccination, affects nutrition, physical activity and medical contacts [18]. Such bias referred to as healthy user or healthy adherer effect is challenging to adjust for statistically.

Future Directions

The best dose for influenza vaccination remains unclear. Recently, a high-dose formulation is approved in the United States and Canada for medically stable individuals over the age of 65 years. HF results in an upregulated sympathetic nervous system. There is evidence that the sympathetic nervous system activation decreases immune response via the activation and modulation of beta2-adrenergic receptors (β2-AR) [67]. Human T and B lymphocytes express β2-AR. A direct catecholamine effect through β2-AR on cytokine gene regulation decreases responses to vaccines [68]. In vitro models show that increased β2-AR density suppressed IFNγ synthesis [67]. Therefore, it is logical that patients with HF demonstrate reduced vaccine responses as compared to healthy, age matched controls [69]. Of note, it has been shown that beta-blockers, which reduce the sympathetic upregulation in HF, significantly improve the effect of influenza vaccination in HF [70]. In a randomized pilot study of 28 patients with HF, individuals received either standard dose (15 μg/strain) versus double dose (30 μg/strain) influenza vaccine [71]. Double-dose vaccination produced significantly higher immunogenicity at 2–4 weeks, though at 4–6 months post-vaccination, absolute antibody titres were similar between standard and double dose groups but well above seroprotective levels [71]. This study did not assess dose response with respect to clinical outcomes, such as laboratory-confirmed influenza or HF exacerbation. A phase IIIb–IV, multicentre randomized, double-blind, active-controlled efficacy trial showed that

a high-dose, trivalent, inactivated influenza vaccine provided improved protection against laboratory-confirmed influenza illness among adults 65 years of age or older as compared with a standard-dose vaccine [72]. Clearly, there is need for large randomized trials to assess whether a high-dose vaccine strategy will be more effective in reducing CV hospitalization and mortality in CHD and HF patients.

Another unresolved clinical issue is the duration of CV protection after influenza vaccination. In some studies, it extends the epidemic season of influenza up to a year, whereas in other studies, it is limited only to the epidemic season [14, 36, 37, 73]. It has been noticed that early vaccination (September – mid-November in the northern hemisphere) protects against acute MI significantly better than later vaccination (after mid-November; OR 0.90, 95% CI 0.82–1.00, $p = 0.42$), and that repeated vaccination (consecutive 5 seasons) protects better than vaccination only during the current season [13].

Given that immune-mediated inflammation is a key feature of atherogenesis, it is tempting to consider active immunization as a novel approach against inflammation and atherosclerosis. The biggest challenge in this regard has been the identification of antigens that could play the role of targets for immunomodulatory therapy. Apart from vaccinations against exogenous infectious antigens described earlier, there are several studies exploring vaccinations against endogenous antigens, such as LDL and Apo-B, which may hold promise [16, 24, 74].

Conclusion

In patients with CVD, influenza vaccination may reduce CV mortality and MACE. However, available studies had a certain risk of bias and results were not always consistent, so there is a clear need for additional higher-quality data. Moreover, evidence for the primary protective effect of influenza vaccine is scarce. Confirmation of such a benefit could lead to more accurate recommendations for individuals with CVD risk factors. Similarly, there is a lack of large prospective RCTs evaluating the effect of pneumococcal vaccination on primary and secondary CVD prevention.

Nevertheless, given the aging of the population and increasing antibiotic-resistance, vaccination as an inexpensive and safe intervention may become a first-line strategy for the prevention of avoidable infections and their CV complications [18]. The low rates of vaccination call for effective, well-organized public health campaigns. Vaccination of ACS and HF patients even as part of in-hospital practice setting should be considered in order to achieve compliance with current treatment guidelines.

Disclosure Statement

The authors report no conflict of interest.

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