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Review Article

Vaccination: A Cost Effective Strategy for Prevention of Cardiovascular Events?

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Abstract

CV diseases are the leading cause of death globally, despite progress in non-invasive and invasive treatment strategies. Elderly patients > 65 are more prone to infections. Influenza and lower respiratory tract infections increase the risk of acute CV events, trigger AMI and HF exacerbations. Vaccination is an alternative approach to prevent the adverse impact of influenza infection and certain lower respiratory infections like pneumococcal pneumonia on myocardial contractility, fibrosis and atherogenesis. However, the trials addressing this issue are limited and give contradictory conclusions. The current review looks at the evidence available to answer the question.

Keywords: *Vaccination; Cardiovascular Disease*

Abbreviations

HF: Heart Failure; ACS: Acute Coronary Syndrome; AMI: Acute Myocardial Infarction; CV: Cardiovascular; TNF-α: Tumor Necrosis Factor-α; FLUVAC: Flu Vaccination; CAD: Coronary Artery Disease; HR: Hazard Ratio; CDC: Center for Disease Control: ACIP: Advisory Committee on Immunization Practices; IIV: Inactive Influenza Vaccine; STEMI: ST-Elevation Myocardial Infarction; PCV: Pneumococcal Conjugate Vaccine; PPV: Pneumococcal Polysaccharide Vaccine; LDL: Low-Density Lipoprotein

Introduction

Regardless of rapid progress in non-invasive and invasive treatment strategies, CV disease remains the leading cause of death globally. Atherosclerosis is the main cause of cardiac disease and inflammation plays a vital role in the atherosclerotic process, from initiation of atherosclerosis to progression and rupture of atherosclerotic plaques. Inflammatory process in atherosclerosis is multifactorial and involves mostly endogenous triggers, such as oxidized LDL cholesterol. Various infectious agents may act as exogenous agents in triggering atherosclerosis. Some of known pathogens are *Chlamydia pneumoniae*, herpes viruses, *Helicobacter pylori*, *Mycoplasma pneumonia, Porphyromonas gingivalis* and enterovirus [1,2].

Cardiac patients, especially elderly patients (> 65 years) are prone to infection. Use of vaccine is an alternative approach against infection and active immunization (vaccination) is probably the most effective method [3]. It provides secondary protection against CV diseases. The mechanism by which vaccination provides CV protection may be related to the modification of the immune and inflammatory model of atherogenesis [4].

Influenza as trigger for ACS

Trials have demonstrated association between influenza infection and AMI. In a meta-analysis of 16 studies, there was a significant association between recent respiratory infection and AMI depicted in figure 1, suggesting plaque disruption [5].

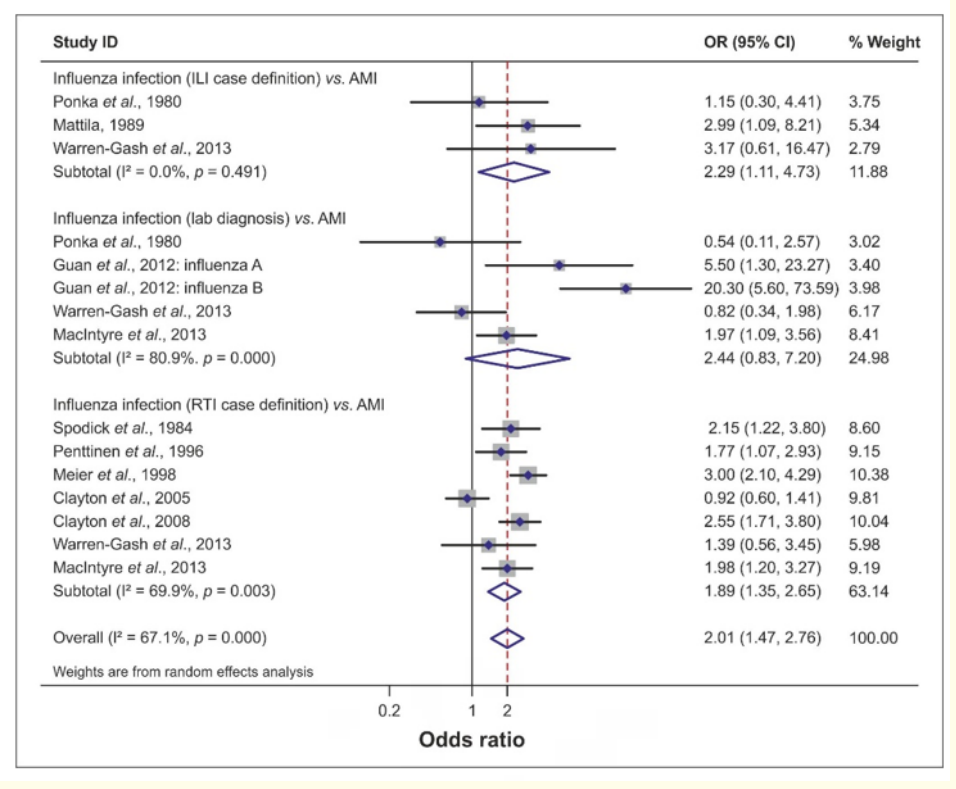

Figure 1: *Pooled results for analysis of infection studies and AMI diagnosis.*

Atherosclerosis involves an inflammatory pathway which culminates in a plaque comprised of a core rich in lipids, pro-inflammatory cells, cytokines and a fibrous cap. Influenza acts by several mechanisms, including release of cytokines which causes a pro-thrombotic state, local disruption of coronary plaques, as well as undesirable physiological effects such as hypoxia and tachycardia, resulting in ACS. Other mechanisms include sympathetic activation with subsequent effects on vascular tone with vasoconstriction, thrombogenesis through the non-specific pro-coagulants, thrombophilic effects of inflammation, epithelial dysfunction and inadequate coronary artery blood flow in presence of increased metabolic demand (supply-demand mismatch) with fever and tachycardia [6]. Figure 2 shows the mechanism by which influenza infection may precipitate CV events. Influenza predisposes patients to develop other infections such as bacterial pneumonia, which may itself be associated with increased CV risk due to prolonged elevation in cytokine levels and a procoagulant state [7].

Influenza vaccination in CVD

Influenza vaccination prevents the adverse impact of infection and inflammation on myocardial contractility, fibrosis and atherogenesis by inhibiting the Sphingomyelinase pathway and preventing plaque instability. It also reduces the production of Proinflammatory cytokines including interleukins, TNF-α, C-reactive protein and thus inhibiting the atherogenic cascade. Vaccination reduces the incidence and/or severity of respiratory infection and thereby prevents HF exacerbations, hospitalization, excess cost and associated morbidity/mortality. Major trials were focused primarily on ACS population; HF outcomes in these trials are limited. A summary of major findings in randomized control trials in CV disease is listed in table 1 [8].

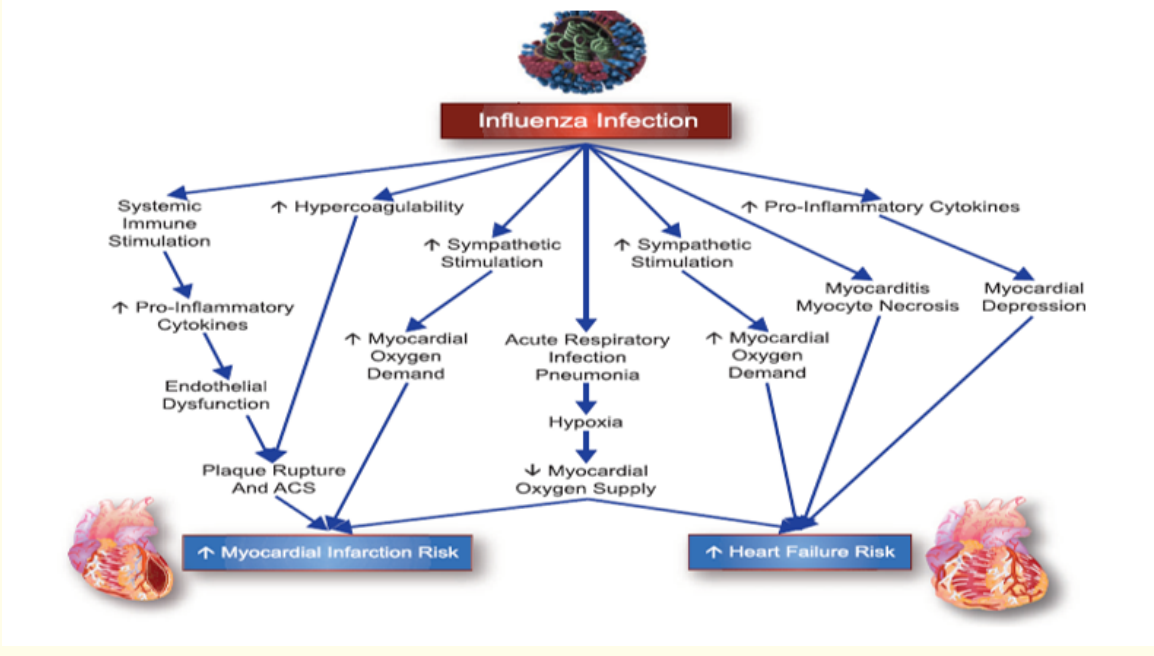

Figure 2: *Mechanisms supporting causal association between influenza infection and CV events.*

Study/First Author (Year)	Total, N	Country	Population	Intervention	Control	Primary Outcome Variable	Results
FLUVACS (2004)	301	Argentina	Inpatients-ACS or planned PCI	Trivalent, inactivated influenza vaccination	No vaccination	CV death (12 months)	RR: 0.34 (95% CI: 0.17 - 0.71) p = 0.002
FLUCAD (2008)	658	Poland	Outpatients-angiographic confirmed CAD	Trivalent, inactivated influenza vaccination	No vaccination	CV death (12 months)	HR: 1.06 (95% CI: 0.15 - 7.56) p = 0.95
Phrommintikul., *et al*. (2011)	439	Thailand	Inpatients-ACS within 8 weeks	Trivalent, inactivated influenza vaccination	No vaccination	Composite major CV events (death, hospitalization for ACS, HF and stroke) (12 months)	HR: 0.70 (95% CI: 0.57 - 0.86) p = 0.004
Van Erman., *et al*. (2013)	28	United States	Outpatients with HF	Double Dose influenza vaccination	Standard dose influenza vaccination	Antibody production by hemagglutinin inhibition assay (2&4 weeks)	3.3 vs. 1.6 for A/H3N2, p < 0.0011.9 vs. 1.1 for A/H1N1, p = 0.0091.7 vs.1 for B/H1N1 p = 0.02*

Table 1: *Randomized control efficacy trial evidence for respiratory vaccination in CV disease.*

In FLUVAC [9] study, the primary endpoint of CV mortality was lower in the vaccination group compared to controls. Notably, fatal, non-fatal HF events were zero in both the vaccination and control groups, whereas Influenza Vaccination in Secondary Prevention from Coronary Ischemic Events in Coronary Artery Disease (FLUCAD) [10] trial showed a reduction in ischemic events in 658 Polish patients with known CAD. Influenza vaccine is found to reduce the cardiac events and improve the survival rate of patients as shown in figure 3 [10]. Another randomized placebo-controlled trial on 439 post-ACS patients showed reduction in major CV events in patients with ACS. However, there was no significant difference in incidence of CV death [11].

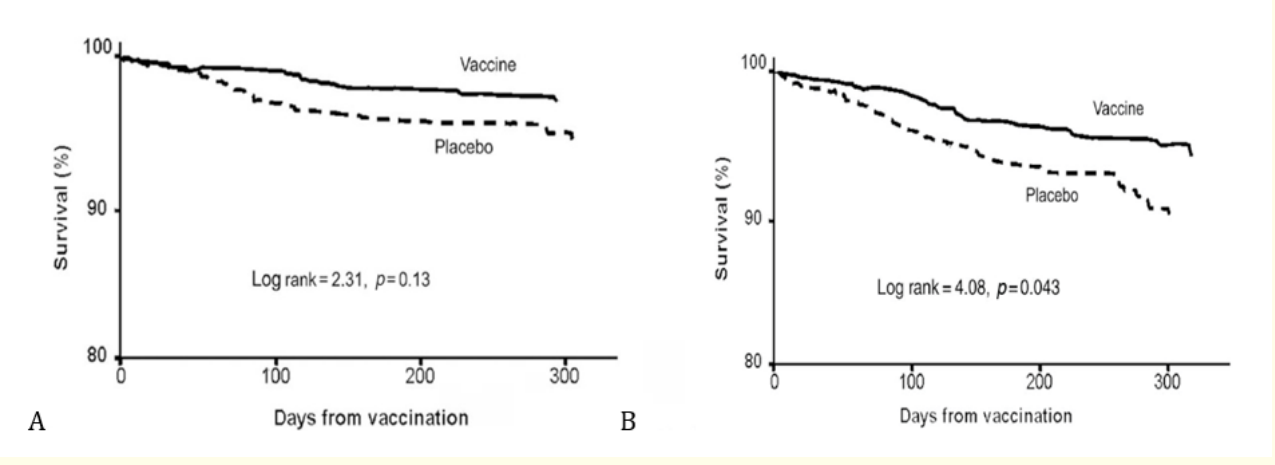

Figure 3: *(A) Graph shows major cardiac event free survival; (B) Graph shows coronary event free survival.*

Poudel S and colleagues studied the effect of influenza vaccination on 82,354 patients with HF. The study concluded that influenza vaccination is associated with a decreased risk of death in individuals, with reduced all cause of mortality 1 year after administration of vaccination (HR: 0.69; 95% CI: 0.51 - 0.87). The effect is more prominent during the influenza season compared with non-influenza season (Figure 4). Influenza vaccination is also associated with lower HF hospitalization (HR: 0.62) [12]. Another cohort study was done by Modin D and colleagues in 2019 involving patients above 18 years of age (n = 134,048) with HF. Follow-up was 99.8% with a median follow-up time of 3.7 years (interquartile range, 1.7 - 6.8 years) and the vaccination coverage of cohort study ranged from 16% to 54% during the study period. In unadjusted analysis, receiving 1 influenza vaccine dose during the study period was associated with a higher risk of death (all-cause death: HR, 1.28; 95% CI, 1.26 - 1.30; $p < 0.001$; CV death: HR: 1.26; 95% CI: 1.23 - 1.28; $p < 0.001$. After adjustment patient receiving ≥ 1 vaccination doses had 18% reduced risk of death (all-cause: HR: 0.82; 95% CI: 0.81 - 0.84; $p < 0.001$; CV causes: HR: 0.82; 95% CI: 0.81 - 0.84; $p < 0.001$) [13].

There are a number of ongoing trials to assess the issue clearly. One such trial is the INVESTED trial [14] to assess efficacy of high dose influenza vaccine to reduce clinical outcomes in high risk CV patients. The trial will enroll approximately 9,300 patients with history of recent HF or AMI hospitalization over four influenza seasons. The patients would receive high dose trivalent or standard dose quadrivalent vaccine. The primary hypothesis to be evaluated is to whether influenza vaccine will reduce composite outcome of all-cause mortality and hospitalization from CV or pulmonary causes.

Another trial Influenza Trial After Myocardial Infarction (IAMI) [15] which is an ongoing trial which aims to randomize 4400 patients with STEMI or NON-STEMI undergoing angiography to either in hospital influenza vaccination or placebo. Primary outcome is a composite of time to all cause death, a new AMI or stent thrombosis at one year.

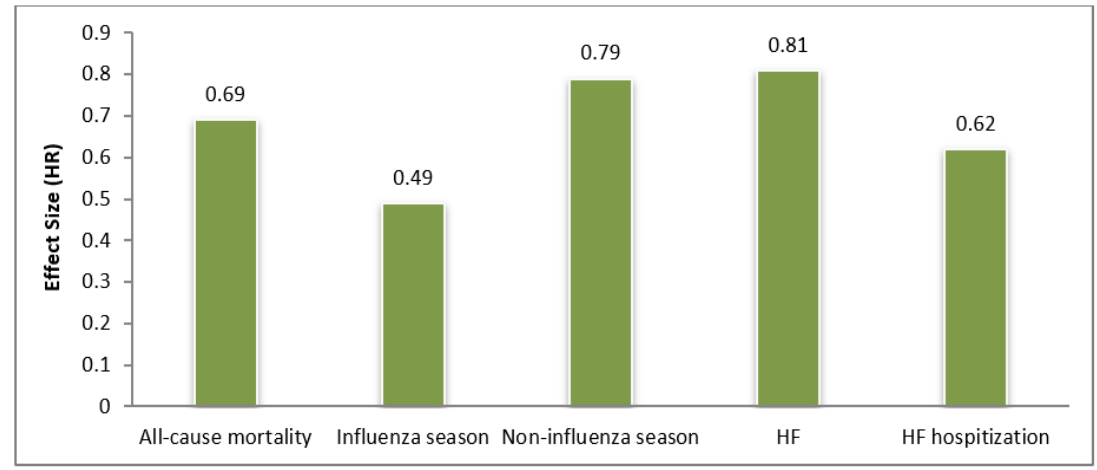

Figure 4: *Administration of influenza vaccine in patients at different conditions.*

Finally, another randomized controlled trial is being conducted by Loeb M and colleagues [16] on 5000 patients from 10 countries with HF. The subjects will receive either inactivated influenza vaccine or placebo annually for 3 years primary outcome is composite of CV death, non-fatal MI, non-fatal stroke and hospitalization for HF.

The above 3 ongoing trials should give definite answers about efficacy of influenza vaccine and its cost effectiveness in preventing CV events.

CDC's ACIP recommends standard-dose IIV or high-dose IIV in patients' ≥ 65 years of age. High-dose vaccination contains 60 mg of hemagglutinin which imparts higher immunogenicity as compared to standard dose which contains 15 mg of hemagglutinin and shows clinical benefit in this age group. Patients with HF may have decreased immune responses to standard dose vaccination [17,18]. According to CDC, Influenza vaccines should be administered to adults in autumn/winter (preferably in October to February). IIV is not recommended to patients who are allergic and have had anaphylactic-type reactions to egg proteins [3].

Pneumonia and CV risk

Acute bacterial pneumonia stresses the heart by increasing myocardial oxygen demand at a time when oxygenation is compromised by ventilation-perfusion mismatch. It raises circulating levels of inflammatory cytokines, which promotes thrombogenesis and impairs ventricular contractility. Factors which contribute to MI include inflammation, hypoxia, anemia, stress and hypotension (Figure 5) [19]. Pneumococcal vaccination is the basic strategy for the prevention of pneumococcal pneumonia in cardiac patients. Vaccination leads to production of IgM antibodies that share binding sites with naturally occurring anti-oxidized LDL antibodies. The conjugated pneumococcal polysaccharide vaccine may directly inhibit the formation of atheroma by preventing LDL oxidation, and thus reduce episodes of new MI and prevent HF [14,20]. Individuals who have not previously received a pneumococcal vaccine, at first, a single dose of PCV13 should be given, followed by PPV23 at least 1 year later, with a booster dose administered 5 years after the first dose of PPV23. The third dose of PPV23 should be administered to people aged 65 years and older. PCV13 protects against 13 of the approximately 90 types of pneumococcal bacteria, whereas PPSV23 protects against 23 types of pneumococcal bacteria [3].

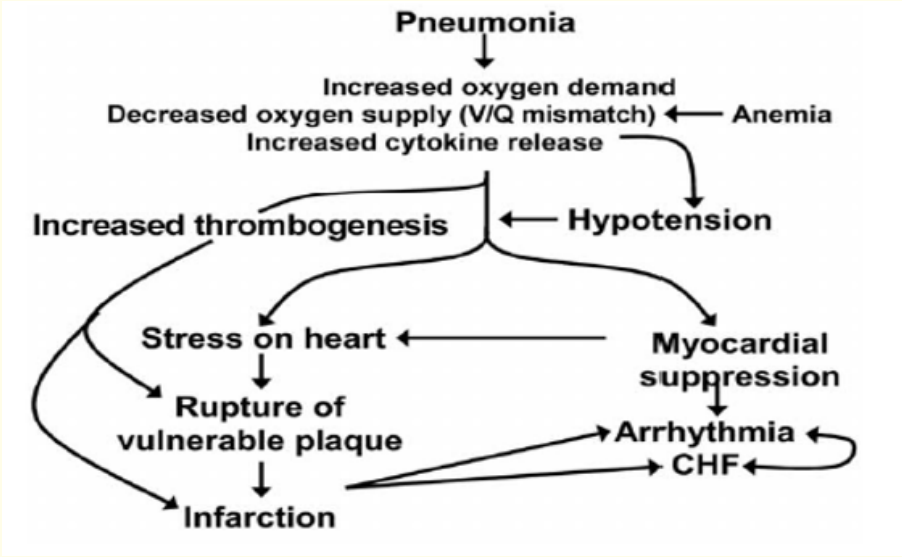

Figure 5: *Pathogenesis of cardiac events in pneumococcal pneumonia.*

In 2015 Ren S and colleagues**,** conducted a meta-analysis to clarify the effects of PPV in CV disease. A total of 23,046 patients receiving vaccination were included in eight observational studies (Figure 6). ACS events in patients of different age groups were recorded. ACS events in patients 65 years and older were reduced [pooled OR: 0.83 (95% CI: 0.71 to 0.97), = 77.0%]. There was no significant difference in ACS events when younger people were included [pooled I^2 = OR = 0.86 (95% CI: 0.73 to 1.01), 81.4%]. PPV was associated with significantly lower odds of ACS events [21]. A meta-analysis of four studies for evaluation of stroke protection, covering a total of 1,92,210 patients, did not find a significantly reduced risk of stroke in all patients (pooled OR: 1.00 (95% CI: 0.89 to 1.12), I^2 = 55.3%), or when restricted to those 65 years and older (pooled OR: 0.96 (95% CI: 0.87 to 1.05), I^2 = 22.5%) [21].

A hospital based case-control study by Lamontagne F involving 43,209 patients showed a 50% decrease in MI with PPV [22]. A population-based cohort study by Eurich DT involving 6,171 patients showed a 60% reduction in ACS events following PPV exposure [23].

PCV13 and inactivated influenza vaccine are immunogenic and can be given simultaneously in adults; administration along with inactive influenza vaccines promotes patient compliance and helps in improving public health.

Pneumococcal vaccine is contraindicated in patients who have a history of allergic reaction to PPV23 or a prior history of allergic reaction to any vaccine that contain diphtheria toxoid. If a patient is having serious acute illness, vaccination is postponed until the patient has recovered from severe health condition [3].

Vaccination in CV diseases guideline recommendations

The HF society of America, European society of cardiology, American heart association, and American college of cardiology/foundation recommends yearly influenza vaccination, specifically in patients with HF without contradictions. Full respiratory vaccination guidelines in CV diseases are listed in table 2 [14,24].

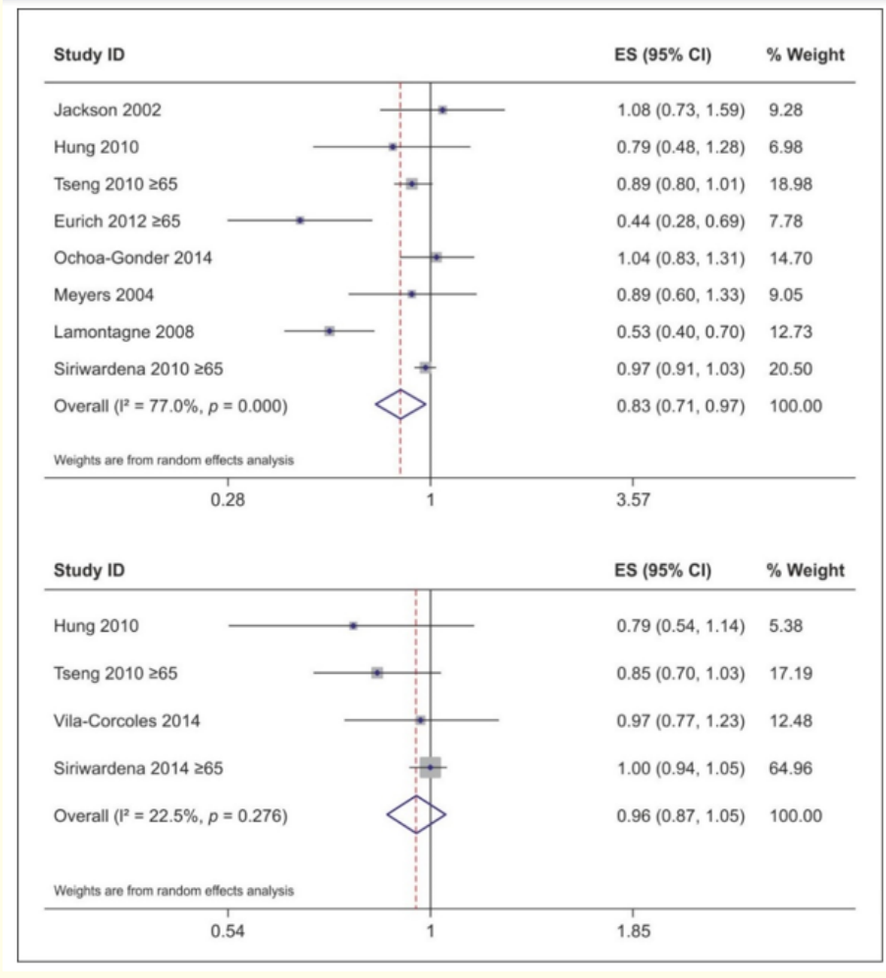

Figure 6: *Primary analysis of PPV and ACS events (upper) and stroke events (down).*

Report	Society	Recommendation and level of evidence
2010 Comprehensive HF practice guidelines	HF Society of America	"Pneumococcal vaccine and annual influenza vaccination are recommended in all patients with HF in the absence of known contraindications". Level of evidence: B
2012 European guidelines on CV Disease Prevention in Clinical Practice	ESC	"Annual influenza vaccinations are recommended for patients with established CV disease".
2013 ACCF/AHA guidelines for the management of HF	ACCF/AHA	''Secondary prevention interventions (e.g. lipids, smoking cessation, influenza and pneumococcal vaccines)". Level of evidence: recommended plan of care for patients with chronic HF
2016 ESC guidelines for the diagnosis and treatment of acute and chronic HF	ESC	"Receive immunization against influenza and pneumococcal disease". Level of evidence: key topics and self-care skills to include in patient education
2016 European guidelines on CV disease prevention in clinical practice	ESC	"Annual influenza vaccination may be considered in patients with established CV disease". Level of evidence: IIb, C

Table 2: *Recommended guidelines on respiratory vaccination in CV disease.*

Conclusion

Center for Disease Control and Prevention (CDC) and CV professional societies recommend annual influenza immunization to overcome the increased risk for influenza-related complications, and autumn or winter is best time for vaccine administration. Pneumococcal vaccine is recommended for high CV risk patients. High quality randomized trials are lacking but there is significant data to endorse immunization in secondary prevention and in high risk individuals for primary prevention. Randomized trials involving influenza vaccine are underway and should provide the final answer in this regard. Vaccination against influenza and pneumococcal infections seems to be a cost-effective measure for secondary prevention of cv events.

Conflict of Interest

None.

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