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EDITORIAL

Flu Vaccination as a Key Prevention Recommendation for Patients at High Cardiovascular Risk: The Next Season's Scenario

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Cardiovascular diseases (CVD) still represent the leading cause of mortality and morbidity in Western countries despite the increasing availability of highly effective strategies to control traditional risk factors in the last years [1]. Therefore, the persistence of other under-recognized risk factors has been hypothesized. Among these, since the beginning of the 1900 the association between seasonal influenza epidemics and major cardiovascular events (MACE) has been repeatedly confirmed [2]. Globally, the World Health Organization estimates that influenza kills almost 650,000 people annually, being a leading cause of death among people of all ages, especially those with comorbidities like CVD [3]. Cardiovascular manifestations associated with influenza include acute coronary syndromes [4–6]. There is indeed a wealth of retrospective and prospective studies showing a temporal relationship with influenza respiratory illnesses preceding acute myocardial infarction (AMI) by a variable time, with the strongest association occurring in the first three days but lasting for months [7]. Indeed, the influenza virus may contribute to prompt acute cardiovascular events by stimulating a potent acute inflammatory response which is a known trigger of acute plaque rupture [8–10]. Moreover, especially in patients at higher cardiovascular risk, influenza virus might destabilize patients through increased metabolic demand, exacerbate underlying CVD through activation of the sympathetic nervous system, inadequate coronary artery blood flow with fever and tachycardia [11]. Furthermore, influenza infection might predispose patients to develop opportunistic infections like bacterial pneumonia, which are associated with increased cardiovascular risk [12, 13]. Other cardiovascular manifestations of influenza include myocarditis, pericarditis, worsening of heart failure (HF) and sudden cardiac death [14]. Influenza-related complications and deaths are much more frequent in patients already suffering from chronic CVD [15]. Therefore, looking at the other side of the coin, it has been suggested that cardiovascular events might be prevented by influenza vaccination [6]. First evidence in this regard came from observational trials showing a general beneficial effect of influenza vaccine on cardiovascular health in patients at high cardiovascular risk [16–19]. After conflicting results of early randomized controlled trials (RCT), in 2013, Udell et al. [20] conducted a meta-analysis of 6 RCT assessing the benefits of influenza vaccine in reducing cardiovascular events within trials of influenza vaccine. The primary outcome was a composite of MACE, including cardiovascular death, hospitalization for acute coronary syndromes (ACS), stroke, HF, or urgent coronary revascularization. The authors found that influenza vaccination was associated with a lower risk of composite cardiovascular events than placebo (in the blinded studies) or standard care without vaccination (among open-label trials). In particular, vaccination was associated with a lower risk of MACE among participants with recent ACS, suggesting that acute cardiovascular patients may benefit the most from the annual influenza vaccine. Later, in 2017 a meta-analysis including 5 RTC showed that influenza vaccination of subjects with chronic CVD reduced mortality and MACE by almost 50% compared to controls [21].

Once highlighted the possible link between viral infection and increased CVD and CV mortality, with the rapid spread of SARS-COV2 during the last 2 years and the possibility of other waves of COVID-19 infections in the fall, receiving an influenza vaccine has become crucial to mitigate the risk associated with overlapping influenza and COVID-19 infections with dramatic effects. This holds particularly true for patients at increased CV risk, which are not only more

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likely to contract the COVID-19, but also more likely to be hospitalized and die because of it [22–24]. Indeed, there is evidence that influenza vaccination is consistently associated with lower mortality in patients affected by COVID-19, independently of age [25]. Moreover, a recent study showed that in the population over 65 years of age, influenza vaccination coverage is strongly correlated with a lower prevalence and better outcome following SARS-CoV-2 infection [26]. Therefore, some studies have suggested that influenza vaccination could be used as a temporary measure to reduce the severity of COVID-19, especially in conjunction with vaccines against SARS-CoV-2 [27, 28].

Recently, the Influenza Vaccination After Myocardial Infarction (IAMI) study [29], a double-blind, RCT conducted in 30 countries showed that influenza vaccination given early after admission for MI can reduce cardiovascular events (the composite of all-cause death, MI, or stent thrombosis) within 12 months of the index event. The vaccinated group also experienced fewer secondary outcomes of all-cause mortality and CV mortality with no increased serious adverse events, confirming that influenza vaccination can to be safely prescribed prior to discharge in patients hospitalized due to MI. The time-to-event curves for vaccination versus placebo separated early after the index hospitalization and then stabilized around 3 months, supporting immediate benefits from vaccination. Even though only few women were enrolled in this trial and it was ended prematurely, which could have enlarged the retrieved effects, the patient enrolled were very well treated, therefore the effect of influenza vaccine has been confirmed in addition to the highest standard of care for secondary prevention. A very recent meta-analysis available consisting of 6 RCT included 9001 adults who were randomized to influenza vaccination vs matching placebo or standard care found that the number of patients needed to vaccinate to prevent a MACE is 56 and even lower for patients recently affected by ACS [30].

Overall data about the beneficial role of influenza vaccine on cardiovascular risk, especially in secondary prevention, suggest that it is as effective as anti-platelet therapy and more effective than other medications such as statins and beta blockers. Therefore, the immunization should contribute to all effects to cardiovascular prevention strategies, being low-cost and widely available.

Clinical guidelines recommend annual influenza vaccination for the general population for influenza-like illness risk reduction, with emphasis on people with CVD. The European Society of Cardiology guidelines and the American Heart Association and the American College of Cardiology joint guidelines suggest a Class I (Level of Evidence B) recommendation for influenza vaccination for all patients with CVD [31, 32] Despite this, the prevalence of vaccination was only 44% in Europe among elderly adults (≥ 65 years) between 2016 and 2017 [33]. An effort should be made by Scientific Societies, also based on recent evidence, to further strengthen the recommendation for influenza immunization as a cardiovascular preventive measure for people at high risk [34], and expert physicians in this field are now called to put the vaccine among indications for all patients, especially those affected by CVD. Moreover, it must be considered that many patients at high cardiovascular risk are old and more susceptible to adverse drug reactions of multiple therapies, therefore sometimes it is hard to get optimal treatment in this population, in which additional options (such as vaccination) might be relevant. Thus, older people should be considered by physicians a high priority group for influenza vaccination to ensure adequate influenza vaccination coverage.

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