European Heart Journal Supplements (2023) **25** (Supplement A), A1–A4
The Heart of the Matter
https://doi.org/10.1093/eurheartjsupp/suac109

ESC
European Society
of Cardiology

What if flu vaccination is the most responsible thing to do for cardiovascular health in the upcoming season?

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'Dangerous liaisons' between influenza virus and cardiovascular diseases

In 2008, cardiovascular disease (CVD) for the first time become the leading cause of mortality in the world, causing ~13% of all deaths globally.[1] Given the rising burden of coronary heart disease (CHD), cardiovascular (CV) prevention through the control of traditional risk factors represents a healthcare priority. Cigarette smoking, elevated serum cholesterol levels, high blood pressure, and diabetes are major risk factors for developing CHD and are recognized as strategic targets for preventive strategies. Despite effective public health strategies and effective treatments in the control of CV risk factors,[2] however, the incidence of CHD is still dramatically high, suggesting the role of other less identified factors such as obesity, physical inactivity, stress, environmental pollution, infections, and inflammation. In this latter regard, since the beginning of the last century, the association between influenza epidemics and major cardiovascular events (MACE)[3] has been repeatedly reported. In this issue of the journal, Caldeira and Nogueira-Garcia provide a complete overview of the evidence retrieved about the relationships between influenza and CVD. Cardiovascular manifestations associated with influenza are multiple, though acute coronary syndrome (ACS) is the most important.[4–6] The risk of ACS related to influenza appears to be greatest in the first few days after infection, but it remains elevated for many weeks.[5] Several possible pathophysiological mechanisms have been suggested to explain the increase in CV events related to influenza. In this issue, Tor Biering-Sorensen *et al*. have addressed this aspect. In synthesis:

- The influenza virus may prompt acute CV events by stimulating a potent acute inflammatory response which may trigger acute plaque rupture.[7–9]
- Influenza infection can destabilize patients with pre-existing CVD through increased metabolic demand, activation of the sympathetic nervous system, and inadequate coronary artery blood flow due to fever and tachycardia.[10]
- Influenza infection also predisposes patients to develop opportunistic infections like bacterial pneumonia, with consequently reduced oxygen supply to the myocardium and increased CV risk.

Cardiovascular manifestations of influenza might also include myocarditis, pericarditis, heart failure (HF), and arrhythmias.[11] For these reasons, in recent years, it has been developed the concept that influenza vaccination can play a preventive action and reduce the development of CV events.[6]

The effect of influenza immunization on cardiovascular death and acute coronary syndromes

As reported in the paper by Carro in this issue, many observational studies have reported the protective effect of the influenza vaccine on MACE and mortality. Previous randomized controlled trials (RCTs) evaluating the effect of the influenza vaccine on CV outcomes in CHD patients had retrieved not uniform results.[12–14] These initial RCTs, however, included a small population sample size and provided short follow-ups.[15] More recent evidence, as summarized in the paper by Aliprandi *et al*. in this issue, has confirmed the efficacy of influenza vaccine in preventing MACE and mortality in secondary prevention as confirmed also by the IAMI (Influenza Vaccination After Myocardial Infarction; NCT02831608) trial.[16] In this specific study, influenza immunization was safely and effectively administered within 72 h after percutaneous coronary angioplasty. A subsequent meta-analysis of the available RCTs involving 4211 patients found that influenza vaccine significantly reduced the risk of MACE [relative risk (RR),

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0.63; 95% confidence interval (CI), 0.51–0.77], all-cause mortality (RR, 0.58; 95% CI, 0.4–0.84) and CV mortality (RR, 0.53; 95% CI, 0.38–0.74) compared with control group, whereas, the risk of myocardial infarction (MI) was comparable across the groups, but with a very low-grade certainty of the evidence.[15] Similarly, another recent meta-analysis found that the influenza vaccine was not associated with a statistically significant reduction of MI (RR, 0.73; 95% CI, 0.49–1.09) compared with control, whereas during a median follow-up of 19.5 months, the influenza vaccine was associated with a lower risk of all-cause mortality (RR, 0.75; 95% CI, 0.60–0.93), CV mortality (RR, 0.82; 95% CI, 0.80–0.84) and MACE (RR, 0.87; 95% CI, 0.80–0.94) compared with control.[17] Also, in this case, it should be noted that one of the reasons that could explain the lack of benefits of MI could be the low incidence of MI in the different RCTs included in the analysis.

Generally, an incremental benefit of influenza vaccination is noted with the increase of CV risk from primary prevention to secondary prevention of ACS. In 2013, Udell *et al*. conducted a meta-analysis of six RCTs comprising only 36.2% of patients with CVD assessing the benefit of the influenza vaccine in reducing CV events. A treatment interaction was detected between participants with and without recent ACS, where vaccination was associated with a lower risk of MACE among participants with recent ACS compared with participants with stable CHD suggesting that acute CV patients with higher risk may benefit the most regarding CV risk reduction from a once-annual influenza vaccine.[18] In view of previous results and of the recent trial IAMI[16] it appears confirmed that the patients who would benefit the most from this intervention are those at high cardiovascular risk, especially patients with a history of CHD.

The effect of influenza immunization on cerebrovascular events and heart failure

Less evidence is available in the setting of stroke. A meta-analysis considering the occurrence of recurrent stroke, thereby reflecting the incidence of stroke in a secondary prevention setting, found that the influenza vaccine was not associated with a significant reduction in the risk of stroke (RR, 0.75; 95% CI, 0.70–1.01).[19] Similarly, there still is no conclusive evidence about the benefit of influenza vaccination in patients affected by HF. Indeed, in the clinical setting of HF, conflicting results have been retrieved so far and the overall available evidence is graded low. In a meta-analysis by Rodriguez *et al*. of six observational studies in patients with HF, influenza vaccination was associated with a significant effect on all-cause mortality (HR, 0.83; 95% CI, 0.76, 0.91), but the vaccine was not associated with a statistically significant effect on all-cause hospitalizations and on CV mortality, according to the pooled analysis of two observational studies.[20] The recent Influenza Vaccine to Prevent Adverse Vascular Events (NCT02762851) trial, tested whether the standard-dose trivalent inactivated influenza vaccine compared with placebo may reduce a composite of adverse CV events in adults with New York Heart Association functional Classes II–IV HF (118) during three consecutive years. The primary outcome, a composite of CV death, non-fatal MI, non-fatal stroke, and hospitalizations for HF over 6 months was not significantly reduced by the influenza vaccine, but there was a significant reduction in MACE during periods of peak influenza circulation in the vaccinated group compared with placebo.[21] A large retrospective Danish study, conducted in 134 048 patients with HF, demonstrated an 18% reduction in mortality linked to flu vaccination. It was also highlighted that the protective efficacy of vaccination is higher when carried out at the beginning of the autumn, probably because of the reduced period in which patients are exposed to the risk of contagion.[22] This mechanism is supported by the fact that the reduction in mortality was directly proportional to the number of vaccinations to which the patients had been subjected during their life. A further study performed on 59,202 patients with HF demonstrated a reduction in hospitalizations for CVD in the flu-vaccinated group compared with controls.[23]

Data retrieved on other specific populations are scarce, therefore more efforts are needed to evaluate the effect of influenza vaccine in subgroups (hypertension, diabetes, peripheral artery disease, cerebrovascular disease, atrial fibrillation, or HF). In this issue, Dirk Muller Wieland provides a broad view of the evidence available for diabetic patients.

Influenza immunization as a key element for cardiovascular prevention during the time of COVID-19

Despite these limitations, based on the overall evidence, it appears today reasonable that influenza vaccination helps decrease mortality, CV mortality, and MACE especially in patients at high CV risk. In a recent meta-analysis, the number needed to treat (NNT) with influenza vaccine for MACE and all-cause mortality prevention were 19 and 48, respectively.[15] Since other medications recommended as secondary prevention have higher NNT (i.e. NNT for aspirin = 50,[24] NNT for statins = 61,[25] NNT for beta-blockers = 48,[26] NTT for angiotensin-converting enzyme inhibitors = 20[27]), influenza vaccination seems to represent a highly effective intervention for reducing adverse events in this population at very high CV risk.[15] Therefore, clinical guidelines recommend annual influenza vaccination for the general population for influenza-like illness risk reduction, with more stringent recommendations for 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.[28,29] Despite this, the prevalence of vaccination rates remains low among individuals with CVD who reside in North America[11] and it was only 44% in Europe among elderly adults (≥65 years) between 2016 and 2017.[30] An effort should be made by Scientific Societies, health authorities, and medical communities, also based on recent evidence, to further strengthen the recommendation for influenza immunization as a CV preventive measure for people at high risk (*Table 1*). The Italian Society for Cardiovascular Prevention has recently stated in its annual consensus document.[31] Expert physicians in this field around the world are now called to consider the seasonal influenza vaccine an urgent and mandatory indication for patients, especially those affected by CVD. Indeed, a key factor in determining vaccine effectiveness is how well the vaccine antigen formulation matches

Table 1 High cardiovascular risk patients candidates to seasonal influenza vaccine

With a previous acute ischaemic event (STEMI and NSTEACS)
With chronic artery disease/previous myocardial revascularization
With high global cardiovascular risk
With Type 1 and Type 2 diabetes
With heart failure
With a previous cerebrovascular accident
With former myocarditis or pericarditis
With valvular disease
With cardiomyopathies
With atrial fibrillation/cardiac arrhythmias
Congenital heart disease
Hypertension (severe or with organ damage)
Chronic kidney disease (eGFR <60 mL/min)
Peripheral artery disease

those of the circulating strains each year. Because each season can see the emergence of a new virulent strain of influenza without sufficient prior population immunity, it is recommended that every individual receive a new vaccine each season.[32]

Furthermore, a time-dependent increase in ACS following infection has been found for other respiratory viruses such as the syncytial, coronavirus, parainfluenza virus, adenovirus, human meta-pneumovirus, and enterovirus infections (incidence ratio, 2.77; 95% CI, 1.23–6.24).[33] From 2020, the association between SARS-CoV-2 infection and CV morbidity and mortality has been extensively investigated. It is now widely accepted that, when suffering from COVID-19, people affected by CVD experience worse outcomes and increased mortality.[34] On the other hand, COVID-19 is associated with an increase in acute CV events, including ACS. As the paper by Dr Raina McIntyre in this issue explains, the interplay of COVID-19 and influenza on health, and particularly CV health is multifaceted. Some recent studies have postulated the underlying mechanisms of COVID-19-related CV injury overlap with influenza infection so that influenza immunization might also improve outcomes in COVID-19.[35–39] There is also evidence that influenza vaccination is consistently associated with lower mortality in patients affected by COVID-19, independently of age.[32] Therefore, the importance of influenza vaccination seems to be further supported by these observations. Thus, during these complex times, national healthcare systems should effectively pursue the flu vaccination campaign, which should not be shaded by the drumming mass media campaign for SARS-CoV-2 immunization. The individual's benefits derived from the combination of the two vaccines should be advocated, especially in people at high CV risk. In parallel, clinical research should continue to provide answers for unsolved issues such as which vaccine would work best in terms of CV protection. Indeed, the INVESTED[40] trial (INfluenza Vaccine to Effectively Stop cardioThoracic Events and Decompensated heart failure; NCT02787044) recently compared for the first time a high-dose trivalent inactivated influenza vaccine to a standard-dose quadrivalent influenza vaccine, over four influenza seasons, in high-risk CV patients with a recent history of MI or hospitalization for HF finding no benefit from the high trivalent dose on the primary endpoint (time to the first occurrence of all-cause death or cardiopulmonary hospitalization). In particular, older people who usually are at high CV risk, but also at higher risk of suffering from side effects of CV medications, might hugely benefit from the influenza vaccine as a CV prevention measure. Despite this, they can also suffer from 'Immunosenescence', so that immunization could be less effective. Moreover, beyond age, there are data showing that patients with established CVD, such as ischaemic and non-ischaemic HF, have a reduced humoral and altered cell-mediated response to standard-dose influenza vaccine.[41–43] This suggests that patients with CVD that are particularly at increased risk for influenza-related complications may not derive sufficient protection with a standard-dose vaccination.[35] Thus, further studies are needed in this regard to find the most effective influenza immunization. More data on people at increased CV risk or affected by specific CV risk factors and CVD other than CHD are awaited, which could further reinforce the indication for annual influenza immunization.

In conclusion, influenza vaccination is a relatively cheap, safe, and evidence-based public health measure that is currently underused in at-risk populations. Influenza vaccination has been shown to be cost-effective in preventing influenza-like illnesses and related bad outcomes, and with the evidence available so far, it is now therefore also likely that the influenza vaccine is a highly cost-effective means of CV prevention, particularly for subjects at high CV risk.

Acknowledgements

None declared.

Funding

This paper was published as part of a supplement financially supported by Sanofi. Manuscripts were accepted after rigorous peer review process that was managed by an expert Guest Editor independently appointed by the Editor-in-Chief. The findings and conclusions contained within are those of the authors and do not necessarily reflect positions or policies of Sanofi.

Conflict of interest: A.B. has nothing to disclose as competing interest, financial support and conflict of interest. M.V. has been a speaker and advisory board member of Sanofi Pasteur.

Data availability

No new data were generated or analysed in support of this research.

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