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Influenza vaccine as part of a heart disease armamentarium in the new cardio-respiratory virus era

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The biological plausibility of the role of influenza vaccine in the prevention of major adverse cardiovascular events (MACE) has long been supported by animal models and epidemiological studies [1,2]. In this issue of *Trends in Cardiovascular Medicine*, Rodrigues et al. provide an overview of four of the most representative systematic reviews and meta-analyses from the past decade that investigated the impact of influenza vaccine on the secondary prevention of cardiovascular (CV) disease (CVD) in patients with varying manifestations of atherothrombosis [3]. The authors found that influenza vaccination was associated with a protective effect in patients with coronary artery disease (CAD) and heart failure (HF).

Specifically in patients with CAD, influenza vaccination was associated with a decrease in all-cause mortality when data from prior meta-analyses were recalculated [4]. The authors elected to synthesize the results only from efficacy trials that reported CV outcomes as primary or secondary endpoints, as opposed to the original meta-analysis which also included safety trials where CV outcomes were ascertained by reviewing appended severe adverse event reports. The rationale for this revision was the strict focus of the current review on patients with established CVD, as some trials enrolled patients with and without a history of CAD. This approach led to an accentuated relative risk (RR) for all-cause mortality of 0.39 (95% CI, 0.30–0.81), which was double in magnitude and now statistically significant compared with what was described previously (RR 0.85 [95%CI, 0.45–1.61]). Interestingly, the original meta-analysis did note that there was heterogeneity in the results when trials were stratified according to their study intent (p-interaction = 0.03), likely in part due to differences in blinding and other quality indicators. Thus, it is important to interpret with caution the overall mortality effects described by Rodrigues et al. among patients with CAD. It is rare to see such a substantial risk reduction in survival at one year in CV outcome trials (CVOTs), hence this observation suggests potential for selection bias, ascertainment bias, or play of chance given the small number of observed events.

Interestingly, the authors' revised meta-analysis approach had less impact on the outcome of MACE. The observed effect of influenza vaccine still seems overly optimistic (RR 0.50 [95% CI, 0.27–0.95]), but more closely approximates earlier results among a broader population with or at risk of CAD (RR 0.64 [95% CI, 0.48–0.86]). As described before, RR estimates for patients with acute coronary syndrome (ACS) and stable CAD were similar in both studies since data were obtained from the same trials with CAD patients only. The underlying hypothesis is that there is potential for greater CV protection from influenza vaccination among patients with relatively acute CV events compared to those with stable CVD. Perhaps this is because of increased vulnerability to the adverse CV effects of superimposed influenza infection, or perhaps there is a potential interaction between vaccination and protection from higher circulating prothrombotic or proinflammatory markers following ACS. All of this remains to be determined, seeing that the former mechanism may explain an increased absolute risk reduction, but not potentiation of the RR reduction.

For patients with HF, only one systematic review of observational studies was available [5]. The authors highlighted the nuances in interpreting the degree of bias surrounding its estimates and component studies that compared outcomes among HF patients with exposure to an influenza vaccine versus unexposed controls. Although a statistically significant risk reduction was seen with all-cause mortality, an unexpected lack of effect was noted for CV mortality. Given the potential overlapping mechanisms by which the influenza vaccine confers cardioprotective benefits in HF and ACS, the latter finding was challenged by the authors based on disease etiology and results from specific cohort studies that were less susceptible to bias. Nevertheless, data derived from observational studies without an active control should at best be considered as hypothesis-generating.

In the absence of published large, multicenter, adequately powered CVOTs assessing the cardioprotective effects of influenza vaccines, meta-analyses can be very useful. However, a meta-analysis does not imply causation and ought to be appraised within the context of its *a priori* criteria, as well as the quality of its underlying studies. As deemed here and by the original syntheses, the quality of the randomized and observational studies in the published literature thus far is relatively low, hence, the high or unclear risk of bias that was ascribed using various assessment tools. This overview underscores the need for adequately powered, multicenter randomized controlled trials to address these findings and

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assess individual CV endpoints among representative patient populations at high risk for influenza infection and recurrent CV events.

To our knowledge, there are currently three ongoing influenza vaccine CVOTs. The **I**nfluenza **V**accine to Prevent Adverse **V**ascular **E**vents (IVVE) trial is enrolling patients with New York Heart Association functional class II-IV HF [6], and the **I**nfluenza Vaccination **A**fter **M**yocardial **I**nfarction (IAMI) trial has targeted patients with MI undergoing coronary angiography [7]. These two trials have randomized patients to influenza vaccine or matched placebo inoculation. The **IN**fluenza **V**accine to **E**ffectively **S**top cardio **T**horacic **E**vents and **D**ecompensated heart failure (INVESTED) trial investigated the comparative effectiveness of two strategies of influenza vaccine among CV patients with a recent history of MI or hospitalization for HF [8]. Despite these ongoing CVOTs, Rodrigues et al. identified that there remains little to no evidence for potential cardioprotection from influenza vaccine among patients with cerebrovascular disease and peripheral artery disease, which carry a large global burden of illness. Specifically, RCTs are needed to clarify whether influenza vaccination reduces pertinent clinical outcomes for patients with these conditions.

Definitive findings from large CVOTs may have considerable clinical impact and health policy implications, given the well-established underuse of influenza vaccination among the general public and in high-risk patients. However, if these trials do not show a reduced risk for recurrent CV events, we will have to scrutinize whether influenza vaccination as a CV intervention is not effective and earlier studies were biased, or whether differences in study design play a role. The experience may be akin to when antimicrobial therapy was tested to determine whether suppression of *Chlamydia pneumoniae* could reduce CV risk among patients with CAD [9,10].

To conclude, the known CV morbidity of influenza, as well as the known efficacy and cost-effectiveness of the vaccine warrant its consideration for CV risk reduction as reviewed by Rodrigues et al. Major medical association guidelines recommend universal vaccination in patients with or at risk of CVD in part based on these data. We eagerly await the results of IVVE, IAMI, and INVESTED, which if successful, may further drive uptake of this undervalued, once-annual intervention in patients with CVD for the added benefit of CV protection. As we settle into the new era of a circulating novel coronavirus with potential for unleashing substantial CV morbidity and mortality among our highest-risk patients, the value of an effective seasonal influenza vaccine seems an all the more critical part of our standard CV protective armamentarium while combating this new respiratory virus threat.

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