EDITORIAL

Influenza Vaccine for Patients With High-risk Cardiovascular Disease

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Influenza and cardiovascular disease (CVD) are 2 of the most common causes of hospitalizations and deaths worldwide. These diseases share a reciprocal relationship because influenza may increase the risk of acute cardiovascular complications and underlying cardiovascular disease may increase the risk of influenza complications. Establishing a causal relationship can strengthen the rationale for wider use of influenza vaccines in patients with CVD worldwide.

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Ecologic studies have examined the relationship between influenza and excess winter mortality, often related to cardiovascular complications, and estimated that the percentage of winter deaths attributable to influenza could range from 4% to 68%.[1,2] However, biases were likely in these studies because the fraction of all-cause outcomes attributed to influenza exceeded measured influenza incidence. Carefully conducted observational studies have suggested that approximately 3% to 6% of hospitalizations and deaths from myocardial infarction may be related to influenza.[1,3] More recently, epidemiologic studies that used self-controlled case series methodology documented 5- to 10-fold temporal increases in the risk of acute myocardial infarction within 1 week of laboratory-confirmed influenza.[4,5] In a 2020 study of 80 261 laboratory-confirmed influenza hospitalizations from 13 states in the US, 12% had acute cardiovascular events, which were most commonly decompensated heart failure and acute ischemic heart disease.[6] These findings are supported by pathogenesis studies in animal models that have linked infection from influenza viruses and other pathogens to atherogenesis with suggested pathways to disease, including hypoxia, increased metabolic demand, atherosclerosis and plaque rupture from inflammation, induction of a prothrombotic state, and direct viral infection.[7,8]

With the amount of evidence indicating a strong association between influenza and cardiovascular morbidity and mortality, the key question is to determine whether influenza vaccination prevents cardiovascular outcomes and deaths. Ecologic studies have observed decreases in cardiovascular diseases associated with vaccination,[1,8] and a meta-analysis of observational studies reported that influenza vaccination was associated with lower risk of all-cause mortality,[9] although biases limit clear interpretation in these noninterventional studies.[1,8,9] Only 4 small randomized clinical trials (<2000 participants total) have evaluated fatal and nonfatal cardiovascular events between vaccinated and comparator groups, and meta-analyses including these trials have shown that influenza vaccination was significantly associated with reduced all-cause cardiovascular events within 1 year of follow-up (absolute risk of CVD mortality, 2.3% vs 5.1%; risk ratio, 0.45 [95% CI, 0.26-0.76][10]; absolute risk of a major CVD event, 2.9% vs 4.7%; risk ratio, 0.64 [95% CI, 0.48-0.86][11]), particularly among patients with coronary syndromes in the past year. However, caution is advised because the findings were inconsistent and were influenced by 2 studies with less than 500 participants in each trial and moderate to high risk of bias.[10,11]

In this issue of *JAMA*, Vardeny and colleagues[12] report findings from the INVESTED trial that compared the relative efficacy of 2 influenza vaccines on outcomes of relevance to the global public health community: death from all causes and cardiopulmonary hospitalizations. This double-blind randomized trial spanned 3 influenza seasons (September 2016-January 2019) and was conducted in 157 sites across the US and Canada. Enrollment was restricted to patients with acute myocardial infarction in the preceding 12 months or hospitalization for heart failure in the preceding 24 months and at least 1 additional high-risk condition. Current influenza vaccines are standardized based on protective properties of the hemagglutinin surface glycoprotein of influenza virus strains. The control vaccine was standard-dose quadrivalent inactivated influenza vaccine containing 4 virus antigens (SD-IIV4). The intervention was high-dose trivalent inactivated influenza vaccine (HD-IIV3) containing 4 times the hemagglutinin content of each of 3 virus antigens compared with the standard dose. A previous randomized trial showed that HD-IIV3 can induce better antibody responses to the hemagglutinin protein and improved protection in patients aged at least 65 years compared with SD-IIV3.[13] Therefore, it was hypothesized that HD-IIV3 would confer greater benefit than SD-IIV4 in participants with underlying CVD.

Among INVESTED participants (n = 5260), of whom the mean age was 65 years, 78% were White, 63% had heart failure, and 37% had prior myocardial infarction, the event rates among a broad range of cardiovascular and pulmonary complications were high, at 42 to 45 per 100 patient-years in both vaccine groups. However, the rates of the primary composite end point of all-cause mortality or cardiopulmonary hospitalization, within-season or across the 3-year study period, were not significantly different between HD-IIV3 recipients (975 primary events [883 hospitalizations and 92 deaths]; event rate, 45 per 100 patient-years) and SD-IIV4 recipients (924 primary events [846 hospitalizations and 78 deaths]; event rate, 42 per 100 patient-years) (hazard ratio, 1.06 [95% CI, 0.97-1.17]).

Three key aspects of the INVESTED trial warrant consideration. First, the study addressed a narrow question: does a higher hemagglutinin antigen content of the standard-dose influenza vaccine reduce all-cause deaths and cardiopulmonary

hospitalizations by an 18% relative risk reduction or more? The study evaluated "relative efficacy" of HD-IIV3 vs SD-IIV4, but not "absolute efficacy" of either vaccine due to lack of a placebo or unvaccinated group. Moreover, the trial assessed nonspecific outcomes rather than laboratory-confirmed influenza. Thus, the findings from this trial should not be interpreted to mean that influenza vaccines are ineffective or that protection conferred by HD-IIV3 is equivalent to SD-IIV4 against laboratory-confirmed influenza in this population.

Second, a meaningful difference between HD-IIV3 and SD-IIV4 against influenza-related cardiovascular outcomes might still exist. The prespecified effect size (relative efficacy of 18%) for HD-IIV3 vs SD-IIV4 against outcomes with very low specificity for influenza was higher than that observed in previous studies.[14] Precise quantification of the effect size is critically relevant for sample size considerations when assessing the comparative efficacy of vaccines against nonspecific outcomes. Compared with the 5260 participants in the INVESTED trial with an unexpectedly large event rate of 42% to 45%, relative efficacy of 5% could still be meaningful and would require enrolling approximately 20 000 participants under the same study assumptions. Lower event rates of 10% to 15% as originally estimated would further increase the sample size requirements.

Relative efficacy is challenging to interpret. With a fixed value for HD-IIV3 relative efficacy, the benefits in terms of averted events vary widely depending on the absolute efficacy of the comparator vaccine (SD-IIV4). In contrast to absolute efficacy of a vaccine of 33% to 67% against laboratory-confirmed influenza,[15] absolute efficacy of inactivated influenza vaccines is unlikely to exceed 5% to 10% for averting nonspecific all-cause deaths and cardiopulmonary hospitalizations, for which influenza-related illness is one of many causes. In contrast, because of the high number of nonspecific events, such as all-cause death and cardiovascular hospitalizations, even small increases in relative efficacy of 5% could substantially increase the number of additional deaths and hospitalizations averted.

Third, including a broad range of cardiopulmonary conditions may have obscured the effect of HD-IIV3 against specific outcomes for which the putative protective benefits might be the greatest, such as acute coronary syndrome.[4,5] Severe cardiopulmonary outcomes requiring hospitalization in the INVESTED study included acute myocardial infarction, heart failure, ischemic chest pain, arrhythmia, cardiac arrest, syncope, pneumonia, chronic obstructive pulmonary disease or asthma exacerbation, pulmonary embolism, and acute stroke. The primary event rate was high (approximately 44%) compared with composite cardiovascular events in vaccinated groups in previous studies (approximately 2.7%).[10,11]

With an aging global population and increasing numbers of people with cardiac diseases, improved prevention efforts to reduce influenza-associated CVD outcomes are overdue. Persons with cardiovascular conditions are at increased risk of influenza virus infection and associated complications due to immunosenescence and, possibly, "inflamm-aging" (ie, a chronic low-level state of inflammation suspected to impair immune responses). However, vaccines are also known to be less effective in these populations and in older adults due to blunted humoral immune responses, and current influenza vaccines are known to have suboptimal effectiveness.[15] Influenza vaccines in development are aimed at overcoming barriers to improving protective immunity.[16] Efforts that hold potential to improve influenza vaccine effectiveness include increasing hemagglutinin content, adding additional strains, ensuring antigenic stability of vaccine strains through use of recombinant or cell culture–grown viruses, mucosal delivery, use of adjuvants, standardizing neuraminidase antigen content, and incorporating antigens against conserved hemagglutinin epitopes (eg, "universal vaccines").[16]

Evidence has accumulated that influenza virus infection of the respiratory tract can trigger acute cardiovascular events. However, gaps include quantifying the magnitude of association between influenza and cardiovascular complications and the attributable fraction of morbidity and mortality associated with these conditions that influenza vaccination can prevent. Multicountry trials evaluating the effect of inactivated influenza vaccine on cardiovascular outcomes that include a placebo group are ongoing (NCT02831608 and NCT02762851) and can inform the vaccine-preventable proportion of these outcomes.[8] There is urgency to better define the relationship between influenza and the cardiovascular system and to reduce CVD morbidity and mortality associated with influenza through influenza vaccines with improved protective benefits. While awaiting the availability of new vaccines with improved efficacy, vaccination with current age-appropriate quadrivalent influenza vaccines that are partially effective (egg-based or cell culture–based IIV4, recombinant vaccine [RIV4], HD-IIV4, or adjuvanted IIV4) is still better than no vaccination, especially for adult patients with underlying conditions, such as cardiovascular disease.

ARTICLE INFORMATION

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