

EDITORIAL COMMENT

The PARADIGM of Influenza Vaccination in Heart Failure Patients*



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Annual seasonal influenza epidemics of variable severity are associated with substantial morbidity and mortality worldwide, with influenza activity peaking during corresponding winter months in temperate climates of the northern and southern hemispheres (1). In the tropics and subtropics, influenza activity occurs year-round, with differences in peak periods. Most influenza disease burden estimates are derived from studies conducted in developed countries. Certain populations are considered to be at increased risk for influenza complications, including infants, the elderly, immunosuppressed persons, pregnant women, and persons with chronic conditions including pulmonary and cardiac disease (2). Prevention of influenza in the United States is focused upon annual influenza vaccination of all persons ≥ 6 months of age, although recommended target populations and different kinds of vaccines and their availability and uses differ worldwide (3). Influenza vaccine effectiveness varies by age group, immune status, and antigenic similarities between circulating influenza virus strains and vaccine strains.

The World Health Organization has estimated that an estimated 3 to 5 million cases of severe influenza and approximately 250,000 to 500,000 deaths occur each year (4). Heart failure (HF) is an

independent prognostic factor for influenza-associated hospitalization or death (5). In the United States, hospitalizations for HF peak during the winter and are lowest during the summer (6). Influenza vaccination has been associated with reductions in HF hospitalization and death in multiple community-based observational studies of patients ≥ 65 years of age and studies of younger adults with high-risk medical conditions (7,8). The U.S. Centers for Disease Control and Prevention, American Heart Association, and European Society of Cardiology recommend annual influenza vaccinations in patients with HF.

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In this issue of *JACC: Heart Failure*, Vardeny et al. (9) assessed influenza vaccination and outcomes in HF patients by using data from the PARADIGM-HF trial (Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure), which randomized 8,442 people with systolic HF to sacubitril and valsartan or enalapril therapy (10). At enrollment, participants were asked about receipt of influenza vaccination in the previous 12 months, and clinical outcomes were assessed during trial follow-up. Among 21% of participants who reported receiving influenza vaccination, vaccination coverage varied widely among different countries, and HF patients who reported being vaccinated had lower mortality.

How might influenza vaccination improve outcomes in HF patients? Patients with HF have limited reserve with which to tolerate respiratory compromise, and prevention of influenza by vaccination as well as reduction of secondary influenza-associated bacterial pneumonia may reduce HF exacerbations. Influenza may be a trigger for myocardial infarction, which may either precipitate HF or lead to severe

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illness in those with pre-existing HF; 2 randomized, controlled trials of influenza vaccination in patients with established coronary disease reported efficacy against cardiovascular death (11). Other potential causes of influenza-associated myocardial damage include accelerated atherosclerosis related to inflammatory response to influenza or to a viral or autoimmune myocarditis.

Influenza vaccination was associated with lower mortality in the PARADIGM-HF trial, but as the authors note, causality cannot be determined by the observational study design. Patients who received influenza vaccination may be more likely to seek other preventive measures. Conversely, older and sicker patients and those with functional impairment may be less able to obtain influenza vaccination and more likely to experience severe influenza complications. Older patients and those with HF can have a blunted immune response to and lower effectiveness of influenza vaccination (12,13), despite a good antigenic match. Confounding biases can exaggerate the apparent benefit of influenza vaccination in observational studies, including reporting that influenza vaccination was associated with lower mortality among elderly people prior to the onset of the influenza season (14). Nevertheless, the benefit of influenza vaccination remains significant, even after adjusting for potentially large confounders over multiple influenza seasons in observational studies (15), as well as in a systematic review of 4 randomized controlled trials (16). Randomized controlled trials of influenza vaccination among groups at increased risk for influenza complications are unethical in countries that recommend vaccination of these high-risk populations. Therefore, evidence from observational studies, surveillance data, modeling, and indirect measures are used to provide estimates of influenza disease burden and vaccine effectiveness.

Several additional observations deserve comment. First, a higher proportion of participants who reported receiving influenza vaccination resided in developed countries with more availability of medical facilities, which may have accounted for higher frequency of HF hospitalizations and specific cardiac care that reduces mortality. Second, patients who were not vaccinated had higher New York Heart Association functional class, higher B-type natriuretic peptide levels, more baseline HF hospitalizations, and lower use of beta-blockers, angiotensin-converting enzyme inhibitors, implantable cardioverter defibrillators, and cardiac resynchronization therapy; and these differences in HF may also have influenced overall outcomes. Finally, self-reported influenza

vaccination in the previous 12 months might be inaccurate compared to confirming vaccination status from records and, even if reliable, might misclassify immunization status. For example, a Canadian patient enrolled in May who was vaccinated during the previous 12 months might not be protected from influenza in the subsequent winter when follow-up outcomes data were collected, unless revaccinated. Therefore, it is challenging to estimate the benefit of influenza vaccination to HF patient outcomes from this study, but the findings are consistent with those from other studies that have reported the effectiveness of influenza vaccination in other cardiac patients (16).

Not surprisingly, enrolling country was the most significant predictor of influenza vaccination, and there was a correlation between proportion of influenza-vaccinated participants and the country's gross domestic product. Participants from the most populous countries (i.e., China and India) had <1% vaccination coverage, and East and Southeast Asian countries had vaccination coverage of <10%. The lack of local data for influenza burden and vaccine efficacy in the most low- and middle-income countries, particularly in Asia and Africa, has hampered development of national influenza policies. Macro-epidemiologic studies have shown that public reimbursement is associated with higher influenza vaccination coverage (17), and persons living in developed countries and countries with national influenza vaccination programs may be more able to access vaccines through the public sector. More accurately determining influenza disease burden in developing and tropical/subtropical countries can provide data for policy makers to consider influenza vaccination programs.

Although influenza may trigger HF exacerbation that requires hospitalization, other respiratory pathogens are also associated with HF. However, in HF patients with influenza, antiviral treatment with a neuraminidase inhibitor started as soon as possible may confer clinical benefit in addition to management of HF. One large meta-analysis of adults hospitalized with the influenza A(H1N1)pdm09 virus infection reported that neuraminidase inhibitor antiviral treatment compared to no treatment and early initiation of antiviral treatment versus later treatment were associated with reductions in mortality risk (18). Availability of antiviral agents and supportive intensive care may improve survival in critically ill influenza patients.

Overall, this study extends observations from previous studies by providing evidence of clinical benefit of influenza vaccination and supports the

current strategy to vaccinate HF patients. The question is, how can influenza vaccination coverage be increased in HF and other cardiac patients? If influenza vaccine is not available or not recommended for cardiac patients in a country, then data are needed on influenza disease burden and the economic impact of influenza for policymakers. Who should be responsible for ensuring annual influenza vaccination of these patients—primary care providers or cardiologists or both? Other strategies to increase influenza vaccination, such as standing orders for influenza

vaccination of cardiac patients at hospital discharge, and annual influenza vaccination of household contacts of HF and other cardiac patients should be considered.

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