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EDITORIAL COMMENT

Vaccinations in Heart Failure

An Expert-Opinion Based Recommendation That Deserves Randomized Validation*

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It is estimated that 6.5 million Americans ≥20 years of age have heart failure (HF). This represents an increase from an estimated 5.7 million U.S. adults with HF based on data from 2009 to 2012. Projections show that the prevalence of HF will increase 46% from 2012 to 2030, resulting in >8 million people ≥18 years of age with HF (1). The prevalence estimates for HF across Asia range from 1.26% to 6.70% (1). In highly populated countries such as Brazil, the prevalence of HF is increasing and is associated with a remarkably high in-hospital mortality rate (2).

In this scenario, HF-related hospital admissions are an ominous event that clearly affect HF natural history. Hospitalizations for HF are responsible for the greatest financial burden of the disease, and incur a significantly increased risk of disease progression or death. The number of primary HF hospitalizations in the United States has recently decreased, whereas secondary HF hospitalizations increased. Common diagnoses for secondary HF hospitalizations include pulmonary disease and infections (3). It is biologically plausible to assume that, if pulmonary infections were a major cause of HF hospitalization, preventing such infections would prevent patients from being admitted for HF. Because the vicious circle of frequent readmissions is a threatening sign of worsening disease, any preventive measure, such as vaccination, would possibly have an impact on patients' prognosis.

The possible mechanisms involved in the benefit of immunization strategies include avoiding viral respiratory infections or even secondary influenza-associated bacterial pneumonia. Atherosclerosis progression or plaque instability triggered by viral inflammation could also be halted by immunization. Last, direct viral myocardial damage through myocarditis or as an indirect trigger to autoimmune myocarditis could precipitate or cause HF admissions.

In summary, vaccination programs in patients with HF makes a lot of sense: there is biological plausibility for the benefit, individual costs are relatively low, population side effects are quite small, and they might be easily applied to many patients simultaneously (as a simple "1-shot strategy"). Indeed, most international renowned entities endorse such recommendations.

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In this issue of *JACC: Heart Failure*, Bhatt et al. (4) have demonstrated that, at 392 centers participating in the American Heart Association–sponsored Get With The Guidelines-HF (GWTG-HF) registry, comprising a population of 313,761 patients with HF, the proposed adoption of routine immunization practices has brought up 3 relevant findings: 1) approximately one-third of patients with HF discharged from these hospitals were not vaccinated for influenza or pneumococcal pneumonia, and this estimation has been stable since 2012; 2) higher vaccination rates paralleled other HF quality of care measures, i.e., the best performers on the hospital level were the smaller, nonacademic, rural centers from the U.S. Northeast region; and 3) vaccination status did not seem to protect patients from clinical outcomes (4). These results definitively deserve in-depth reflection about the role of vaccination in patients with HF.

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Five randomized, clinical trials have investigated the role of influenza vaccination in preventing cardiovascular events, presumably by decreasing pulmonary infections. These trials have focused primarily on patients with coronary artery disease and the information regarding the HF population is surprisingly limited. From the 2 positive trials that have compared vaccination against no vaccination, the FLUVACS (Flu Vaccination Acute Coronary Syndromes) study did not investigate a subgroup of patients with HF; the data on fatal and nonfatal HF events were zero in both groups (5). In the second "positive" trial, Phrommintikul et al. (6) have found a benefit in a composite endpoint of major cardiovascular events, including death, hospitalization for acute coronary syndromes, HF, and stroke, but the rate of HF hospitalizations were similar between the 2 groups (1.8% vs. 4.6%; hazard ratio: 0.69; 95% confidence interval: 0.49 to 1.01; $p = 0.111$) (6). The other 3 clinical trials on patients with established coronary artery disease or a high-risk elderly population have shown no protection of influenza vaccination in cardiovascular deaths (7–9). It is noteworthy that the prevalence of patients with HF in these trials was low. Therefore, data from randomized, clinical trials addressing the specific clinical effectiveness of influenza vaccination in HF are surprisingly scarce, and not systematically or consistently validated. The larger body of evidence comes from a number of observational studies in elderly patients, in younger adults with high-risk medical conditions, or from administrative datasets, which are, by definition, potentially prone to intractable bias (10). The scenario of pneumococcal vaccination and HF outcomes is not different, if not even less defined. Our current knowledge of the relationship between pneumococcal vaccination and HF-related benefits or harm is also based only on retrospective and observational data.

One contemporary dataset of patients with HF under optimal medical therapy comes from observational data derived from the PARADIGM-HF (Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure Patients) trial (11). This nested study examined the predictors of receiving influenza vaccination and the relationship between vaccination and outcomes in a propensity-adjusted model. Predictors of receiving influenza vaccine included country (greatest in the Netherlands, Great Britain, and Belgium and least in Asia), white race, presence of implanted defibrillator, older age, lower New York Heart Association functional class, lower heart rate, and a history of diabetes. In this analysis, vaccination was associated with a 19% decrease in the relative risk of death, but this benefit cannot be dissociated from the inherent patients' risk and selection biases, as well as regional differences in quality of care that patients with HF received. Although this substudy represents comprehensive data exclusively on patients with HF looking into influenza vaccination effects, the observational study design cannot determine a causal effect on vaccination protection, as acknowledged by the authors.

The study from Bhatt et al. (4) adds controversy to the current knowledge in the field, because one of their main findings in fact did suggest that vaccination status was not associated with a benefit in clinical outcomes. These results come with the strength of the largest contemporary HF sample already evaluated to address immunization efficacy. Several aspects related to the observational nature of the study design, however, might explain in part this lack of effect. Importantly, the group that did not receive vaccination was somewhat sicker (lower ejection fraction, higher heart rate, more smokers), a subset of patients with HF that presumably could realize a greater benefit with immunization. There were wide regional variations in adherence to vaccination, a factor that might unpredictably influence quality of care. Finally, the voluntary nature of the GWTG-HF Program and the fact that patients who refused to receive a vaccination were not adequately computed may have also distorted final results.

Several frontiers have to be explored to better understand the risks and benefits of respiratory vaccination in patients with HF. In elderly patients, vaccine effectiveness is about one-half of that in healthy middle-aged adults and varies depending on the study population. Patients with HF also present a blunted response, with reduced humoral and altered cell-mediated responses to influenza vaccine, which may decrease the degree to which those with HF are protected by yearly vaccinations (12). Systematic reviews have demonstrated that the influenza vaccine decreases the incidence of pneumonia, hospital admissions, and deaths in elderly patients, but whether patients with HF indeed benefit from vaccination remains a matter of debate. Will the already weakened immune system in patients with HF adequately respond to different vaccine formulations and what is the best timing in the disease process to vaccinate? These are also unanswered questions.

The best available evidence so far is mainly based on expert opinion and observational data, and current findings from Bhatt et al. (4) might have shifted the existing understanding. International guidelines

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are consensual to recommend influenza and pneumococcal immunization in patients with HF, but this may be far from an equipoise clinical practice. Randomized, controlled data are definitely needed to thoroughly assess the relationship between vaccination and clinical outcomes in patients with HF.

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REFERENCES

1. Benjamin EJ, Virani SS, Callaway CW, et al. Heart disease and stroke statistics-2018 update: a report from the American Heart Association. Circulation 2018;137:e67–492.

2. Wajner A, Zuchinali P, Olsen V, Polanczyk CA, Rohde LE. Causes and predictors of in-hospital mortality in patients admitted with or for heart failure at a tertiary hospital in Brazil. Arq Bras Cardiol 2017;109:321–30.

3. Blecker S, Paul M, Taksler G, Ogedegbe G, Katz S. Heart failure-associated hospitalizations in the United States. J Am Coll Cardiol 2013;61:1259–67.

4. Bhatt AS, Liang L, DeVore AD, et al. Vaccination trends in patients with heart failure: insights from get with the guidelines-heart failure. J Am Coll Cardiol HF 2018;6:844–55.

5. Gurfinkel EP, Leon de la Fuente R, Mendiz O, Mautner B. Flu vaccination in acute coronary syndromes and planned percutaneous coronary interventions (FLUVACS) Study. Eur Heart J 2004;25:25–31.

6. Phrommintikul A, Kuanprasert S, Wongcharoen W, Kanjanavanit R, Chaiwarith R, Sukonthasarn A. Influenza vaccination reduces cardiovascular events in patients with acute coronary syndrome. Eur Heart J 2011;32:1730–5.

7. Ciszewski A, Bilinska ZT, Brydak LB, et al. Influenza vaccination in secondary prevention from coronary ischaemic events in coronary artery disease: FLUCAD study. Eur Heart J 2008;29:1350–8.

8. De Villiers PJ, Steele AD, Hiemstra LA, et al. Efficacy and safety of a live attenuated influenza vaccine in adults 60 years of age and older. Vaccine 2009;28:228–34.

9. Govaert TM, Thijs CT, Masurel N, Sprenger MJ, Dinant GJ, Knottnerus JA. The efficacy of influenza vaccination in elderly individuals. A randomized double-blind placebo-controlled trial. JAMA 1994;272:1661–5.

10. Lang PO, Mendes A, Socquet J, Assir N, Govind S, Aspinall R. Effectiveness of influenza vaccine in aging and older adults: comprehensive analysis of the evidence. Clin Interv Aging 2012;7:55–64.

11. Vardeny O, Claggett B, Udell JA, et al. Influenza vaccination in patients with chronic heart failure: the PARADIGM-HF Trial. J Am Coll Cardiol HF 2016;4:152–8.

12. Vardeny O, Sweitzer NK, Detry MA, Moran JM, Johnson MR, Hayney MS. Decreased immune responses to influenza vaccination in patients with heart failure. J Card Fail 2009;15:368–73.

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