

## Editorial

## Vaccination in Heart Failure: An Approach to Improve Outcomes

## La vacunación en la insuficiencia cardiaca: una estrategia que mejora el pronóstico

Nikolaos P.E. Kadoglou,<sup>a</sup> John Parissis,<sup>b</sup> Petar Seferovic,<sup>c</sup> and Gerasimos Filippatos<sup>b,d,\*</sup><sup>a</sup> Centre for Statistics in Medicine - Botnar Research Centre, University of Oxford, Oxford, United Kingdom<sup>b</sup> Heart Failure Unit, Attikon University Hospital, National and Kapodistrian University of Athens, Athens, Greece<sup>c</sup> Belgrade University School of Medicine, Department of Cardiology, Clinical Center of Serbia, Belgrade, Serbia<sup>d</sup> School of Medicine, University of Cyprus, Nicosia, Cyprus

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## INFECTIONS AND HEART FAILURE

Heart failure (HF) remains a severe cardiovascular disease with increasing prevalence and high morbidity and mortality worldwide.<sup>1</sup> There is an unmet need to improve prognosis and reduce the socioeconomic impact of HF management.<sup>2</sup> In addition to pharmaceutical regimens and interventions, lifestyle measures tailored to the underlying causes of HF exacerbations may help to achieve these goals. Among the precipitating factors for HF worsening, respiratory infections play a leading role.<sup>3</sup> The underlying pathogenic organisms of respiratory infections are predominantly influenza viruses and pneumococcal bacteria.<sup>4</sup> Currently, a purely causative relationship between HF and influenza and/or pneumococcal infection has not been proven. However, frequent, infection-induced HF exacerbations that follow a seasonal, periodic fashion imply an association between those organisms and the development and progression of HF.<sup>5</sup>

## INFLUENZA VACCINATION AND HEART FAILURE

Influenza vaccination is an effective measure to reduce all-cause mortality among high-risk persons during seasonal influenza epidemics.<sup>6</sup> The high-risk population includes mostly elderly individuals with significant comorbidities predisposing them to respiratory infection. Most but not all community-based studies support the timely implementation of anti-influenza vaccination for primary and secondary prevention of cardiovascular events in high-risk populations.<sup>7</sup> Patients with already established cardiovascular disease may also benefit from anti-influenza vaccination.<sup>8</sup> The studies performed to date might have been biased by unmeasured confounders and study population variance, leading to the aforementioned discrepancies.<sup>9</sup> The underlying pathogenic mechanisms of HF exacerbations during infections may involve direct myocardial injury, inflammation, and fluid shifts. However, they remain mostly speculative. In this context, a cause-effect relationship between vaccination and reduced morbidity and mortality is missing<sup>10,11</sup> (Figure).

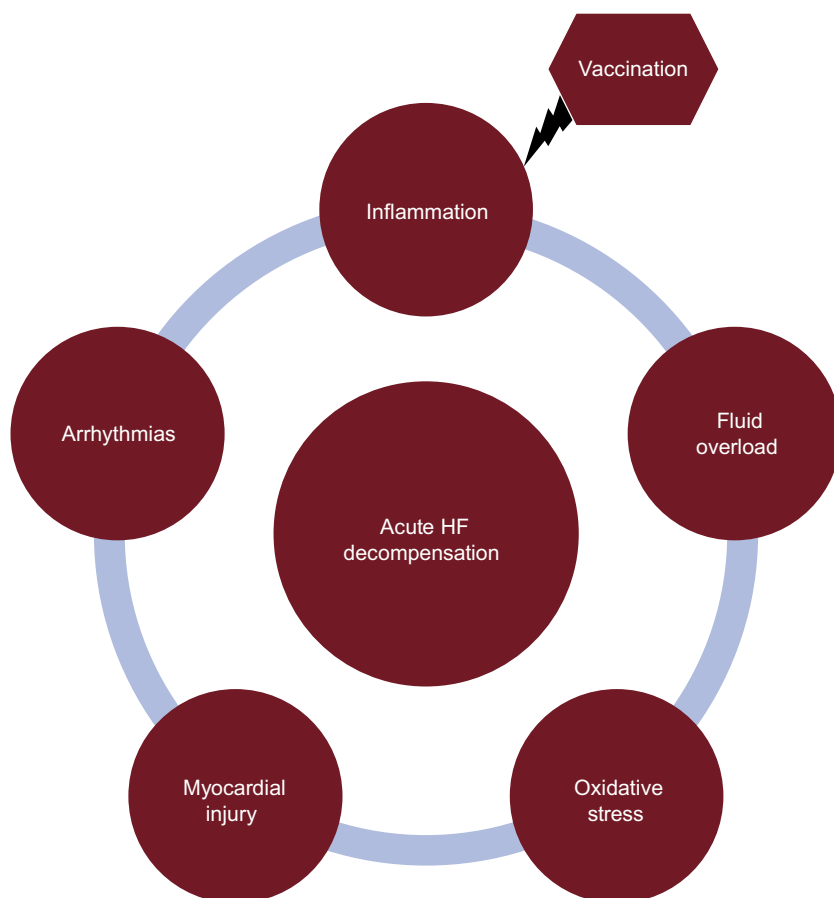
In HF patients, anti-influenza vaccination confers considerable benefits regarding the frequency and severity of HF exacerbations,<sup>12</sup> especially when other comorbidities coexist.<sup>13</sup> It is well-known that patients at higher risk derive greater benefit from vaccination.<sup>14</sup> Thus, HF patients, who have multiple comorbidities, are expected to gain more cardioprotection from anti-influenza vaccination. In a large (59 202 HF patients), self-controlled case series study, the anti-influenza vaccination was associated with a lower hospitalization rate for cardiovascular diseases.<sup>15</sup> Regarding the seasonal epidemics of respiratory infections, the initial concept for vaccination in HF patients was to provide protection only during the influenza season (December to April). However, a growing body of evidence underpinned a persistent reduction in hospitalization of vaccinated HF patients throughout the year,<sup>16</sup> not only during the “flu season”, as previously reported.<sup>9</sup> This is an extremely important finding, since it emphasizes the role of immunity on HF progression and supports immunization strategies throughout the year. Most importantly, there is accumulated data from population-based studies, documenting survival benefits in anti-influenza vaccinated heart failure patients.<sup>16,17</sup> A subanalysis of the PARADIGM-HF trial, which was designed to assess the efficacy of sacubitril/valsartan vs enalapril in patients with symptomatic HF and reduced ejection fraction (< 40%), outlined the important contribution of vaccination on survival after a median follow-up of 27 months.<sup>18</sup> Independently of other confounders, anti-influenza vaccination determined survival in the propensity adjusted models.

## PNEUMOCOCCAL VACCINATION AND HEART FAILURE

Pneumococcal disease is common among older adults. A growing body of evidence supports the association of pneumococcal pneumonia and HF development.<sup>19</sup> Patients admitted to hospital with pneumococcal pneumonia frequently have concurrent acute myocardial infarction or new/worsening HF.<sup>20</sup> Conversely, pneumococcal vaccination reduces the incidence of pneumonia and seems to lower cardiovascular morbidity and mortality in older individuals.<sup>21</sup> To our knowledge there is no study assessing solely antipneumococcal vaccination in an HF cohort. For instance, a recent multicenter study demonstrated lower 30-day and 1-year mortality in HF patients who received the recommended care including medications and vaccinations (influenza and pneumococcal).<sup>22</sup> Unambiguously,

\* Corresponding author: Department of Cardiology, University of Athens, Attikon, University Hospital, Rimini 1, 12461 Athens, Greece.

E-mail address: geros@otenet.gr (G. Filippatos).



**Figure 1.** Precipitating factors for acute heart failure decompensation. Potential interaction of anti-influenza and/or antipneumococcal vaccination with acute heart failure decompensation. HF, heart failure.

**Table**  
Guideline Recommendations of the International Cardiology Societies on Anti-influenza and Antipneumococcal Vaccination in the Heart Failure Population

Report	Society	Recommendation and level of evidence
2010 comprehensive heart failure Practice guideline <sup>25</sup>	Heart Failure Society of America	"Pneumococcal vaccine and annual influenza vaccination are recommended in all patients with HF in the absence of known contraindications" Level of evidence: B
2013 ACCF/AHA guidelines for the management of heart failure <sup>26</sup>	ACCF/AHA	"Secondary prevention interventions (eg, lipids, smoking cessation, influenza and pneumococcal vaccines)" Level of evidence: recommended plan of care for patients with chronic HF
2016 European guidelines on cardiovascular disease prevention in clinical practice <sup>24</sup>	ESC	"Annual influenza vaccination may be considered in patients with established cardiovascular disease" Level of evidence: IIb, C
2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure <sup>5</sup>	ESC	"Receive immunization against influenza and pneumococcal disease" Level of evidence: key topics and self-care skills to include in patient education

ACCF, American College of Cardiology Foundation; AHA, American Heart Association; ESC, European Society of Cardiology; HF, heart failure.

the immunogenicity and safety of different antipneumococcal vaccination types and doses requires further investigation.<sup>23</sup> Thus, there is a shortage of robust evidence about the efficacy of antipneumococcal vaccination in the HF population.

## COMMENTS

Both European and American cardiology societies recommend immunization against influenza and pneumococcal infection in the

context of patients' skills and professional behaviors. In particular, the Heart Failure Association of the European Society of Cardiology (ESC) has recently "advised both vaccines on local guidance and immunization practice".<sup>5</sup> In the ESC guidelines for cardiovascular disease prevention, "annual influenza vaccination may be considered in patients with established cardiovascular disease" (level of evidence: IIb, C).<sup>24</sup> However, as the authors declared, that recommendation is primarily focused on acute myocardial infarction prevention. In the Heart Failure Society of America guidelines, pneumococcal vaccination and annual influenza

vaccination were recommended in 2010 in all HF patients (level of evidence: B).<sup>25</sup> In 2013, the American Heart Association also recommended influenza and pneumococcal vaccination among secondary prevention interventions.<sup>26</sup> Notably, those recommendations were based on expert consensus, since there are no randomized controlled trials and the evidence derives from large, observational studies or population-based registries, which have mostly enrolled patients with cardiovascular disease. Last but not least, immunization has been listed among the key topics and self-care skills in the recent recommendations of the Heart Failure Association of the ESC<sup>5</sup> (Table).

Therefore, the available data suggest the advisability of vaccination in the HF population but they have not been validated and systematically analyzed. On the other hand, it seems unethical to apply a large, blind, randomized, controlled trial in order to test vaccination efficacy in HF patients, as it would require a sample without vaccination. Moreover, the necessary dosage of effective vaccines needs further investigation. There is an ongoing, clinical trial (NCT02787044)<sup>27</sup> aiming at the comparative evaluation of the high dose trivalent influenza vaccine vs standard dose quadrivalent influenza vaccine in high-risk cardiovascular patients, such as those with recent myocardial infarction or HF hospitalization. In parallel, the wide variety in vaccination rates in different countries constitutes another important issue of health care systems. The PARADIGM-HF trial and other registries have documented higher vaccination rates in developed rather than undeveloped countries. Hence, several aspects should be clarified to obtain robust evidence that will support a wide recommendation of vaccination in HF population.<sup>28</sup>

## CONCLUSIONS

Both influenza and pneumococcal infection are associated with high cardiovascular morbidity and mortality. Vaccination against these infections seems to be a cost-effective, preventive measure, improving survival and reducing cardiovascular events in high-risk populations, such as those with HF. However, large-scale trials are required to clarify the safety and efficacy of anti-influenza and antipneumococcal vaccinations in HF conditions.

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## CONFLICTS OF INTEREST

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## REFERENCES

- Chioncel O, Lainscak M, Seferovic PM, et al. Epidemiology and one-year outcomes in patients with chronic heart failure and preserved, mid-range and reduced ejection fraction: an analysis of the ESC Heart Failure Long-Term Registry. *Eur J Heart Fail*. 2017;19:1574–1585.
- Ponikowski P, Anker SD, AlHabib KF, et al. Heart failure: preventing disease and death worldwide. *ESC Heart Fail*. 2014;1:4–25.
- Platz E, Jhund PS, Claggett BL, et al. Prevalence and prognostic importance of precipitating factors leading to heart failure hospitalization: recurrent hospitalizations and mortality. *Eur J Heart Fail*. 2017. <https://doi.org/10.1002/ehf.901>.
- Babb R, Chen A, Ogunniyi AD, et al. Enhanced protective responses to a serotype-independent pneumococcal vaccine when combined with an inactivated influenza vaccine. *Clin Sci (Lond)*. 2017;131:169–180.
- Ponikowski P, Voors AA, Anker SD, et al. Authors/Task Force Members; Document Reviewers. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail*. 2016;18:891–975.
- de Diego C, Vila-Córcoles A, Ochoa O, et al. EPIVAC Study Group. Effects of annual influenza vaccination on winter mortality in elderly people with chronic heart disease. *Eur Heart J*. 2009;30:209–216.
- Barnes M, Heywood AE, Mahimbo A, Rahman B, Newall AT, Macintyre CR. Acute myocardial infarction and influenza: a meta-analysis of case-control studies. *Heart*. 2015;101:1738–1747.
- Clar C, Oseni Z, Flowers N, Keshtkar-Jahromi M, Rees K. Influenza vaccines for preventing cardiovascular disease. *Cochrane Database Syst Rev*. 2015;5:CD005050.
- Alla F, Zannad F, Filippatos G. Epidemiology of acute heart failure syndromes. *Heart Fail Rev*. 2007;12:91–95.
- Kadoglou NPE, Bracke F, Simmers T, Tsiodras S, Parissis J. Influenza infection and heart failure—vaccination may change heart failure prognosis? *Heart Fail Rev*. 2017;22:329–336.
- Flaherty JD, Bax JJ, De Luca L, et al. Acute Heart Failure Syndromes International Working Group. Acute heart failure syndromes in patients with coronary artery disease early assessment and treatment. *J Am Coll Cardiol*. 2009;53:254–263.
- Nichol KL, Nordin J, Mullooly J, Lask R, Fillbrandt K, Iwane M. Influenza vaccination and reduction in hospitalizations for cardiac disease and stroke among the elderly. *N Engl J Med*. 2003;348:1322–1332.
- Fang YA, Chen CI, Liu JC, Sung LC. Influenza vaccination reduces hospitalization for heart failure in elderly patients with chronic kidney disease: a population-based cohort study. *Acta Cardiol Sin*. 2016;32:290–298.
- Uhnou I, Linde A, Pauksens K, Lindberg A, Eriksson M, Norrby R. Swedish Consensus Group. Treatment and prevention of influenza: Swedish recommendations. *Scand J Infect Dis*. 2003;35:3–11.
- Mohseni H, Kiran A, Khorshidi R, Rahimi K. Influenza vaccination and risk of hospitalization in patients with heart failure: a self-controlled case series study. *Eur Heart J*. 2017;38:326–333.
- Kopel E, Klempfner R, Goldenberg I. Influenza vaccine and survival in acute heart failure. *Eur J Heart Fail*. 2014;16:264–270.
- Liu IF, Huang CC, Chan WL, et al. Effects of annual influenza vaccination on mortality and hospitalization in elderly patients with ischemic heart disease: a nationwide population-based study. *Prev Med*. 2012;54:431–433.
- Vardeny O, Claggett B, Udell JA, et al. PARADIGM-HF Investigators. Influenza vaccination in patients with chronic heart failure: The PARADIGM-HF Trial. *JACC Heart Fail*. 2016;4:152–158.
- Ahmed MB, Patel K, Fonarow GC, et al. Higher risk for incident heart failure and cardiovascular mortality among community-dwelling octogenarians without pneumococcal vaccination. *ESC Heart Fail*. 2016;3:11–17.
- Musher DM, Rueda AM, Kaka AS, Mapara SM. The association between pneumococcal pneumonia and acute cardiac events. *Clin Infect Dis*. 2007;45:158–165.
- Ren S, Newby D, Li SC, et al. Effect of the adult pneumococcal polysaccharide vaccine on cardiovascular disease: a systematic review and meta-analysis. *Open Heart*. 2015;2:e000247.
- Wu WC, Jiang L, Friedmann PD, Trivedi A. Association between process quality measures for heart failure and mortality among US veterans. *Am Heart J*. 2014;168:713–720.
- Jackson LA, Gurtman A, van Cleeff M, et al. Immunogenicity and safety of a 13-valent pneumococcal conjugate vaccine compared to a 23-valent pneumococcal polysaccharide vaccine in pneumococcal vaccine-naïve adults. *Vaccine*. 2013;31:3577–3584.
- Piepoli MF, Hoes AW, Agewall S, et al. Authors/Task Force Members. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J*. 2016;37:2315–2381.
- Lindenfeld J, Albert NM, Boehmer JP, et al. Heart Failure Society of America. HFSA 2010 Comprehensive Heart Failure Practice Guideline. *J Card Fail*. 2010;16:e1–e194.
- Yancy CW, Jessup M, Bozkurt B, et al. American College of Cardiology Foundation; American Heart Association Task Force on Practice Guidelines. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2013;62:e147–e239.
- National Institute for Health and Clinical Excellence. INfluenza Vaccine to Effectively Stop Cardio Thoracic Events and Decompensated Heart Failure (INVESTED) trial. Available at: <https://www.investedtrial.org/>. Consulted 20 Jan 2018.
- Gheorghiadu M, Filippatos G. Reassessing treatment of acute heart failure syndromes: the ADHERE Registry. *Eur Heart J Suppl*. 2005;7(Suppl B):B13–B19.