

Vaccine-Associated Atrial Fibrillation

Zaki Al-yafeai¹, Mohamed Ghoweba², David Aziz², Anil Ananthaneni³, Shafik Hanna-Moussa², and Muhie Sabayon²

¹LSU Health Shreveport

²Affiliation not available

³Louisiana State University Health Sciences Center Shreveport

March 31, 2022

Abstract

Aim: Vaccines have been mainly described to provide cardioprotective effects with rare reports showing rare association with myopericarditis. However, vaccines have not been well studied regarding its effects on heart rhythm disorders. **Methods:** we used vaccine adverse event reporting system (VAERS) between 1990-2021 to search for atrial fibrillation and other less prevalent arrhythmia. Disproportionality signal analysis was conducted by measuring reporting odds ratio (ROR) with 95% confidence interval (CI). **Results:** Over 1,300,000 adverse events were reported between 1990-2021. Among these events, atrial fibrillation was reported 2149 times in association with various vaccines. 90% of atrial fibrillation was associated with COVID-19 vaccines with ROR of 13.18 (CI 95%: 11.3 to 15.4) (P<0.0001). Interestingly, influenza vaccines, polyvalent polysaccharide pneumococcal (PPSV23) vaccine, pneumococcal 13-valent (PCV13) vaccine, zoster vaccine, and tetanus-containing vaccines were significantly associated with reduced atrial fibrillation. Finally, our analysis showed that COVID-19 vaccines were associated with much higher incidence of other cardiac arrhythmias compared with other vaccines. **Conclusions:** While vaccines have not been linked to heart rhythm disorders, the introduction of COVID-19 vaccines in 2020 showed significant association with atrial fibrillation. This study showed unprecedented detrimental effect of COVID-19 vaccines on atrial fibrillation and warrants the need to take that into consideration when prescribing COVID-19 vaccines.

Vaccine-Associated Atrial Fibrillation

Zaki Al-Yafeai¹111Department of Internal Medicine, Louisiana State University Health Sciences Center-Shreveport, Shreveport, LA. These authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation ²Department of Medicine, CHRISTUS Good Shepherd/Texas A&M College of Medicine, Longview, TX. These authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation [#] Equal contribution. [#], Mohamed Ghoweba^{2#}, David Aziz¹, Anil Ananthaneni¹, Shafik Hanna-Moussa², and Muhie Dean Sabayon²

Corresponding author:

Zaki Al-Yafeai, MD PhD

Department of Internal Medicine

Louisiana State University Health Sciences Center-Shreveport

1501 Kings Hwy, Shreveport, LA. 71103

Key words: Atrial fibrillation, Vaccine, COVID-19, Arrhythmia

What is already known about this subject:

The role of inflammation in atrial fibrillation emerging

Some pathogens and vaccines have been described to be associated with AF

Comprehensive study of the role of vaccines in AF is lacking

What this study adds:

COVID-19 Vaccines are significantly associated with AF.

Compared to other vaccines, COVID-19 is also reported with arrhythmic disorders.

Other vaccines (tetanus, flu, zoster, PPV... etc.) vaccines have proactive effect against AF.

Abstract:

Aim: Vaccines have been mainly described to provide cardioprotective effects with rare reports showing rare association with myopericarditis. However, vaccines have not been well studied regarding its effects on heart rhythm disorders.

Methods: we used vaccine adverse event reporting system (VAERS) between 1990-2021 to search for atrial fibrillation and other less prevalent arrhythmia. Disproportionality signal analysis was conducted by measuring reporting odds ratio (ROR) with 95% confidence interval (CI).

Results: Over 1,300,000 adverse events were reported between 1990-2021. Among these events, atrial fibrillation was reported 2149 times in association with various vaccines. 90% of atrial fibrillation was associated with COVID-19 vaccines with ROR of 13.18 (CI 95%: 11.3 to 15.4) ($P < 0.0001$). Interestingly, influenza vaccines, polyvalent polysaccharide pneumococcal (PPSV23) vaccine, pneumococcal 13-valent (PCV13) vaccine, zoster vaccine, and tetanus-containing vaccines were significantly associated with reduced atrial fibrillation. Finally, our analysis showed that COVID-19 vaccines were associated with much higher incidence of other cardiac arrhythmias compared with other vaccines.

Conclusions: While vaccines have not been linked to heart rhythm disorders, the introduction of COVID-19 vaccines in 2020 showed significant association with atrial fibrillation. This study showed unprecedented detrimental effect of COVID-19 vaccines on atrial fibrillation and warrants the need to take that into consideration when prescribing COVID-19 vaccines.

Introduction:

Over the last few decades, Atrial Fibrillation (AF) has been a rapidly growing global health problem becoming the most common sustained cardiac arrhythmia(1). Consequences include decreased cardiac output and thrombus formation(2, 3). On electrocardiogram, it is characterized by the presence of rapid, irregular, fibrillatory waves varying in size, shape, and duration. AF is associated with a plethora of cardiac and non-cardiac conditions including hypertension, ischemic heart disease, congestive heart failure, valvular heart disease, inflammatory states, hyperthyroidism, obesity, alcohol use disorder, infections, and sepsis(4).

Influenza and Herpes Zoster (HZ) infections were shown to increase the rate of development of AF(5-7). The relationship between atrial fibrillation with *Helicobacter pylori* and *Chlamydia pneumoniae* infections remains debatable(8-11). Particularly interesting, sepsis has been implicated in the increasing number of hospitalizations of patients with new-onset AF(12-14).

Pathophysiologically, AF likely originates from the underlying inflammatory process that occurs with infections and sepsis leading to the release of a wide-range of inflammatory mediators including high-sensitivity C-reactive protein (CRP), Interleukin-6 (IL-6), Interleukin-8 (IL-8), and Tumor Necrosis Factor- α (TNF- α). These in turn act directly or through exerting oxidative stress to trigger atrial electrical remodeling with decreased atrial refractory period, conduction heterogeneity, abnormal calcium and ionic handling, as well as atrial ectopy. Far less understood is the variation in AF incidence between types of infections being highest in pneumonia, while more recurrence and a long-term prognosis being observed with gastrointestinal infections. This might be related to different cytokine profiles involved with each type of infection(15).

The novel coronavirus disease-2019 (COVID-19) seems to be the culprit in a significant proportion of reported atrial fibrillation cases over the last one and a half years. Atrial fibrillation is the most commonly encountered cardiac arrhythmia in the disease. This could be explained by the associated inflammatory/cytokine storm, hypoxemia, direct cardiotoxic effects, sympathetic nervous system overactivity, or secondary to therapeutic agents and drug-drug interactions(16).

While the correlation with infections and sepsis has been well-established, the relationship between atrial fibrillation and vaccinations is yet to be fully elucidated. Influenza vaccine has been noted to decrease the risk of development of AF while the anthrax vaccine adsorbed (AVA) and the smallpox vaccines showed no increased risk(5, 7, 17, 18). Our aim in this study is to shed the light on the reported incidence of atrial fibrillation with different widely-used vaccines.

Methods:

The Vaccine Adverse Event Reporting System (VAERS) is a well-established and publicly accessible database used for monitoring adverse events associated with vaccinations. This system has data starting from 1990 and is updated regularly. It accumulates reports from around the globe on vaccine quality complaints as reported by health care professionals, producers, and from those having received the vaccine. In particular, it identifies name of the vaccine, the adverse reaction seen, the severity of the reaction and other related information. Ethics committee approval was not needed for the use of this system since it is anonymous. In the present study we comprehensively evaluated the incidence of cardiac arrhythmias in association with all vaccines (COVID, Zoster, Influenza, Pneumococcal, Hepatitis B, TDAP, TD, TTX, Smallpox, Anthrax, Typhoid, Meningococcal, Hepatitis A, Lyme, MMR, Yellow Fever, HPV, Japanese Encephalitis virus, Poliovirus, Varicella).

We looked for arrhythmia adverse events (AEs) using standardized medical terms according to the Medical Dictionary for Regulatory Activities, the list of terms included “atrial fibrillation”, “long QT”, “atrial flutter”, “ventricular tachycardia”; “ventricular fibrillation”, “supraventricular tachycardia”, “sick sinus syndrome”, “bundle branch block” and “heart block”.

The association between the use of vaccines with arrhythmia adverse events was assessed by disproportionality signal detection analysis using the reporting odds ratio (ROR). ROR is a measure of the magnitude of association between an exposure to a given vaccine and the odds of patients experiencing a specific adverse event, compared to the odds of the same event occurring with all other vaccines in the database. ROR was considered significant when the lower limit of the 95% confidence interval (CI) was >1.0 .

Results:

The patient characteristics of reported cases are shown in table 1. Overall, no significant sex differences existed with a nearly equal proportion of reported adverse events in males and females. Patients at the age of 50 years and above constituted about 85% of cases with the remainder falling in the 19-49 age group. Serious adverse events occurred in 823 cases compared to 739 non-serious events, while 81 cases (4.9 %) had an outcome of death. In the majority of cases (913 patients), onset of adverse events was within the first seven days following vaccine administration. This was followed by 243 patients developing adverse events later than one month following administration. Onset within 8-14 and 15-30 days occurred in 101 and 161 patients, respectively. Table 2 further characterizes vaccine-associated AF and showing that COVID-19 vaccines reported the most frequent reported AF (84%) among all other vaccines.

As shown in figure 1 and table 3, individuals who received the COVID-19 vaccine had a significantly higher risk of developing atrial fibrillation with a ROR (CI 95%) of 13.18 (11.3 to 15.4) with $P < 0.0001$. Interestingly, the risk of atrial fibrillation was significantly decreased in those receiving the zoster with ROR (CI 95%) of 0.6, (0.5-0.75, $P < 0.0001$), Flu (0.43, 0.36-0.5, $P < 0.0001$), PPV13 (0.4, 0.26-0.65, $P = 0.0001$), and PPSV23 (0.4, 0.28-0.53, $P < 0.0001$) vaccines. Those who were administered the tetanus vaccines had the least likelihood of developing atrial fibrillation with an ROR of 0.3 (0.2-0.6, $P < 0.0001$). Further analysis revealed that Pfizer and Moderna COVID-19 vaccines were responsible for more than 90% of COVID-19

vaccine-associated AF likely due to widespread use of these types of vaccines in the united states (table 4).

A wide array of arrhythmias other than atrial fibrillation was reported following vaccine administration. Supraventricular Tachycardia (SVT) was the most common with 438 cases followed by atrio-ventricular blocks (262), bundle-branch blocks (238), ventricular tachycardias (220), among others. In about two thirds of these cases, patients had received the COVID-19 vaccine. COVID-19 was the suspected culprit in 50.5% of Long QT and 80.3% of atrial flutter cases. Sick Sinus Syndrome (SSS) was the least reported with only 14 cases. Notably however, 92.8% of patients with SSS had received the COVID-19 vaccine (table 5).

Discussion:

While the link between infection and atrial fibrillation is still poorly characterized, the impact of vaccine on this disease is largely unknown. Our study comprehensively analyzed all reported vaccine-related atrial fibrillation and demonstrated for the first time an unknown association between vaccines and atrial fibrillation. Particularly, we show that, among all vaccine, COVID-19 vaccines are significantly associated with the risk of atrial fibrillation with reported odds ratio of almost 10 compared to patients who didn't take any of the COVID-19 vaccines. Additionally, almost all cardiac rhythm disorders that reported in VAERS were primarily shown to be associated with COVID-19 vaccines compared to other vaccines.

The role of inflammation in atrial fibrillation is an emerging field. Inflammation contributes to pathogenesis of AF via structural and electrophysiological alterations of the atrium that enhances the susceptibility for AF development(19, 20). Myocarditis and pericarditis have been linked to increase risk of AF(21). Several proinflammatory signaling are described to mediate atrial fibrillation. For example, the NLRP3 inflammasome, a classic pathway mediating IL-18 and IL-1 β production, has been shown to be increased on AF patients(22). Systematically, AF incidence is known to be elevated critically ill and septic patients(12). Additionally, upregulation of inflammatory markers has been correlated with AF(23).

Since several studies have supported the role of inflammation in AF, different groups have demonstrated that certain infections may participate in atrial fibrillation development. Beside the posing risk of sepsis as mentioned above, pneumococcal pneumonia has been shown to increase the risk of new onset AF(24). *H. pylori* was shown to be associated with high incidence of AF(25). Viral infections such as influenza, hepatitis C, and Zika viruses were correlated with elevated risk of atrial fibrillation(5, 26, 27). While COVID-19 vaccines-associated arrhythmia is a novel finding in this study, the underlying mechanism are unknown. COVID-19 vaccines have been reported to increase the risk of myocarditis and pericarditis which may explain the enhanced risk of AF after COVID-19 vaccines, however, further studies are warranted to delineate the underlying the mechanisms that drive this process.

Although our study uncovered a novel association between vaccines and arrhythmias, certain limitations are notable. While VAERS provides important data, multiple reservations arise such as under-reporting, inaccuracy and incomprehensiveness. Additionally, the population characteristics regarding cardiac history and other cardio-metabolic profile are unknown.

In conclusions, our findings showed that COVID-19 vaccines are strongly associated with AF and other arrhythmias. We recommend obtaining electrocardiogram for certain population who are at high risk for AF before receiving the vaccine. Further studies are required to study rhythm disorders with COVID-19 vaccines regarding which population are at higher risk for AF.

References:

1. Morin DP, Bernard ML, Madias C, Rogers PA, Thihalolipavan S, Estes NA, 3rd. The State of the Art: Atrial Fibrillation Epidemiology, Prevention, and Treatment. *Mayo Clinic proceedings*. 2016;91(12):1778-810.
2. Carlisle MA, Fudim M, DeVore AD, Piccini JP. Heart Failure and Atrial Fibrillation, Like Fire and Fury. *JACC Heart failure*. 2019;7(6):447-56.

3. Safavi-Naeini P, Rasekh A. Thromboembolism in Atrial Fibrillation: Role of the Left Atrial Appendage. *Cardiac electrophysiology clinics*. 2020;12(1):13-20.
4. Zimetbaum P. Atrial Fibrillation. *Annals of internal medicine*. 2017;166(5):ITC33-ITC48.
5. Chang TY, Chao TF, Liu CJ, Chen SJ, Chung FP, Liao JN, et al. The association between influenza infection, vaccination, and atrial fibrillation: A nationwide case-control study. *Heart rhythm*. 2016;13(6):1189-94.
6. Cha MJ, Seo HM, Choi EK, Lee JH, Han K, Lee SR, et al. Increased Risk of Atrial Fibrillation in the Early Period after Herpes Zoster Infection: a Nationwide Population-based Case-control Study. *Journal of Korean medical science*. 2018;33(22):e160.
7. Liprandi AS, Liprandi MIS, Zaidel EJ, Aisenberg GM, Baranchuk A, Barbosa ECD, et al. Influenza Vaccination for the Prevention of Cardiovascular Disease in the Americas: Consensus document of the Inter-American Society of Cardiology and the World Heart Federation. *Global heart*. 2021;16(1):55.
8. Tang RB, Dong JZ, Liu XP, Ma CS. Inflammation and atrial fibrillation: is Chlamydia pneumoniae a candidate pathogen of atrial fibrillation? *Medical hypotheses*. 2006;67(3):462-6.
9. Tetta C, Moula AI, Matteucci F, Parise O, Maesen B, Johnson D, et al. Association between atrial fibrillation and Helicobacter pylori. *Clinical research in cardiology : official journal of the German Cardiac Society*. 2019;108(7):730-40.
10. Andrew P, Montenero AS. Is Helicobacter pylori a cause of atrial fibrillation? *Future cardiology*. 2006;2(4):429-39.
11. Andrew P, Montenero AS. Is there a link between atrial fibrillation and certain bacterial infections? *Journal of cardiovascular medicine*. 2007;8(12):990-6.
12. Kuipers S, Klein Klouwenberg PM, Cremer OL. Incidence, risk factors and outcomes of new-onset atrial fibrillation in patients with sepsis: a systematic review. *Critical care (London, England)*. 2014;18(6):688.
13. Rath B, Niehues P, Leitz P, Eckardt L. [Atrial fibrillation in patients with sepsis and non-cardiac infections]. *Herzschrittmachertherapie & Elektrophysiologie*. 2019;30(3):256-61.
14. Keller M, Meierhenrich R. [New onset atrial fibrillation in patients with sepsis]. *Der Anaesthesist*. 2017;66(10):786-94.
15. Boos CJ. Infection and atrial fibrillation: inflammation begets AF. *European heart journal*. 2020;41(10):1120-2.
16. Manolis AS, Manolis AA, Manolis TA, Apostolopoulos EJ, Papatheou D, Melita H. COVID-19 infection and cardiac arrhythmias. *Trends in cardiovascular medicine*. 2020;30(8):451-60.
17. Perez-Rubio A, San Roman JA, Eiros Bouza JM. The impact of influenza vaccination on cardiovascular disease. *Medicina clinica*. 2021;157(1):22-32.
18. McNeil MM, Duderstadt SK, Sabatier JF, Ma GG, Duffy J. Vaccination and risk of lone atrial fibrillation in the active component United States military. *Human vaccines & immunotherapeutics*. 2019;15(3):669-76.
19. Zhou X, Dudley SC, Jr. Evidence for Inflammation as a Driver of Atrial Fibrillation. *Frontiers in cardiovascular medicine*. 2020;7:62.
20. Hu YF, Chen YJ, Lin YJ, Chen SA. Inflammation and the pathogenesis of atrial fibrillation. *Nature reviews Cardiology*. 2015;12(4):230-43.
21. Morgera T, Di Lenarda A, Dreas L, Pinamonti B, Humar F, Bussani R, et al. Electrocardiography of myocarditis revisited: clinical and prognostic significance of electrocardiographic changes. *American heart journal*. 1992;124(2):455-67.

22. Yao C, Veleva T, Scott L, Jr., Cao S, Li L, Chen G, et al. Enhanced Cardiomyocyte NLRP3 Inflammasome Signaling Promotes Atrial Fibrillation. *Circulation*. 2018;138(20):2227-42.
23. Richter B, Gwechenberger M, Socas A, Zorn G, Albinni S, Marx M, et al. Markers of oxidative stress after ablation of atrial fibrillation are associated with inflammation, delivered radiofrequency energy and early recurrence of atrial fibrillation. *Clinical research in cardiology : official journal of the German Cardiac Society*. 2012;101(3):217-25.
24. Ruiz LA, Serrano L, España PP, Martinez-Indart L, Gómez A, González B, et al. New-onset atrial fibrillation in patients with pneumococcal pneumonia. Impact of timing and duration on short- and medium-term mortality. *The Journal of infection*. 2021;82(1):67-75.
25. Tetta C, Moula AI, Matteucci F, Parise O, Maesen B, Johnson D, et al. Association between atrial fibrillation and *Helicobacter pylori*. 2019;108(7):730-40.
26. Yang YH, Chiang HJ, Yip HK, Chen KJ, Chiang JY, Lee MS, et al. Risk of New-Onset Atrial Fibrillation Among Asian Chronic Hepatitis C Virus Carriers: A Nationwide Population-Based Cohort Study. *Journal of the American Heart Association*. 2019;8(22):e012914.
27. Abdalla LF, Santos JHA, Barreto RTJ, Souza EME, D'Assunção FF, Borges MA, et al. Atrial fibrillation in a patient with Zika virus infection. *Virology journal*. 2018;15(1):23.

Acknowledgment: None.

Funding: The authors declare that this work was not supported by any funds or grants.

Competing Interests: The authors have no relevant financial or non-financial interests to disclose

Data Availability: The datasets from the current study are available from the corresponding author upon request

Hosted file

Data.pptx available at <https://authorea.com/users/472173/articles/563194-vaccine-associated-atrial-fibrillation>