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Review

Benefits and Harms of COVID-19 Vaccines in Cardiovascular Disease: A Comprehensive Review

Chung-Yen Chen [1,2,3] **Ta-Chen Su** [2,3,4]

[1]Department of Environmental and Occupational Medicine, National Taiwan University Hospital Yunlin Branch, Douliu, Taiwan
[2]Department of Environmental and Occupational Medicine, National Taiwan University Hospital, Taipei, Taiwan
[3]Institute of Environmental and Occupational Health Sciences, College of Public Health, National Taiwan University, Taipei, Taiwan
[4]Division of Cardiology, Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan

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Correspondence to
Ta-Chen Su
Department of Environmental and Occupational Medicine, National Taiwan University Hospital, No. 8 Chung-Shan South Rd., Taipei 100, Taiwan.
Email: tachensu@gmail.com

ORCID iDs
Chung-Yen Chen
https://orcid.org/0000-0003-4715-2258
Ta-Chen Su
https://orcid.org/0000-0001-7523-7166

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ABSTRACT

Patients with a history of cardiovascular disease (CVD) who contract coronavirus disease 2019 (COVID-19) tend to have a worse prognosis and more severe cardiovascular side effects. COVID-19 vaccines, which are intended to prevent COVID-19, may also potentially reduce the severity and complications (including cardiovascular sequelae) of COVID-19, especially in patients with a history of CVD. However, there have also been reports of cardiovascular side effects from COVID-19 vaccines of various brands and types. The purpose of this study is to review the benefits and harms of COVID-19 vaccines in relation to CVD. In this thorough review of the most current evidence on the benefits and harms of COVID-19 vaccines, we present information about the characteristics of cardiovascular complications. Most of the evidence focuses on myocarditis or pericarditis, which are most strongly associated with mRNA vaccines and predominantly occur in young males within days of receiving the second dose. Meanwhile, post-vaccination myocardial infarction is more common in older males, and the first dose of adenoviral vector vaccines appears to play a greater role in this complication. This information may guide us in formulating alternative options and implementing targeted surveillance. Gaining more knowledge about the potential benefits and harms of COVID-19 vaccines will improve our ability to make informed decisions and judgments about the balance of these factors.

Keywords: COVID-19; Vaccines; Atherosclerosis; Cardiovascular diseases

INTRODUCTION

Intriguing yet interweaving interplays among cardiovascular disease (CVD), coronavirus disease 2019 (COVID-19), and vaccines have garnered much attention during the COVID-19 pandemic (**Fig. 1**). Detailed evidence suggests that patients with a history of CVD who contract COVID-19 tend to have a worse prognosis than those without a history of CVD. For example, the American College of Cardiology has published a health policy statement that

Conflict of Interest
The authors have no conflicts of interest to declare.

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All data generated or analyzed during this study are included in this published article.

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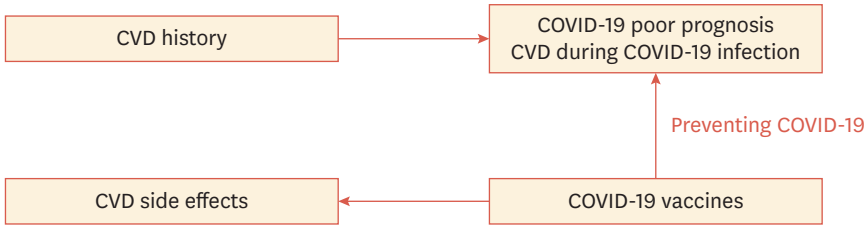

Fig. 1. Schematic diagram of the relationship among atherosclerotic CVD, COVID-19, and vaccines.
CVD, cardiovascular disease; COVID-19, coronavirus disease 2019.

considers certain cardiovascular clinical risks for severe COVID-19 outcomes when allocating and prioritizing COVID-19 vaccines. These risks include unplanned hospitalization for CVD within the past 6 months, pulmonary hypertension (New York Heart Association class III or higher), adult congenital heart disease (physiological stage C or higher), severe peripheral arterial disease, obstructive coronary artery disease, heart failure (stage C or higher), morbid obesity (body mass index >40 kg/m^2), and poorly controlled cardiovascular risk factors (namely, hypertension, diabetes, and obesity).[1]

A study of approximately 30,000 COVID-19 patients found that those categorized as high-risk according to the atherosclerotic cardiovascular disease (ASCVD) risk score, which is calculated using parameters including age, sex, race, blood pressure, blood lipid levels, diabetes, smoking history, hypertension treatment, and statin and aspirin usage, had a significant 4.6-fold increase in the likelihood of severe COVID-19 outcomes compared with the low-risk group. This suggests that the 10-year ASCVD risk score can be helpful in identifying the risk of COVID-19 complications and guiding the allocation of preventive resources and intensive treatment.[2]

In addition, more cardiovascular events accompanied by higher-severity COVID-19 infections have been observed in patients with ASCVD. According to an up-to-date systematic review and meta-analysis that included 37 studies and more than 20,000 participants, the pooled prevalence of myocardial injury among COVID-19 patients is as high as 22.33%. The global burden of acute myocardial infarction (AMI) associated with COVID-19 is also evident from the fact that mortality is 8-fold higher among COVID-19 patients with AMI. The mortality rate is also about 3 times higher among COVID-19 patients with hypertension and with a history of coronary artery disease (CAD).[3] Myers et al.[4] also demonstrated a significantly increased risk of COVID-19-associated AMI in patients with a history of ASCVD and/or familial hypercholesterolemia (both confirmed and suspected cases). Patients with both ASCVD and familial hypercholesterolemia are exposed to an exceedingly higher risk of AMI when infected with COVID-19.[4]

Pathological studies have provided a mechanistic link between COVID-19 infection and related cardiovascular complications. Angiotensin-converting enzyme 2 (ACE2), the receptor for which has been proven to play a key role in the entry and invasion of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) into cells, is also known to be a major regulator of the renin-angiotensin-aldosterone system (RAAS) and is highly expressed in vital organs such as the heart, kidney, lung, gastrointestinal tract, and endothelium. Direct viral infection of endothelial cells has been observed under microscopy, followed by endotheliitis (i.e., diffuse endothelial inflammation) and endothelial dysfunction. These processes can lead to the acceleration and exacerbation of ASCVD.[5,6] Cardiomyocyte injury and resulting myocarditis could also be caused by a similar pathway, either via ACE2 receptors or indirectly

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through infection-mediated vasculitis. Dysregulation of the RAAS is also an etiology of ASCVD mediated by ACE2. Stress (Takotsubo) cardiomyopathy, as well as myocardial injury secondary to an oxygen supply and demand mismatch related to the physiological stress of infection itself, are also potential mechanisms of myocardial ischemia in COVID-19.[7]

Vuorio et al.[8] proposed a 2-hit model for the development of COVID-19-associated ASCVD, including both familial hypercholesterolemia (or other cardiovascular and cardiometabolic diseases) and COVID-19. Familial hypercholesterolemia contributes to chronic dysfunction through elevated levels of low-density lipoprotein cholesterol and lipoprotein (a), while COVID-19 contributes to the acute development of ASCVD through endothelial cell infection and cytokine storm. These 2 factors mutually facilitate endothelial dysfunction, inflammation, and hypercoagulation, ultimately triggering microvascular and macrovascular thrombosis. An important implication of this model is that treatment with statins and other lipid-lowering therapies may be a feasible strategy for combating the cardiovascular outcomes of COVID-19 infection.[8]

On the one hand, COVID-19 vaccines, which are intended to prevent COVID-19, may also potentially reduce the severity and complications—cardiovascular sequelae included—of COVID-19, especially in patients with a CVD history. On the other hand, there have been reports of cardiovascular side effects from COVID-19 vaccines of various brands and types. The purpose of this study is to review the benefits and harms of COVID-19 vaccines concerning CVD.

TYPES OF VACCINES AND CARDIOVASCULAR SIDE EFFECTS

As of December 2022, the World Health Organization has granted emergency use authorization for 11 vaccines. These vaccines can be classified according to their platform (**Table 1**). There are 2 mRNA-based vaccines that encode the spike protein of SARS-CoV-2:

Table 1. Comparison of cardiovascular side effects among types of vaccine platforms

Variables	mRNA	Adenoviral vector	Inactivated whole virus	Protein subunit
Brands	Moderna's Spikevax*, Pfizer/BioNTech's Comirnaty*	Oxford/AstraZeneca's Vaxzevria, India Serum Institute's Covishield, Johnson & Johnson's Janssen*, and CanSino's Convidecia	Bharat Biotech's Covaxin, Sinopharm's Covilo, and Sinovac's CoronaVac	Novavax's Nuvaxovid* and India Serum Institute's COVOVAX
Mechanisms	Encodes the spike protein of SARS-CoV-2	Packages the SARS-CoV-2 coding sequence in a recombinant adenovirus	Inactivated SARS-CoV-2 with adjuvant	Contains isolated and purified SARS-CoV-2 proteins
Pooled vaccine effectiveness[9]				
Infection	3 doses: 96% 2 doses: 77% 1 dose: 59%	2 doses + 1 dose mRNA: 88% 2 doses: 74% 1 dose: 61%	2 doses: 57% (n.s.)	-
Symptomatic infection	3 doses: 98% 2 doses: 91% 1 dose: 55% (n.s.)	1 dose: 43% (n.s.)	2 doses: 72% (n.s.) 1 dose: 48% (n.s.)	-
Severe infection	2 doses: 99% 1 dose: 96%	2 doses: 96%	2 doses: 88% 1 dose: 66% (n.s.)	-
Hospital admission	3 doses: 95% 2 doses: 81%	2 doses: 81% 1 dose: 80%	-	-
Cardiovascular side effects	Myocarditis, pericarditis, AMI, arrhythmia, stress cardiomyopathy, thrombosis thrombocytopenia	Myocarditis, pericarditis, AMI, thrombosis, thrombocytopenia	Type 1 Kounis syndrome	-

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; AMI, acute myocardial infarction; n.s., non-significant.
*Approved or authorized for use by the United States Food and Drug Administration.

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Moderna's Spikevax and Pfizer/BioNTech's Comirnaty. Four vaccines utilize a non-replicating viral vector, which packages the SARS-CoV-2 coding sequence in a recombinant adenovirus vector. Of these, 2 use the Oxford/AstraZeneca formula (Vaxzevria and Covishield), while the others are Janssen from Johnson & Johnson and Convidecia from CanSino. Three vaccines contain the inactivated whole virus, including Covaxin from Bharat Biotech, Covilo from Sinopharm, and CoronaVac from Sinovac. Two vaccines are composed of a protein subunit, both using the Novavax formula (Nuvaxovid and COVOVAX). As of the end of 2022, 4 of these 11 vaccines have been approved or authorized for use in the United States by the US Food and Drug Administration: the 2 mRNA vaccines, the Novavax protein subunit vaccine, and Johnson & Johnson's Janssen viral vector vaccine.

According to a systematic review and network meta-analysis, an mRNA booster significantly improves protection against infections, symptomatic infections, and related hospital admissions, regardless of the type of vaccine received for the first 2 doses. For the Delta and Omicron variants, a 3-dose regimen of an mRNA vaccine has 93% effectiveness against hospitalization, and a 2-dose regimen of an adenovirus vector vaccine followed by an mRNA booster has 77% effectiveness against infection.[9] A systematic review and meta-analysis of 11 studies showed that receiving 3 doses of a COVID-19 vaccine significantly reduced the risk of contracting the Omicron variant by 56% compared to being unvaccinated and by 40% compared to receiving a 2-dose schedule.[10] According to a large case-control study, the Moderna mRNA vaccine has high effectiveness against the Delta variant: 80.2% in the first 90 days and 68.9% in the second 90 days. However, its effectiveness against the Omicron variant is less clear: 44.0% in the first 90 days, decreasing to only 23.5% in the second 90 days. Nevertheless, 3 doses of the Moderna mRNA vaccine still have high effectiveness (over 99%) in preventing hospital admissions for both variants.[11]

There is an ongoing debate about whether the vaccines have flattened the epidemic curve, especially as new waves and variants of SARS-CoV-2 have rapidly emerged. However, concerns about adverse events related to the vaccines have been raised, initially in Israel, due to elevated incidence rates of myocarditis and pericarditis in adolescents and young adults after vaccination.[12]

Although considered the most effective type of vaccine by some experts, mRNA vaccines have been associated with reports of more cases and types of cardiovascular adverse events than other types of vaccines. Post-mRNA vaccination myocarditis/pericarditis is a major issue, probably associated with the CD4 cytokine reaction of T cells induced by the vaccines.[12] Similar findings have previously been observed in vaccines of other pathogens, including meningococcus, typhoid, Japanese encephalitis, and anthrax.[12] Thrombosis of cerebral vessels and thrombocytopenia, specifically idiopathic thrombocytopenia and acquired thrombotic thrombocytopenia purpura, have also been reported. Possible mechanisms of thrombosis include aggregation of platelets, inflammation of the brain endothelium, and impairment of the blood-brain barrier; all could be associated with stimulation of the spike protein encoded by the mRNA vaccines. The vaccines can also produce anti-platelet autoantibodies, leading to thrombocytopenia.[13] Other reported cardiovascular complications of mRNA vaccines include AMI, arrhythmia, and stress cardiomyopathy (**Table 1**).[12]

The primary cardiovascular side effects after receiving viral vector vaccines are thrombosis with thrombocytopenia syndrome or vaccine-induced immune thrombotic thrombocytopenia (VITT). These conditions are strongly related to the development

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of anti-platelet and anti-platelet factor 4 (PF4) antibodies, which may be induced by inflammation following vaccination or by the binding of viral proteins in the vaccines to PF4. ethylenediaminetetraacetic acid, which is contained in some vaccines, is also thought to contribute to these conditions by increasing vascular permeability and the spread of vaccine components.[13] There have also been documented cases of myocarditis, pericarditis, and AMI following vaccination with adenoviral vector vaccines (**Table 1**).[12] One case of type I Kounis syndrome, which is an allergic vasospastic angina caused by endothelial dysfunction, was reported in Turkey following vaccination with an inactivated vaccine.[12,14]

MYOCARDITIS/PERICARDITIS AND VACCINES

As of the end of 2022, the United States' Vaccine Adverse Event Reporting System (VAERS) contained reports of 3,177 cases of myocarditis, 2,244 cases of pericarditis, and 73 cases of endocarditis among a population of more than 268 million people who had received at least 1 dose of a vaccine, out of a total of 665 million doses administered.[15] According to official statistics from the Taiwan Center for Disease Control's VAERS, 238 cases of myocarditis/pericarditis were identified in Taiwan between March 2021 and February 2022. Of these patients, 203 (85.3%) were hospitalized, 49 (20.6%) received intensive care, 9 were treated with extracorporeal membrane oxygenation, and 4 died. The highest rates of myocarditis/pericarditis were observed in male adolescents under 18 years of age who received the second dose of the BNT vaccine (126.79 cases per million doses) and young adults under 24 years of age who received the Moderna vaccine (93.84 cases per million doses).[16]

Ho et al. reviewed 29 studies and identified 314 cases of myocarditis, 59 cases of myopericarditis, and 8 cases of pericarditis following vaccination. Those diseases are the most commonly reported cardiovascular events after receiving mRNA vaccines. All but 2 cases of pericarditis (1 from a randomized controlled study and 1 from a case series) and another case of myocarditis from a case series study were associated with mRNA vaccines. The 3 exceptions were related to adenovirus vector vaccines (2 with the Johnson & Johnson vaccine and 1 with the Oxford/AstraZeneca vaccine). As with other studies, most patients who developed post-vaccination myocarditis were young males without previous medical histories, with almost 80% of cases occurring in individuals under 30. The most common clinical presentations included chest pain, dyspnea, fever, fatigue, and myalgia. All cases of myocarditis presented with elevated troponin levels, while pericarditis cases showed normal troponin levels, but elevated C-reactive protein levels and erythrocyte sedimentation rates. ST-segment elevation was the most common abnormality on electrocardiography. Reduced left ventricular ejection fraction (LVEF) and regional wall motion abnormalities were features seen on echocardiography, but nonspecific changes or normal findings could also be present. The prognosis was generally good, with only 1 patient dying.[12,17]

According to a recent systematic review and meta-analysis, the estimated incidence rate of myocarditis is 14.80 cases per million people or 8.84 cases per million doses, with a significant risk elevation of 39% among those who were vaccinated compared to their unvaccinated counterparts. Myocarditis mainly affects males and people under 40, with 3.44 and 2.20 higher risks in those groups, respectively. The second dose is associated with a higher incidence of myocarditis than the first or third dose. mRNA vaccines have a significantly higher incidence of myocarditis than adenoviral vector and inactivated vaccines. The Moderna and BNT vaccines are associated with increases of 3.13 and 1.57 times in the likelihood of myocarditis, respectively.[18]

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Pillay et al.[19] reviewed 46 studies to analyze the incidence, risk factors, case characteristics, and short- and long-term outcomes of myocarditis/pericarditis following vaccination. They found that the incidence of myocarditis after the second dose was highest in male adolescents (50–139 cases per million) and young male adults under 30 (28–147 cases per million). However, there is currently insufficient evidence to draw any conclusions about the incidence of myocarditis or pericarditis after the third dose. The incidence of myocarditis from the Moderna vaccine is probably higher than that of the Pfizer-BNT vaccine in men and women under 40, but no significant differences have been noted for the remaining population. The incidence of myocarditis or pericarditis is not significantly different according to whether the second dose is the same vaccine type as the first dose or a different vaccine type. Extending the dosing interval to more than 30 days might reduce the risk of myocarditis or pericarditis. Insufficient information is available about the immunocompromised population. Most cases of myocarditis were in men, with a median age of 20–29, onset within 2–4 days on average, and more than 70% occurring after receiving the second dose. Most cases presented with chest pain and troponin elevation, but only a few patients showed an LVEF <50%. Most patients were hospitalized, while only a few were admitted to the intensive care unit (ICU). The most common treatment was non-steroidal anti-inflammatory drugs, but beta-blockers, angiotensin-converting enzyme inhibitors, colchicine, H2 antagonists, steroids, and intravenous immunoglobulin G are also feasible options. Long-term follow-up found that about 50% of cases were symptom-free, and some remaining patients still showed abnormal findings on echocardiography.[19]

Larson et al. were among the first to describe a series of 8 patients hospitalized due to chest pain (most commonly described as constant, non-positional, and non-pleuritic pain) and diagnosed with myocarditis. All symptoms appeared within 2–4 days of receiving an mRNA vaccination, with all but 1 patient experiencing symptoms after the second dose. Elevated troponin values were observed in all patients. The most common feature on electrocardiography was diffuse ST-segment elevation. Only 2 patients had decreased LVEF, but all had segmental or diffuse wall motion abnormalities. Five of the patients were hemodynamically stable, and the remaining 3 received intensive care but were eventually discharged in stable condition.[20]

Mansanguan et al.[21] identified 7 cases of myocarditis, pericarditis, or myopericarditis among more than three hundred adolescents under 18 who received the second dose of the BNT mRNA vaccine. The clinical presentation included fever, chest pain, chest discomfort, pericardial effusion, headache, palpitations, and dyspnea. Three of the patients developed pericardial effusion. Electrocardiographic abnormalities included diffuse ST-segment elevation with PR depression, premature atrial complex, and junctional escape rhythm. Only 1 patient was admitted to the ICU, and all patients fully recovered and were discharged within 2 weeks.[21]

In a large case-control study conducted in France during May and October 2021, the risk of myocarditis and pericarditis was found to be significantly elevated during the first week after the second-dose vaccination of BNT (8.1 times and 2.9 times the risk, respectively) and Moderna vaccines (30 times and 5.5 times the risk, respectively). A history of hospitalization due to myocarditis or pericarditis within the past 5 years or a history of SARS-CoV-2 infection within the past 30 days further increased the risk. The Moderna vaccine generated more excess cases of myocarditis and pericarditis attributed to vaccination in almost every sex and age group. For young adolescents under 18, 1.9 excess cases of myocarditis per 100,000 doses could be attributed to the second dose of the BNT vaccine. For young adults under 25, it was

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estimated that 4.7 and 17 excess cases of myocarditis per 100,000 doses could be attributed to the second dose of the BNT and Moderna vaccines, respectively.[22]

A self-controlled case series study conducted in England between December 2020 and August 2021 found an increased risk of myocarditis associated with the first dose of the AstraZeneca and BNT vaccines, as well as both the first and second doses of the Moderna vaccine. The researchers estimated 2, 1, and 6 extra myocarditis events per 1 million population within 28 days following the first dose of the AstraZeneca, BNT, and Moderna vaccines, respectively. Ten additional cases of myocarditis following the second dose of the Moderna vaccine were also noted. In contrast, the researchers estimated 40 excess cases of myocarditis following COVID-19 infection, greatly outweighing the effect of the vaccines.[23]

Although myocarditis is more prevalent in young males, we have experience treating an 81-year-old woman who complained of dyspnea and was diagnosed with post-vaccination myocarditis and dilated cardiomyopathy. A comparison with previous chest X-ray imaging showed a significantly enlarged heart (**Fig. 2A**). Serial electrocardiograms showed sinus rhythm with premature atrial complex in a bigeminy pattern, left atrial enlargement, ST and T wave abnormalities, and a prolonged QT interval. Twenty-four-hour Holter monitoring recorded rare paroxysmal non-sustained atrial fibrillation (<0.01%), occasional ventricular ectopic beats (0.6%), and frequent supraventricular ectopic beats (38.8%, mostly in bigeminy). Findings from an echocardiogram included a dilated left atrium and ventricle, as well as global hypokinesia with severely reduced left ventricular systolic function (LVEF <20%) (**Fig. 2B**).

The most supported hypothesized mechanisms for myocarditis following mRNA vaccines are as follows: 1) hyperimmunity or inflammation triggered by the spike protein, mRNA strand, or other triggers; 2) delayed hypersensitivity induced by antibodies and immune complexes; 3) hypersensitivity related to significant eosinophilia, which has been observed in smallpox vaccine myocarditis but has not been adequately proven for mRNA COVID-19 vaccines; 4) hypersensitivity to vaccine vehicle components like polyethylene glycol or lipid nanoparticles; 5) molecular mimicry of the viral spike protein with some kind of myocardial protein; and 6) direct toxicity mediated by the spike protein. As stated by Heymans and Cooper,[24] "the generation of autoantibodies and hormone-related factors contribute to the sex-specific differences." One hypothesis that explains the predominant incidence of myocarditis in young males is associated with testosterone, which may increase viral binding to myocytes and inhibit anti-inflammatory function. This mechanism has already been supported for Coxsackie virus-induced myocarditis, but remains an unanswered question for COVID-19 vaccines.[12,19]

To summarize, cardiac symptoms such as chest pain, dyspnea, and palpitation after vaccination should raise the alarm for the possibility of myocarditis/pericarditis, especially if they occur in young males a few days after the second dose of a vaccine. Elevated troponin levels, abnormal electrocardiographic patterns, abnormal cardiac function on echocardiography, and cardiac magnetic resonance imaging can help with the diagnosis and confirmation of these conditions.[25]

MYOCARDIAL INFARCTION (MI) AND VACCINES

By the end of 2022, the United States' VAERS had reported 1,896 cases of MI, 1,159 cases of AMI, and 1,314 cases of angina pectoris.[15]

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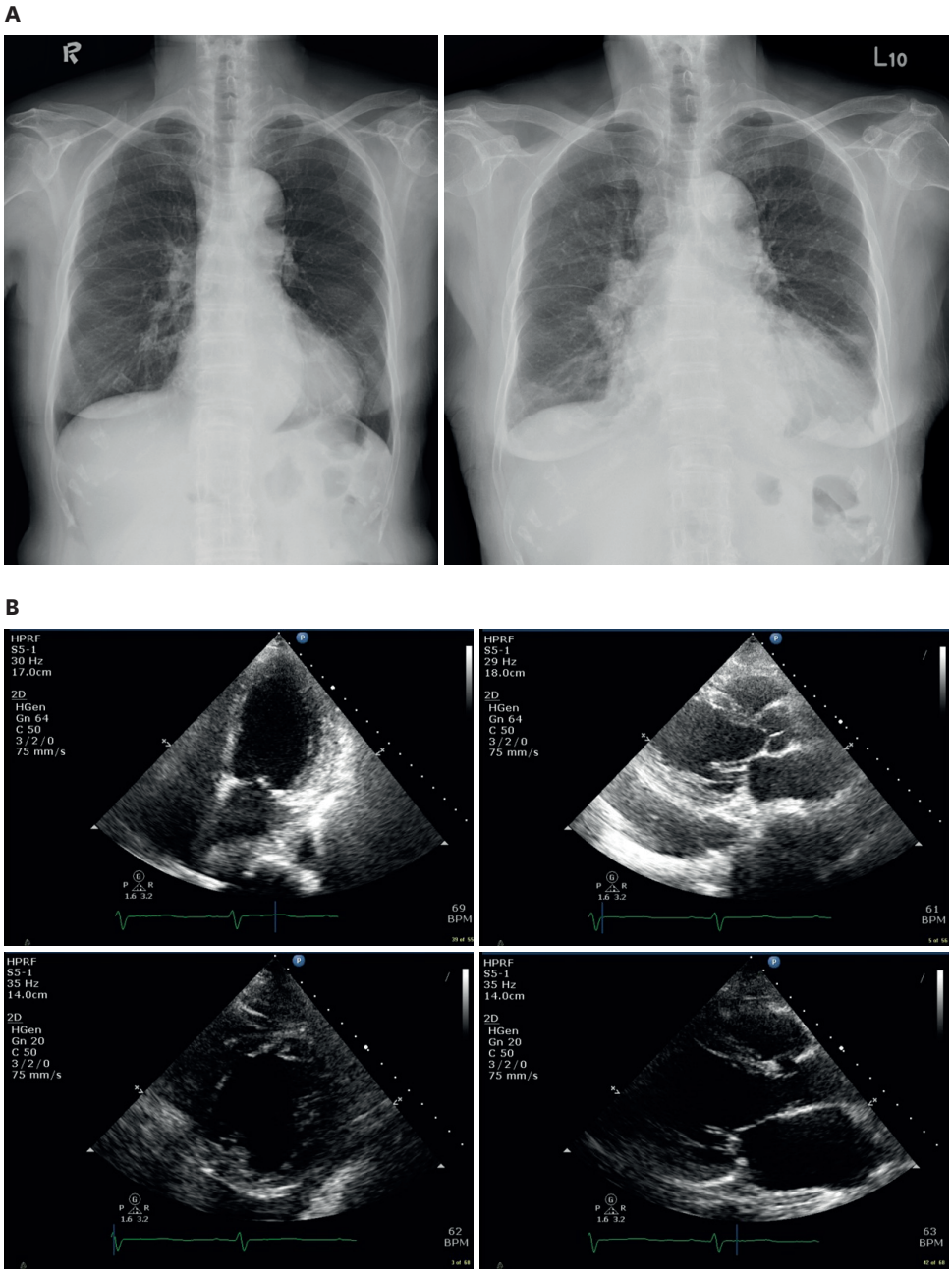

Fig. 2. An 81-year-old woman with post-vaccination myocarditis and dilated cardiomyopathy. (A) Cardiomegaly on a chest X-ray (left: baseline image, right: at disease onset). (B) A dilated left atrium and ventricle, as well as global hypokinesia in the echocardiogram.

An analysis of data from Israel's National Emergency Medical Services (EMS) found that there was a 25% or greater increase in the volume of EMS calls for both cardiac arrest and acute coronary syndrome among the population under 40 from January to May 2021, compared to the same period in 2019 and 2020. The weekly emergency call counts for cardiac arrest and acute coronary syndrome were significantly associated with the rates of the first and second vaccination doses. However, this intriguing temporal association does not automatically imply a causal relationship, especially when it is impossible to distinguish the effect of

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infection and vaccination in the current setting. Nonetheless, the findings still raise concerns about the potential for severe cardiovascular complications from vaccines.[26]

A recent systematic review retrieved 29 studies regarding the relationship between COVID-19 vaccines and MI. Eighteen studies reported events after AstraZeneca viral vector vaccines, 14 presented information on complications after Pfizer BNT vaccines, and nine reported MI cases after Moderna vaccines. Among these studies, 69% of cases were reported after the first dose and 14% after the second; furthermore, 44% reported ST-segment elevation, and 26% reported non-ST segment elevation. Of these reported MI patients, 29% died.[27]

A cohort study in a Singapore medical center enrolled 29 patients with AMI starting within 14 days after COVID-19 vaccination (primarily within 24 hours), of which 5 cases were complicated with heart failure, 2 had cardiogenic shock, and 3 required intubation. There was also 1 case of mortality. The cases of myocarditis in the same cohort tended to be in younger patients and to develop more frequently after the second dose. In contrast, cases of AMI tended to be in older patients and to occur after the first dose.[28]

A French cohort study found that the risk of AMI increased by 29% after the first dose of the adenoviral-based Oxford AstraZeneca vaccine, while the risk of pulmonary embolism increased by 40%. No significant increase in risk was found for either of the mRNA vaccines (BNT and Moderna).[29]

According to a Korean retrospective cohort study conducted by Kim et al.,[30] a full vaccination schedule significantly reduced the risk of both AMI and ischemic stroke for COVID-19 patients by 52% and 60%, respectively. Similar trends were observed among all subgroups, regardless of sex, medical history, and COVID-19 severity.[30]

Baronti et al.[31] performed detailed postmortem laboratory and pathological studies and cardiac magnetic resonance imaging on 5 cases of mortality associated with post-vaccination MI. A thrombotic lesion of the coronary artery was found in all 5 cases. The absence of anti-PF4 excluded the diagnosis of VITT. All 5 cases carried at least 1 pro-thrombotic mutation. While these findings do not establish a causal relationship between COVID-19 vaccines and MI, they point towards further hints in the puzzle.[31]

In conclusion, the evidence for a relationship between COVID-19 vaccines and MI is less clear than with myocarditis. Some studies have observed distinctive characteristics among cases, such as older patients more frequently experiencing onset after the first dose of viral vector vaccines. This, as stated by Zafar et al.,[27] suggests that the immune response may play a smaller role in vaccine-induced MI than in myocarditis. Instead, it is more plausible to include a demand-supply mismatch in the explanation, especially among elderly patients or those with comorbidities who are more susceptible to the stress of vaccination.[27] However, further studies are still needed to understand this issue comprehensively.

ARRHYTHMIA AND VACCINES

As of the end of 2022, the United States' VAERS had reported 1,248 cases of arrhythmia and 4,026 cases of atrial fibrillation. Kumar et al.[32] analyzed VAERS data from early January 2022. Out of 2,611 atrial fibrillation events, 315 were new-onset cases. There was a slight excess of

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male cases compared to female cases, and the onset time following the first dose was slightly higher than following the second dose. Most cases were aged over 40.[32]

An English study by Patone et al.[23] estimated a 93% increased risk of arrhythmia following the second dose of the Moderna vaccine. The AstraZeneca and BNT vaccines did not significantly increase the risk of arrhythmia. However, COVID-19 infection increased the risk of arrhythmia by 11.73 times in the first 7 days, 6.57 times in the second 7 days, 2.30 times in the third 7 days, and 1.67 times in the fourth 7 days.[23]

A multicenter study in Thailand found that the AstraZeneca vaccine increased the incidence of supraventricular tachycardia by 73% in patients with cardiac implantable electronic devices. A 4.16-fold increase in ventricular tachycardia was also observed. This result, however, may not be applicable to the general population without histories of cardiovascular comorbidities.[33]

STRESS CARDIOMYOPATHY AND VACCINES

As of the end of 2022, the United States' VAERS had reported 95 cases of stress cardiomyopathy. A recent systematic review and meta-analysis included 10 case reports of individuals with an average age of 62 years, of whom 90% were male. Eighty percent had received mRNA vaccines, and 20% had received the AstraZeneca adenoviral vector vaccine. Fifty percent experienced onset of the condition following the first dose and 40% following the second dose. All cases had an elevated level of troponin and electrocardiographic abnormalities, and 90% had an LVEF below 50%. Despite these symptoms, all patients recovered without any irreversible consequences. Several mechanisms have been proposed for the development of Takotsubo cardiomyopathy in these cases. These mechanisms include vasospasm and direct myocardial injury caused by excess stress-induced catecholamine release. Other potential contributing factors include cytokine response, inflammation, and endothelial dysfunction. Additionally, it is suggested that viral spike proteins may interfere with the balance of the RAAS.

CONCLUSION

Bozkurt et al. compared the public health burden of COVID-19 infection, hospitalization, severe cases, and mortality, which can be prevented to some extent through vaccination, with the risk of post-vaccination myocarditis. The authors stated that the former outweighs the latter.[34] However, it is self-evident that the benefits of collective preventive strategies may not persuade many individuals to cooperate with and adopt these policies, especially when they have a genuine fear of perceived risks.

By thoroughly reviewing the most current evidence on the benefits and harms of COVID-19 vaccines, we provide information about the characteristics of cardiovascular complications. Most of the evidence has focused on myocarditis and pericarditis, which are most strongly associated with mRNA vaccines and predominantly occur in young males within days of receiving the second dose. This information may guide us in formulating alternative options, such as avoiding mRNA vaccines for young males and implementing targeted and proactive surveillance. Meanwhile, post-vaccination MI occurs more frequently in older men, and

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the first dose of adenoviral vector vaccines plays a greater role. This may lead to a different preventive strategy for MI compared to myocarditis/pericarditis.

As discussed above, increased risks of CVD and non-CVD complications are observed in COVID-19 patients with a history of CVD. The key information to determine whether the benefits of vaccination outweigh post-vaccination side effects involves the safety and efficacy of the vaccines. Ye et al.[35] conducted a self-controlled case-series study to compare the risk of major cardiovascular events before and after BNT and CoronaVac vaccination. They found that both mRNA and inactivated viral vaccines did not increase CVD risk and actually reduced the risks in specific periods, such as 2–4 weeks after the first dose of the BNT vaccine (incidence rate ratio [IRR]=0.40; 95% confidence interval [CI], 0.18–0.93), 0–2 weeks (IRR=0.43; 95% CI, 0.24–0.75) and 2-4 weeks (IRR=0.54; 95% CI, 0.33–0.90) after the first dose of the CoronaVac vaccine. The findings remained consistent in different subgroups of sex, age, and underlying CVD (including coronary heart disease and cerebrovascular disease).[35] Raxwal et al.[36] enrolled 330 CVD patients, including those with CAD, hypertension, congestive heart failure, diabetes, arrhythmia, and stroke, to follow major and minor complications after their vaccination. Among 221 patients who received Moderna, only 1 was diagnosed with deep vein thrombosis (0.5%). Of the 92 patients who received Pfizer, 1 patient was diagnosed with pulmonary embolism (1.1%). No other major CVD complications were reported in these patients or the other 17 patients who received Johnson & Johnson. Interestingly, mRNA vaccines have higher efficacy (14.0% and 13.0% of patients infected for Moderna and Pfizer, respectively), but also higher rates of complications (50% and 43.5%). In comparison, the adenoviral vaccine has lower efficacy (35.3% infection) and lower rates of complications (35.3% and without major CVD events).[36] Although evidence is still scarce, this implies that for CVD patients, the benefits of vaccination outweigh its side effects.

In addition, as concerns about the so-called “long COVID” symptoms with a duration of more than 4 weeks or even 12 weeks, including long-term cardiovascular outcomes, rise,[37] recent evidence on vaccination reducing the likelihood of these symptoms furnishes hope.[38-40]

However, there are still many unknown aspects of the cardiovascular complications of COVID-19 vaccines. By gathering adverse event registrations, conducting epidemiological analyses of cases, completing comprehensive surveys of risk factors, and performing detailed mechanistic studies, we may gain more knowledge about these complications in the near future. We hope this will improve our judgment and decision-making when balancing the benefits and harms of these vaccines.

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