Review

Clinical cardiovascular emergencies and the cellular basis of COVID-19 vaccination: from dream to reality?

Yiran E. Li[1], Shuyi Wang[2], Russel J. Reiter[3], Jun Ren[1,*]

[1] Shanghai Institute of Cardiovascular Diseases, Department of Cardiology, Zhongshan Hospital, Fudan University, Shanghai, 200032, China
[2] Department of Emergency, Shanghai Tenth People's Hospital, Tongji University, Shanghai, 200072, China
[3] Department of Cellular and Structural Biology, UT Health San Antonio, San Antonio, USA

ABSTRACT

Objectives: SARS-CoV-2 is responsible for the global COVID-19 pandemic, with little prevention or treatment options. More than 600 million mortalities have been documented from SARS-CoV-2 infection, with the majority of fatalities occurring among elderly patients (aged >65 years). A number of vaccines have been developed in an effort to restrain the rapid spread of SARS-CoV-2. Considering the widespread administration of these vaccines, substantial side or undesired effects in multiple organ systems have emerged, necessitating essential critical care. Herein, we tabulate the adverse cardiovascular responses resulting from COVID-19 vaccines.
Design or Methods: We searched PubMed for articles published through April, 2022, with the terms "SARS-CoV-2", "COVID-19", "cardiovascular", "SARS-CoV-2 vaccines", "COVID-19 vaccines", "myocarditis", "pericarditis", "thrombosis", "thrombocytopenia", "vaccine-induced thrombotic thrombocytopenia", "acute coronary syndrome", "myocardial infarction", "hypertension", "arrythmia", "postural orthostatic tachycardia syndrome", "Takotsubo cardiomyopathy", "cardiac arrest" and "death". We mainly selected publications from the past 3 years, but did not exclude widely referenced and highly regarded older publications. Besides, we searched the reference lists of articles identified by above search method and chose those we considered relevant.
Results: COVID-19 vaccines evoke rare but fatal thrombotic events, whereas messenger RNA\055based vaccines appear to be associated with risks of pericarditis/myocarditis, with the latter being more predominant in young adults following the second dose. Reports of other cardiovascular responses, including hypertension, arrhythmia, acute coronary syndrome, and cardiac arrest, have also been indicated.
Conclusion: The undesired cardiovascular complications remain infrequent, giveng the large number of vaccinations inoculated to general population. And lower mortality takes precedence over the undesired cardiovascular complications.

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Introduction

COVID-19 first emerged in Wuhan, China, in December 2019, resulting in a rapid spread in the outbreak of pneumonia. The pandemic has affected millions of individuals and claimed more than 6 million lives worldwide, leading to massive health, social, and economic issues (Cascella *et al.,* 2022). Patients with COVID-19 often experience fatigue, fever, cough, pneumonia, and acute respiratory distress syndrome at the advanced stages (Shirani *et al.,* 2020). Except for respiratory symptoms, COVID-19 might be directly or indirectly linked to severe cardiovascular complications, such as palpitation, chest pain, and acute cardiovascular injury (Driggin *et al.,* 2020). SARS-CoV-2 disrupts the renin-angiotensin-aldosterone system and upregulates angiotensin 2 and proinflammatory cytokines, with detrimental sequelae on vascular endothelium. In particular, systemic inflammatory response syndrome is often noted in patients with COVID-19, offering a possible machinery for multiple organ failure, including the heart (Shiravi *et al.,* 2022).

Alarmingly, several risk factors negatively impact clinical sequelae of COVID-19, such as aging and pre-existing health problems (e.g., chronic respiratory disease, diabetes mellitus, cardiovascular disease, cancer, and obesity) (Huang *et al.,* 2020). Although programs are launched to determine the optimal COVID-19 manage-

* Corresponding author.
   E-mail address: jren_aldh2@outlook.com (J. Ren).

Table 1
Available data on the efficacy of current vaccines.

Vaccine name	Company	Category	Efficacy (%)
BNT162b2	Pfizer/BioNTech	mRNA	α: 78-95
			β: 75
			δ: 42-79
			o: 29-62
mRNA-1273	Moderna	mRNA	α: 84-99
			β: 96
			δ: 76-84
			o: 37-75
AZD1222	Oxford/AstraZeneca	adenovirus vector	α: 79
			δ: 60-67
			o: 29-43
Ad26.COV2.s	Johnson & Johnson	adenovirus vector	δ: 47-79
Sputnik V	Gamaleya	adenovirus vector	δ: 81

Data and contents listed here are extracted from Abu-Raddad et al. (2021); Andrews et al. (2022); Chemaitelly et al. (2021); Fiolet et al. (2022); Pouwels et al. (2021); Sheikh et al. (2021); Tang et al. (2021).

ment, no definitive curative therapy is available. At this time, prevention remains the main focus for the management of COVID-19. The development of effective vaccines is vital to control the COVID-19 pandemic and reduce the mortality risk in already infected patients. However, adverse reactions, such as headache, fever, fatigue, injection site reaction, and rare, although devastating, cardiovascular complications are observed following vaccine inoculation. Due to the wide inoculation, it is essential to understand the potential adverse events, risks, and advantages of COVID-19 vaccines (Jeet Kaur et al., 2021; Kaur et al., 2021; Shiravi et al., 2021). Here, we explore cardiovascular side effects following COVID-19 inoculation, including myocarditis/pericarditis, and thrombotic events in addition to rare cases of arrhythmia, hypertension, acute coronary syndrome, and cardiac arrest.

Short history of COVID-19 vaccines and clinical benefits

The rapid spread of COVID-19 necessitated effective vaccines to control this pandemic. More than 4 billion COVID-19 vaccines have been administered worldwide. Approximately 24% of the world population has received at least one dose of the vaccine (Mathieu et al., 2021). Indeed, the development of COVID-19 vaccine progressed faster than any other such treatment in history. To date, 117 SARS-CoV-2 vaccine candidates have reached clinical trials, and 194 vaccines were evaluated in preclinical studies (Joshi et al., 2021). SARS-CoV-2 vaccines are classified into four categories, including DNA and RNA, viral vector, inactivated virus, and protein-based vaccines (Chung et al., 2020). DNA and RNA COVID-19 vaccines comprise a genetically modified nucleotide sequence encoding SARS-CoV-2 to elicit an immune response, enveloped in lipid nanoparticles to reduce degeneration and increase translation efficiency. Viral vector vaccines incorporate part of the gene sequence of COVID-19 virus into a safe virus to construct a fusion type of the two viruses. Therefore, they possess both the infectivity of vector virus and antigenicity of SARS-CoV-2. Inactivated COVID-19 vaccines originated from native SARS-CoV-2, which process immunogenicity but render replication defective. Protein-based vaccines use harmless fragments of protein or protein shells that imitate SARS-CoV-2 to prompt a safe immune response (Haimei, 2021). DNA delivered within a nonreplicating recombinant adenovirus vector-based system is a formulation used by Johnson & Johnson, Sputnik V, and AstraZeneca vaccines, whereas the Moderna and Pfizer vaccines use messenger RNA (mRNA) and lipid nanoparticle delivery (Table 1). All these vaccines encode SARS-CoV-2 spike (S) protein, ultimately evoking enhanced human immunity.

Pfizer/BioNTech vaccine trial indicated that the effectiveness against symptomatic COVID-19 was 52% within 12 days following the first dose and subsequently elevated to 95% after the second dose (Polack et al., 2020). A comparable situation was found with the Oxford/AstraZeneca vaccine, with 76% protection against symptomatic COVID-19 following 22 days from the first dose, which increased to 81% following the second dose, which was administered 12 weeks after the first vaccination (Hung and Poland, 2021). These findings suggested that receiving the second dose of vaccine strengthens the immune reaction and is essential to provide additional protection from COVID-19 (Table 1). In addition, a recent report claimed that a third dose of vaccine was effective in further lowering the risk of COVID-19 infection and related illness by 11.4- and 10-fold, respectively. This study also suggested the effect of booster shots in reducing δ variant infection (Patalon et al., 2022). However, more work is needed to evaluate the decision-making for booster doses. Notably, most of the newly reported SARS-CoV-2 cases in the United Kingdom were caused by the o variant. Lower risks of hospital admission and death were confirmed for the o variant than infections from the δ variant (Bager et al., 2022). Evaluation of vaccine effectiveness reported a moderate decrease in vaccine-offered protection of hospitalization in confirmed o infection compared with the δ variant. The new variants BA.2.12.1, BA.4, and BA.5 are believed to escape neutralizing antibodies evoked by vaccination and infection, indicating the likelihood of new variants of o to mutate in the direction of immune escape. Previous studies noted a substantial decrease in vaccine efficacy against symptomatic infection (Andrews et al., 2022; Sheikh et al., 2022). Nevertheless, mRNA vaccine boosters are still deemed highly protective against hospitalization or mortality in the o infection cases (Andrews et al., 2022; Nyberg et al., 2022).

Cardiovascular complications of COVID-19 vaccines

Myocarditis and pericarditis

Among reported adverse reactions, myocarditis/pericarditis is the most frequently reported cardiovascular comorbidity for mRNA vaccines, especially following the second vaccination (Figure 1). The disease ranges from mild asymptomatic inflammation of the heart to severe heart failure and even death (Albert et al., 2021; Parra-Lucares et al., 2021). A total of 2984 incidences of myocarditis and 2081 cases of pericarditis were reported in the Vaccine Adverse Event System (VAERS) (Table 2) (Centers for Disease Control [CDC], 2022). Compared with healthy individuals, the odds ratio of developing pericarditis was 1.27 following Pfizer vaccine administration as opposed to 5.39 for those uninoculated patients with SARS-CoV-2 (Barda et al., 2021). The a.ge of individuals who experienced postvaccination myocarditis ranged from 14 to 67, with 79% cases being those who under 30 years. Furthermore, the majority of patients were male (65.1%) (Shaw et al., 2021).
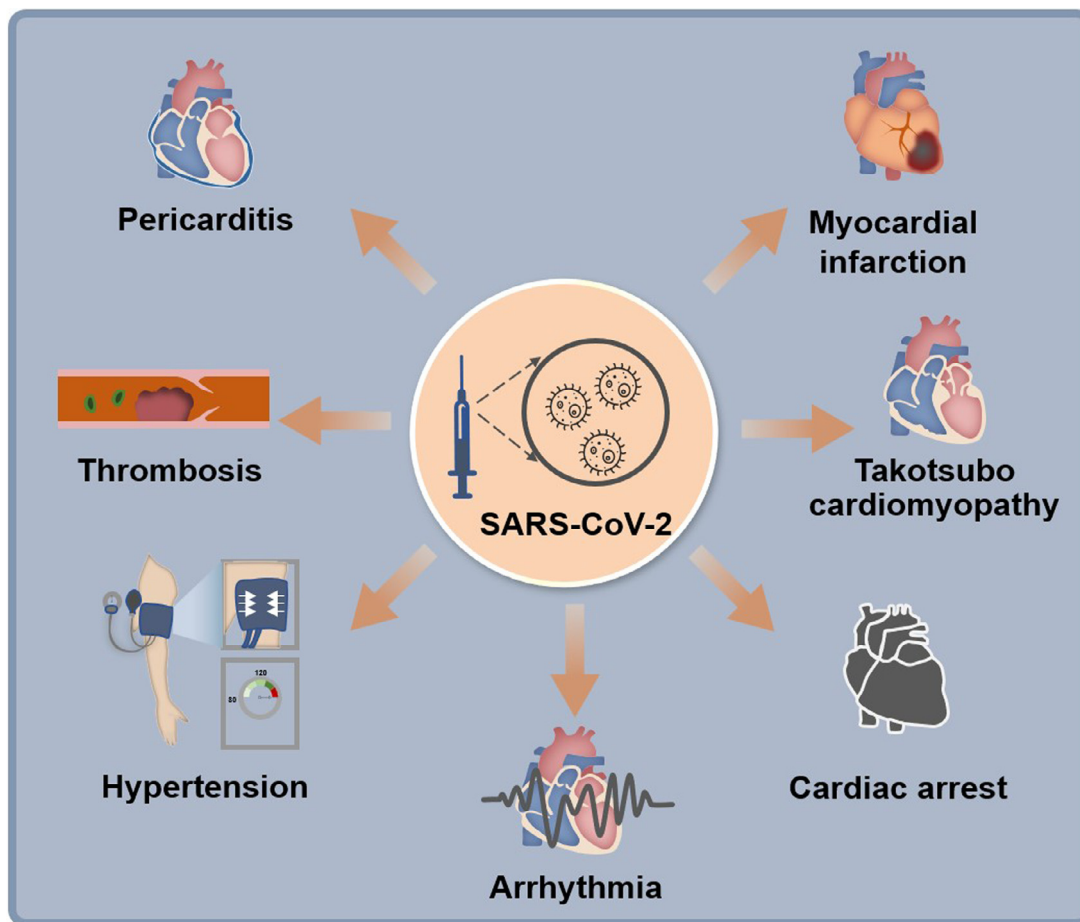
Figure 1. The various cardiovascular complications of COVID-19 vaccine. Numerous cardiovascular comorbidities such as myocarditis/pericarditis, thrombosis and thrombocytopenia, acute coronary syndrome, hypertension, arrhythmia, Takotsubo cardiomyopathy, cardiac arrest, and death have been reported in individuals who received a COVID-19 vaccine.

Table 2
Common cardiovascular adverse events reported in VAERS as of Jul 2022 in the United States.

Cardiovascular complication	Number of cases	Cases per million vaccines	Pfizer/BioNTech	Moderna	Johnson & Johnson	Unknown
Myocarditis	2984	4.94	1897	980	94	13
Pericarditis	2081	3.45	1217	745	108	11
Thrombosis	5052	8.36	2177	1580	1159	136
Thrombocytopenia	1195	1.98	536	354	152	153
Pulmonary embolism	4144	6.86	1806	1600	634	104
DVT	3001	4.97	1270	1107	561	63
CVST	233	0.39	87	81	60	5
Hypertension	8276	13.70	3898	3228	711	439
Hypertensive crisis	108	0.18	49	46	7	6
Hypertensive urgency	91	0.15	50	34	6	1
Myocardial infarction	2021	3.35	937	748	206	130
Acute myocardial infarction	1325	2.19	681	526	89	29
Angina pectoris	1403	2.32	800	416	114	73
Arrhythmia	1343	2.22	681	505	67	90
Palpitation	17,473	28.93	8869	6683	1263	658
Tachycardia	7517	12.45	3722	2963	472	360
Atrial fibrillation	4163	6.89	1994	1826	243	100
Sinus tachycardia	782	1.30	411	279	64	28
Supraventricular tachycardia	639	1.06	322	257	35	25
Takotsubo cardiomyopathy	102	0.17	56	39	5	2
Cardiac arrest	1722	2.85	826	632	140	124
Death	14,088	23.33	6360	5704	1290	734

Total doses of vaccines = 604 million doses,
CVST, cerebral venous sinus thrombosis 379000000; DVT, deep veinous thrombosis; VAERS, vaccine adverse event system.

Two large-scale retrospective studies were conducted in Israel examining the development of myocarditis in individuals inoculated with the Pfizer vaccines. Mevorach and colleagues examined more than 5.1 million recipients 21 days after the first vaccination and 30 days after the second vaccination (Mevorach *et al.,* 2021). They recorded 136 events of myocarditis, with one mortality. Moreover, the difference in the risk of myocarditis between the first and second vaccination was 1.76 per 100,000 individuals. In another study, Witberg and colleagues reported a myocarditis incidence rate of 2.3 in 100,000 individuals receiving the Pfizer vaccine, and the incidence was increased to more than 10 per 100,000 at a younger age (aged 16 to 29) (Witberg *et al.,* 2021). Furthermore, Diaz and colleagues examined over 2 million vaccinated individuals and identified 37 pericarditis cases, with a median symptom onset time of 20 days (Diaz *et al.,* 2021) (Table 4).

Pericarditis or myocarditis events associated with COVID-19 vaccines are more frequent in younger adults. This seeming discrepancy may be due to a stronger immune response to the vaccine and more common reactogenicity in youngsters, favoring a shift in the maximal background incidence of cardiac inflammation diseases toward younger ages after vaccination (Fazlollahi *et al.,* 2022). Moreover, males are more prone to pericarditis and myocarditis after COVID-19 vaccination, although the difference is less pronounced for pericarditis. Sex hormones appear to play a major role in the pathophysiology behind the gender bias. Notably, testosterone possesses an inhibitory capacity against anti-inflammatory cells. In particular, it evokes proinflammatory M1 macrophage activity and strengthens the immune response of Th1 lymphocytes (Di Florio *et al.,* 2020, Fairweather *et al.,* 2013). In contrast, estrogen plays an inhibitory role in proinflammatory T lymphocytes, leading to a reduction in cellular immune reactions. This notion should help to explain the higher incidence of pericarditis or myocarditis in vaccinated postmenopausal women (Kytö *et al.,* 2014).

The pathophysiology underneath cardiac sequelae of COVID-19 vaccine remains undefined. As shown in Figure 2, a nonspecific inflammatory response from exposure to the nucleotide sequence and cross-reactivity of antibodies has been speculated due to molecular mimicry between SARS-CoV-2-encoded S protein and similar human protein sequences, such as α-myosin vital in myocardial contraction (Vojdani and Kharrazian, 2020). In addition, antibodies against self-antigens reported in myocarditis patients (e.g., antiproteolipid protein 1, antiendothelial antigen, or antiaquaporin 4) were detected in patients with vaccine-induced myocarditis, supporting the presence of a myocarditis mechanism mediated by autoantibodies generation (Sette and Crotty, 2021; Vojdani and Kharrazian, 2020). Moreover, although nucleoside modifications of mRNA lowered their innate immunogenicity, the immune response to mRNA may still be aberrant in individuals with genetic susceptibility. In these individuals, the immune system may detect mRNA in the vaccine as an antigen, leading to immunologic and proinflammatory cascades to favor the development of myocarditis.

Clinically, pericarditis or myocarditis is characterized by chest pain, palpitations, and tachypnea, followed by fever, cough, and headache. These symptoms appear within a few days after vaccination against COVID-19, especially after the second dose (Kim *et al.,* 2021). Nevertheless, the consequences of myocarditis or pericarditis are temporary and usually do not require specific treatment. Supportive care for symptomatic control includes colchicine and nonsteroidal anti-inflammatory drugs. Also, glucocorticoids and immunoglobulins are given to patients with a poor response to reduce the immune reaction evoked by vaccinated antigen (Berg *et al.,* 2019; Deftereos *et al.,* 2020; Kamarullah *et al.,* 2021). Inadequate literature is available, along with the short follow-up duration for prognosis of pericarditis or myocarditis following inoculation. Long-term evaluation is required to reveal the pathophys-

iological nature of inoculations. Information garnered from these studies would help to identify strategies to strengthen safety and improve prognosis for inoculation.

Thrombosis and thrombocytopenia

COVID-19 vaccines, especially in the adenoviral platform, have been associated with the development of thrombotic thrombocytopenia (Figure 1) (Calcaterra *et al.,* 2022; Cines and Bussel, 2021). VAERS reported 5052 undefined thrombosis, 4144 pulmonary embolisms, 3001 deep venous thromboses, 1195 thrombocytopenias, and 233 cerebral venous sinus thromboses among 604 million doses of SARS-CoV-2 vaccines in the United States (Table 2) (CDC, 2022; Hana *et al.,* 2022). In an independent study from Norway, Schultz and colleagues reported five cases of thrombotic thrombocytopenia among 130,000 individuals who were inoculated with the AstraZeneca vaccine and four of those were female (Schultz *et al.,* 2021). A study on recipients of the AstraZeneca vaccine noted that the morbidity rate of thrombotic cases was 1.97-fold higher than the general population, including a higher incidence in adults aged <50 years than those aged >50 (Marcucci and Marietta, 2021). Moreover, Greinacher and colleagues identified 11 patients with a median age of 36 years, who were experiencing thrombotic adverse reactions following the AstraZeneca vaccination (Greinacher *et al.,* 2021). Nine of these patients tested positive for antibodies against platelet factor 4 (PF4), and the remaining two were not evaluated. Five patients were found with high D-dimer levels as well as abnormal international normalized ratio, prothrombin time, and fibrinogen levels, suggesting the presence of disseminated intravascular coagulation. The term vaccine-induced thrombotic thrombocytopenia (VITT) was offered for this unique pathology, albeit with yet uncertain pathophysiological mechanisms (Aleem and Nadeem, 2022).

The antibodies against PF4 are produced as part of the immune stimulation and inflammatory reaction induced by vaccination, which activates massive platelets and facilitates clotting (Figure 2) (Haimei, 2021; Scully *et al.,* 2021); although, thromboxane A2 (TxA2) and COX-2 genes may also be involved. It is believed that the generation of S protein by COVID-19 vaccination prompts the generation of TxA2 and COX-2 in megakaryocytes. TxA2 stimulates the COX-2 expressing platelets, contributing to platelet activation and aggregation and ultimately, thrombotic inflammation (Rocca *et al.,* 2002). Also, following intravenous injection, double-stranded DNA borne by the adenoviral vector-based COVID-19 vaccine may inadvertently interact with platelets because of microtrauma and microbleeding at the injection site. Moreover, the ethylenediaminetetraacetic acid content in vaccine preparations increases vascular permeability at the injection site, resulting in the rapid spread of vaccine components into the bloodstream (Tsilingiris *et al.,* 2021). Platelet activation and aggregation in turn contribute to the release of cytokines, binding of platelets to endothelial cells, and consequently, activation of endothelial cells by higher vascular cell adhesion molecule-1 levels. Interactions between endothelial cells and platelets then facilitate platelet aggregation and thrombogenesis (Atasheva *et al.,* 2019; Calcaterra *et al.,* 2022; Chen *et al.,* 2021).

The main pathological feature of coagulopathy evoked by VITT includes arterial and venous thrombosis, along with thrombocytopenia and particular abnormalities of blood tests. The onset time of symptoms is around 5-14 days after inoculation (Hwang *et al.,* 2021). As for the management, all thrombotic events in vaccinated patients should be treated with nonheparin anticoagulant or intravenous immunoglobulin if no special contraindication is present. On the contrary, given that VITT shares similarities with heparin-induced thrombocytopenia, the use of heparin or platelet transfusion treatment may promote disease progression and should not be considered for patients with such risk (Islam *et al.,* 2021;
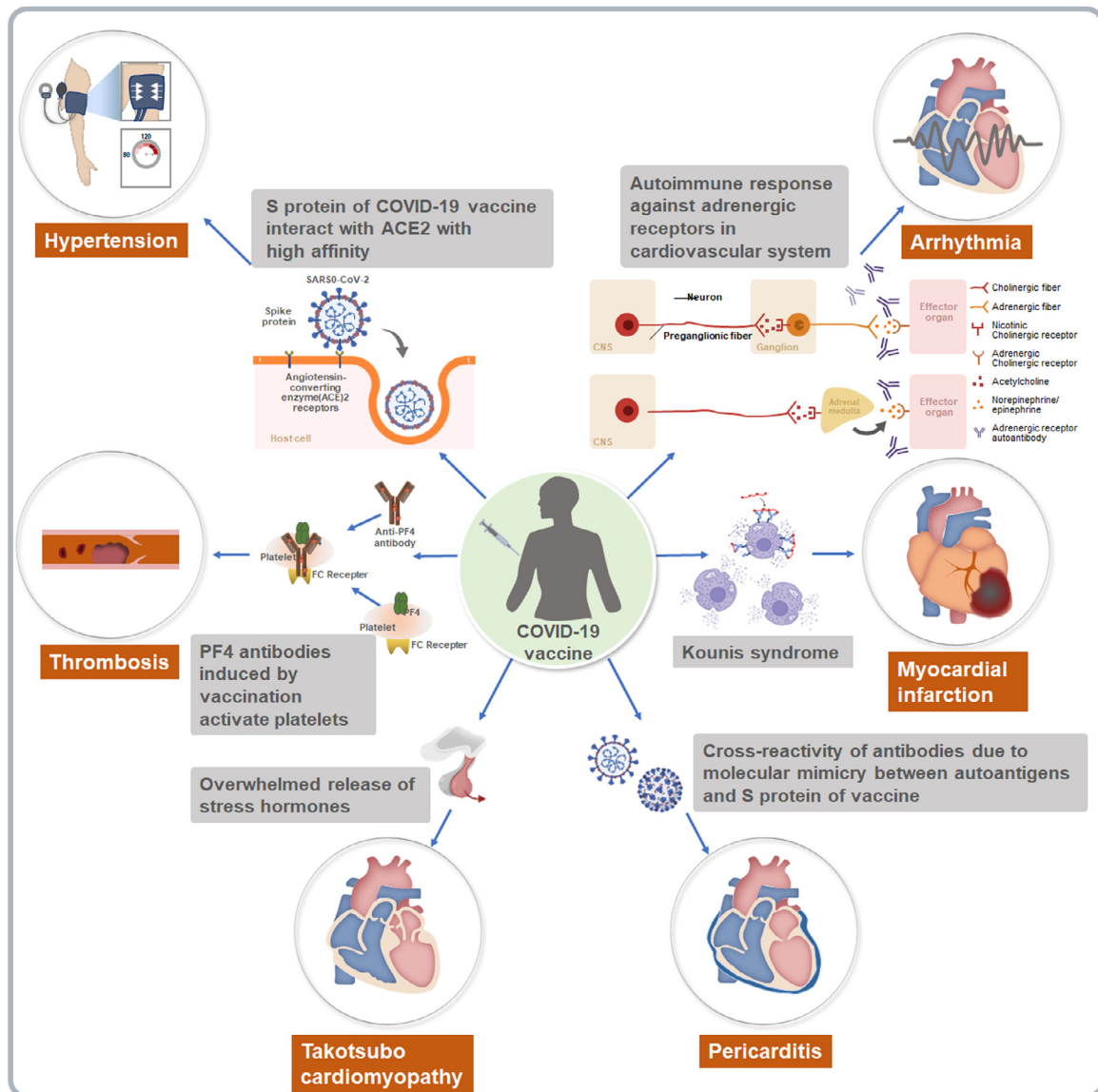
Figure 2. Proposed mechanisms for COVID-19 vaccine-induced cardiovascular complications.
Hypertension might be induced by the interaction between S protein of COVID-19 vaccine and ACE2 with high affinity. Acute coronary syndrome is related to Kounis syndrome which is an allergic reaction to the vaccines. Overwhelming emotional disturbance and stress triggered by COVID-19 vaccine may evoke overwhelmed catecholamine release, inflammatory reaction elicited if the vaccine sensitizes patients to catecholamines; such a response may lead to Takotsubo cardiomyopathy. Myocarditis/pericarditis may be the result of the cross-reactivity of antibodies due to the molecular mimicry between autoantigens and encoded S protein in vaccines. Thrombosis is associated with S protein production causing megakaryocytes to produce COX-2 and TxA2. Moreover, antibodies against PF4 are made as part of the immune stimulation and the inflammatory reaction induced by vaccination, which activates massive platelet formation and facilitates clotting. Arrhythmia is linked to the autoimmune response against adrenergic receptors in the cardiovascular system.
Abbreviations: ACE2, angiotensin-converting enzyme 2; PF4, platelet factor 4; S protein, spike protein.

Talasaz *et al.*, 2021). Most importantly, being aware of this new, unusual postvaccination syndrome is essential, and further exploration of its etiological mechanisms is warranted.

Other cardiovascular complications associated with COVID-19 vaccines

Hypertension

COVID-19 vaccinations may be associated with the development of high blood pressure (BP) (Figure 1). VAERS reported a sum of 8276 events of hypertension, 108 episodes of hypertensive crisis, and 91 cases of hypertensive urgency in the United States (Table 2) (CDC, 2022). A case series has indicated a sum of 941 hypertensive cases, 14 events of hypertensive crisis, and four cases of hyperten-

sive urgency in individuals vaccinated with the AstraZeneca from the United Kingdom (Table 3). The incident rate of hypertension was identified to be linked to vaccination in different age groups and sexes. The prevalence of women was 73%, and the mean age was 43 ± 11 years (Jeet Kaur *et al.*, 2021). In addition, Zappa and colleagues documented that among 113 participants after inoculation of the first dose of Pfizer/BioNTech vaccine, six patients displayed an average increase in systolic or diastolic BP by >10 mm Hg in the first 5 days (Table 4) (Zappa *et al.*, 2021). A number of factors appear to play a role in vaccine-associated hypertension, such as stress, injection-induced pain, the "white coat" effect, and comorbidities, including the hypertensive state of the patients. Another possible scenario is that the S protein of the COVID-19 vaccine may interact with angiotensin-converting enzyme (ACE) 2

Table 3

Adverse cardiovascular events based on the case series drug analysis by UK government for AstraZeneca vaccine.

Cardiovascular complication	Total number of cases	Cases per million vaccines	Fatal cases
Myocarditis	105	1.84	1
Pericarditis	162	2.84	0
Thrombosis	1712	30.04	33
Thrombocytopenia	868	15.23	6
Pulmonary embolism	1582	27.75	100
DVT	1173	20.58	9
CVST	207	3.63	22
Hypertension	941	16.51	0
Hypertensive crisis	14	0.25	0
Hypertensive urgency	4	0.07	0
Myocardial infarction	386	6.77	51
Acute myocardial infarction	79	1.39	13
Angina pectoris	219	3.84	0
Arrhythmia	134	2.35	3
Palpitation	5157	90.47	1
Tachycardia	1242	21.79	0
Atrial fibrillation	311	5.46	0
Sinus tachycardia	69	1.21	1
Supraventricular tachycardia	41	0.72	0
Takotsubo cardiomyopathy	5	0.09	0
Cardiac arrest	167	2.93	35
Death	301	5.28	301

Total doses of vaccines = 57 million doses,

DVT, deep veinous thrombosis; CVST, cerebral venous sinus thrombosis.

with a high affinity, thus exaggerating the risk of hypertension after COVID-19 vaccination because the vaccines take effect by introducing S protein into the body to trigger a self-immune reaction (Figure 2) (Nesci, 2021). As a key member of the renin-angiotensin-aldosterone system, activation of ACE leads to elevated systemic vascular resistance and electrolyte imbalance, resulting in elevated BP. The binding of S protein to ACE2 leads to internalization and degradation of these receptors (Angeli *et al.*, 2021). Loss of ACE2 activity may result in a drastic and rapid decline in the production of angiotensin 1-7 due to angiotensin 2 inactivation (Verdecchia *et al.*, 2020b). The resulting imbalance between angiotensin 1-7 (deficiency) and angiotensin 2 (overactivity) may have an effect on hypertension (Brojakowska *et al.*, 2020; Verdecchia *et al.*, 2020a, 2020b). It is suggested that prevaccination BP control and postvaccination screening should be implemented for elderly patients with severe cardiovascular comorbidities or a history of hypertension.

Acute coronary syndrome

Acute coronary syndrome (especially myocardial infarction [MI]) is one of the most devastating and life-threatening cardiac comorbidities. It has been reported that patients vaccinated with AstraZeneca, Pfizer, and Moderna developed MI following vaccination after an interval ranging from 15 minutes to 2 days (Figure 1). More importantly, most symptoms of MI develop after the first dose (Aye *et al.*, 2021; Barda *et al.*, 2021). Preliminary clinical trials in the Food and Drug Administration briefing documents indicated that the incidence rate of MI was 0.03% and 0.02% after receiving Moderna or Pfizer vaccines, respectively. The odds ratio for developing MI was 1.07 for individuals who received the Pfizer vaccine compared with 4.47 for individuals with SARS-CoV-2 (Barda *et al.*, 2021). The risk of MI following inoculation increases with age (Li *et al.*, 2021b; FDA briefing: Document: Pfizer-BioNTech, 2021). Males were mainly affected and accounted for 80% of the cases, with an average age of 65 in a study (Table 4) (Aye *et al.*, 2021). Moreover, VigiBase database of the World Health Organization identified 32 (0.66% of all cardiovascular complications) patients with MI, 16 (0.33%) patients with acute MI, and 13 (0.27%) patients with angina pectoris (Jeet Kaur *et al.*, 2021). A total of 2021 cases of MI and 1325 episodes of acute MI were reported

in the United States by VAERS (Table 2) (CDC, 2022). Moreover, a case series, by the UK government, of the AstraZeneca vaccine reported 386 (51 fatal) events of MI, 79 (13 fatal) events of acute MI, and 219 (nonfatal) events of angina (Table 3) (AstraZeneca, 2021). As for the mechanisms underlying MI following COVID-19 inoculation, several theories offer explanations for vaccine-induced cardiovascular events. Similar mechanisms responsible for the aforementioned vaccine-induced thrombotic events may explain the MI complication (Greinacher *et al.*, 2021; Wise, 2021). Another possible contributing factor is the Kounis syndrome, an acute coronary syndrome occurring in the setting of mast cell activation and degranulation, including allergic or hypersensitivity and anaphylactoid reactions to vaccines (Figure 2) (Kounis, 2006). Indeed, almost all current vaccines contain excipients (e.g., trometamol, polysorbate 80, and aluminum hydroxide), which may elicit hypersensitivity responses (Kounis *et al.*, 2022).

Pathophysiologically, Kounis syndrome is associated with inflammatory mediators, such as histamine, platelet-activating factors, arachidonic acid products, as well as various chemokines and cytokines released during mast cell activation (Şancı *et al.*, 2022). Hyperallergy may elicit myocardial ischemia, and MI occur through several mechanisms, such as allergic vasospasm, atherosclerotic plaque erosion, and stent occlusion with mast cells and/or eosinophils infiltrating thrombus (Özdemir *et al.*, 2021). Moreover, alterations in hemodynamics, including increased BP or tachycardia, have been reported in certain cases after vaccine administration (Palacios *et al.*, 2020). These might be induced by vaccines or psychological factors associated with vaccination, elevating myocardial oxygen demand. Notably, the supply-demand mismatch might lead to the untimely cardiac events among the recipients (Boivin and Martin, 2021). In addition, inflammatory reactions tied to immune response to vaccination may exacerbate coronary plaque to rupture (Panthong *et al.*, 2022). Elderly patients with other related comorbidities, such as hypertension and a history of coronary artery disease, are more prone to high stressors; this could initiate more frequent episodes of myocardial ischemia after vaccination (Boivin and Martin, 2021). Generally, the data are incomplete and inconclusive to establish a definitive link between COVID-19 vaccines and MI. Further research is needed to establish the causal relationship.

Table 4

Details of studies reporting cardiovascular diseases post-COVID-19 vaccine. Study cohort characteristics, comorbidities, clinical presentation, diagnostic evaluation, and outcome are all summarized.

Case series	Myocarditis and pericarditis after vaccination for COVID-19 (Diaz et al., 2021)	Acute myocardial infarction following COVID-19 vaccination (Aye et al., 2021)	Thrombotic Thrombocytopenia after COVID-19 vaccination (Schultz et al., 2021)	Hypertension after vaccination for COVID-19 (Zappa et al., 2021)	Case report	Arrhythmia after COVID-19 vaccination: A case report (Reddy et al., 2021)	Takotsubo cardiomyopathy following COVID-19 vaccination: A case report (Crane et al., 2021)
Characteristics cases, n	20	35	5	6	Characteristics cases, n	1	1
Male, %	15 (75%)	28 (80%)	1 (20%)	2 (33%)	Gender	Male	Male
Median age (range), years	36 (26.3-48.3)	65 (59-74)	39 (32-54)	48 (35-52)	Age	42	72
Vaccine type	Pfizer-BioNTech: 9 (45%) Moderna: 11 (55%)	Pfizer-BioNTech:30 (86%) Moderna: 1 (3%) AstraZeneca: 4 (11%)	AstraZeneca	Pfizer-BioNTech	Vaccine type	Pfizer-BioNTech	AstraZeneca
Hypertension	5 (25%)	22 (63%)	1 (20%)	5 (83%)	Hypertension	-	Yes
Hyperlipidemia	-	19 (54%)	0	2 (33%)	Hyperlipidemia	Yes	Yes
Diabetes mellitus	2 (10%)	18 (51%)	0	1 (17%)	Diabetes mellitus	-	Yes
Smoking	-	12 (34%)	-	-	Smoking	No	-
Previous history of CAD	1 (5%)	7 (20%)	0	1 (17%)	Previous history of CAD	-	Yes
COVID-19 PCR positive	-	-	0	-	COVID-19 PCR positive	No	No
Time between last vaccine and symptoms onset, median days (range)	3.5 (3-10.8)	1 (1-2)	8 (7-10)	5 (3-5)	Time between last vaccine and symptoms onset (days)	1	1
Symptoms post-second dose	16 (80%)	6 (33%)	-	2 (33%)	Symptoms post-second dose	-	-
Chest pain	-	-	-	0	Chest pain	No	Yes
Other symptoms (e.g., myalgia, fatigue, fever)	-	-	5 (100%)	5 (83%)	Other symptoms (e.g., myalgia, fatigue, fever)	Yes	Yes
Abnormal ECG	9 (45%)	20 (57%)	-	-	Abnormal ECG	-	Yes
Abnormal echocardiogram	-	25 (89%)	-	-	Abnormal echocardiogram	Yes	Yes
LVEF < 50%	5 (25%)	-	-	-	LVEF < 50%	No	No
Median length of hospitalization, days (range)	2 (2-3)	-	10 (2-15)	-	Length of hospitalization	-	10
Treatment regimen	NSAIDs (75%), and colchicine (45%)	Discharged on β-blockers (77%), aspirin (96%), P2Y12 antagonist (76%), ACEI (54%), statin (80%)	Low molecular weight heparin (80%), heparin (20%), methyl-prednisolone (40%), prednisolone (20%)	CCB (33%), ACEI (33%), β-blocker (50%), diuretic (17%)	Treatment regimen	Lifestyle modifications	Antiplatelet therapy, including a P2Y12 antagonist

ACEI, ACE-inhibitor; CAD, coronary artery disease; CCB, calcium-channel blocker; ECG, electrocardiograph; LVEF, left ventricular ejection fraction; NSAIDs, nonsteroidal anti-inflammatory drugs; PCR, polymerase chain reaction.

Arrhythmias

Multiple reports have noted an increased incidence of various arrhythmias following vaccination against SARS-CoV-2 (Figure 1). According to the World Health Organization VigiBase database, Kaur and colleagues identified 717 incidents of palpitations, 185 of which were considered serious cases (Jeet Kaur et al., 2021). A total of 17,473 palpitation episodes were reported in the United States by VAERS (Table 2) (CDC, 2022). Moreover, the case series of the AstraZeneca vaccine reported 5157 cases of palpitation, with only 1 fatal report in the United Kingdom (AstraZeneca, 2021). The most common arrhythmias reported include tachycardia, atrial fibrillation, sinus tachycardia, and supraventricular tachycardia (Table 3) (Jeet Kaur et al., 2021). Also, a 31-year-old male with Marfan syndrome recovering from Bentall surgery and mitral valve replacement developed atrial fibrillation following Vero cell vaccination. The electrocardiogram showed atrial fibrillation with fast ventric-

ular response as the patient experienced palpitation 8 hours following vaccine administration (Li et al., 2021a). However, it remains unclear whether these arrhythmia events are solely associated with SARS-CoV-2 vaccination or were potential cardiac complications that occurred coincidently with vaccination.

Postural orthostatic tachycardia syndrome was identified in a healthy patient 6 days after the first dose of the Pfizer vaccine (Table 4) (Reddy et al., 2021). One possible mechanism is an autoimmune response against adrenergic receptors in the cardiovascular system, resulting in compromised vasoconstrictor reaction and postural tachycardia (Figure 2) (Li et al., 2014; Reddy et al., 2021). Mustafa et al. (2012) noted compromised BP self-regulatory processes of plasma angiotensin 2 and baroreflex responses, resulting in attenuated vasoconstrictor capacity and orthostatic tachycardia. Patients exhibiting continuous symptoms can be treated with lifestyle modifications, such as increased sodium intake and appli-

cation of compression socks. Indeed, postural orthostatic tachycardia syndrome is a syndrome difficult to diagnose. Additional work is needed to understand the arrhythmic side effects induced by COVID-19 vaccines.

Takotsubo cardiomyopathy

As a transient and acute syndrome, Takotsubo cardiomyopathy is characterized by diastolic and systolic left ventricular abnormalities, accompanied by regional wall movement dysfunction beyond the distribution of a single coronary artery. Takotsubo cardiomyopathy is most common in postmenopausal women, with a risk of 9.9% of major cardiac events and a 5.6% patient mortality rate per year (Templin *et al.*, 2015). A total of 102 Takotsubo cardiomyopathy events were reported in the United States according to VAERS (Table 2) (CDC, 2022). Moreover, case series of AstraZeneca vaccine reported five events of Takotsubo cardiomyopathy in the United Kingdom although, none were fatal (Table 3) (AstraZeneca, 2021). Vidula and coworkers (2021) noted Takotsubo cardiomyopathy in a 60-year-old female, 4 days after the second dose of the Pfizer vaccine. The patient had a stent placed in left anterior descending artery 3 years ago, and echocardiography showed normal left ventricular function and wall movement 5 months earlier. She presented with exertional chest pain and new inferolateral T wave inversions on electrocardiogram. In addition, echocardiography indicated a mild decrease in left ventricular function and apical akinesis, without obstructive disease on coronary angiography (Vidula *et al.*, 2021). Nevertheless, pathogenicity remains poorly understood. As illustrated in Figure 2, unlike heart damage with classical infection, vaccines elicit a systemic inflammatory reaction that sensitizes patients to catecholamines, leading to the development of disequilibrium between parasympathetic and sympathetic tones, manifested as Takotsubo cardiomyopathy (Almas *et al.*, 2021; Fearon *et al.*, 2021; Singh *et al.*, 2013). It is possible that overwhelming emotional disturbance and stress triggered by COVID-19 vaccine evoke overwhelming epinephrine and norepinephrine release from adrenal glands and sympathetic nerves, resulting in catecholamine-mediated microvascular dysfunction, myocardial stunning, and increased cardiac workload, typical of Takotsubo cardiomyopathy (Crane *et al.*, 2021; Fearon *et al.*, 2021; Ghadri *et al.*, 2018b). Most patients with Takotsubo cardiomyopathy experience rapid left ventricular recovery; although, the early clinical stage might be difficult to diagnose because of thrombotic complications, acute heart failure, arrhythmias, and even death (Ghadri *et al.*, 2018a). General treatment should include casual risk management and symptom control.

Given the complex pathophysiology of Takotsubo cardiomyopathy, anticatecholamine therapies, such as β-blockers would be recommended, although no prospective optimal therapeutics are available. Similarly, ACE inhibitors or angiotensin 2 type 1 receptor blockers might be considered in the setting of left ventricular dysfunction (Sattar *et al.*, 2020).

Cardiac arrest and death

Postvaccination cardiac arrest and death have been reported (Figure 1). VAERS identified a total of 6181 deaths in COVID-19 vaccine recipients compared with more than 0.89 million deaths in COVID-19 patients in the United States. The case series of the AstraZeneca vaccine recorded 301 deaths in COVID-19 vaccine recipients compared with 0.15 million deaths in patients with COVID-19 in the United Kingdom (AstraZeneca, 2021). Individuals with cardiac arrest following vaccine administration were 1722 in the United States (Table 2) and 167 in the United Kingdom (Table 3), reported by VAERS and AstraZeneca vaccine case series, respectively (CDC, 2022). The number of mortalities from COVID-19 pandemic (as measured by excess deaths) was largest in the regions of South Asia, North Africa, the Middle East, and eastern Europe. At the country level, the highest numbers of cumulative excess deaths due to COVID-19 were estimated in India, the United States, Russia, Mexico, Brazil, Indonesia, and Pakistan. However, the mortality of COVID-19 was significantly lower in sub-Saharan Africa, possibly due to low median age and low proportion of vulnerable elderly patients. As of May 2022, 74.4% of patients who died of COVID-19 infection in the United States were older than 65 years. Moreover, 65% of COVID-19 deaths in the United States were White, 16% were Hispanic, 14% were Black, and 3% were Asian, with a male/female ratio of 1.2. Compared with death after COVID-19 vaccination, the male/female ratio was close to one (1.04). The mean age was 52.74 years (range 22-91). The ratio of mortality from COVID-19 vaccination ≤50 years to that >50 years was 0.8 (Maiese *et al.*, 2022).

Edler et al. (2021) reported that three patients died within 15 days following vaccination. Postmortem examination noted recurrent MI and pulmonary embolism as the possible cause of death in two individuals. The third patient died of severe SARS-CoV-2 infection within 10 days of inoculation. Given the observed mortality, recommendations for vaccination in the elderly (aged >80 years) should be reconsidered. In patients with multimorbidity in a suboptimal situation before vaccination, vaccine-drug and vaccine-disease interactions in polypharmacy users might have contributed to worsened health outcomes (Qamar *et al.*, 2022). The general vaccination response and potential immune stimulation might be sufficient to trigger decompensation of underlying diseases and prompt death (Thomas *et al.*, 2021). The availability of guideline-based treatment (antihistamines, epinephrine) should be double-checked before vaccination. In addition, full autopsies are recommended to confirm the causal relationship between inoculation and death, especially in those who were otherwise healthy or not critically ill (Edler *et al.*, 2021). Recent studies suggest that thrombosis combined with VITT might be the main cause of mortality (Junapudi *et al.*, 2021). Other causes of death that can be considered include vaccine-related include myocarditis, MI, acute disseminated encephalomyelitis (inflammation of the nervous system related to demyelination), and complications of rhabdomyolysis (muscle damage, inducing myoglobin excretion by the kidney and acute renal failure) (Maiese *et al.*, 2022). However, no evidence has revealed a direct causal link between vaccine administration and cardiac arrest or death in vaccine recipients.

Conclusions and precautions for vaccine usage

Accumulating evidence documents a number of cardiovascular comorbidities, including myocarditis/pericarditis, thrombosis and thrombocytopenia, acute coronary syndrome, hypertension, arrhythmia, Takotsubo cardiomyopathy, cardiac arrest, and death in individuals receiving COVID-19 vaccines. Nevertheless, direct causality between inoculation and adverse reactions remains poorly elucidated. All available data were derived from reporting systems and case reports. Moreover, cardiovascular side effects remain infrequent, considering the large number of vaccinations administered to the general population. The ultimate benefit of COVID-19 vaccine administration still outweighs the risk of cardiovascular adverse reactions. With inoculation, major events of infection, hospitalization, and death may be avoided for COVID-19 infection. Close monitoring for vaccine effectiveness and safety is required to lower vaccination reluctance by the general population.

Patients with serious cardiovascular conditions, such as symptomatic atherosclerotic cardiovascular disease, poorly controlled atrial fibrillation, heart failure, and a history of heart transplantation, should be given more careful consideration before receiving a vaccine because these populations are considered at high risk for COVID-19 complications. Safety evaluation of COVID-19 vaccine is a rather daunting task that requires utmost attention. Health care workers should be attentive to potential cardiovascular comor-

bidities during the postvaccination period; this is essential so that probable pathophysiological events can be managed in a timely manner. It is also important that a worldwide database on COVID-19 vaccine side effects should be implemented to collect precise data. Furthermore, regional modulatory systems should regulate vaccine inoculation and monitor the occurrence of complications.

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Author contributions

YEL was involved in the acquisition, analysis, and interpretation of data and drafting of the manuscript. SW, RR, and JR were involved in study concept and design and medical writing assistance. All authors read and approved the final manuscript.

Availability of data and materials

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

Consent for publication

Not applicable.

Declarations of competing interests

The authors have no competing interests to declare.

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Supplementary materials

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