Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

International Journal of Infectious Diseases 124 (2022) 1–10

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

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

ARTICLE INFO

Article history:
Received 26 June 2022
Revised 29 August 2022
Accepted 30 August 2022

Keywords:
SARS-CoV-2
COVID-19 vaccines
Cardiovascular
Myocarditis
Pericarditis
Thrombotic thrombocytopenia

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.

© 2022 The Author(s). Published by Elsevier Ltd on behalf of International Society for Infectious Diseases.
This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/)

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).

https://doi.org/10.1016/j.ijid.2022.08.026
1201-9712/© 2022 The Author(s). Published by Elsevier Ltd on behalf of International Society for Infectious Diseases. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/)

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).

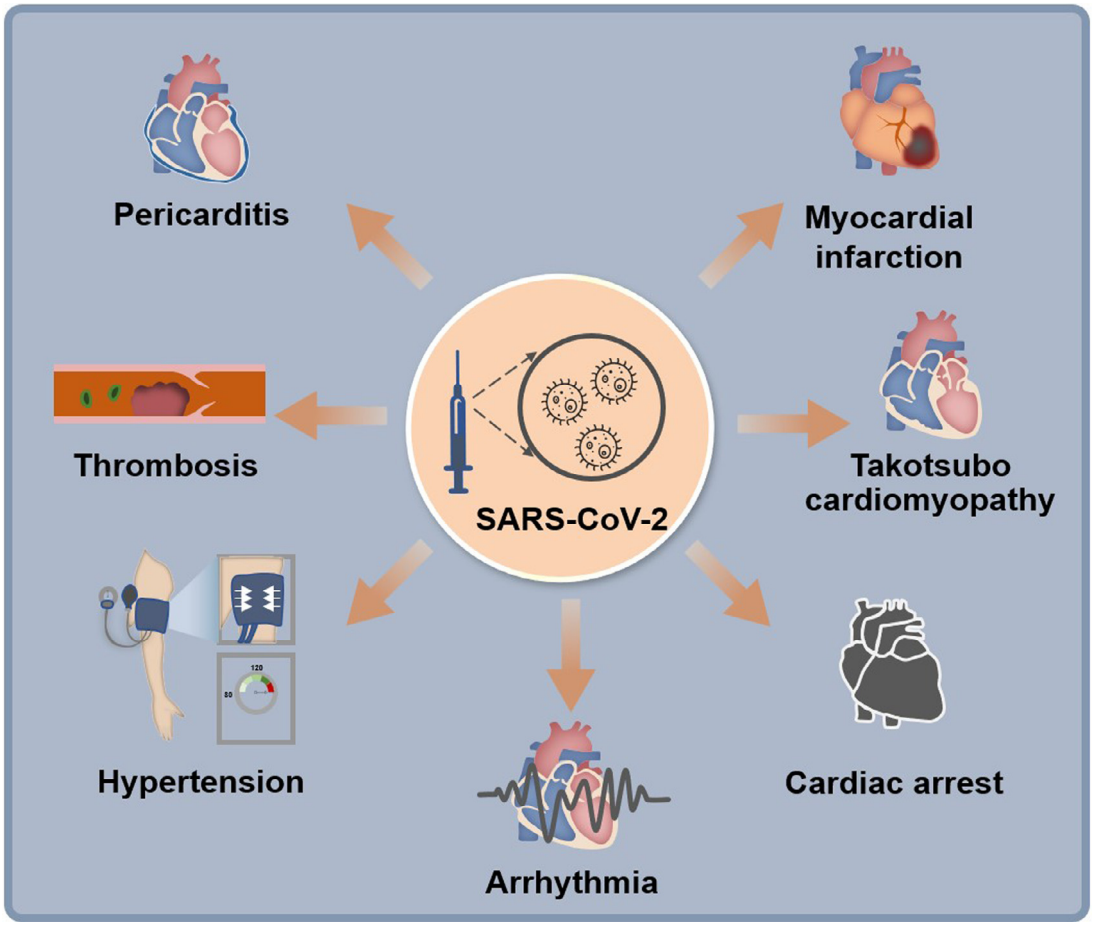

Figure 1. The various cardiovascular complications of COVID-19 vaccine. Numerous cardiovascular comorbidities such as myocarditis/pericarditis, thrombosis and thrombocytopenia, acute coronary syndrome, hypertension, arrhythmia, Takotsubo cardiomyopathy, cardiac arrest, and death have been reported in 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 pathophysiological 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 veinous 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;

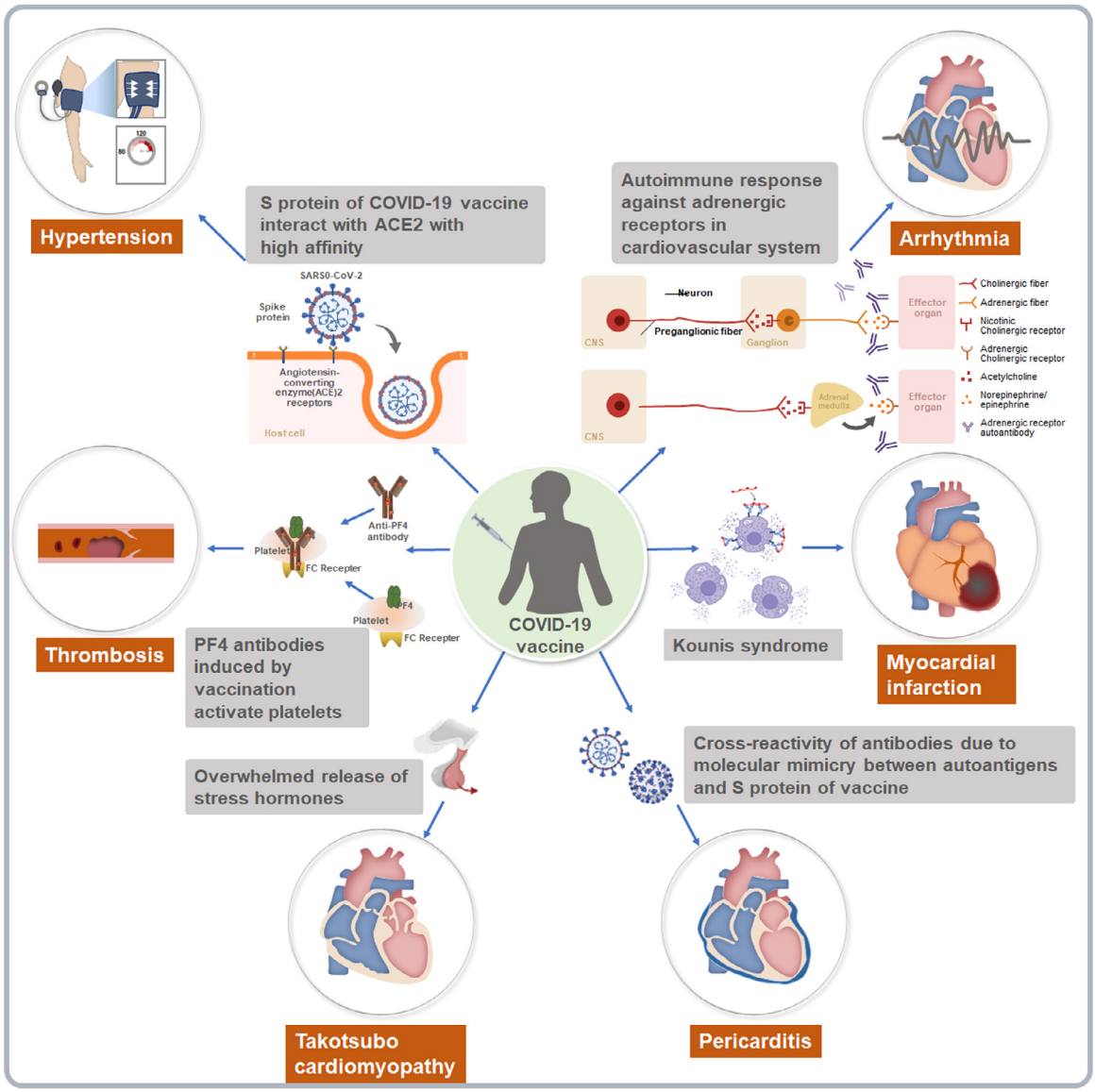

Figure 2. Proposed mechanisms for COVID-19 vaccine-induced cardiovascular complications.
Hypertension might be induced by the interaction between S protein of COVID-19 vaccine and ACE2 with high affinity. Acute coronary syndrome is related to Kounis syndrome which is an allergic reaction to the vaccines. 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 hypertensive 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%), methylprednisolone (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 ventricular 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 $\leq$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 administrated 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.

Funding

Work in our groups was supported in part by the Natural Science Foundation of China (82000351).

Ethics approval and consent to participate

Not applicable.

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.

Acknowledgments

The authors sincerely appreciate Dr, Yu Duan from Xijing Hospital, the Air Force Medical University (Xi'an, China) for his skillful assistance in graphics work.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2022.08.026.

References

Abu-Raddad LJ, Chemaitelly H, Butt AA. National Study Group for COVID-19 Vaccination. Effectiveness of the BNT162b2 Covid-19 Vaccine against the B.1.1.7 and B.1.351 Variants. N Engl J Med 2021;385:187–9.
Albert E, Aurigemma G, Saucedo J, Gerson DS. Myocarditis following COVID-19 vaccination. Radiol Case Rep 2021;16:2142–5.
Aleem A, Nadeem AJ. Coronavirus (COVID-19) vaccine-induced immune thrombotic thrombocytopenia (VITT). StatPearls. Florida: StatPearls publishing; 2022.
Almas T, Khedro T, Haadi A, Ahmed R, Alshaikh L, Al-Awaid AH, et al. COVID-19-induced takotsubo cardiomyopathy: venturing beyond the obvious. Ann Med Surg (Lond) 2021;65.
Andrews N, Stowe J, Kirsebom F, Toffa S, Rickeard T, Gallagher E, et al. Covid-19 vaccine effectiveness against the omicron (B.1.1.529) variant. N Engl J Med 2022;386:1532–46.
Angeli F, Spanevello A, Reboldi G, Visca D, Verdecchia P. SARS-CoV-2 vaccines: lights and shadows. Eur J Intern Med 2021;88:1–8.
AstraZeneca. COVID-19 vaccine AstraZeneca analysis print. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/972833/COVID-19_AstraZeneca_Vaccine_Analysis_Print.pdf, 2021 (accessed 29 August 2021).
Atasheva S, Yao J, Shayakhmetov DM. Innate immunity to adenovirus: lessons from mice. FEBS Lett 2019;593:3461–83.
Aye YN, Mai AS, Zhang A, Lim OZH, Lin N, Ng CH, et al. Acute myocardial infarction and myocarditis following COVID-19 vaccination [published online ahead of print, 2021 Sep 29]. QJM 2021:hcab252.
Bager P, Wohlfahrt J, Bhatt S, Stegger M, Legarth R, Møller CH, et al. Risk of hospitalisation associated with infection with SARS-CoV-2 omicron variant versus delta variant in Denmark: an observational cohort study. Lancet Infect Dis 2022;22:967–76.
Barda N, Dagan N, Ben-Shlomo Y, Kepten E, Waxman J, Ohana R, et al. Safety of the BNT162b2 mRNA Covid-19 vaccine in a nationwide setting. N Engl J Med 2021;385:1078–90.
Berg J, Lovrinovic M, Baltensperger N, Kissel CK, Kottwitz J, Manka R, et al. Non-steroidal anti-inflammatory drug use in acute myopericarditis: 12-month clinical follow-up. Open Heart 2019;6.
Fairweather D, Cooper LT, Blauwet LA. Sex and gender differences in myocarditis and dilated cardiomyopathy. Curr Probl Cardiol 2013;38:7–46.
Boivin Z, Martin J. Untimely myocardial infarction or COVID-19 vaccine side effect. Cureus 2021;13:e13651.
Brojakowska A, Narula J, Shimony R, Bander J. Clinical implications of SARS-CoV-2 interaction with renin angiotensin system: JACC review topic of the week. J Am Coll Cardiol 2020;75:3085–95.
Calcaterra G, Bassareo PP, Barilla' F, Romeo F, Mehta JL. Concerning the unexpected prothrombotic state following some coronavirus disease 2019 vaccines. J Cardiovasc Med (Hagerstown) 2022;23:71–4.
Cascella M, Rajnik M, Aleem A, Dulebohn SC, Di Napoli R. Features, evaluation, and treatment of coronavirus (COVID-19). StatPearls. Florida: StatPearls publishing; 2022.
Centers for Disease Control and Prevention (U.S.). The Vaccine Adverse Event Reporting System (VAERS) 2022. https://wonder.cdc.gov/, (accessed 4 August 2022).
Chemaitelly H, Yassine HM, Benslimane FM, Al Khatib HA, Tang P, Hasan MR, et al. mRNA-1273 COVID-19 vaccine effectiveness against the B.1.1.7 and B.1.351 variants and severe COVID-19 disease in Qatar. Nat Med 2021;27:1614–21.
Chen PW, Tsai ZY, Chao TH, Li YH, Hou CJ, Liu PY. Addressing vaccine-induced immune thrombotic thrombocytopenia (VITT) following COVID-19 vaccination: a mini-review of practical strategies. Acta Cardiol Sin 2021;37:355–64.
Chung YH, Beiss V, Fiering SN, Steinmetz NF. COVID-19 vaccine frontrunners and their nanotechnology design. ACS Nano 2020;14:12522–37.
Cines DB, Bussel JB. SARS-CoV-2 vaccine-induced immune thrombotic thrombocytopenia. N Engl J Med 2021;384:2254–6.
Crane P, Wong C, Mehta N, Barlis P. Takotsubo (stress) cardiomyopathy after ChAdOx1 nCoV-19 vaccination. BMJ Case Rep 2021;14.
Deftereos SG, Giannopoulos G, Vrachatis DA, Siasos GD, Giotaki SG, Gargalianos P, et al. Effect of colchicine vs standard care on cardiac and inflammatory biomarkers and clinical outcomes in patients hospitalized with coronavirus disease 2019: the GRECCO-19 randomized clinical trial. JAMA Netw Open 2020;3.
Di Florio DN, Sin J, Coronado MJ, Atwal PS, Fairweather D. Sex differences in inflammation, redox biology, mitochondria and autoimmunity. Redox Biol 2020;31.
Diaz GA, Parsons GT, Gering SK, Meier AR, Hutchinson IV, Robicsek A. Myocarditis and pericarditis after vaccination for COVID-19. JAMA 2021;326:1210–12.
Driggin E, Madhavan MV, Bikdeli B, Chuich T, Laracy J, Biondi-Zoccai G, et al. Cardiovascular considerations for patients, health care workers, and health systems during the COVID-19 pandemic. J Am Coll Cardiol 2020;75:2352–71.
Edler C, Klein A, Schröder AS, Sperhake JP, Ondruschka B. Deaths associated with newly launched SARS-CoV-2 vaccination (Comirnaty®). Leg Med (Tokyo) 2021;51:101895.
Fazlollahi A, Zahmatyar M, Noori M, Nejadghaderi SA, Sullman MJM, Shekarriz–Foumani R, et al. Cardiac complications following mRNA COVID-19 vaccines: a systematic review of case reports and case series. Rev Med Virol 2022;32:e2318.
FDA briefing: Document: Pfizer-BioNTech. COVID-19 vaccine. Vaccines and related biological products advisory committee meeting. https://www.fda.gov/media/144245/download, 2021 (accessed 16 July 2021).
Fearon C, Parwani P, Gow-Lee B, Abramov D. Takotsubo syndrome after receiving the COVID-19 vaccine. J Cardiol Cases 2021;24:223–6.
Fiolet T, Kherabi Y, MacDonald CJ, Ghosn J, Peiffer-Smadja N. Comparing COVID-19 vaccines for their characteristics, efficacy and effectiveness against SARS–CoV-2 and variants of concern: a narrative review. Clin Microbiol Infect 2022;28:202–21.
Ghadri JR, Kato K, Cammann VL, Gili S, Jurisic S, Di Vece D, et al. Long-term prognosis of patients with takotsubo syndrome. J Am Coll Cardiol 2018a;72:874–82.
Ghadri JR, Wittstein IS, Prasad A, Sharkey S, Dote K, Akashi YJ, et al. International expert consensus document on takotsubo syndrome (Part I): clinical characteristics, diagnostic criteria, and pathophysiology. Eur Heart J 2018b;39:2032–46.
Greinacher A, Thiele T, Warkentin TE, Weisser K, Kyrle PA, Eichinger S. Thrombotic thrombocytopenia after ChAdOx1 nCov-19 vaccination. N Engl J Med 2021;384:2092–101.
Haimei MA. Concern about the adverse effects of thrombocytopenia and thrombosis after adenovirus-vectored COVID-19 vaccination. Clin Appl Thromb Hemost 2021;27.
Hana D, Patel K, Roman S, Gattas B, Sofka S. Clinical cardiovascular adverse events reported post-COVID-19 vaccination: are they a real risk? Curr Probl Cardiol 2022;47.
Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497–506.
Hung IFN, Poland GA. Single-dose Oxford-AstraZeneca COVID-19 vaccine followed by a 12-week booster. Lancet 2021;397:854–5.

Hwang SR, Wang Y, Weil EL, Padmanabhan A, Warkentin TE, Pruthi RK. Cerebral venous sinus thrombosis associated with spontaneous heparin-induced thrombocytopenia syndrome after total knee arthroplasty. Platelets 2021;32:936–40.
Islam A, Bashir MS, Joyce K, Rashid H, Laher I, Elshazly S. An update on COVID-19 vaccine induced thrombotic thrombocytopenia syndrome and some management recommendations. Molecules 2021;26.
Jeet Kaur R, Dutta S, Charan J, Bhardwaj P, Tandon A, Yadav D, et al. Cardiovascular adverse events reported from COVID-19 vaccines: a study based on WHO database. Int J Gen Med 2021;14:3909–27.
Joshi G, Borah P, Thakur S, Sharma P, Mayank PR, Poduri R. Exploring the COVID-19 vaccine candidates against SARS-CoV-2 and its variants: where do we stand and where do we go? Hum Vaccin Immunother 2021;17:4714–40.
Junapudi SS, Junapudi S, Ega K, Chidipi B. Major cardiac concerns in therapy and vaccinations for COVID-19. Metabol Open 2021;11.
Kamarullah W, Nurcahyani Mary Josephine C, Bill Multazam R, Ghaezany Nawing A, Dharma S. Corticosteroid therapy in management of myocarditis associated with COVID-19; a systematic review of current evidence. Arch Acad Emerg Med 2021;9:e32.
Kaur RJ, Dutta S, Bhardwaj P, Charan J, Dhingra S, Mitra P, et al. Adverse events reported from COVID-19 vaccine trials: a systematic review. Indian J Clin Biochem 2021;36:427–39.
Kim HW, Jenista ER, Wendell DC, Azevedo CF, Campbell MJ, Darty SN, et al. Patients with acute myocarditis following mRNA COVID-19 vaccination. JAMA Cardiol 2021;6:1196–201.
Kounis NG. Kounis syndrome (allergic angina and allergic myocardial infarction): a natural paradigm? Int J Cardiol 2006;110:7–14.
Kounis NG, Koniari I, Mplani V, Kouni SN, Plotas P, Tsigkas G. Acute myocardial infarction within 24 hours after COVID-19 vaccination: is Kounis syndrome the culprit? Am J Cardiol 2022;162:207.
Kytö V, Sipilä J, Rautava P. Clinical profile and influences on outcomes in patients hospitalized for acute pericarditis. Circulation 2014;130:1601–6.
Li H, Yu X, Liles C, Khan M, Vanderlinde-Wood M, Galloway A, et al. Autoimmune basis for postural tachycardia syndrome. J Am Heart Assoc 2014;3.
Li K, Huang B, Ji T, Xu SG, Jiang W. A postoperative man with Marfan syndrome with palpitations and chest pain after receiving the SARS-CoV-2 vaccine. Infect Drug Resist 2021a;14:2953–6.
Li X, Ostropolets A, Makadia R, Shaoibi A, Rao G, Sena AG, et al. Characterizing the incidence of adverse events of special interest for COVID-19 vaccines across eight countries: a multinational network cohort study. BMJ 2021b;373:n1435.
Maiese A, Baronti A, Manetti AC, Di Paolo M, Turillazzi E, Frati P, et al. Death after the administration of COVID-19 vaccines approved by EMA: has a causal relationship been demonstrated? Vaccines (Basel) 2022;10:308.
Marcucci R, Marietta M. Vaccine-induced thrombotic thrombocytopenia: the elusive link between thrombosis and adenovirus-based SARS-CoV-2 vaccines. Intern Emerg Med 2021;16:1113–19.
Mathieu E, Ritchie H, Ortiz-Ospina E, Roser M, Hasell J, Appel C, et al. A global database of COVID-19 vaccinations. Nat Hum Behav 2021;5:947–53.
Mevorach D, Anis E, Cedar N, Bromberg M, Haas EJ, Nadir E, et al. Myocarditis after BNT162b2 mRNA vaccine against Covid-19 in Israel. N Engl J Med 2021;385:2140–9.
Mustafa HI, Raj SR, Diedrich A, Black BK, Paranjape SY, Dupont WD, et al. Altered systemic hemodynamic and baroreflex response to angiotensin II in postural tachycardia syndrome. Circ Arrhythm Electrophysiol 2012;5:173–80.
Nesci S. SARS-CoV-2 first contact: spike-ACE2 interactions in COVID-19. Chem Biol Drug Des 2021;98:207–11.
Nyberg T, Ferguson NM, Nash SG, Webster HH, Flaxman S, Andrews N, et al. Comparative analysis of the risks of hospitalisation and death associated with SARS–CoV-2 omicron (B.1.1.529) and delta (B.1.617.2) variants in England: a cohort study. Lancet 2022;399:1303–12.
Özdemir İH, Özlek B, Özen MB, Gündüz R, Bayturan Ö. Type 1 Kounis syndrome induced by inactivated SARS-COV-2 vaccine. J Emerg Med 2021;61:e71–6.
Palacios R, Patiño EG, de Oliveira Piorelli R, Conde MTRP, Batista AP, Zeng G, et al. Double-blind, randomized, placebo-controlled chase III clinical Trial to evaluate the efficacy and safety of treating healthcare professionals with the adsorbed COVID-19 (inactivated) vaccine manufactured by Sinovac - PROFISCOV: a structured summary of a study protocol for a randomised controlled trial. Trials 2020;21:853.
Panthong S, Vimonsuntirungsri T, Thapanasuta M, Wanlapakorn C, Udayachalerm W, Ariyachaipanich A. Acute coronary syndrome after inactivated SARS-COV-2 vaccine. Int Heart J 2022;63:388–92.
Parra-Lucares A, Toro L, Weitz-Muñoz S, Ramos C. Cardiomyopathy associated with anti-SARS-CoV-2 vaccination: what do we know? Viruses 2021;13:2493.
Patalon T, Gazit S, Pitzer VE, Prunas O, Warren JL, Weinberger DM. Odds of testing positive for SARS-CoV-2 following receipt of 3 vs 2 doses of the BNT162b2 mRNA vaccine. JAMA Intern Med 2022;182:179–84.
Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and efficacy of the BNT162b2 mRNA COVID-19 vaccine. N Engl J Med 2020;383:2603–15.
Pouwels KB, Pritchard E, Matthews PC, Stoesser N, Eyre DW, Vihta KD, et al. Effect of Delta variant on viral burden and vaccine effectiveness against new SARS-CoV-2 infections in the UK. Nat Med 2021;27:2127–35.
Qamar N, Rukh G, Khan SN. Vaccines for COVID-19: an insight on their effectiveness and adverse effects. J Med Virol 2022;94:3554–60.
Reddy S, Reddy S, Arora M. A case of postural orthostatic tachycardia syndrome secondary to the messenger RNA COVID-19 vaccine. Cureus 2021;13:e14837.
Rocca B, Secchiero P, Ciabattoni G, Ranelletti FO, Catani L, Guidotti L, et al. Cyclooxygenase-2 expression is induced during human megakaryopoiesis and characterizes newly formed platelets. Proc Natl Acad Sci U S A 2002;99:7634–9.
Şancı E, Örçen C, Çelik OM, Özen MT, Bozyel S. Kounis syndrome associated with BNT162b2 mRNA COVID-19 vaccine presenting as ST-elevation acute myocardial infarction. Anatol J Cardiol 2022;26:69–74.
Sattar Y, Siew KSW, Connerney M, Ullah W, Alraies MC. Management of takotsubo syndrome: a comprehensive review. Cureus 2020;12:e6556.
Schultz NH, Sørvoll IH, Michelsen AE, Munthe LA, Lund-Johansen F, Ahlen MT, et al. Thrombosis and thrombocytopenia after ChAdOx1 nCoV-19 vaccination. N Engl J Med 2021;384:2124–30.
Scully M, Singh D, Lown R, Poles A, Solomon T, Levi M, et al. Pathologic antibodies to platelet factor 4 after ChAdOx1 nCoV-19 vaccination. N Engl J Med 2021;384:2202–11.
Sette A, Crotty S. Adaptive immunity to SARS-CoV-2 and COVID-19. Cell 2021;184:861–80.
Shaw KE, Cavalcante JL, Han BK, Gössl M. Possible association between COVID-19 vaccine and myocarditis: clinical and CMR findings. JACC Cardiovasc Imaging 2021;14:1856–61.
Sheikh A, Kerr S, Woolhouse M, McMenamin J, Robertson C. EAVE II Collaborators. Severity of omicron variant of concern and effectiveness of vaccine boosters against symptomatic disease in Scotland (EAVE II): a national cohort study with nested test-negative design. Lancet Infect Dis 2022;22:959–66.
Sheikh A, McMenamin J, Taylor B, Robertson C. Public Health Scotland and the EAVE II Collaborators. SARS-CoV-2 Delta VOC in Scotland: demographics, risk of hospital admission, and vaccine effectiveness. Lancet 2021;397:2461–2.
Shirani K, Sheikhbahaei E, Torkpour Z, Ghadiri Nejad M, Kamyab Moghadas B, Ghasemi M, et al. A narrative review of COVID-19: the new pandemic disease. Iran J Med Sci 2020;45:233–49.
Shiravi AA, Ardekani A, Sheikhbahaei E, Heshmat-Ghahdarijani K. Cardiovascular complications of SARS-CoV-2 vaccines: an overview. Cardiol Ther 2021;11:13–21.
Shiravi AA, Saadatkish M, Abdollahi Z, Miar P, Khanahmad H, Zeinalian M. Vitamin D can be effective on the prevention of COVID-19 complications: a narrative review on molecular aspects. Int J Vitam Nutr Res 2022;92:134–46.
Singh K, Marinelli T, Horowitz JD. Takotsubo cardiomyopathy after anti-influenza vaccination: catecholaminergic effects of immune system. Am J Emerg Med 2013;31 1627.e1–4.
Talasaz AH, Sadeghipour P, Kakavand H, Aghakouchakzadeh M, Kordzadeh-Kermani E, Van Tassell BW, et al. Recent randomized trials of antithrombotic therapy for patients with COVID-19: JACC state-of-the-art review. J Am Coll Cardiol 2021;77:1903–21.
Tang P, Hasan MR, Chemaitelly H, Yassine HM, Benslimane FM, Al Khatib HA, et al. BNT162b2 and mRNA-1273 COVID-19 vaccine effectiveness against the SARS–CoV-2 Delta variant in Qatar. Nat Med 2021;27:2136–43.
Templin C, Ghadri JR, Diekmann J, Napp LC, Bataiosu DR, Jaguszewski M, et al. Clinical features and outcomes of takotsubo (stress) cardiomyopathy. N Engl J Med 2015;373:929–38.
Thomas SJ, Moreira ED, Jr Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine through 6 months. N Engl J Med 2021;385:1761–73.
Tsilingiris D, Vallianou NG, Karampela I, Dalamaga M. Vaccine induced thrombotic thrombocytopenia: the shady chapter of a success story. Metabol Open 2021;11.
Verdecchia P, Cavallini C, Spanevello A, Angeli F. COVID-19: ACE2 centric infective disease? Hypertension 2020a;76:294–9.
Verdecchia P, Cavallini C, Spanevello A, Angeli F. The pivotal link between ACE2 deficiency and SARS-CoV-2 infection. Eur J Intern Med 2020b;76:14–20.
Vidula MK, Ambrose M, Glassberg H, Chokshi N, Chen T, Ferrari VA, et al. Myocarditis and other cardiovascular complications of the mRNA-based COVID-19 vaccines. Cureus 2021;13:e15576.
Vojdani A, Kharrazian D. Potential antigenic cross-reactivity between SARS-CoV-2 and human tissue with a possible link to an increase in autoimmune diseases. Clin Immunol 2020;217.
Wise J. COVID-19: European countries suspend use of Oxford-AstraZeneca vaccine after reports of blood clots. BMJ 2021;372:n699.
Witberg G, Barda N, Hoss S, Richter I, Wiessman M, Aviv Y, et al. Myocarditis after COVID-19 vaccination in a large health care organization. N Engl J Med 2021;385:2132–9.
Zappa M, Verdecchia P, Spanevello A, Visca D, Angeli F. Blood pressure increase after Pfizer/BioNTech SARS-CoV-2 vaccine. Eur J Intern Med 2021;90:111–13.