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Review

Cardiovascular implications of the COVID-19 pandemic

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ABSTRACT

The COVID-19 pandemic has rapidly emerged as one of the biggest public health concerns of the 21st century. Although it was initially reported as a cluster of pneumonia cases, it quickly became apparent that COVID-19 is not merely a respiratory tract infection. Its clinical course is often complicated by cardiovascular manifestations including venous and arterial thrombosis, electrical disturbances, and myocardial damage. In addition, the cardiovascular system is involved not only during infection but also preceding the contraction of the virus; having cardiovascular comorbidities indicates significant vulnerability to the pathogen. As longer-term data continue to accumulate, we now have concerns over its lasting cardiovascular effects after recovery. Moreover, there have been substantial collateral effects on the epidemiology of cardiovascular diseases. Reports of adverse cardiovascular events from vaccination have emerged as new hurdles to our efforts to bring an end to the pandemic. As such, the association between COVID-19 and the cardiovascular system and cardiovascular practice in general is expansive. In this review, we provide an overview of the knowledge and considerations in this field, based on the evidence available at the time of this writing.

Introduction

Since the first case was identified in Wuhan, China in December 2019, coronavirus 2019 (COVID-19) has rapidly spread across the globe, representing the largest pandemic humanity has faced since the Spanish flu a century ago. As of September 2021, there have been at least 218 million confirmed cases of COVID-19 worldwide [1]. Approximately 2.8% of the world's population have been infected. Besides posing direct health consequences to the patients, COVID-19 has influenced our daily lives, leading to unforeseen secondary effects both within and outside healthcare.

The bidirectional relationship between infectious diseases and the cardiovascular system has been well established in previous literature. However, we have come to realize that our current understanding is insufficient to effectively manage severe acute respiratory syndrome coronavirus **2** (SARS-CoV-2) infection. In addition, the pandemic has resulted in secondary effects to cardiovascular practice. As COVID-19 becomes more common in daily clinical practice, every cardiovascular professional must keep up to date with the latest findings in this broad field. Here in this review, we will summarize potential cardiovascular problems in each phase of illness: preceding contraction of the virus, during acute infection, and after recovery. In addition, we will broaden our scope outside of COVID-19 infection itself to collateral consequences of the pandemic, touching briefly on the vaccines as well. In each of the topics, we will focus on the cardiovascular aspects and summarize what has been made clear and what needs further investigation.

Role of cardiovascular comorbidities on the clinical course

Pre-existing cardiovascular disease, along with older age and other non-cardiovascular comorbidities, is an established risk for adverse outcomes in COVID-19 patients. An early prospective cohort study of 5279 infected people in New York revealed that patients with cardiovascular disease were more likely to take a severe clinical course. Heart failure was one of the most substantial risks for critical illness (odds ratio 1.9, CI 1.4 to 2.5) [2]. Also, in a multicenter cohort study from the UK of 20,133 inpatients, chronic cardiac disease was the most prevalent comorbidity and was associated with mortality [3]. Similar findings have been reported from many other regions of the world [4–7]. More recently, a large meta-analysis that included 51 studies with a total of 48,317 patients suggested that the increased risk is consistent across all ages [8]. Although younger patients had a lower prevalence of cardiovascular diseases, they were at a higher risk for morbidity from COVID-19 compared to elderly patients with similar conditions.

Although evidence on severe illness in COVID-19 patients with cardiovascular comorbidities is abundant, many of these early studies did not distinguish between different heart conditions. Ac-

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Table 1
Prevalence and Mechanism of Cardiovascular Complications Caused by COVID-19.

	Prevalence	Common mechanism	COVID-specific mechanism
Venous Thrombosis Pulmonary Embolism	High	• Immunothrombosis • Reduced mobility • Hypoxia	• Endothelial damage • Prominent NET formation
Myocardial Infarction	Low	• Immunothrombosis	• Prominent NET formation
Arrhythmia	Intermediate	• Inflammatory electrophysiological disturbance • Sympathetic activation • Volume / electrolyte imbalance	Unlikely
Myocardial Injury	High	• O2 supply-demand ischemia	Unlikely
Myocarditis Endocarditis Pericarditis	Low	Insufficient data	Insufficient data

NET, neutrophil extracellular trap.

cording to data currently available, heart failure, although the term itself incorporates a broad spectrum of etiologies and severity, appears to pose the highest risk. Surprisingly, based on an analysis of a large, multicenter database of 8383 American COVID-19 patients with heart failure, nearly one in four died during hospitalization [9]. In a large multi-national cohort study of 20,954 patients, the adjusted risk ratio for in-hospital mortality was 1.19 for heart failure and 1.41 for severe (i.e. New York Heart Association III/IV) heart failure [10]. Of note, after adjustment for age, sex, body mass index, diabetes, hypertension, chronic kidney disease, and chronic obstructive pulmonary disease, the increased risk was not significant for other heart disease subtypes, including ischemic heart disease, arrhythmias, and valvular heart diseases. Further studies to determine the association across different heart disease subtypes are warranted.

Given the profound influence that cardiovascular comorbidities have on the clinical trajectory of COVID-19, a thorough review of the patient's medical history must be conducted. By doing so, the risk for progressive disease would be better estimated, which would in turn enable timely escalation of therapeutic interventions. Also, efforts to encourage patients with cardiac comorbidities to get vaccinated must be continued. In areas of the world where vaccines are in short supply, priority needs be determined based on different cardiovascular conditions and their severity [11].

Cardiovascular complications during acute infection

In the wake of the pandemic in Wuhan, China, SARS-CoV-2 infections were reported as a cluster of pneumonia cases, mainly affecting the lungs. However, it quickly became evident that the infection has far-reaching effects on other parts of the body as well. Since then, both basic and clinical researchers have re-explored the close connection between the immune system and the cardiovascular system [12].

Previous investigations have suggested that various types of cardiovascular complications may occur in COVID-19 patients. According to a meta-analysis of 17 cohort studies with a total of 5815 patients, the most common cardiovascular complications were heart failure, myocardial injury, cardiac arrhythmia, and acute coronary syndrome [13].

The true incidence for each complication is difficult to estimate. There is significant heterogeneity in disease severity and treatment among various studies. Therefore, it is a matter of ongoing debate which, if any, cardiovascular complications are particularly frequent in COVID-19 compared to other types of infections. Interestingly, a recent multi-national cohort study of 16,511 patients pointed out that besides pulmonary embolism, serious cardiac complications including myocarditis, myocardial infarction, and new-onset heart failure were rare, occurring in only 2.0% of hospitalized patients [10] (Table 1).

Venous thrombosis and pulmonary embolism

The presence of venous thrombosis in COVID-19 patients is common, particularly in those with a critical illness [14–16]. According to a recent systematic review of 16 studies, the estimated incidence of venous thromboembolism was 7.4% [17]. Another systematic review analyzed 27 studies and concluded that the pooled incidence rate was 16.5% [18]. This large deviation demonstrates the presence of substantial heterogeneity among various studies. Contributing factors may include differences in the study population (e.g. disease severity and patient demographics) and clinical practices [e.g. anticoagulation prophylaxis and accessibility of computed tomography pulmonary angiography (CTPA) testing].

The development of venous thrombosis in COVID-19 patients probably involves etiologies familiar to other respiratory infections, such as hypoxia and reduced mobility [19,20]. However, the incidence of venous thrombosis is significantly higher in COVID-19 compared to seasonal influenza, suggesting that mechanisms exclusive to COVID-19 may also be present [21]. Here, the angiotensin-converting enzyme 2 (ACE2) receptor may play a unique role in the process. Via the ACE2 receptor, the SARS-CoV-2 virus enters the vascular endothelium, triggering endothelial inflammation and the exposure of von Willebrand factor (vWF) [22–24]. vWF plays a role in adhesion and aggregation of platelets and contributes to thrombosis [25]. In addition, neutrophils, which also express ACE2 receptors, are activated by the virus and release neutrophil extracellular traps (NETs) [12]. NETs are key mediators of immunothrombosis that activate factor XII and trigger the coagulation cascade [26]. In fact, studies on blood neutrophils and lung specimens of COVID-19 patients have suggested that prominent NET formation was a distinguishing feature in COVID-19 [27,28].

The establishment of an optimal anticoagulation strategy to prevent thrombotic complications continues to be a work in progress. During the early days of the pandemic, clinicians experimentally began administering prophylactic anticoagulation to COVID-19 patients upon hospital admission. Meanwhile, a retrospective analysis of 449 severe COVID-19 patients in China showed that anticoagulant therapy with low molecular weight heparin (LMWH) was associated with a better prognosis [29]. Following this trend, several academic institutions recommended routine prophylactic anticoagulation with LMWH in all hospitalized COVID-19 patients without contraindications [30,31]. The strategy was later justified by a large nationwide cohort study of 4297 COVID-19 patients in the USA [32]. The research revealed that early prophylactic administration of heparin was associated with a 34% increased chance of survival without an increased risk of serious bleeding. Still, even with the routine administration of prophylactic-dose anticoagulation, venous thrombosis remained a major question [33]. Whether higher doses of anticoagulation pro-

phylaxis would be more effective and still be safe remained a mystery among clinicians.

The most recent randomized clinical trials (RCT) hint against routine therapeutic-dose anticoagulation. The INSPIRATION RCT compared the effects of intermediate-dose and standard-dose prophylactic anticoagulation in 562 COVID-19 patients treated in the intensive care unit (ICU) [34]. The trial revealed that intermediate-dose anticoagulation showed no improvement in the composite outcome of thrombosis, extracorporeal membrane oxygenation (ECMO) treatment, or mortality. Instead, it resulted in more bleeding. Similar findings came from the ACTION RCT, where 615 COVID-19 patients with elevated D-dimer were randomized to receive either therapeutic-dose or prophylactic-dose anticoagulation [35]. The study also failed to show improvement in clinical outcomes with therapeutic-dose anticoagulation. Again, therapeutic-dose anticoagulation was associated with a significant increase in bleeding compared to prophylactic-dose. In contrast to the two RCTs, the REMAP-CAP, ACTIV-4a, and ATTACC multi-platform RCT suggested that benefits of therapeutic-dose anticoagulation might depend on disease severity [36,37]. The study suggested that therapeutic-dose anticoagulation improved survival rate in the noncritically ill patients but not in critically ill patients. Within the noncritically ill patients, although therapeutic-dose anticoagulation improved outcomes regardless of the patient's D-dimer level at baseline, the benefit was more prominent in those with high D-dimer levels. Altogether, the three RCTs have reemphasized that individualized adjustments based on disease severity, D-dimer levels, and bleeding risks are crucial.

In addition, the development of a diagnostic algorithm for pulmonary embolism (PE) in COVID-19 patients also continues to be a work in progress. In particular, the appropriate D-dimer threshold for selecting patients for CTPA is still controversial. CTPA is the golden diagnostic standard for PE in general. However, it is often overused, leading to unnecessary risks of radiation exposure and contrast nephropathy [38]. In the case of COVID-19, it also poses the risk of viral transmission to the medical staff. Some studies argue that the conventionally used cut-off value (500 or 1000 ng/mL) is too low, while others argue that setting a higher cut-off value would reduce the sensitivity of the test [18,39,40]. To further complicate the problem, the efficacy of pre-test prediction scores such as the Well criteria has been questioned in COVID-19 patients [41,42]. Given the high prevalence of PE, it may be reasonable to maintain a low threshold for conducting CTPA until reliable evidence becomes available.

Myocardial infarction

Since the early phases of the pandemic, multiple cohort studies have shown that COVID-19 might trigger acute myocardial infarction (AMI) [15,43]. In addition to cohort studies, the self-controlled case series (SCCS) method has been used to evaluate the risk of AMI associated with COVID-19. An SCCS compares incidence rates of an outcome (i.e. AMI) relative to an exposure (i.e. COVID-19) in one person at different time periods. Using the method, a Danish study of 5119 patients diagnosed with COVID-19 estimated that the incidence rate of AMI was five times higher during the 14 days after COVID-19 diagnosis [44]. In a recent nationwide study from Sweden that analyzed 86742 patient records, the incidence rate ratio for AMI was 2.9 for the first week following COVID-19 onset, compared with control intervals [45]. The researchers simultaneously conducted a matched cohort study to compare the risk with the background population. Compared to matched controls, COVID-19 patients had an odds ratio of 3.4 for the two weeks following COVID-19. The studies have confirmed that COVID-19 patients are at an increased risk for AMI, particularly within the first two weeks of onset.

The detailed mechanism of AMI onset in COVID-19 is unclear. Infections and subsequent inflammation may trigger coronary thrombosis through multiple mechanisms, including inflammatory cell infiltration into the atherosclerotic plaques, systemic platelet activation, coronary vasoconstriction, and endothelial dysfunction [46]. Indeed, it has been validated in previous literature that acute respiratory infections in general increase the risk of acute coronary syndromes [47–49]. According to a meta-analysis of 16 case-control studies, recent respiratory tract infection, including influenza, was significantly associated with AMI [50]. In COVID-19 patients, NET formation may also be playing a specific role. A small case series study compared the coronary thrombus aspirates of 5 AMI patients with COVID-19 and 50 control patients without COVID-19 [51]. NETs were detected in all COVID-19 patients, whereas in the control group, only 68% were positive. The median density of NETs was significantly higher in COVID-19 patients as well (61% vs. 19%).

The treatment algorithm of AMI for COVID-19 patients is the same as that for non-COVID-19 patients [52]. For suspected ST-elevation myocardial infarction, the patient should undergo emergent coronary angiography (CAG) plus an ad-hoc percutaneous intervention if the diagnosis is confirmed. One thing to keep in mind though, is the need to limit exposure with the patient. Unless the patient is proven COVID-19-negative, emergent CAG procedures should be conducted with minimal staff members with proper personal protective equipment.

COVID-19-triggered AMI in individuals with high coronary risks may become a public health concern in the coming days. Interestingly, authors of the meta-analysis mentioned above also analyzed the benefits of influenza vaccination in preventing AMI and estimated that the effectiveness of flu vaccines in AMI prevention was 29%, comparable to that of other preventative measures such as statins (36%) and antihypertensives (15-18%) [50]. The merits of vaccination go beyond preventing the original viral infection to its possible cardiovascular complications.

Arrhythmia

A wide variety of arrhythmias are reported in the acute phase of COVID-19. In a global survey of electrophysiology professionals, atrial fibrillation was the most common arrhythmia, reported by 142 out of 683 respondents (21%) [53]. On the other hand, life-threatening arrhythmias were rarely reported. For instance, malignant ventricular tachycardia and ventricular fibrillation were reported by only 4.8% of respondents. In a worldwide case series of 4526 COVID-19 patients, 18% had an arrhythmia during hospitalization, most of which were newly discovered [54]. Of those who developed an arrhythmia, the incidence of atrial tachycardia was 81.8%, and the incidence of ventricular tachycardia was 20.7%. Drug-induced QT prolongation and Torsade de Pointes once used to be a clinical issue in the early days of the pandemic when hydroxychloroquine and azithromycin were experimentally used as COVID-19 treatment [55]. With solid evidence against their effectiveness, these drugs are no longer recommended. As such, the initial retrospective studies may have overestimated the actual burden of arrhythmias in COVID-19 patients, especially for ventricular tachycardias.

Although the pathophysiology of arrhythmias in COVID-19 patients remains uncertain, it is likely precipitated by systemic immunoinflammatory response. Inflammatory cytokines prolong the action potential duration (APD) of the myocardium, hence a prolonged QT interval on electrocardiogram. Combined with sympathetic activation, they may trigger ventricular arrhythmias. Also, the cytokines also induce delayed after depolarizations (DADs), increasing the frequency of ectopic activities and subsequent atrial arrhythmias [56–58]. Other underlying factors may include

electrolyte disturbances and intravascular volume imbalances in severely ill COVID-19 patients.

Based on such assumptions, it is no surprise that the frequency of arrhythmia is associated with disease severity. In the aforementioned case series study, 43% of patients who developed arrhythmias were mechanically ventilated [54]. Furthermore, an analysis of 700 COVID-19 patients showed that patients treated in the ICU were 10 times more likely to develop atrial fibrillation, bradycardia, or non-sustained ventricular tachycardia compared to those in the general ward [59]. Myocardial injury, an indicator of poor prognosis, was also associated with malignant arrhythmias in patients receiving intensive care [60].

Management of arrhythmias does not differ significantly in the context of COVID-19 infection and should be based on evidence-based guidelines. For instance, in the case of atrial fibrillation, treatment should address rate control, rhythm control, and anticoagulation.

Other complications

Other reported cardiovascular complications of COVID-19 include heart failure, endocarditis, pericarditis, and myocarditis. The definition of heart failure is often ambiguous and inconsistent among studies, making it difficult to determine its significance in COVID-19 patients. According to a large multi-national cohort study of 20954 patients, new-onset heart failure occurred in only 1.2%, more frequently in patients with pre-existing heart conditions [10]. Reports of endocarditis and pericarditis are limited to case reports [61,62]. Although myocardial injury is a common finding in COVID-19 patients, other clinical features of myocarditis, such as electrocardiographic and echocardiographic abnormalities, are relatively rare [17,63].

Myocardial injury and cardiovascular biomarkers

In the context of COVID-19, myocardial injury usually refers to the elevation of cardiac troponin regardless of its etiology. Previous studies have shown that it is a common finding in COVID-19 patients. The reported incidence of elevated troponin varies widely, from 4.8% in patients with only mild symptoms to 54% in critically ill patients [17].

The level of troponin is shown to be closely related to disease severity and mortality of COVID-19. In an initial report from China, myocardial injury was more prevalent among ICU patients compared to non-ICU patients (22.2% vs. 2.0%) [64]. Furthermore, troponin elevation was not only associated with mortality but also with a greater risk of non-cardiovascular complications such as sepsis, acute kidney failure, and major bleeding [65]. Another multicenter study reported that although troponin-I was only mildly elevated (e.g. $<$0.03-0.09 ng/ml) in a majority of patients, even subtle elevations were significantly associated with mortality [66]. Surprisingly, patients exhibiting myocardial injury without prior cardiovascular disease had worse outcomes compared to those with a history of cardiovascular disease, but no myocardial injury [60].

The association between myocardial injury and critical illness is not unique to COVID-19; It has been previously demonstrated in other infections, including community-acquired pneumonia and seasonal influenza [67,68]. In a retrospective cohort study of 321 hospitalized patients with H7N9 influenza, 45.8% showed elevated troponin, and myocardial injury was associated with in-hospital mortality [68]. Moreover, troponin has been proposed as a prognostic marker for critically ill patients with early sepsis [69] and other acute respiratory diseases [70].

Myocardial injury in COVID-19 is usually a result of supply-demand ischemia from immune-mediated systemic inflammation. Some studies suspect myocardial damage caused by direct invasion of SARS-CoV-2, but this notion lacks quality evidence. Several *in vitro* studies have supported that human iPS-derived cardiomyocytes are susceptible to direct infection by SARS-COV-2 [71,72]. On the contrary, in histopathological analysis of 39 autopsy cases of COVID-19 patients, a high viral load of SARS-CoV-2 in the cardiac tissue was present in 16 (41%) patients, but it was detected in the interstitial cells rather than the cardiomyocytes [73]. Furthermore, none of them had concomitant infiltrates of inflammatory cells.

Other parameters routinely used in daily cardiovascular practice may also be effective in predicting prognosis. One of such biomarkers is D-dimer. In an early study of 191 Chinese patients with COVID-19, D-dimer greater than 1 μg/mL was associated with increased in-hospital mortality [74]. Of note, levels of D-dimer and cardiac troponin rose progressively in non-survivors as the condition deteriorated, while these values stayed around the normal range in survivors. N-terminal prohormone of brain natriuretic peptide (NT-proBNP) is another biomarker that is under investigation. In a large cohort study of 3080 patients in Spain, NT-proBNP was independently associated with mortality even after adjusting for relevant confounders, including chronic heart failure and acute decompensated heart failure during hospitalization [75].

Routine examination of these biomarkers as a prognostic marker in COVID-19 patients is controversial, as it may result in over-testing. In the case of cardiac troponin, other than relative ischemia from oxygen supply-demand imbalance from severe inflammatory response, its elevation may also involve other mechanisms such as acute coronary syndrome, pre-existing heart disease, renal impairment, and various cardiomyopathies. As such, biomarker tests are often difficult to interpret in clinical practice, requiring comprehensive review of the patient with physical examinations and other diagnostic tools. If biomarker tests are to be conducted for prognosis prediction, pre-test assessment of the patient's broader clinical picture is essential to avoid being misled by the result.

Long-term cardiovascular consequences

Patients who have successfully recovered from COVID-19 may experience persistent symptoms after the infection. The complications of COVID-19 in the chronic phase are referred to as "long COVID syndrome" and have been a focus of research. According to a study of 179 individuals who recovered from COVID-19, 87.4% reported persistence of at least one symptom on a standardized questionnaire [76]. The most frequent manifestations were fatigue (53%), dyspnea (43%), arthralgia (27%), and chest pain (21%).

Within the scope of cardiology, ongoing myocardial inflammation is an area of an emerging issue. According to a large cohort study of 1597 young athletes with prior COVID-19 infection, 2.3% were suspected of having myocarditis on cardiovascular magnetic resonance (CMR) imaging, although only 0.31% were symptomatic [77]. Other imaging studies have also suggested an ongoing myocardial inflammation months after the acute infection. In one cohort study, 100 individuals who recovered from COVID-19 were scanned with CMR imaging approximately two to three months after infection [78]. Up to 78% showed abnormal T1 and/or T2 findings, and this finding was independent of pre-existing cardiac conditions or the clinical severity of COVID-19 infection. In another cohort study of 148 COVID-19 recovered patients who were troponin-positive during admission, 26% exhibited myocarditis-like pattern on CMR imaging, and a third of those showed signs of ongoing inflammation [79]. In the two studies, left ventricular ejection fraction was preserved or only mildly reduced. However, a recent study suggested that left ventricular global longitudinal strain (LVGLS), a more sensitive marker of subclinical myocardial dys-

function, might be reduced even in patients who were only mildly ill [80].

Previous studies have suggested that the after-effects of infection are not unique to COVID-19. For instance, in patients with community-acquired pneumonia, the resolution of symptoms require more than a month [81]. However, symptoms aside, they may also be at an increased risk for cardiovascular diseases 10 years after recovery [82]. Further studies with more extended follow-up periods are critical to determine whether outpatient monitoring should be continued in the convalescent phase of COVID-19.

Secondary effects on cardiovascular practice

Epidemiological changes to cardiovascular diseases

The ongoing pandemic has altered people's lifestyles and attitudes toward healthcare, affecting the distribution and presentation patterns of all types of disorders [83,84]. Cardiovascular diseases are no exception. The epidemiology of acute cardiovascular diseases was drastically affected particularly in the first wave of the pandemic when strict social distancing measures were implemented in many countries.

It appears that patients with acute cardiovascular events have been unable to or have hesitated to seek medical help during waves of the pandemic. In a nationwide retrospective study from Austria, following the outbreak at the beginning of March 2020, there was a 39.4% reduction in admissions for acute coronary syndromes [85]. Similar findings have been observed in the UK, Italy, and the USA [86–88]. In contrast, other studies have revealed that overall cardiovascular deaths increased despite the reduction in hospital presentations. In New York, deaths caused by ischemic heart disease from January to June 2020 were 2.39 times that of the same period in 2019 [89]. According to a large study using national statistics data of all adult deaths in the UK, the pandemic caused an excess acute cardiovascular mortality of 2085 (+8%), mostly occurring at home [90]. Another study from the UK confirmed that thromboembolic deaths increased outside the hospitals despite a decrease in in-hospital deaths [91]. These observed increases in out-of-hospital mortality from acute cardiovascular events may be due to 1. fear of catching the virus during hospital visits, and 2. overwhelmed healthcare system in the initial phase of the pandemic.

Lifestyle alterations, especially sedentary behavior, may also result in epidemiological changes to cardiovascular conditions. The importance of physical activity is well documented in all kinds of cardiovascular conditions [92]. Amidst the pandemic, acute venous thromboembolism (VTE i.e. PE and deep venous thrombosis) in the non-COVID-19 population is particularly concerning. A multicenter Chinese study of 3358 VTE patients compared the population before and during the pandemic and evaluated changes in VTE risk factors. Compared to the control period, proportion of trauma and surgery-induced VTE was lower during the pandemic period, whereas the proportion of VTE from inactivity was significantly higher during the pandemic period (30.7% vs. 22.6%) [93]. Similar observations were seen in other areas with different COVID-19 containment policies [91,94,95].

Stringent social distancing measures, such as lockdowns and stay-at-home orders, are still necessary in many parts of the world where vaccination distribution is inadequate. However, physical inactivity leads to development and progression of multiple cardiovascular conditions. It also increases the infection risk of COVID-19 and is associated with severe outcomes [96,97]. Especially when such policies are being implemented, emphasizing the risk of sedentary lifestyles, and promoting regular exercise is crucial.

Changes to outpatient cardiovascular care

The long-term consequences of changes in patient behavior are of growing concern [98]. First, patients with chronic cardiovascular conditions have avoided medical care visits during the pandemic [99]. Close outpatient follow-up enables optimal cardiovascular risk factor control through timely prescription adjustments and is associated with an improved prognosis of cardiovascular diseases [100,101]. The shift away from regular in-person visits poses a great risk to continuity of care. Second, fewer health checkups and testing are conducted, resulting in delays in diagnoses and interventions [84]. The importance of appropriate healthcare visits must be more widely recognized by the public.

Some clinicians see the pandemic not as a public health crisis but rather as a chance for digital transformation in healthcare. As an example, information and communication technology (ICT) has been promoted in cardiovascular outpatient care to avoid direct patient-physician contact [102]. However, as some people are unfamiliar with newer technologies, accessibility issues need to be resolved. A study conducted during the pandemic analyzed the demographics of 2940 patients with cardiovascular conditions who were scheduled for a telemedicine encounter [103]. Those who completed video telemedicine visits were significantly more likely to be male and had higher incomes than those who did not use video. The ongoing trend toward ICT-based healthcare will continue, but the issue of digital divide may be the rate-determining step in its widespread use.

Cardiovascular adverse reactions of vaccination

COVID-19 vaccines have been rapidly developed and are being distributed around the globe to tackle the pandemic. Even with increased prevalence of new, potentially more transmissible variants such as Delta, the vaccines continue to offer protection against severe disease [104]. The four vaccines predominantly distributed in the USA and Europe are commonly referred to by the manufacturer name: Pfizer-BioNTech, Moderna, AstraZeneca, and Johnson & Johnson/Janssen. These vaccines adopted fairly new technologies to achieve rapid development and large-scale production [105]. They introduce the genetic information (either mRNA or DNA) of the antigen to the immune system, instead of the antigen itself. Although the incidence is presumably extremely low, cardiovascular side effects of the vaccines are of growing concern: myocarditis and thrombosis (Fig. 1).

Cases of acute myocarditis have been reported in individuals who were vaccinated with mRNA vaccines, namely Pfizer-BioNTech and Moderna. According to an analysis based on Centers for Disease Control and Prevention's (CDC) vaccine safety monitoring system, as of June 2021, there have been 1226 reports of myocarditis after vaccination [106]. It occurred most frequently in young males (highest in age range 12–24 years) after the second shot. Ninety-two percent of them manifested within one week, and the median time until onset was two days. The patient typically presented with acute chest pain and substantially elevated troponin levels [107,108]. The clinical course was usually mild and none had died. Although the incidence of this adverse event is still under investigation, the benefits still clearly outweigh the risks. The Advisory Committee on Immunization Practices estimated that even in younger individuals, for every one million second-dose of vaccination, 560 hospitalizations and 138 ICU admissions from COVID-19 might be avoided, compared to only 40 cases of myocarditis [106].

Rare thrombotic events and thrombocytopenia have occurred after first doses of vaccination with viral-vectored vaccines. Vaccine classified in this type are Oxford-AstraZeneca vaccine and Johnson & Johnson/Janssen's single-shot vaccine. Some refer to the syndrome as vaccine-induced immune thrombocytopenia and

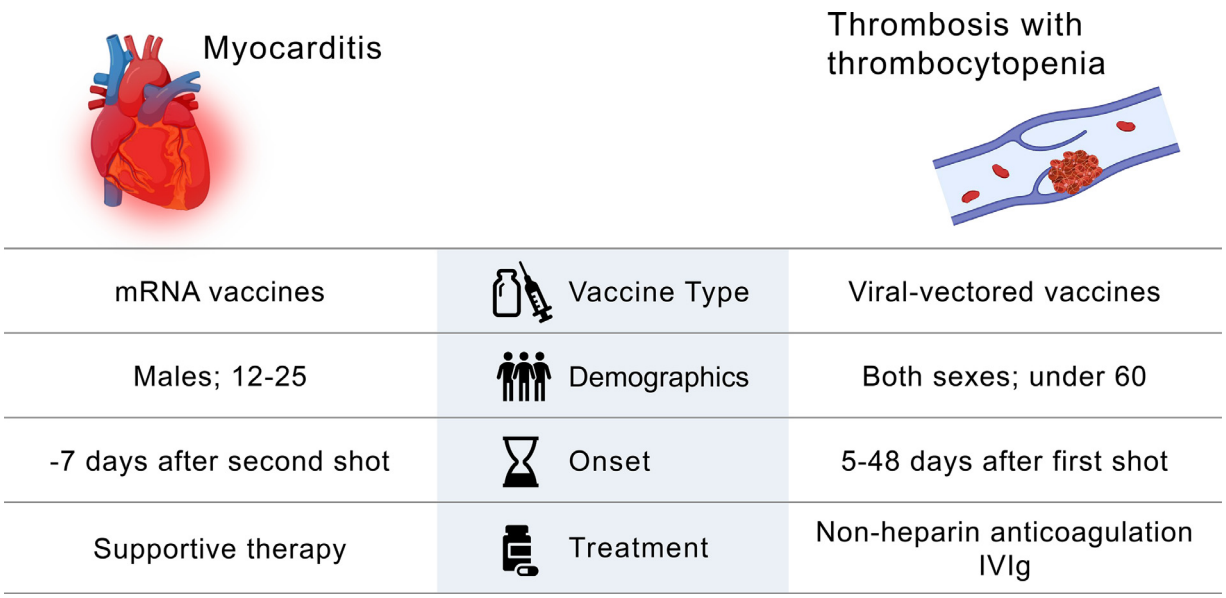

Fig. 1. Possible cardiovascular adverse reactions of COVID-19 vaccination.

thrombosis (VITT) [109]. In many ways, the reported manifestations resembled heparin-induced thrombocytopenia (HIT). Even though it occurs without exposure to heparin, the patients exhibited positive anti-platelet factor 4 (PF4) antibodies, the very antibodies detected in HIT. According to a recent cohort study of 294 VITT cases, the patients were relatively young (85% were <60 years old) and presented 5 to 48 days after the first dose of vaccination [110]. Overall mortality was 22%, and death occurred more frequently in patients with cerebral venous sinus thrombosis and severe coagulation abnormality. While optimal treatment remains unclear, based on deduction from HIT, intravenous immunoglobulins and/or non-heparin-based anticoagulants are recommended [111,112]. Plasma exchange may also be considered for those with poor responses to initial therapy [113]. As is the case with mRNA vaccines, the World Health Organization (WHO) concluded that benefits of vaccination clearly outweigh the potential risks [112].

Safety monitoring is undoubtedly critical in this global vaccination campaign of an unprecedented scale. However, based on reports thus far, the vaccines' benefits are much greater than their risks. In fact, newest studies have shown that the risks for developing the cardiovascular events (myocarditis and thrombosis) are higher after SARS-CoV-2 infection itself than after vaccination [114,115]. Keeping up with the latest safety guidance from reliable sources such as the CDC and the WHO, rather than the lay press, is critical to enable rational decision-making regarding vaccination.

Conclusion

We have described multiple topics of interest with regards to the close relationship between COVID-19 and the cardiovascular system/practice. We have seen that COVID-19 is associated with cardiovascular disorders in every step of its infection. In addition, we have demonstrated that the pandemic has had significant secondary impacts on cardiovascular care. Due to the fast-moving nature of this field, the recommendations made in this review are subject to change quickly. We must continue to keep a close eye on the latest findings. Accumulation of new knowledge and experience will enable us to emerge stronger from this pandemic.

Declaration of Competing Interest

None.

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