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REVIEW ARTICLE

Global Perspective on COVID-19 Therapies, Cardiovascular Outcomes, and Implications for Long COVID: A State-of-the-Art Review

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Abstract

The COVID-19 pandemic has resulted in many therapies, of which many are repurposed and used for other diseases in the last decade such in Influenza and Ebola. We intend to provide a robust foundation for cardiovascular outcomes of the therapies to better understand the rationale for the clinical trials that were conducted during the COVID-19 pandemic, and to gain more clarity on the steps moving forward should the repurposing provide clinical benefit in pandemic situations. With this state-of-the-art review, we aim to improve the understanding of the cardiovascular involvement of the therapies prior to, during, and after the COVID-19 pandemic to provide meaningful findings to the cardiovascular specialists and clinical trials for therapies, moving on from the period of pandemic urgency.

Keywords: COVID-19, Investigational therapies, Cardiovascular, Clinical trials, Long covid

1. Introduction

At the end of 2019, an outbreak of pneumonia with unknown etiology occurred in Wuhan, a city in the Hubei province in China.[1] The patients were later on found to have developed pneumonia due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The outbreak spread rapidly and was announced to be a Public Health Emergency of International Concern by the WHO at the end of January and known as coronavirus disease 2019 (COVID-19).[2] Approximately 80 % of COVID-19 patients suffer from mild respiratory infections and do not require hospitalization. However, about 15 % of the patients suffer from moderate to severe pneumonia requiring supportive therapy and close monitoring. The remaining 5 % suffer from serious conditions and require intensive care treatment.[3] Acute respiratory distress syndrome (ARDS) and multiple organ dysfunction syndrome (MODS) are serious complications of COVID-19 which are associated with high morbidity and mortality with no successful therapy for COVID-19 till date.[4]

Various clinical trials were conducted around the world for the discovery of an effective treatment for COVID-19 as part of emergency use authorization (EUA) by the Food and Drug Administration (FDA). These therapies are being assessed for their risk−benefit profile and may be associated with severe adverse effects that may overlap with the clinical features of COVID-19.[6] Drugs such as hydroxychloroquine (HCQ) and chloroquine (CQ),

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earlier assessed as an emerging therapy in COVID-19, has increased the likelihood of cardiac arrhythmias.[5] Therapies should be used carefully in patients with underlying cardiovascular conditions and echocardiography must be done in severely ill patients before their use.[6,7] Careful use of these drugs with other drugs that are associated with prolongation of QT intervals (e.g. azithromycin) and cardiac arrhythmias should be considered.[8-10] Similarly, lopinavir-ritonavir can also prolong the QT interval and increase the possibility of bradycardia in the elderly and severely-ill COVID-19 patients, having been eliminated as an emerging therapy since evidence that the risks outweighed the benefits.[11] Various interactions among drugs and diseases should be taken into account before their use in COVID-19 patients. In this review, we appraised emerging drugs in the management of COVID-19 and their potential cardiovascular implications.

2. Methods

A scoping review was performed using Medline and Scopus to identify relevant articles. The following search terms were used using Boolean logic: cardiovascular, in combination with COVID-19, corticosteroids, remdesivir, favipiravir, ivermectin, oleandrin, convalescent plasma, monoclonal antibodies, recombinant ACE-2, cytokine inhibitors, interferon, and stem cells. The search was conducted independently for each therapy or drug and the final results were 322 articles. Studies were incorporated which reported the cardiovascular outcomes. The authors independently screened the titles and abstracts to determine eligibility. Lateral entries were selected by conducting an umbrella review of the reference list of the selected studies.

3. Cardiovascular effects of COVID-19 therapies

Therapies for the treatment of COVID-19 have been approved by the Food and Drug Administration (FDA) in the United States. Of these therapies, remdesivir was promising whereas other therapies were tentatively effective. Fig. 1 identifies select emerging therapies and their targets in the viral life cycle of severe acute coronavirus 2 syndrome (SARS-CoV-2).

3.1. Corticosteroids

Corticosteroids are well-tolerated in treating COVID-19 and are being examined for their therapeutic efficacy at different stages of the disease.[12] Their downside includes an increased risk of secondary infections.[13] Corticosteroids work by reducing the expression of ACE2 and TMPRSS2, which facilitates the entry of the virus into host cells.[14] They may also be effective in treating complications like secondary pericarditis, myocarditis, and acute respiratory distress syndrome (ARDS).[12,15] An Argentine trial evaluated high-dose dexamethasone for ARDS.[16] However, the treatment comes with risks, including hypertension and insulin resistance.[17]

3.2. Favipiravir

Favipiravir acts as an RNA-dependent RNA polymerase inhibitor and shows broad antiviral activity against various RNA viruses.[18,19,20] It is approved in Japan primarily for influenza.[21,22] Early studies indicate its efficacy against SARS-CoV-2.[19] A trial conducted by Peking University involved multiple centers and looked into its effectiveness in COVID-19.[24,25] The drug has been associated with possible mild QT prolongation, although the evidence is limited.[23]

3.3. Remdesivir

Remdesivir is an FDA-approved drug used for hospitalized COVID-19 patients but has been associated with hepatotoxicity.[26-30] One study reported that some patients fared better without the drug.[32] It can also cause hypokalemia, which may lead to cardiac arrhythmias.[31]

3.4. Ivermectin

Ivermectin is known for its anti-parasitic properties and has demonstrated antiviral activity in vitro.[33-35] It is approved by the FDA for treating parasitic infections but has not been endorsed for COVID-19 treatment.[36,42] Generally, side effects are mild and often associated with parasite load.[37-40] A study observed no significant new ECG abnormalities in a cohort with pre-existing cardiac issues.[41]

3.5. Oleandrin

Oleandrin, a cardiac glycoside derived from the *Nerium oleander* L. plant, is known for its cytotoxic properties and used in treating cardiac issues.[43] It operates by inhibiting the Na−K ATPase enzyme and other cellular pathways.[44] In Vero cell experiments against COVID-19, it substantially reduced viral production.[45] The compound also has anti-

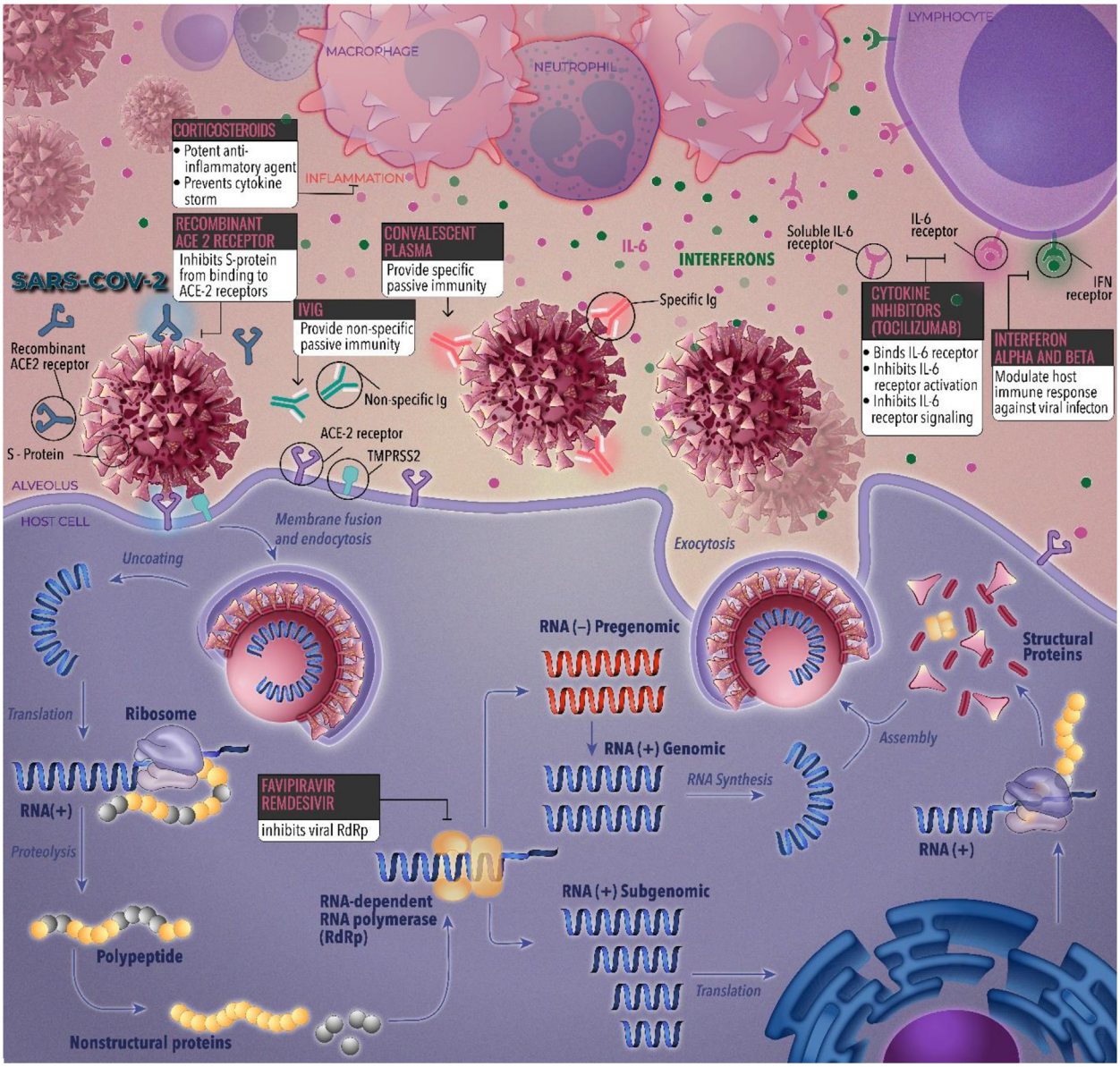

Fig. 1. Drug targets of select emerging therapies across the viral life cycle of SARS-CoV-2.

inflammatory effects potentially beneficial in COVID-19 management.[46,47] However, it can cause side effects like cardiac arrhythmias.[48,49]

3.6. Immunoglobulin therapy

Convalescent plasma and immunoglobulins have shown limited effectiveness in treating COVID-19 despite Emergency Use Authorization (EUA) by the FDA.[50] Previous uses in other disease outbreaks had minor side effects but were generally safe.[51-54] Transfusion-associated cardiac overload (TACO) is an identified risk, especially in vulnerable populations.[55,56] Human monoclonal antibodies targeting IL-6 pathways are under study but may lead to dyslipidemia.[57]

3.7. Recombinant ACE-2

Angiotensin converting enzyme-2 (ACE-2) is a form of transmembrane metallo carboxypeptidase which is closely related to ACE, the main enzyme in RAS. This is also a primary treatment method for hypertension and other similar cardiac conditions. Recombinant ACE-2 is created through genetic modification of human ACE-2 (genetic sequencing: Gln 18- 247 Ser 740) bound with polyhistidine at the C-terminal.[58] ACE-2 is a precursor to angiotensin, a

protein that is crucial in regulation of blood pressure, vascular health and vasomotor tone. ACE2 is present in various areas in the human body, including the vascular endothelial cells in lung and cardiac cells, kidney tubules, small and large intestines. A depletion of ACE-2 is strongly associated with hypertension, heart failure, coronary artery disease, diabetes. A recombinant vaccine combining elements of avian viruses with SARS-CoV-2 has been developed for intranasal administration.[59] Promising results have been shown in animal studies.[60,61]

3.8. Cytokine inhibitors

COVID-19 often triggers a cytokine storm, leading to severe complications.[62-65] Various IL-1 receptor antagonists, such as Anakinra and Canakinumab, are being trialed for their ability to mitigate this response.[66-68] The drugs have shown promising results in reducing inflammation and improving clinical outcomes.[68,69] The CANTOS trial further validates the cardiovascular safety profile of canakinumab.[70] Tocilizumab, an IL-6 receptor antagonist, has also shown efficacy but requires monitoring due to potential cardiovascular effects and drug interactions.[71-75] Clinical trials with TNF-alpha blockers like adalimumab are also underway.[67]

3.9. Interferon alpha

Pegylated Interferon -Alpha, which was previously used in the management of SARS & MERS, was studied for the treatment of COVID-19.[76,77] However, in a study involving 295 patients with chronic HCV, adverse cardiovascular effects were reported. There were six patients who had cardiac effects during the interferon therapy and four others who reported adverse effects within one year of the therapy.[78] Increase in TNF-α during INF-α therapy may be the cause and underlying mechanism for the adverse cardiac effects.[79] Another study of 194 patients with chronic hepatitis C reported cardiovascular complications (18 %) with pegylated interferon-alpha therapy.[80] The arrhythmogenic property may be attributed to local inflammation in the conduction system induced by interferon.[81,82] Hence, prudent use of interferon alpha was recommended in high-risk patients of COVID-19.

3.10. Interferon-beta

Interferon beta has been used in the treatment of multiple sclerosis.[83] Studies on the efficacy of treatments for SARS and MERS provide insight into options for potential repurposing of these drugs for SARS-CoV-2 treatment.[84,85] However, it was reported that interferon beta, especially type 1 interferons, accelerates atherosclerotic changes.[86] A randomized clinical trial of 81 patients of COVID-19 reported 28.4 % of adverse cardiovascular events.[87] This called for further detailed assessment of cardiovascular risk in patients treated with Type-1 IFN.

3.11. Stem cells

When severe, COVID-19 is a systemic illness characterized by hyper-inflammation, cytokine storm, and elevations of cardiac injury biomarkers.[4] Structurally, both viruses use the ACE2 receptor to enter cells and bind with similar affinities to ACE2, therefore given these similarities to SARS-CoV, it is plausible that SARS-CoV-2 could also use ACE2 to enter adult cardiomyocytes.[88] One study utilized human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) as a model to examine the mechanisms of cardiomyocyte-specific infection by SARS-CoV-2.[88] Another study aimed to test whether the viral RNA of SARS-CoV-2 can be transmitted via extracellular vesicles (EVs) into cardiomyocytes.[89] A case series by Singh et al. explored the safety and effectiveness of intravenous allogeneic cardiosphere-derived cells (CDCs).[90]

4. Discussion

While pulmonary involvement is predominant in COVID-19, and as we move on from the COVID-19 pandemic, there are accumulating evidence of severe manifestations of the cardiovascular system. This may be of essence as we cater to cases of long COVID. The role of underlying cardiovascular conditions in precipitating the cardiovascular involvement during and after COVID-19 infection is of concern but remains unclear. Associations with acute kidney injury has been observed in nearly 60 % of COVID-19 who are hospitalized.[91] Suspected contributors include i) acute hypoxemia, tachycardia and hypoxemia due to the pulmonary involvement in COVID-19 leading to type 2 myocardial involvement, ii) induction of hypercoagulability leading to acute atherothrombosis and acute coronary syndrome, iii) stress-induced cardiomyopathy known as Takotsubo syndrome, and iv) direct or indirect myocardial injury due to viral invasion.[91] Fig. 2 summarizes the potential cardiovascular adverse outcomes due to COVID-19 therapies.

Using clinicaltrials.gov as a reference, various studies have utilized the following primary outcomes: time to 2-point reduction of symptoms, time

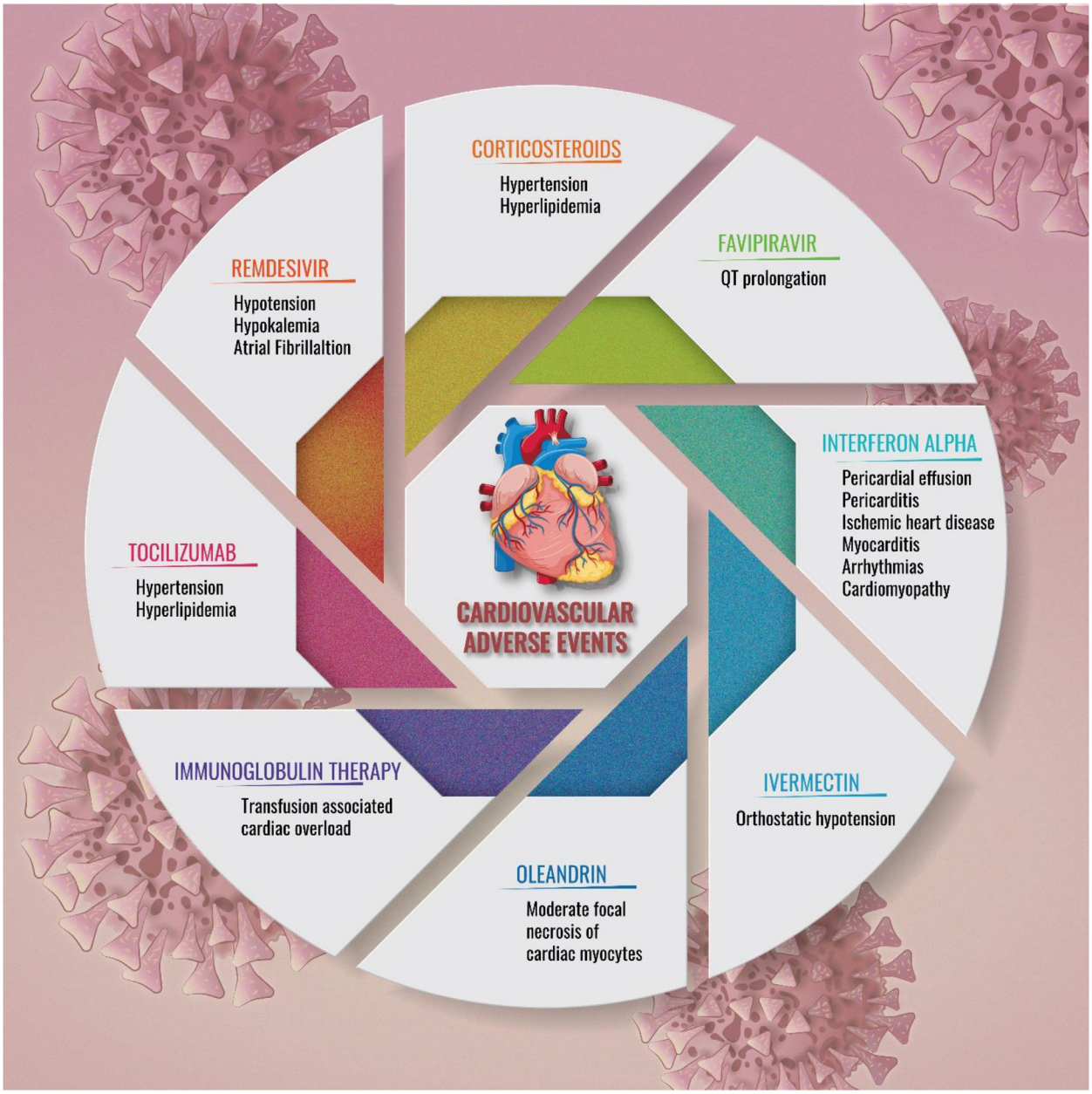

Fig. 2. Adverse cardiovascular outcomes of therapies in COVID-19.

to return of olfactory sensation, and whether or not the patient will require ICU treatment of invasive mechanical ventilation during the hospital course. Aside from corticosteroids, numerous studies established the efficacy of antiviral drugs such as favipiravir and remdesivir. For these two therapeutic treatments over hundreds of trials worldwide were conducted; the common primary outcomes comprised time to repeat negative testing on RT-PCR of a nasopharyngeal swab for SARS-CoV-2. Other treatment approaches were considered including ivermectin, oleandrin, recombinant ACE-2, and cytokine inhibitors such as tocilizumab.

The World Health Organization defines Long COVID as "the continuation or development of new symptoms 3 months after the initial SARS-CoV-2 infection, with these symptoms lasting for at least 2 months with no other explanation".[92] The use of the mentioned therapies in patients with long COVID, who are experiencing cardiovascular manifestations, has both potential benefits and risks. Careful consideration must be taken when planning the

course of treatment for such patients. The following are implications of the discussed treatments:

1. **Interferon Alpha**: This treatment has been linked to adverse cardiovascular events such as ischemic heart disease, arrhythmias, and cardiomyopathy. Although it could potentially inhibit viral replication, its use should be approached with caution in patients who have a history of cardiovascular disease or are at high risk for such conditions. Regular monitoring for cardiac effects during and after therapy is necessary.
2. **Interferon Beta**: Despite its potential antiviral efficacy, this treatment may accelerate atherosclerotic changes, which could lead to increased cardiovascular risks. Therefore, the potential benefits need to be weighed against these risks, particularly in patients with pre-existing cardiovascular conditions or who are at high risk of such conditions.
3. **Stem cells**: Preliminary evidence indicates potential benefits of stem cell therapies in severe cases of COVID-19, with associated reductions in pro-inflammatory biomarkers. However, more robust, large-scale trials are needed to establish the safety and efficacy of these therapies in the management of long COVID with cardiovascular manifestations.

In general, patients with long COVID experiencing cardiovascular manifestations are recommended the following:

- **Prioritize comprehensive care**: Because long COVID can affect multiple organ systems, patients, and their primary care providers should prioritize comprehensive, multidisciplinary care. This care team might include a primary care doctor, cardiologist, neurologist, pulmonologist, and possibly a mental health professional.
- **Engage in cardiovascular protective activities**: This includes following a heart-healthy diet, engaging in regular physical activity, avoiding tobacco and excessive alcohol, managing stress, and keeping other health conditions like diabetes and hypertension under control.
- **Active monitoring**: Regular follow-ups with healthcare providers for the monitoring of cardiovascular health and the effectiveness of treatment interventions are essential. This can help in early identification and management of potential complications.
- **Participate in rehabilitation programs**: Some patients with long COVID may benefit from participating in rehabilitation programs, which can provide specialized physical and occupational therapy to help manage persistent symptoms and improve daily functioning.
- **Stay informed about emerging treatments**: The knowledge about long COVID is continuously evolving, and new treatments are being tested. It is pertinent for patients to stay informed about these developments and discuss potential benefits and risks with their healthcare provider.

The ongoing research on long COVID is critical in understanding the disease and its effects better, which would pave the way for the development of more targeted and effective therapies. Until then, personalized care, close monitoring, and maintaining a healthy lifestyle are key to managing the condition.

5. Conclusion

The review provides a global perspective for the potential cardiovascular involvement and outcomes of COVID-19 therapies, while presenting implications for long COVID. With many treatments being repurposed for COVID-19 and used for different diseases earlier, there is ample data during, prior to, and after the COVID-19 pandemic that is indicative of the potential cardiovascular outcomes. While clinical trials are underway addressing the growing medical needs of those afflicted with long-term outcomes of the disease and therapies, this review provides a comprehensive view into the cardiovascular interactions of the therapies in context with COVID-19.

Author contributions

The authors contributed and are assigned authorship as per ICMJE guidelines.

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Conflicts of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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