VIEWPOINT

Challenges in Pharmacological Management of Cardiovascular Diseases in Covid-19: do Benefits Outweigh Risks?

Samuel de Sousa Pedro, Fernanda Carla Ferreira de Brito, Christianne Bretas Vieira Scaramello

Universidade Federal Fluminense, Instituto Biomédico, Niterói, Rio de Janeiro, RJ – Brazil.

Introduction

Cardiovascular diseases (CVD) are the main cause not only of global mortality but also of reduced quality of life. They cover ischemic heart disease, stroke, heart failure, peripheral artery disease, and various other heart and vascular conditions. In 2017, CVDs caused about 17.8 million deaths worldwide, corresponding to 330 million years of life lost and another 35.6 million years of life with disabilities. Almost 80% of deaths occur in low- and middle-income countries, such as Brazil, where the occurrence of CVDs and their risk factors are on the rise as a result of an ongoing epidemiological transition.[1] In low-income countries CVDs greatly affect working-age populations, and the total economic loss resulting from this group of diseases is high, representing 2% of Gross Domestic Product. In addition, the disability caused by CVDs has economic consequences at multiple levels: individual, family, economic agents, public institutions, government, and society as a whole.[2]

Recent studies also show that chronic conditions, such as CVD, increase the risk of aggravation and death associated with the new coronavirus 2019 disease (COVID-19), whose outbreak was characterized as a pandemic by the World Health Organization (WHO) in March 2020. The new coronavirus is a betacoronavirus called SARS-CoV-2 (Severe Acute Respiratory Syndrome coronavirus 2), phylogenetically identical to other coronaviruses capable of determining acute respiratory distress syndrome (ARDS), which is responsible for numerous deaths. The most common symptoms of COVID-19 include fever, cough, dyspnea, myalgia, fatigue, diarrhea, sore throat, chest pain, confusion, and lethargy. Acute and chronic cardiovascular complications have also been observed in the course of COVID-19, being attributed to several mechanisms, such as relative ischemia, systemic inflammation mediated by pathogens, with increased levels of several biomarkers. In this context, studies point to the relevance not only of chronic conditions, such as hypertension, but also of the age and immunological status of the host, characterizing a complex, multifactorial, and bidirectional model that can comprehend the drugs used to treat these pathologies.[3]

It is important to note that there is no vaccine for prophylaxis, nor specific drug therapy for the treatment of COVID-19. The repositioning of medications such as chloroquine, hydroxychloroquine, and some antivirals has been considered for the treatment of this disease.[4] However, the clinical effectiveness of this approach has not yet been adequately proven. In addition, the literature points out that the combination of lopinavir / ritonavir antivirals alters cardiac conduction, with prolongation of the QT interval and atrioventricular block.[5] This change in heart rate is also seen in the use of chloroquine / hydroxychloroquine, which can contribute to the development of cardiomyopathy in patients with rheumatic diseases.[4] These cardiotoxic effects are particularly uninteresting in patients with CVDs, such as those using β-blockers, with which these drugs may have a pharmacodynamic drug interaction with regard to atrioventricular conduction.

Lifestyle changes and cardiovascular pharmacotherapy play a truly important role in the management of CVDs across their spectrum. Drug therapy has

Keywords

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Mailing Address: Scaramello, Christianne
Rua Prof. Hernani Mello, 101. Postal Code: 24210-130, São Domingos, Niterói, Rio de Janeiro, RJ – Brazil.
E-mail: chrisbretas@gmail.com

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proven to be a life-saving or life-prolonging tool in some cases, as well as to improve the quality of life in others, as a result of its role in improving debilitating symptoms.[6] The reduction of blood pressure using one or more drugs in association is fundamental for the prevention and treatment of CVDs. Globally, 62% of cerebrovascular diseases and 49% of ischemic heart diseases were attributed to suboptimal blood pressure control. Similarly, the development of drugs to control serum lipid levels has had an important impact on the prevention and treatment of these diseases. Statins can reduce the risk of cardiovascular events by 20%, and the benefits of therapy increase with their duration. In addition, antiplatelet drugs, such as low-dose acetyl salicylic acid, play an important role in preventing ischemic heart disease and stroke. As the mechanism of action of the main pharmacotherapeutic options for the prevention of CVDs (antihypertensives, hypolipemiants and antiplatelet agents) are independent, fixed dose combinations of these substances are adopted.[7]

Although the different classes of antihypertensive drugs have similar efficacy for preventing the vascular results of interest, the literature points that β-blockers appear to be inferior to others for the prevention of major cardiovascular events, such as stroke and renal failure. In the case of heart failure prevention, while diuretics appear to be superior, calcium channel blockers are inferior; however, for stroke prevention they are superior. The combination of these agents with angiotensin-converting enzyme inhibitors (ACEI) has proven to be more effective in preventing CVDs than the ACEI-diuretic association.[8] However, the benefit not only of ACE inhibitors but also of angiotensin receptor blockers (ARB) in the course of COVID-19 is controversial.[3] In view of the above, the aim of the present review was to analyze the risk-benefit ratio of cardiovascular pharmacotherapy in patients with COVID-19.

Methods

The electronic databases LILACS, MEDLINE and SCOPUS were consulted, crossing the term COVID-19 with the different CVDs individually, as well as with the different pharmacological groups associated with the treatment of these pathologies, without delimiting the time for the research that was conducted in April 2020. Figure 1 illustrates the selection process of the researched studies and the number of publications found at each stage.

A total of 84 results were found, from which articles that were not available in English and / or Portuguese were excluded. Studies were also discarded after reading the titles and abstracts, as well as after reading the full text. After screening, 15 articles were selected because they showed a direct relationship with the subject of the present study.

Results and Discussion

Antithrombotic and Statins

Antithrombotics include anticoagulants, antiplatelet agents, and fibrinolytics. These agents are prescribed in several situations related to hemostasis disorders that favor the formation of thrombi. Anticoagulants can be for oral use, such as warfarin and xabans, or for parenteral use, such as high and low molecular weight heparins (LMWHs). [9,10]

Statins are drugs used to treat dyslipidemia, reducing the risk of cardiovascular disease.[7] These agents, as well as antiplatelet inhibitors of P2Y12 activity (clopidogrel and ticagrelor) and oral anticoagulants, present pharmacokinetic interactions with lopinavir / ritonavir, antiviral agents evaluated in prospective studies, as well as ribavirin and remdesivir, leading to the need for revision of the therapeutic regimen to avoid toxicity if used in combination. The literature also points to an interesting anti-inflammatory effect of statins to mitigate the course of COVID-19.[11]

Anticoagulant therapy with heparins, mainly with LMWHs, such as enoxaparin, seems to be associated with a better prognosis in patients with severe COVID-19 provided they meet the criteria for sepsis-induced coagulopathy or with markedly high D-dimer levels. All of this is due to the risk of disseminated intravascular coagulation and venous thromboembolism.[9,10] Although COVID-19 is characterized by hyperfibrinolysis, studies that attempt to restore fibrinolytic function have not been reported.[12]

The literature points to an association between viral load and the severity of COVID-19 so that individuals with a higher viral load can develop severe acute lung injury, requiring hospitalization in an intensive care unit with poor prognosis. Mortality of patients developing ARDS is 49%. Many patients with COVID-19 develop multiple organ failure. The main causes of death are ARDS, septic shock with multiple

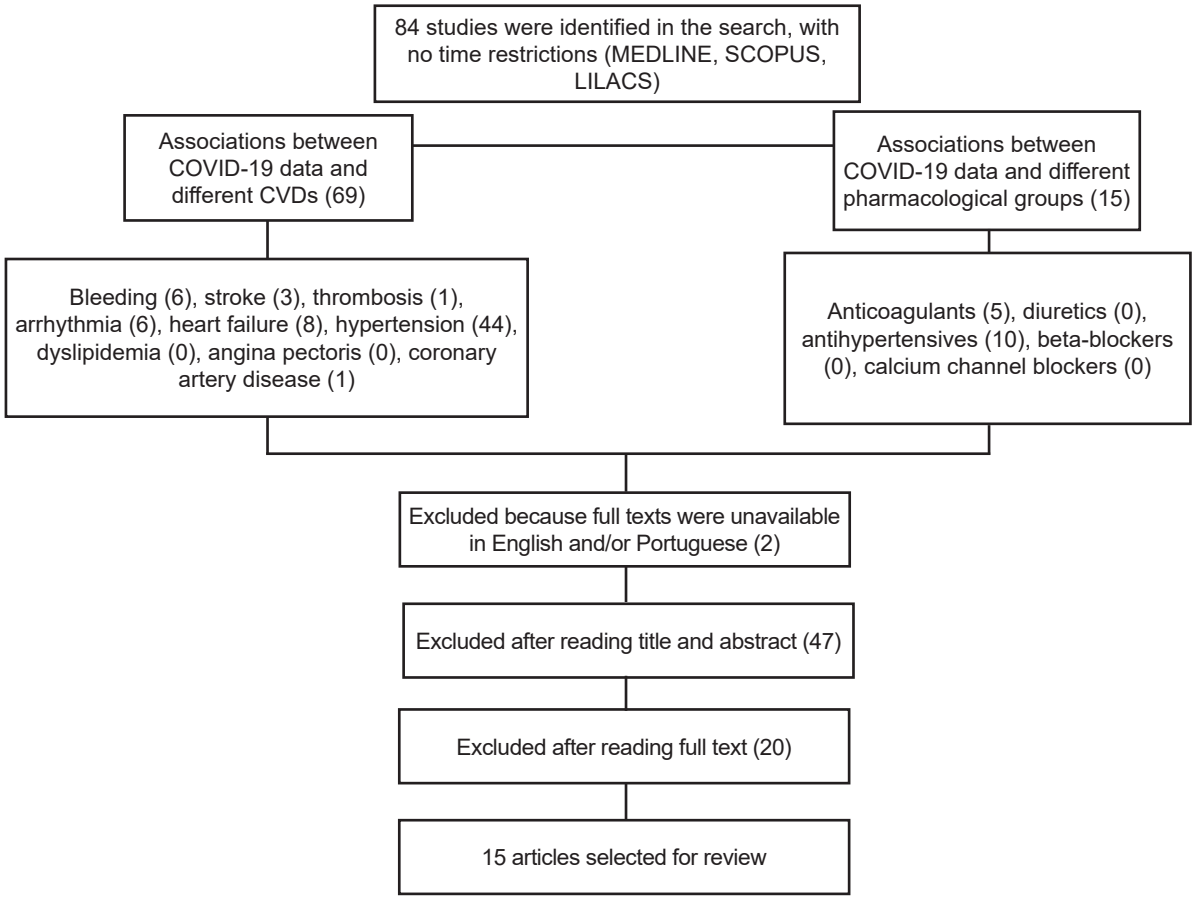

Figure 1 – Flowchart of the selection process of the searched studies. The number of articles in each stage is indicated in parentheses.

organ failure, disseminated intravascular hemorrhage/coagulopathy, acute hepatic/renal heart injury and secondary bacterial infections. Consistent with clinical observations, the lungs are the organs that suffer the most damage, followed by moderate injury to heart, liver, kidney, and brain. Patients with high plasma/plasminogen levels and pre-existing conditions seem to present a mechanism that contributes to increase the susceptibility to infection and fatality by the new coronavirus. Therefore, targeting hyperfibrinolysis with antiplasmin compounds (broad spectrum or specific) may prove to be a promising strategy to improve the clinical outcome of patients with comorbidities. Clinical trials with several protease inhibitors are being conducted in China; however, there are no suitable animal models of COVID-19 with underlying medical conditions to test new therapeutic agents.[10]

In the fibrinolysis process, plasmin generates soluble D-dimer and D-monomer from the proteolytic cleavage of fibrin. The activity of this enzyme can be detected in bronchial-alveolar lavage (BAL), including in healthy individuals. However, significantly increased levels of D-dimer and D-monomer are found in patients with ARDS, who also have a higher expression of α2-antiplasmin, a specific plasmin inhibitor. Thus, while the fibrinolytic activity decreases by half, the level of D-dimer increases, showing a nonproportional change between the level of expression and activity of plasmin and antiplasmin in favor of fibrin degradation in ARDS patients. In addition, the literature points to a prominent reduction in platelets in individuals with COVID-19. Therefore, in this context, the idea that the administration of antiproteases can be beneficial is reinforced. On the other hand, based on laboratory and pathological results, hypercoagulation occurs, as evidenced by the presence of microthrombi along the blood vessels of multiple organs. It is not known whether fragmented hemorrhage coexists with areas

infected with the new coronavirus.[10] The best prognosis for LMWH therapy in severe cases of COVID-19 is attributed to the uncoordinated coexistence of hyperproteolysis and hypercoagulation.

The endothelial cell dysfunction induced by coronavirus infection results in increased production of thrombin, which generates a hypercoagulable state. Moreover, hypoxia found in severe COVID-19 may stimulate thrombosis, not only increasing blood viscosity, but also a signaling pathway dependent on the hypoxia-inducible transcription factor. The anti-inflammatory effect of LMWH can also add benefit to its use. In China, a dose considered prophylactic (Table 1) was used, with hemorrhagic complications being uncommon and generally mild. However, it is important to consider whether a higher dose of LMWH could be convenient in non-Asian patients with severe COVID-19. Since the decline in platelet count and the prolongation of prothrombin time correlate with increased mortality and hypofibrinogenemia is not common in sepsis, the criteria for sepsis-induced coagulopathy are important to guide anticoagulant therapy, as well as high levels of D-dimer, which acts as an indirect marker of coagulation activation, even because the activation of coagulation contributes to the compartmentalization of pathogens, reducing their invasion. Anticoagulation in patients without significant coagulopathy is associated with a potential risk.[9] Therefore, anticoagulant therapy performed mainly with LMWH appears to be associated with a better prognosis in severe cases of COVID-19 in patients who clearly meet sepsis-induced coagulopathy criteria or have significantly high levels of D-dimer.[9]

Table 1 – Therapeutic regimen recommended for the control of ARDS in patients with COVID-19

Drug	Dosage
Unfractionated heparin [9]	10000-15000 U/day
Enoxaparin[9]	40-60 mg every 24h
Acetazolamide[21]	250mg every 12h
Nifedipine[21]	30mg every 12h (prolonged release)
Sildenafil[21]	20-50mg every 8h
Tadalafil[21]	10mg every 12h

Drugs that Modulate the Renin-Angiotensin-Aldosterone System

The Renin-Angiotensin-Aldosterone System (RAAS) plays a crucial role in the homeostasis of blood volume, and consequently, of systemic blood pressure. Its actions are mediated by Angiotensin II (Ang II) via the AT1 and AT2 receptors, which in vascular smooth muscle generate vasoconstriction and vasodilation, respectively. The cleavage of Angiotensin I (Ang I) by ACE accounts for the formation of Ang II. On the other hand, the homologous ACE2 enzyme converts Ang I to Ang 1-9, which is an inactive metabolite, and Ang II to Ang 1-7, a peptide that can act via the MAS receptor (MasR) playing an anti-inflammatory, antifibrotic and vasodilator role. ACE2 is expressed in several tissues such as heart, lung, kidney, spleen, liver, brain, among others, presenting about 40% homology to ACE (figure 2). The affinity of Ang II for its binding site in the ACE2 enzyme is 400 times greater than the affinity of this same peptide for the binding site in ACE.[13,14]

It is known that ACE2 participates in the process of cell invasion by the SARS virus, in which the S protein (Spike) present in the virion binds to this transmembrane enzyme, promoting its internalization via endocytosis with the virus. This interaction configures an important and limiting process in its replication cycle. In addition, with endocytosis and consequent decrease in the density of this enzyme in the tissue membrane, there is a decrease in the degradation of the Ang II substrate by the former and consequently the formation of Ang 1-7 product, which favors the process of pulmonary fibrosis. Studies show that the mechanism adopted by the new coronavirus is similar, corroborating the clinical findings that ARDS is highly prevalent in COVID-19.[14,15] Furthermore, in silico studies have shown that, due to mutations, this virus has a greater affinity for ACE2 than other SARS, which may be related to a greater dynamics of infection by the new coronavirus.[15]

Atri et al.,[11] also described that the expression of ACE2 is encoded on the X chromosomes, which may explain the sexual differences pointed out in the epidemiology of COVID-19, which seems to affect more males than females.[11]

In the pathophysiology of heart failure, changes in the density of ACE2 and the increase of its expression in the heart are also identified, which may reflect a compensatory effect in the face of cardiac remodeling and hypertrophy, favoring the increase in the local concentration of Ang 1-7. Thus, the deleterious effects

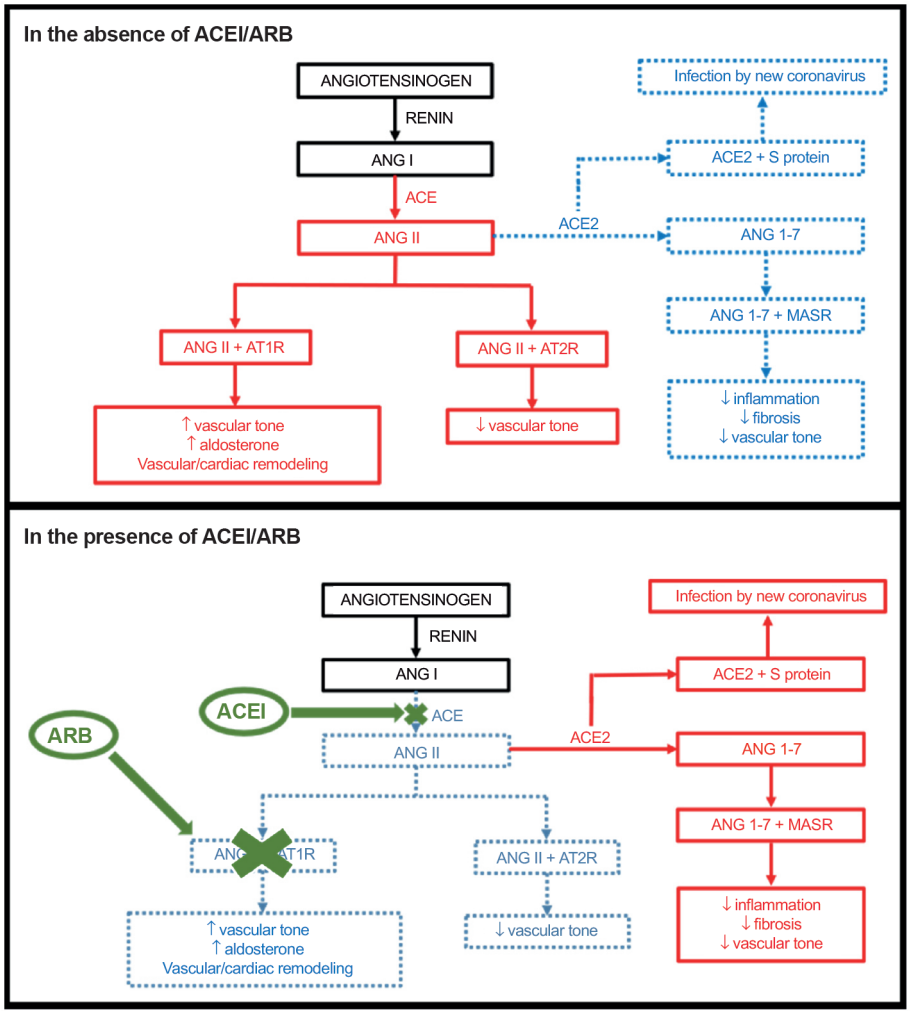

Figure 2 – Schematic representation of the renin-angiotensin-aldosterone system in two different situations: in the absence and in the presence of pharmacological interventions using angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II AT1 receptor blockers (ARBs). For each situation there is a highlighted axis (red) and a faded axis (blue). Angiotensinogen is produced in the liver as a renin (enzyme secreted by the kidney) substrate and generates angiotensin I (ANG I), an inactive peptide. Through the action of angiotensin-converting enzyme (ACE), ANG I is converted into angiotensin II (ANG II), which determines its effects by binding to its receptors AT1 (AT1R) and AT2 (AT2R). The action of angiotensin-converting enzyme 2 (ACE2) on ANG II leads to the production of angiotensin 1-7 (ANG 1-7), which determines various effects by binding to Mas receptors (MASR). Also, ACE2 is able to bind to S protein in the virion, favoring cell invasion by the new coronavirus.[13,14]

of COVID-19 on the cardiovascular system may also involve reducing the availability of ACE2 in the heart. It was observed that the coronavirus increases myocardial inflammation, causing cardiac dysfunction possibly due to a decrease in the cardioprotective effects associated with the ACE2-Ang1-7-MasR axis.[17] Lippi et al., in their meta-analysis, demonstrated that cardiac Troponin I concentrations were significantly increased in patients infected with the new coronavirus, showing possible cardiac injury.[18] In turn, Guan et al., observed that 13.7% of 1099 patients with COVID-19 had increased Creatine-Kinase, and 37.2%, a high concentration of lactate dehydrogenase.[19] In addition, cardiac injury is further supported by a decrease in oxygen supply due to pulmonary insufficiency.[17]

In view of this, it is worth discussing the use of drugs that negatively modulate the RAAS and can simultaneously increase the expression of ACE2 during the course of COVID-19. The expression / activity relationship of ACE2 regarding the use of ARB and ACEI is still unclear. However, studies in different experimental models (healthy rats, with acute

myocardial infarction or with heart failure) indicate that drugs belonging to these therapeutic classes, such as enalapril and lisinopril, would be able to increase the gene expression of ACE2 in the heart. Losartan, on the other hand, showed an increase in protein expression and enzyme activity in healthy hearts.[13,20] The literature also points that other therapeutic classes encompassing drugs such as spironolactone, ibuprofen, thiazolidinediones, atorvastatin, and fluvastatin also modulate positively the activity and / or protein expression of this enzyme in some tissues.[15,20]

ACEI / ARB are therapeutic classes widely used by the hypertensive population, as well as indicated for patients with heart failure, and, according to the literature, their actions on ACE2 are indirect. The mechanism of action of ACE inhibitors, such as lisinopril, encompasses their ability to bind to ACE, inhibiting its activity and, therefore, the formation of Ang II. ARBs, like losartan, are AT1 receptor antagonists, binding to this pharmacological receptor and preventing its activation by Ang II. Thus, both classes are able to decrease vasoconstriction mediated by this active peptide and blood volume, justifying the antihypertensive effect, as well as reducing the cardiac remodeling observed in heart failure and apparently predisposing patients to infection with the new coronavirus, although the latter association is still uncertain (figure 2).[17] As Ibuprofen also increases the expression of ACE2, the WHO (World Health Organization) requested caution and the suspension, when possible, of the use of this non-steroidal anti-inflammatory as an analgesic and antipyretic for the treatment of disease symptoms. However, it should be noted that there is greater evidence of RAAS and Ang II activity, to the detriment of Ang 1-7, in patients infected with the new coronavirus due to ACE2 endocytosis, which is then correlated to viral load and pulmonary damage. From this perspective, intervention with ARB and ACE inhibitors in patients with COVID-19 and CVD could then be positive, due to the fact that the decrease in overactivation of RAAS and the favoring of the ACE2 pathway, with higher production of Ang 1-7, have the additional potential to mitigate lung injury.[20] Thus, there is a duality associated with the negative modulation of RAAS and the consequent increase in the expression of ACE2 in the course of COVID-19: the possible facilitation of host infection by the new coronavirus versus the attenuation of the deleterious effects of the disease by increasing the availability of Ang 1-7.

Therefore, the use of camostat, a protease inhibitor approved for the treatment of chronic pancreatitis, can increase the safety of drugs that increase ACE2 expression. This substance seems to inhibit the TMPRSS2 transmembrane protease present in the host cell membrane that favors the access of the viral genome to the cellular machinery for replication via S protein - ACE2 interaction. A randomized, placebo-controlled study is being conducted to verify the effects of this agent in COVID-19.[11]

Figure 2 illustrates the RAAS, in the absence or in the presence of pharmacological interventions covering ACEI and ARB, as well as its point of intersection with the infection by the new coronavirus.

Other Cardiovascular Drugs

The review by Solaimanzadeh, published on March 20, 2020, points to the benefit of using other drugs with action on the cardiovascular system such as nifedipine, a calcium channel blocker used as an antihypertensive and anti-anginal agent, acetazolamide, an example of a diuretic inhibitor of carbonic anhydrase, used in acute mountain sickness, in edematous conditions and in glaucoma, as well as phosphodiesterase inhibitors commonly prescribed for erectile dysfunction, such as sildenafil and tadalafil, in patients with COVID-19. This is because all these drugs are useful in the treatment of high-altitude pulmonary edema (HAPE). Both conditions exhibit a reduced proportion of partial arterial oxygen pressure to fractional inspired oxygen, with concomitant hypoxia and tachypnea, reduced levels of carbon dioxide and the presence of irregular infiltrates in the lung fields. Likewise, elevated levels of fibrinogen in both conditions are likely to be an epiphenomenon of edema formation rather than activation of clotting. Thus, both COVID-19 and HAPE converge to ARDS. Acetazolamide is then useful as it potently reduces hypoxic pulmonary vasoconstriction, improves minute ventilation, and expired vital capacity, as does nifedipine and phosphodiesterase inhibitors, which are also drugs that reduce pulmonary pressure.[21]

Table 1 shows the dosage of cardiovascular drugs that may be useful for patients with ARDS in the course of COVID-19.

Final Considerations

To date, there is no evidence on the risk-benefit ratio of the use of most cardiovascular drugs in patients with COVID-19. The evidence that points to benefits is particularly related to the improvement of ARDS and not to the treatment of CVD per se. The use of antiplatelet drugs seems to be inadvisable, not only due to the pharmacokinetic drug interaction with lopinavir / ritonavir, an association that may prove to be effective in the treatment of COVID-19, as also observed for statins, but also because it may lead to reduced levels of platelets and bleeding. Due to the pharmacodynamic drug interaction with these promising antivirals, β-blockers may also be inadvisable.

In order to especially mitigate ARDS, the use of nifedipine, acetazolamide, phosphodiesterase inhibitors, and LMWH seems to be recommended, provided that, in the case of the latter, eligibility criteria are clear.

Many experts warn that discontinuing antihypertensive pharmacotherapy is a dangerous choice and the clinical benefit associated with the use of ACEI / ARB in patients with heart failure is also widely described. As the literature points to the dual effect of these agents in patients with COVID-19 by promoting ACE2 overload in tissues such as the lungs, favoring virus infection, but also reducing the severity of lung injury, perhaps the risk-benefit ratio may suggest the maintenance of pharmacotherapy with these agents for patients with CVD during the course of COVID-19. In this context, it may also be interesting to maintain statins in dyslipidemic patients who do not use the lopinavir / ritonavir association.

In view of all these considerations, it is important to point out that it is mandatory that the health team remains attentive to the clinical manifestations because the studies associated to the disease caused by the new coronavirus still include a relatively small number of individuals, with much to be elucidated about the polynomial COVID-19-ARDS-CVD-cardiovascular pharmacotherapy.

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Conception and design of the research: Pedro SS, Scaramello CBV. Acquisition of data: Scaramello CBV. Writing of the manuscript: Pedro SS, Scaramello CBV. Critical revision of the manuscript for intellectual content: Brito FCF, Scaramello CBV.

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This study is not associated with any thesis or dissertation work.

Ethics Approval and Consent to Participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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