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Effects of angiotensin II receptor blockers and angiotensin-converting enzyme inhibitors on COVID-19: a narrative review of the literature

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ABSTRACT

Introduction: An outbreak of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is currently affecting worldwide. The association between this virus and the upregulation of Angiotensin-Converting Enzyme 2 (ACE2) has been suggested as a potential as an important factor in the development of Coronavirus Disease- 19 (COVID-19).

Objective: To describe the relationship between some antihypertensive treatments and COVID-19.

Methods: A research was conducted with the components of the PIO (Population, Intervention, Outcomes) strategy, including the literature of the last 20 years available in central PubMed, Web of Science, Scopus, and Embase databases. All relevant articles that assessed the epidemiological relationship between SARS-CoV-2 and hypertension, the treatment and outcomes of the patients who have this comorbidity, as well as the relationship between the RAA axis and COVID-19 were included in the analysis.

Results: A total of 292 items were found in the databases. After a thorough analysis, 17 papers were selected, including in vitro and in vivo tests, clinical trials, and epidemiological studies related to the topic analyzed.

Conclusion: Due to the systemic benefits of antihypertensive drugs targeting the RAA axis, and the lack of evidence of these treatments being a risk factor, It is not recommended to withdraw these medications from hypertensive patients infected with SARS-CoV 2, unless there is a clinical indication.

Keywords: coronavirus; COVID-19; hypertension; angiotensin-converting enzyme inhibitors; angiotensin receptor antagonists.

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Efectos de bloqueadores del receptor de angiotensina II e inhibidores de la enzima convertidora de angiotensina en COVID-19: una revisión narrativa de la literatura

RESUMEN

Introducción: el surgimiento y diseminación del coronavirus tipo 2 del síndrome respiratorio agudo severo (SARS-CoV-2), actualmente, afecta a la mayoría de los del mundo. La asociación entre este virus y la regulación positiva de la enzima convertidora de angiotensina 2 (ACE2) se ha sugerido como un factor potencial en el desarrollo de la enfermedad por coronavirus-19 (COVID- 19).

Objetivo: describir la relación entre algunos tratamientos antihipertensivos y la COVID-19.

Métodos: se revisaron los componentes de la estrategia PIO (población, intervención, resultados). Se incluyeron todos los artículos relevantes de los últimos 20 años disponibles en las bases de datos centrales PubMed, Web of Science, Scopus y Embase, que describen la relación epidemiológica entre SARS-CoV-2 e hipertensión, el tratamiento y el desenlace de los pacientes quienes tienen esta comorbilidad, así como la relación entre el eje renina-angiotensina-aldosterona y COVID-19.

Resultados: se encontraron inicialmente 292 artículos en las bases de datos, para finalmente seleccionar 17 artículos, incluyendo exámenes in vivo e in vitro, ensayos clínicos y estudios epidemiológicos relacionados con el tema analizado.

Conclusión: debido a los beneficiosos efectos sistémicos del tratamiento antihipertensivo, cuyo blanco es el sistema renina-angiotensina- aldosterona, y a la falta de evidencia acerca de estos medicamentos en cuanto a la inducción de SARS-CoV-2, no se recomienda suspender o contraindicar el tratamiento con estos fármacos en pacientes hipertensos positivos para COVID-19, a menos que haya una indicación clínica.

Palabras clave: coronavirus; infecciones por coronavirus; virus del SARS; hipertensión; inhibidores de la enzima convertidora de angiotensina.

Efeitos dos bloqueadores do receptor da angiotensina II e inibidores da enzima de conversão da angiotensina no COVID-19: uma revisão narrativa da literatura

RESUMO

Introdução: Um surto de Síndrome Respiratória Aguda Grave Coronavirus 2 (SARS-CoV-2) está afetando atualmente em todo o mundo. A associação entre esse vírus e a suprarregulação da Enzima Conversora da Angiotensina 2 (ACE2) tem sido sugerida como um fator potencial importante no de-senvolvimento da Doença do Coronavírus-19 (COVID-19).

Objetivo: Descrever a relação entre al-guns tratamentos anti-hipertensivos e COVID-19.

Métodos: Foi realizada uma pesquisa com os com-ponentes da estratégia Population, Intervention, Resultados (PIR), incluindo a literatura dos últimos 20 anos disponível nas bases de dados centrais PubMed, Web of Science, Scopus e Embase. Todos os artigos relevantes que avaliaram a relação epidemiológica entre SARS-CoV-2 e hipertensão, o trata-mento e resultados dos pacientes que apresentam essa comorbidade, bem como a relação entre o eixo RAA e COVID-19 foram incluídos na análise.

Resultados: Foram encontrados 292 itens nas bases de dados. Após análise aprofundada, foram selecionados 17 artigos, entre testes in vitro e in vivo, en-saios clínicos e estudos epidemiológicos relacionados ao tema analisado.

Conclusão: Devido aos be-nefícios sistêmicos dos medicamentos anti-hipertensivos direcionados ao eixo RAA e à falta de evi-dência desses tratamentos serem um fator de risco, não é recomendado retirar esses medicamentos de pacientes hipertensos infectados com SARS-CoV 2, a menos que haja um indicação clínica.

Palavras-chave: coronavírus; COVID-19; hipertensão; inibidores da enzima de conversão da angio-tensina; antagonistas do receptor da angiotensina.

INTRODUCTION

On January 30th, 2020, the World Health Organization declared a public health emergency of international concern (PHEIC) due to Coronavirus Disease-19 (COVID-19) caused by the Severe Acute Syndrome Coronavirus 2 (SARS-CoV-2 virus) (1).

This virus belongs to the family Coronaviridae (1), classified as Baltimore IV, its genetic material is a single strain of positive RNA (2). Members of this family cause pathology in humans, other mammals, and birds, and its effects can range from a common cold (3) to more severe symptoms and have even caused pandemic outbreaks in the past, e.g. the MERS-CoV (Middle East respiratory syndrome-related coronavirus) outbreak in 2012 (4), the SARS-CoV (Severe acute respiratory syndrome coronavirus) outbreak in 2002 (5) and finally the SARS-CoV-2 pandemic in 2019 (6). The symptoms, mortality, and associated risk are different depending on the virus (7,8).

Phylogenetic analysis of the virus shows a close relationship with two bat-derive SARS-like coronaviruses (more than 80% of homology) as well as an important relationship with SARS-CoV (more than 70% of homology). These codification processes allowed the study and comparison of SARS-CoV with SARS-CoV-2 (9).

It is widely documented that the Spike (S) protein of SARS-CoV binds to the Angiotensin-Converting Enzyme 2 (ACE2), for attachment and entry to the host cell (10). Recent research by Markus Hoffmann and colleagues provided evidence that host cell entry of SARS-CoV-2 also depends on ACE2 (9,11). Additionally, it was reported that SARS-CoV-2 does not use dipeptidyl peptidase 4 (DPP4) to enter the cell, as did MERS-CoV (12).

ACE2 is widely expressed in human organs, such as the lung (specifically in type 2 alveolar cells), intestine, heart, testis, and kidney (13-15). Its broad distribution may explain the multi organic burden of COVID-19 (16,17). Therefore, it is particularly important to develop a deeper understanding of the ACE2-SARS-CoV-2 interaction and its detrimental effects.

In addition to ACE2, another essential host molecule for this viral infection is a membrane protease known as Transmembrane Serine Protease 2 (TMPRSS2), this enzyme is expressed in different body tissues including the heart and lungs, and cleaves the viral S protein enhancing and allowing the viral entry (18,19).

Due to the interaction between SARS-CoV-2 and ACE2, a generalized concern was raised about withdrawing the administration of drugs dealing with the RAA axis, like Angiotensin-Converting Enzyme inhibitors (ACEIs) such as captopril, ramipril, and li-

sinopril, or like Angiotensin II receptor blockers (ARBs) such as losartan, valsartan and olmesartan (20).

This review aims to analyze whether patients should continue the antihypertensive treatment, taking into account the potential relationship between antihypertensive drugs and COVID-19.

METHODOLOGY

To find relevant studies, an exhaustive research was conducted on studies published in the last twenty years, searching in the central PubMed, Web of Science, Scopus, and Embase databases. According to the objectives, controlled descriptors based on the different PIO strategy (a variant of PICO strategy) items (21) connected by boolean operators "OR" and "AND" for a combination of the components were used, and the search term: ("ACE2" OR "hypertension" OR "RAAS" OR "RAS") AND ("COVID-19" OR "SARS-CoV-2") was employed, without language or any other restriction. To identify missing studies, extra searches in the reference lists of selected studies were performed. According to the work schedule, two reviewers independently screened and selected the pertinent papers following the eligibility criteria and the study selection to ensure the quality and reliability of the search protocol. Papers assessing in vitro and in vivo laboratory studies were accepted, as well as those addressing human population studies. Due to the recent outbreak, studies related to the action mechanism of SARS-CoV-2 and its associated receptors were included, and due to the similarities with the past SARS-CoV, articles referring to this virus were also covered. Articles assessing hypertension and SARS-CoV-2, or antihypertensive drugs and COVID-19 were included. Duplicated items, not yet peer-reviewed, not indexed journals, letters, not related to the objective of this review, published before 2002, papers with confounding factors, and not found were categories of exclusion. Studies in a language other than English were also excluded due to the authors' limitations with other languages. High quality, replicable, relevant articles, adequate sample size, appropriate research design, and analysis to answer the important questions were inclusion criteria.

Proceeding with the schedule, the five researchers extracted the relevant data from included studies, and disagreements were subsequently discussed. The information was classified into the following categories: COVID-19 disease/ACE2 and SARS-CoV-2/Hypertension and SARS-CoV-2/Antihypertensive drugs targeting the RAA axis and novel coronavirus.

Even though it is more commonly used in systematic reviews, PIO strategy was used to define the objective of this literature review:

Patient or problem: Infected SARS-CoV-2 patients with hypertension.

Intervention: Any kind of pharmacological intervention, both in human patients and experimental animal models of clinical pharmacology, targeting the RAA axis, especially showing lung and cardiac outcomes.

Outcome: the proportion of patients treated with ARBs or ACEIs that develop severe forms of the disease or death and possible mechanisms for these outcomes.

Initially, a total of 292 articles were found using the above-mentioned search terms. 80 duplicated items were excluded, resulting in 212 papers. After the first abstract screening, 126 items were eliminated for not meeting the criteria; 22 editorial/letter, 104 non-pertinent, and after an additional and detailed revision of the abstract 12 articles were rejected: 5 not yet peer-reviewed and 7 investigations not in English were dismissed; leaving 74 articles subjected to a thorough, comprehensive and detailed evaluation full-text and analysis of which 17 articles which met the inclusion criteria were included as shown in Figure 1.

RESULTS

Classical and non-classical RAA axis

It is important to describe the RAA axis without the influence of SARS-CoV-2, given its relevance to understanding the relationship with COVID-19. This axis is composed of two branches (classical axis and non-classical), and targets multiple tissues, regulating blood pressure, inflammation, urinary output, aldosterone secretion, among other body functions (22,23).

The classical RAA axis is acutely activated in states of hypovolemia or hypotension, promoting vasoconstriction, sodium retention, and other mechanisms, ultimately resulting in higher blood pressure. However, if it is chronically activated, (as seen in patients with hypertension), a pro-inflammatory response is favored (24), as shown in Figure 2. Angiotensin (Ang) II is the main effector of this axis and executes its physiological actions by binding to angiotensin receptors type I (AT1R) (22,23).

Otherwise, the non-classical RAA axis is composed of the ACE2/Ang(1-7)/MasR (24). ACE2 hydrolyzes Ang II to yield the active peptide Ang (1-7) (24,25), and also hydrolyzes Ang I to Ang (1–9) which is then cleaved to angiotensin (1–7), this molecule is the main effector of the non-classical axis; its vasodilator, antihypertensive and positive inotropic effects play an important role in myocardial and systemic protection (Figure 2) (25). Hypertension is a condition with a high prevalence worldwide. Therefore, drugs that alter the RAA axis are used widely in order to treat this disease (22).

Figure 1. Selection and filtration process

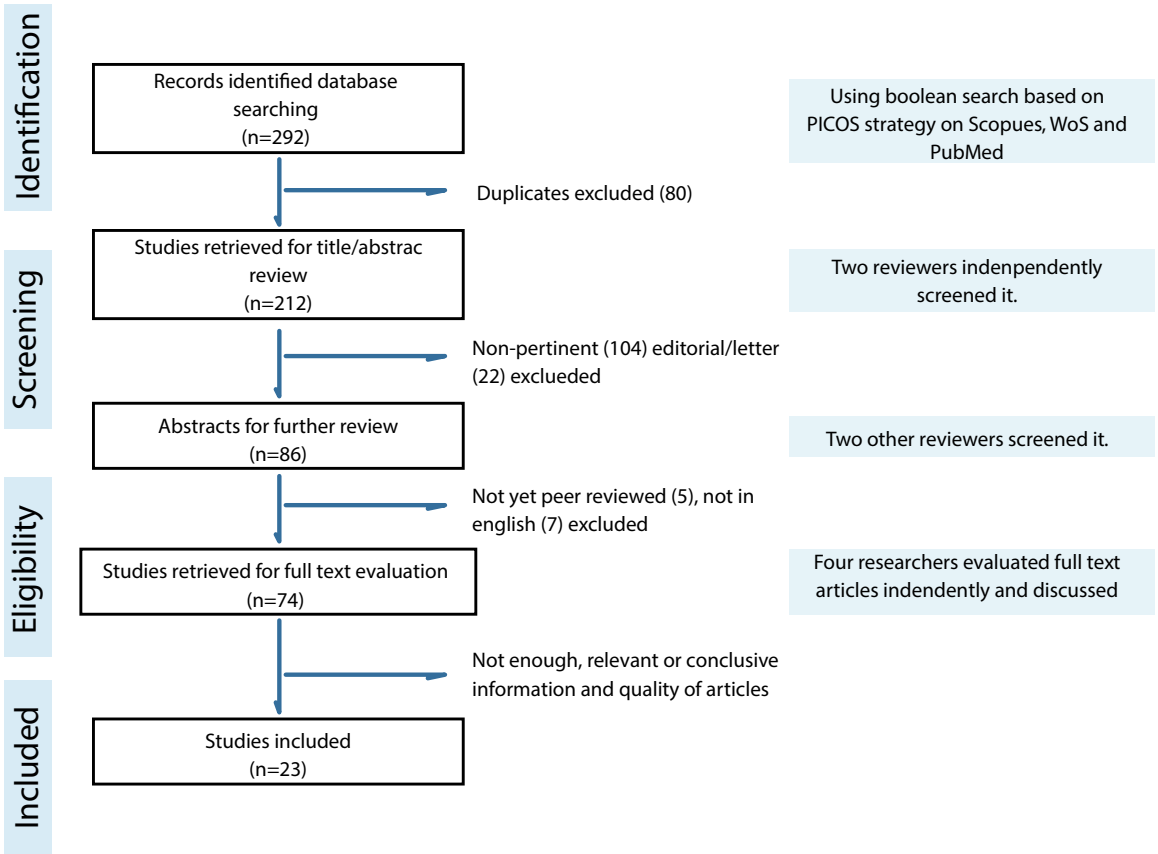
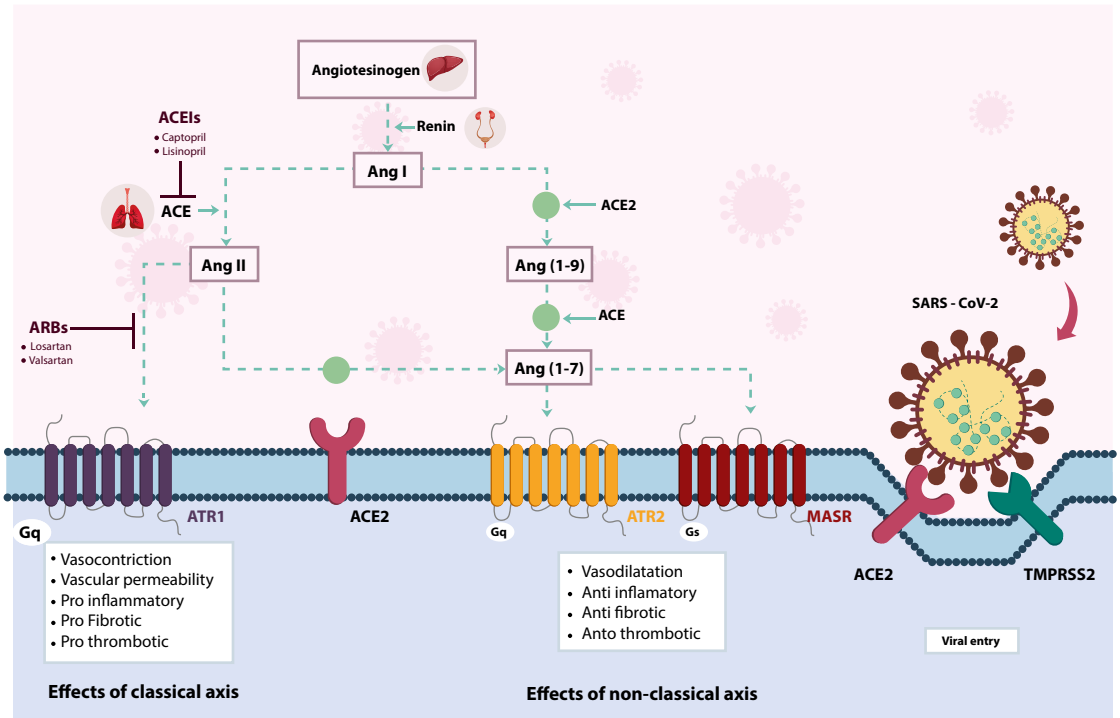


Figure 2. Renin-angiotensin-aldosterone axis and viral entry



Note: The liver pre-enzyme angiotensinogen is converted into angiotensin I through the action of renin, an enzyme produced and secreted by the kidney in response to low sodium concentration or low blood pressure. The inactive decapeptide Ang I can follow two paths: the one of the classical axis, and the one of the non-classical system, in the former one, Ang I, mainly through the action of enzyme pulmonary enzyme ACE, gets converted into Ang II, the main effector of this axis, and can either use the receptor ATR1 to do all the effects enlisted or can be broken further down by ACE2 to become Ang (1-7), the main effector of the non-classical system. Another way to get to Ang (1-7) is by converting Ang I into Ang (1-9), by ACE2, which then gets cleavage by ACE. The main effector of the non-classical axis uses the receptor ATR2 and MAS, in order to do the actions enlisted in the image. ARBs act by not allowing Ang I to use ATR1, whereas ACEI acts by directly inhibiting the enzyme ACE, thus both affect directly the classical axis and indirectly promote the non-classical one. On the other hand, SARS-CoV-2 interacts with two host proteins, ACE2 and TMPRSS2 to enter the cell.

Conventions: Ang: angiotensin. ATR: Angiotensin receptor. ACE: angiotensin-converting enzyme. MASR: MAS receptor. ACEIs: angiotensin-converting enzyme inhibitors. ARBs: Angiotensin receptor blockers. SOURCE: This graphic is property of the authors.

Ang (1-7) has beneficial effects on diabetes, hypertension, renal and cardiovascular diseases antagonizing the role of Ang II (26). Deficiency or inhibition of ACE2 increases nuclear factor kappa-light-chain-enhancer of activated B cells (NFkB) mediated inflammation, endothelial dysfunction, and enhances prothrombotic and atherogenic activity (27,28).

Extrapulmonary pathology

The RAA axis studied in COVID-19 disease takes importance not only in lung injury but also in cardiovascular damage; both SARS-CoV and SARS-CoV-2 cause downregulation of ACE2 in cardiac tissue, compromising this organ (28). This pathway might exacerbate previous cardiovascular pathologies (29).

In theory, it is not only possible to be predisposed to cardiovascular diseases depending on ACE2 variations, but also to be at a higher risk of a severe SARS-CoV-2 infection, that is to say that polymorphisms on ACE2 could affect the affinity for the S protein of SARS-CoV-2, determining the severity of the infection based on the patient's genetics (30).

Besides affecting the lung and cardiovascular systems, SARS-CoV-2 pathology could have a systemic effect: pro-inflammatory cytokine storm is related to poor prognosis in patients with COVID-19 due to an augmented profile of interleukin 2, 6, 7, chemokine ligand 2, and tumor necrosis factor-α (TNF-α) expression (31,32), this could contribute to the lung disease by causing endothelial dysfunction, which may lead to capillary leakage, interstitial edema, and respiratory failure with subsequent fibrosis. Some authors have even explored the possibility to treat severe patients with mesenchymal stem cells for their immunomodulatory function, thus preventing the systemic cytokine storm (33). These cytokines were involved in the progression of hypertension in different studies.

In addition, a deficiency of pulmonary ACE2 may exacerbate respiratory distress, hypertension, and TGF.b/Smad signaling pathway, mediating fibrosis in animal models after viral infection (28), which may promote the general inflammation in a patient affected with SARS-CoV-2 (29).

Hypertension

A large number of studies have demonstrated that the severe illness and deaths by SARS-CoV-2 infection are principally reported in patients older than 60 years old, as well as patients with underlying diseases such as hypertension, diabetes, cardiovascular, gastrointestinal, and cerebrovascular diseases (34,35). Several of these disorders are associated with the dysregulation of the RAA axis (31) emphasizing its importance.

Multiple studies are converging towards hypertension as the most prevalent comorbidity in patients with COVID-19. Some authors proposed this disease as a risk factor for the development of severe and lethal outcomes (36-38).

On the other hand, hypertension is a very prevalent disease worldwide; especially in Asia, where a lot of investigations on COVID-19 are being held, the number of hypertensive patients in China is similar to that of infected by SARS-CoV-2. Furthermore, it is important to mention that people with hypertension often have other coexisting risk factors such as diabetes and advanced age (39).

Does ACEI and ARB treatment increase susceptibility to SARS-Cov-2 infection?

A common antihypertensive target is the RAA classical axis, that is the case of ACEIs, which act by decreasing Ang II and increasing bradykinin, and of ARBs, that work by preventing Ang II from binding to its receptors. Despite the molecular similarities between ACE and ACE2, ACEI only inhibits the former but not the latter due to their different active sites (40). This important aspect allows these drugs to increase the beneficial non-classical axis, while blunting the classical one.

Studies, although scarce, from animal models and human beings established that treatment with ACEIs or ARBs lead to an up-regulation of ACE2 expression in lung tissue (38,41,42): in previous studies, researchers have found a 5-fold and 3-fold increase in ACE2 expression using lisinopril and losartan, respectively. Moreover, Rico-Mesa et al. (43) demonstrated that patients treated with Olmesartan have increased secretion of urinary ACE2.

Furthermore, since ACE2 expression is increased in the pathophysiology of diabetes, hypertension, and myocardial infarction (44) and because patients suffering from these diseases happen to be at a higher risk of developing severe complications due to SARS-CoV-2 infection, it has been important to consider if overexpression of ACE2 due to the use of these drugs could be a risk factor, as it would theoretically increase the numbers of receptors for the virus (38) and hence it's been important to analyze whether physicians should either stop or modify the treatment.

Initially, some authors hypothesized to stop supplying these drugs (45,46), however, Singh et al (47), shed light on the problem by stating that an increase in ACE2 expression may not result in more viral entry since there is a limited amount of intracellular TMPRSS2. Co-expression of ACE2 and TMPRSS2 does not happen in all ACE2-expressing cells, hence the overall local and systemic effect of this increased enzyme, and therefore upregulation of Ang(1-7), after the administration of these drugs, is beneficial (38).

Moreover, the pharmacological interventions in this axis can increase the soluble form of ACE2, which in turn could specifically block the binding domain in the Spike viral protein, this way preventing the virus from entering the cells (38).

In summary, evidence studied suggested the administration of ACEIs and/or ARBs does not increase the risk of SARS-CoV-2 infection. Consequently, those patients who were previously prescribed with these antihypertensives should not stop their medication, unless there are other clinical reasons to. However, further studies are needed to prove these drugs could reduce the risk of infection of the novel coronavirus in healthy people, therefore they should not be administered for preventive aims.

Is ARB and ACEI treatment beneficial for SARS-CoV-2 infected hypertensive patients?

Once inside the cell, SARS-CoV-2 downregulates the ACE2 protein, which then upregulates Ang II; this increases the actions of the classical axis, thus promoting constriction in both pulmonary vasculature and bronchi, and enhancing overall tissue inflammation caused by SARS-CoV-2 infection (48-50). The over-accumulation of this hormone could lead to acute respiratory distress syndrome (ARDS) (34).

In Addition to the loss of ACE2 by endocytosis, the increased Ang II binds to AT1R upregulating ADAM17 (a disintegrin and metalloproteinase 17), which mediates shedding and proteolysis of ACE2 resulting in an extra membrane-bound ACE2 loss (35,51). As a consequence, this upregulates the classical RAA system leading to the positive feedback of ADAM17 and perpetuating the detrimental effects of this axis (31).

There is evidence that ACEIs and ARBs are not only important to block the classical RAA axis, but also to upregulate the non-classical axis, increasing the levels of Ang (1-7) and decreasing Ang II, therefore having a beneficial impact on the patient (20,52). For these reasons, RAA axis inhibitors provide cardiovascular and renal benefits in patients who are under this medication and get diagnosed with COVID-19.

Can RAA axis inhibitors be used as treatment for COVID-19?

Some authors have recommended ACEIs and ARBs to treat COVID-19, since theoretically this could not only downregulate the ACE/Ang II/AT1R pathway and upregulate ACE2/Ang (1-7)/AT2R/MasR pathway (51), but also it could increase the amount of soluble ACE2, and decrease the levels of Ang II, therefore, lowering the pro-inflammatory state. It has been shown that younger males have greater amounts of ACE2 expression

than older adults, a known population at risk, thus this treatment may emulate ACE2 expression in young people (47). In this way, Ang (1-7) upregulation can prevent lung fibrosis through its vasodilatory, anti-proliferation, antifibrotic, and anti-inflammatory effects, limiting the disease progression (28).

Human studies have suggested that the use of these drugs significantly reduced mortality in patients with sepsis (53), and also reduced rates of death and endotracheal intubation in patients with viral pneumonia. Some RAA-axis-inactivated animal models demonstrated symptom relief in severe acute pneumonia and respiratory failure, through inhibition of vasoconstriction mechanisms (43,54).

In addition, a pilot trial in ten intensive care units in the U.S.A. showed that administration of recombinant human ACE-2 (rhACE-2) raised levels of Ang (1-7) and lowered levels of proinflammatory cytokine interleukin-6 in patients with ARDS (51). Therefore, rhACE-2 is another molecule proposed as a treatment for infection with SARS-CoV-2.

These results support the result of recent clinical studies where hospitalized COVID-19 patients that received ACEI/ARB treatment had a lower risk of mortality (55-57). While there is no solid evidence on the effectiveness of either ACEIs, ARBs or rhACE-2 in treatment of COVID-19; it is important to encourage researchers to do randomized clinical trials to demonstrate the impact of this therapeutic intervention.

DISCUSSION

This study presents an approach of the relationship between some antihypertensive treatments and COVID-19. The strength of this review is related to the use of a PIO strategy that provides a rigorous analysis of different studies that answer the described problem and support the exposed results.

In this context, the angiotensin-converting enzyme II (ACE2) is not only involved in the regulation of the RAA system, but it also participates as a gateway to SARS-CoV-2 (28). It is of great importance to understand these two processes together and to determine the effects of the most frequent pharmacological interventions dealing with this system, such as ARBs and ACEIs.

As a consequence of the short time elapsed since the onset of the novel coronavirus, some scientists hypothesized suspending RAA axis inhibitors despite the few studies that supported it, however, mounting evidence confirms otherwise due to the great risks assumed by stopping these antihypertensive treatments. Many older patients are treated with RAA axis inhibitors due to left ventricular dysfunction

or hypertension, discontinuing medication in these patients may result in heart failure (58).

Hypertension is a highly prevalent disorder; thus the burden of a greater incidence of strokes and myocardial infarctions (50), caused by discontinuing radically the treatments could have catastrophic results to the health system, in the context of an ongoing pandemic. Therefore, multiple cardiology associations, such as Heart Failure Society of America (HFSA), American College of Cardiology (ACC), American Heart Association (AHA) and European Society of Cardiology (ESC) Hypertension Council suggested the non-suspension of treatments with ACEIs and ARBs in those patients who, prior to SARS-CoV-2 infection, were already taking these medications (43). In addition, there is not enough evidence to establish whether these medications could have a preventive role for those who are not yet taking them.

As of treatment, some authors have hypothesized the beneficial role of medication affecting the RAA axis, taking into account that in the pathogenesis of COVID-19, Ang II is one the main mediators and that blunting the non-classical axis could have cardiopulmonary benefits, however, this needs to be studied to a greater extent.

If the ACE2 upregulation in some pulmonary and cardiovascular disease is an important risk factor for contracting COVID-19, or if it plays a protective role before the infection in these patients, is yet to be determined. Although further epidemiological studies are needed to assess the odds ratio, with the literature review performed in this text, one could think that this overexpression is a protective factor.

Other important information that is not yet widely studied is the participation of TMPRSS2 in relation with the comorbidities, that is to say, if there is an upregulation of this protease in some prevalent associated diseases such as hypertension, diabetes, or chronic obstructive pulmonary disease.

CONCLUSION

It is evident that in those hypertensive patients who have not been infected with SARS-CoV-2, the possible theoretical "benefits" of stopping their treatment, derived from downregulating the amount of ACE-2, and therefore "preventing" the viral entrance, do not outweigh the great cardiovascular risks of uncontrolled hypertension, this is because these medications may play a protective role in these patients due to the activation of the non-classical axis, therefore withdrawing the drugs might have a negative impact on their health.

Regarding patients already infected with SARS-CoV-2, there is not enough evidence to support

the discontinuation of ARB and ACEI drugs unless there are other clinical reasons to stop their use (56). It is believed that the protective effects of the medication could be also applicable to these patients, thus withholding medication might not be a good option overall. It is worth mentioning that there is no solid evidence assessing their preventive use on patients who were not previously prescribed these medications and therefore further investigation must be carried out.

LIMITATIONS

- Only articles in English were taken into account.

- Due to the emerging character of the pandemic, information may rapidly become outdated.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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