Fast-track publication and care management: exploring the evidence for the use of RAS Inhibitors in patients with hypertension and COVID-19

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A debate exists in Social Science about whether the truth and the quality of the institutions of a given society are better known in normal conditions, of the current operation, or in exceptional, critical scenarios. Maybe both types of conditions are equally knowledge-inducers, but it is certain that they allow us to know or reveal different things. What potential knowledge could the coronavirus pandemic bring about?

Boaventura Souza Santos, Vírus: tudo que é sólido se desfaz no ar (p.1)[1].

On March 11, 2020, the World Health Organization (WHO) declared COVID-19 a pandemic. The disease was caused by a novel coronavirus, Coronavirus 2 of Severe Acute Respiratory Syndrome, SARS-CoV-2[2]. The high incidence, the high number of deaths and the prolonged time of the pandemic, with alternating infectious variants, turned COVID-19 into one of the greatest health challenges ever faced in the world.

Science and research production followed the rapid pace of the pandemic, quickly analyzing the virus distribution and behavior among the population. The need for information for clinical decision-making stimulated the conduction of experimental and epidemiological studies, and accelerated underway changes to the rules of article publication, made available on websites in the form of preprint manuscripts, fast-track publications, papers with no peer review or opinion pieces[3]. This process allowed, on the one hand, rapid access to scientific information by the lay media and public health authorities, and, on the other hand, adoption of new therapeutic guidelines by frontline professionals in the course of the pandemic, with increasing learning that, in turn, dropped mortality rates. However, information without sound evidence led to misguidance in the management of the pandemic, both clinically and politically[3].

COVID-19 expanded scientific production and modified science production and disclosure, a movement that Nature magazine called a "science torrent": websites and scientific journals were flooded with research on coronavirus[4]. Between December 30, 2019, and January 23, 2022, 865,054 publications on COVID-19 were made available by more than 33,000 organizations located in 206 countries[5]. Out of that amount, more than 80,000 publications (9.6%) were preprinted, especially in medRxiv, SSRN, and Research Square databases. The papers firstly focused on the spread of the disease, the outcome for hospitalized patients, as well as on diagnostic methods and testing; and, as the pandemic progressed, they were replaced, by research within the mental health area, vaccines, and treatment[4]. More than two-thirds of the articles published on the MedRxiv website in 2020 were on COVID-19, and scientific journals accelerated the evaluation of articles on the topic[4].

By late 2021, advances in the knowledge of COVID-19 were unquestionable. Proven and effective vaccines and new treatments were approved, regulated, and implemented, controlling the pandemic[6]. The virus elimination is not a scenario so far foreseen, but rather one of each nation setting its own and acceptable level of coexistence with COVID-19 in this

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interconnected world and, the manner in which knowledge will be generated and applied to practice[6].

In Brazil, this debate gained expanded contours due to the tension between experts' associations, scientific and regulatory agencies, and the Ministry of Health that challenged the technical opinions of clinical guidelines on the prevention and treatment of COVID-19[7]. Public health emergencies are a challenge to regulatory agencies due to the combination of demand for urgent and rapid access to vaccines and medicines, the healthcare system operating at the limit of its capacity, a frightened population, and healthcare professionals jeopardized[8]. The Brazilian healthcare system regulation body is the National Health Surveillance Agency (Anvisa). The agency, during the pandemic, prioritized registers and clinical studies on COVID-19, issued emergency use permits, conducted epidemiological analyses, and issued extraordinary notes to speed up the registration of diagnostic tests, medicines, and biological products for COVID-19 prevention and treatment[8].

A further important agency in the evaluation of the incorporation of new technologies in Brazil is Conitec (National Commission for the Incorporation of Technologies in the Unified Health System), a body that advises the Ministry of Health in the incorporation, exclusion or alteration of new drugs, products, and procedures by the Unified Health System (SUS) and contributes to the elaboration or alteration of Clinical Protocols and Therapeutic Guidelines (PCDT) evaluated and issued by the Secretariat for Science, Technology, Innovations and Strategic Inputs (SCTIE)[9]. Conitec accelerated the time for evaluation of COVID-19 therapies, setting at ten days the public consultation deadline, and rapidly approved the incorporation of vaccines to prevent the disease[10]. The Guidelines for Hospital Treatment of Patients with COVID-19[11] are counted among the guidelines published. The Guidelines for outpatient pharmaceutical treatment of patients with COVID-19 and the Guidelines for hospital treatment were developed and disclosed, but, in an unprecedented decision, were given no approval from the SCTIE, especially for issues involving Hydroxychloroquine, Ivermectin and inferences regarding vaccines[7].

Pepe, Novaes and Osorio de Castro[8] warned that regulation on the use of new interventions in emergency scenarios should be built as

> a viable compliance between the urgency of the epidemic and the need for approval, surveillance or scrutiny by the regulatory authority. [...] Worldwide, the making of decisions about the use of medicines is uncertain and, at times, a response to external and internal pressures on the countries, influenced by the scientific motion that involves intense research of various types, often of questionable quality, generating sometimes conflicting or inconclusive results. (p.4698-99)

Within this pandemic scenario, extended beyond the biological field to reach economic, social, political dimensions, not to mention science and knowledge production, the use of well-known medications, widely studied and used, was also questioned. Such is the case of renin-angiotensin system inhibitors (RASIs)[3], which will be evaluated in this article.

Knowledge of the role of the cardiovascular system and, more specifically, of the renin-angiotensin-aldosterone system (RAS) in COVID-19 and the therapeutic implications of treating hypertensive patients with COVID-19 were the subject matter of studies during the pandemic. Hypotheses were formulated and tested, and the guidelines published by professional associations and regulatory agencies were changed regarding the use of drugs that act on the RAS in hypertensive patients with COVID-19.

This paper aims to document and analyze the research trajectory, scientific communication, and formulation of clinical guidelines and standards by regulatory agencies and experts' societies on the use of hypertensive medications that act on RAS (angiotensin-converting enzyme inhibitors – ACEIs and angiotensin receptor blockers – ARBs) in hypertensive patients with COVID-19, from the onset of the pandemic to March 2021.

METHOD

This paper is an integrative literature review. The sources of information included preclinical studies, editorials of scientific journals, brief communications, epidemiological studies, and review papers that analyzed the effect of COVID-19 in

animal models and hypertensive patients, as well as Clinical Guidelines for Hypertension and COVID-19.

Scielo and PubMed databases were used and the initial keywords were: "COVID -19 AND Heart"; "COVID -19 AND Cardiovascular Diseases" in the Portuguese, English, and Spanish languages, published from May 2020 to June 2020. Following this first literature survey that evidenced the interaction of SARS-CoV-2 with RAS in patients with cardiovascular diseases, the authors did a second survey, focusing on hypertension. The second survey aimed at studies that enabled the understanding of the different mechanisms and relations between SARS-CoV-2 and RAS in patients on ARB and ACEI for the management of systemic hypertension, as well as the corresponding therapeutic implication of such relation, reported in experts' consensuses and in the establishment of clinical guidelines. The keywords used in this second survey were: "COVID-19 and Antihypertensive drugs", "Angiotensin Receptor Blocker", "Angiotensin Converting Enzyme Inhibitor", "ACE2", "Angiotensin1-7". The timeframe was extended to cover the first studies on SARS caused by other coronaviruses, from 2004 to March 31, 2021. We registered, if available, the publication timespan, from submission of the paper to its acceptance, if the database was of open access, and if the article was published as a preprint.

Searches in Google assessed the lay media coverage on the subject with the keywords "Covid", "hypertension", "antihypertensive drugs", on dates next to the publishing of the articles analyzed.

COVID-19, hypertension and RAS

COVID-19 is a viral infectious disease caused by SARS-CoV-2, with patients presenting few or no symptoms in about 80% of the cases. After the viremia phase, the disease progresses to either a cure or an inflammatory phase, with different clinical features and severity, such as a hypercoagulable condition, respiratory, or renal failure. Approximately 15% of patients require hospitalization due to respiratory symptoms and 5% present the severe form of the disease, with Severe Acute Respiratory Syndrome (SARS) and multisystem manifestations. Severe illness is more likely to occur in senior adults or when presenting underlying clinical comorbidities. Arterial Systemic Hypertension (ASH) is one of the most prevalent risk factors for severe disease[12]. In Brazil, high blood pressure affects approximately 25% of the population, and the prevalence increases with age (49%, on average for individuals aged 55 to 64 years and 60% for those aged over 65)[9].

The main physiopathological mechanism of ASH is the deregulated hyperactivity of RAS, a system that plays a major role in the cardiovascular, hydric, and saline homeostasis of the body[13], with the marked activity of its main enzyme, ACE. In the classic pathway[13], pressure, beta-adrenergic or molecular stimulus liberates renin in the juxtaglomerular apparatus, and renin cleaves the hepatic angiotensinogen precursor, transforming it into Angiotensin I (AngI). AngI, in turn, is converted, by the ACE action, preferably located in the pulmonary endothelial cells, into Angiotensin II (AngII), a peptide that acts on the AT1 receptor and produces vasoconstrictive, oxidative, and pro-fibrotic effects. The action of AngII in the AT2 receptor causes the opposite effect, i.e., vasodilation and antiproliferative activity[13]. (Figure 1)

Cano et al.[13] note that, for nearly three decades, researchers have been finding other peptides and alternate RAS pathways, compounding integrated axes that maintain and regulate the system, located in different system organs, acting independently by both autocrine and paracrine mechanisms. One of these axes is formed by the cleavage of AngI into the peptide Ang1-7, through a variant of the ACE, the ACE2. The ACE2 also converts AngII into Ang1-7. Ang1-7, through the MAS receptor, causing vasodilation, nitric oxide production; natriuresis, and diuresis, counteracting the effect of the AngII in the AT1 receptor (Figure 1). ACE2 is the gateway for SARS-CoV-2 to enter the body.

The virus enters the human cells by binding its Spike surface protein (protein S) to the ACE2 receptor, a process facilitated by the activation of transmembrane serine protease 2 (TMPRSS2)[12]. The amount of ACE2 in the cardiac striated muscle tissue is higher in hypertensive patients, and this could explain the greater severity of the disease in hypertensive patients.

ACE2 also constitutes the immune system and is highly concentrated in the lung and heart, which could explain the damage of COVID-19 to the cardiovascular and respiratory systems[12]. Cardiac damage is expressed in differently reported

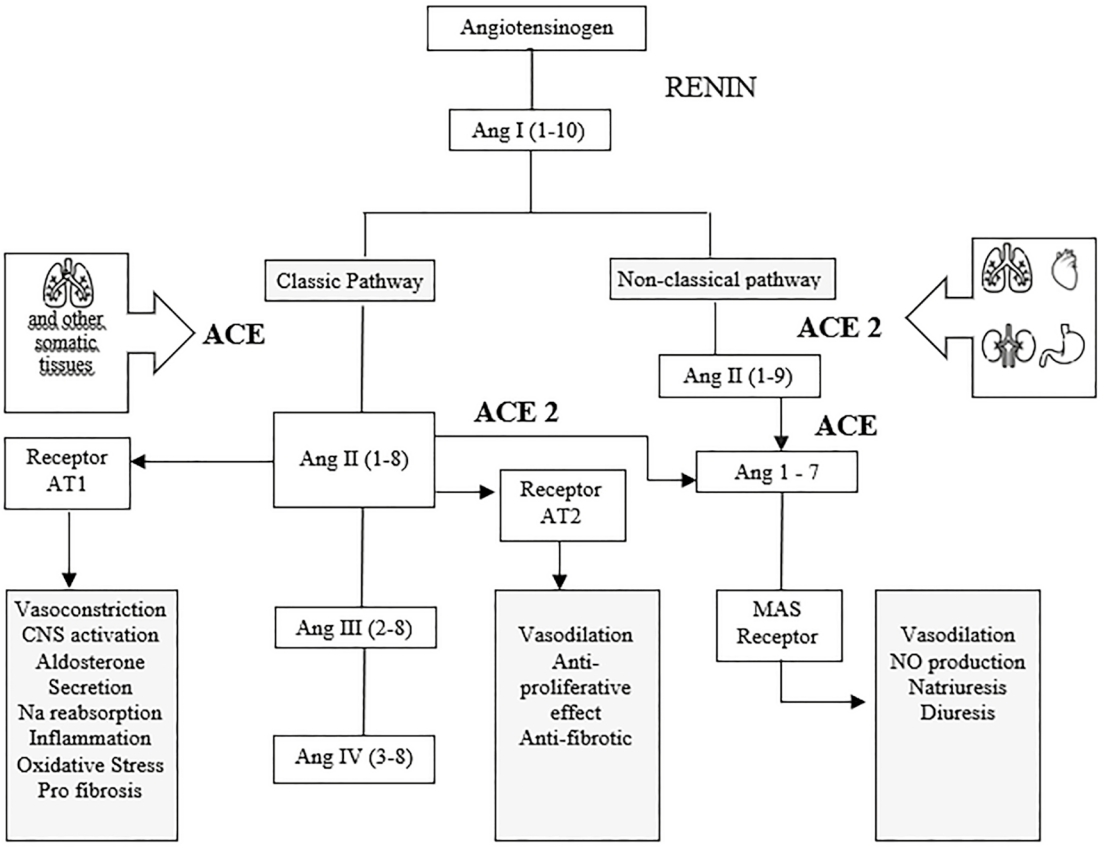

Figure 1. Renin-angiotensin aldosterone system, classic, non-classical pathways and main activities (Adapted and translated from CANO et al., 2020[13]).

ways, such as myocardial injury, heart failure, arrhythmias, myocarditis, and shock[12]. Costa et al., in a review article[12], reported that the damages to the cardiovascular system are probably multifactorial and may be caused either by an unbalanced relation between high metabolic demand and low cardiac reserve or by systemic inflammation and thrombogenesis. The major risk of cardiovascular complications in hypertensive patients infected with SARS-CoV-2 is unquestionable, worsening their prognosis, whether considering the risk of complications or death.

In addition to the pathophysiological alteration of ARS in hypertensive patients, medications for ASH may target ARS, modulating it. It is the case of ACEIs and ARBs that reduce ACE activity and, as a result, increase ACE2 activity.

A controversy emerges: whether or not to withdraw ACEIs and ARBs in patients with COVID-19

Fang et al.[14] published a short notice on March 8, 2020, in the scientific journal The Lancet, postulating that the treatment with ACEIs/ARBs would be harmful to hypertensive patients due to the increased ACE2 concentration they induce, acting as an adjuvant facilitating mechanism for severe systemic manifestation of the COVID-19 in hypertensive patients. The assumption was grounded on both the pathophysiology of COVID-19 and the ACEIs and ARBs mechanisms of action when there was more to learn about the RAS role in hypertensive patients with COVID-19 than the knowledge then existing. The authors based their notes on three

observational studies. The studies evaluated the clinical progress of patients hospitalized for COVID-19 and found a high prevalence of diabetic and hypertensive patients. The use of medications or their impact on the clinical outcome was not assessed in those studies.

For the authors, the higher expression of ACE2 in diabetic and hypertensive patients on ACEIs and ARBs would increase the chance of developing the severe form of the disease. Based on this hypothesis, they recommended the withdrawal of ACE inhibitors and suggested they should be replaced with calcium channel blockers (CCB), drugs that would not intervene with the ACE2 activity. Although this hypothesis was refuted by subsequent studies[15], the full note was still available in March 2022, with open access. This publication was one of the three examples used by Bagdasarian et al.[3], calling attention to the risk that opinion pieces, published at moments of anxiety and rapid search for information, be interpreted as a fact. In this case, misinformation reached the media and also the institutional agencies (such as the WHO), transmitting uncertainty to the medical community and the public in general, fostering the risk of a social lack of trust in the public health systems.[3]

Covid-19 and RAS: the paths followed by the scientific literature and expert recommendations

Twenty-nine publications were selected for the integrative review. Papers on cardiovascular conditions other than hypertension and not focusing on RAS were discarded. Detailing the selected productions, six were experimental/pre-clinical papers; seven were retrospective observational studies; one was a prospective cohort study; one was a clinical trial; six were integrative review papers; one was a meta-analysis; and four were short notices (Figure 2). Three guidelines or expert consensus were also included.

The epidemiological association between hypertension and increased risk of severe disease opened the way to studies investigating the role of RAS and RAS inhibitor drugs in hypertensive patients with COVID-19. The letter to the editor, published in the Lancet magazine, with Fang et al.[14] hypotheses, suggesting that the use of ACEIs would be contraindicated for patients with COVID-19, was readily debated by the experts' societies. In Brazil, the Brazilian Society of Hypertension published a positioning note ten days after Fang et al.[14] publication on March 21, 2020, refuting the authors' hypothesis and supporting the importance of maintaining ACEIs and ARBs based on pathophysiology studies[16]. In May 2020, 17 experts published a review paper in the Brazilian Archives of Cardiology, aiming to provide guidance for evidence-based cardiovascular management of patients with COVID-19, including hypertension management[12]. The paper was submitted and accepted on the same day, April 3, 2020.

In the social construction of knowledge, one notes that the rapid dissemination of alarming news by the non-specialist media, particularly in a pandemic scenario, contrasts with the longer time required for science to make sound recommendations. This time gap would justify the fast-track approval of expert consensus. Meanwhile, issues such as whether to withdraw or maintain RASIs; whether their effect would be harmful or protective; what mechanisms were involved in this association; the controversial conclusions of the studies; the lack of sufficient information were conveyed in podcasts[17], reports[18], TV sketches[19], YouTube animations[20]. The content sought to bring, to the public in general, the relevance of carefully evaluating the inferences made from poor associations or non-substantiated hypotheses without considering the confounding factors and the complex nature of COVID-19, a systemic disease. A key question, however, was posed: what is the role of ACE2 in understanding and mitigating the severe effects of SARS-CoV2 infection?

Observational studies, from the onset of the pandemic, associated lethality with hypertension. In a retrospective observational study published in August 2020, with more than 1000 patients enrolled, Huang et al.[21] attributed the highest lethality to the pathophysiology and inflammatory disorders related to hypertension, as well as to the fact that the virus enters the cell through ACE2 receptors. Considering ACEIs and ARBs in hypertensive patients with COVID, the authors indicated that their effect was at least

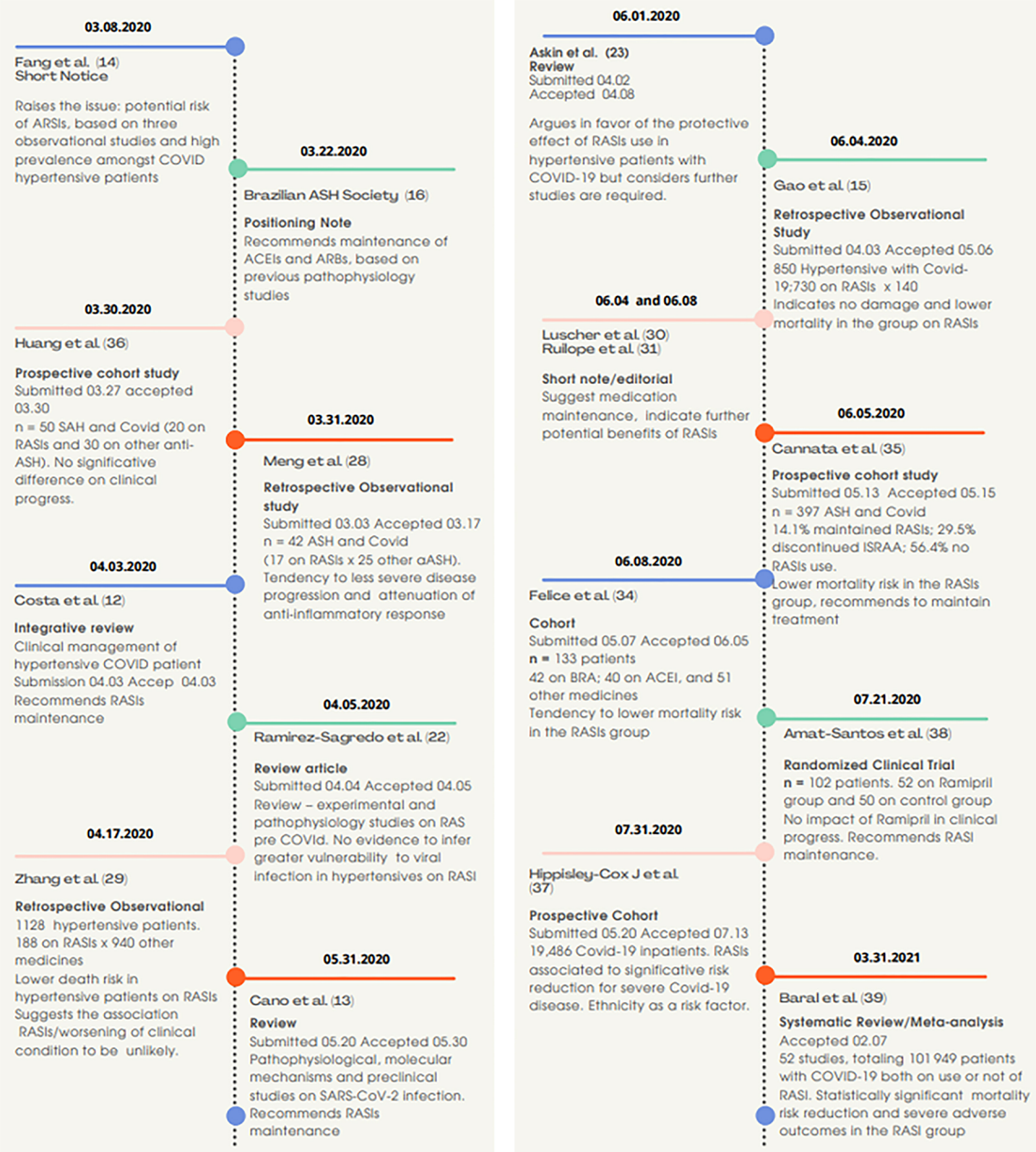

Figure 2. Covid-19, arterial hypertension and use of Angiotensin Renin System Inhibitors. Knowledge production, March 8, 2020, to March 1, 2021.

controversial: on the one hand, increased expression of ACE2 in the lung tissue could increase the risk of severe disease, but on the other hand, its down-regulation role on RAS would confer protection.

The respiratory, cardiovascular, renal systems, and gastrointestinal tract hold greater concentrations of ACE2[13]. ACE2, in addition to its role in RAS, integrates the immune system, protecting the lungs, kidneys and heart from the inflammatory effects of AngII. The enzyme catalyzes AngII into Ang1-7 that, binding to the MAS receptor, increases vasodilation and reduces fibrosis and inflammatory effects, resulting in protection of the cardiovascular, pulmonary and renal systems, precisely the ones most affected in the SARS of COVID-19 (Figure 1). In animal models, ACE2 reduction in pulmonary tissue aggravates acute pulmonary failure[22]. This pathophysiological evidence would corroborate

the hypothesis that connects ACE2 reduction to clinical COVID progress due to the loss of its protective effect. In hypertensive patients, the class of antihypertensive treatment instituted and its action on RAS would mediate the complications of infection[23].

In June 2020, Gao et al.[24], investigating the hypothesis of antihypertensive treatment mediation in the outcome of hypertensive patients with COVID-19, published a retrospective observational study with 2877 patients, 850 of whom were hypertensive. The aim was to analyze the risk of severe disease and death risk of hypertensive patients compared to non-hypertensive patients, evaluating, secondarily, whether untreated hypertensive patients, compared to the ones medicated, would have a higher risk of severity when contaminated with COVID-19. The authors concluded that hypertensive patients stood a greater chance of developing the severe and critical form of COVID-19, with twice a greater risk of death compared to non-hypertensive patients. Regarding the risks associated with drug treatment in hypertensive patients infected by the SARS-CoV-2, RASIs, such as ARBs and ACEIs, tended to be protective, showing better clinical outcomes.

Thus, the higher amount of ACE2, secondary to the use of BRAs and ACEIs, would increase the infective viral load at the onset of the clinical condition[12]. This was basically the ground for Fang et al.[14] inferential arguments in favor of withdrawing those medications, and replacing them with CCB. However, following the infection, the massive destruction and reduction of ACE2 would aggravate the clinical condition, leading to pro-thrombotic and systemic inflammatory effects, presenting as the cytochemical storm and eventually resulting in death[12]. In fact, RAS is complex and polymorphic[13].

One month following Fang et al. publication[14], six researchers in the fields of chemical and pharmaceutical sciences and internal medicine of the University of Chile published a review paper on the available knowledge concerning the relation between coronavirus infection, RAS, and antihypertensive drugs. The authors intended to scientifically test the hypothesis of aggravation of the disease from maintenance of antihypertensive drugs acting on RAS, aiming to establish the actual risks of using such medications in patients with COVID-19[22]. The study was assessed under the fast-track process, submitted on April 4, accepted the following day, and published in *Revista Chilena de Cardiologia* as a special article, evidencing the relevance of the subject. In the review paper, the authors analyzed papers on preclinical models, and pharmacology and clinical studies published from 1999 to 2020. They found little information to support a correlation between the prolonged use of the medications and increased ACE2 expression and/or activity[22]. The authors pointed out that ACE2 expression in hypertensive patients does not mean, necessarily, greater susceptibility to the viral infection[22].

Studies in mice, in the same review article[22], showed that reduced ACE2 concentration in the pulmonary tissue aggravated acute respiratory failure. The authors found, therefore, correspondence between the pathophysiological findings in experimental studies[22] and clinical findings in observational studies[24], which signaled, in mid-2020, the beneficial effect of high ACE2 expression during the inflammation phase and, possibly, a protective role against injuries to target-organs.

One argument emphasized in Ramirez-Sagredo et al.[22] integrative review was the protective effect of the treatment with ACEIs. In animal models, Losartan, an ARB, would potentially reduce the pulmonary rate of injury. A further aspect highlighted in the review was the two forms of ACE2. One is an enzyme that acts as a receptor for the Spike protein of SARS-CoV-2, and the other is a soluble form that does not have the binding site of the Spike protein in the cellular membrane. This latter form has a low concentration in the organism compared to the former one and can act as a competitor-interceptor of the virus, preventing its binding to the Spike protein[22].

RAS complexity, demonstrated in biokinetic studies almost twenty years ago[17], is shown in the balanced and counterbalanced performance of ACE, ACE2, and neprilysin levels. According to the levels of peptides generated in cleavage (AngII, Ang1-7, Ang1-9), vasodilation or vasoconstriction prevails. Due to this dynamic interaction and the different activation sites of ACE and ACE2 enzymes, the use of antihypertensive agents acting on RAS would not compromise ACE2 functions. Ramirez-Sagredo et al.[22] integrative review strengthened such proposal, presenting experimental studies that found an association between increased ACE2

expression using Enalapril, and a cardio-protective effect in animal models of hypertension and acute myocardium infarction.

Vuille-Dit-Bille et al.[26], in a study of human physiology conducted in 2015 on the effect of ACEIs on ACE2, found increased RNAm levels of ACE2 in the intestinal lumen in patients on those medications as compared to control patients. In another pre-COVID study published in 2016, Gu et al.[27] suggested, based on animal models and samples from pediatric patients, that ACE2 would have a pulmonary protective effect in infection caused by the syncytial respiratory virus (SRV). This effect was demonstrated by the association between the aggravation of the SRV condition and reduction of ACE2 plasmatic levels (in an animal model) and lessening of the pulmonary condition severity in rats infected with SRV receiving recombinant ACE2, with reduced pulmonary inflammatory response and viral load. There was, therefore, strong evidence in preclinical studies that increased ACE2 during the infection would be beneficial.

Clinical Studies

Retrospective studies were the first to be conducted due to the facility in data collection and the smaller timeframe to generate associative hypotheses. They were carried out in a country of higher hospitalization density, i.e., with easy access to clinical data in medical records. On March 31, under the Fast-Track system (published 23 days after submission of the original manuscript), Meng et al.[28] published an observational, retrospective study, including 417 patients, 51 of whom were hypertensive. The study was motivated by previous results of ecological studies suggesting hypertension as a risk factor for death. It investigated the role of RASIs, given the high prevalence of use of those medications, and their acknowledged role in other viral respiratory infections by SRV and other Coronavirus species. Nine patients not on antihypertensive medication were excluded from the study. Out of the 42 remaining patients, 17 were on RASIs and 25 were on a different medical therapy for hypertension. Considering the group of patients who were not on ARBs or ACEIs, 12 were sub-classified as patients in a severe condition (48%) and one died. Among the patients on ACEIs or ARBs, as few as four (23.5%) were considered to be in a severe condition and no deaths were reported. Patients on ACEIs and ARBs had a smaller inflammatory response, better cellular immune response, and lower viral load. Therefore, the major outcomes were control of hypertension, regulation of the immune function, and inhibition of inflammatory responses. The authors considered that to be the first clinical study on the influence of RASIs in patients with COVID-19, presenting data in favor of the use of those medications; however, limited by its design and sample size.

A further retrospective study of Chinese researchers, published in April in the magazine Circulation Research[29], enrolled 1,128 adult patients with hypertension hospitalized in Hubei, China, with COVID-19 diagnosis, 188 of whom were on ACEIs or ARBs, and 940 in different drug therapies. The mortality rate was reduced in patients on ACEI or ARB (adjusted hazard ratio, 0.37; CI 95%; CI 0.15-0.89; p = 0.03). The findings were considered non-conclusive.

In June 2020, Gao et al.[24] published a retrospective observational study in the European Heart Journal, investigating the influence of hypertension treatment on the mortality risk in COVID-19 patients. The letter of the publisher, Thomas Luscher, a Cardiology professor, opened the journal with the provoking heading "The Saga continues: is COVID-19 a cardiopulmonary disease?"[30] and followed by the editorial of Ruilope et al.[31] on the subject, showing that not only the use of antihypertensive drugs acting on RAS was in debate, but the etiology and pathogeny of the disease itself as well.

Gao et al.[24] study enrolled 1,786 patients admitted to a COVID-dedicated hospital in Wuhan. Out of the total number of patients, 29.5% were hypertensive and the mortality risk in those patients was twice as high as compared to those with normal blood pressure. The study also evaluated the relationship between the different types of drug therapy for ASH and the clinical progress of COVID-19. The authors concluded that no harm was connected with the use of ARBs and ACEIs and warned that the results were still "preliminary" and would have "to be evaluated with caution"[24] (p.2064), warning about the uncertainty that still involved the subject. The paper was a Fast-Track publication, submitted on April 3, accepted on May 6, and published on June 4.

In the study justification[24], the authors pointed to the studies in human and animal models that found increased serum levels of ACE2 following the use of ACEIs and ARBs, and suggested there were studies in both directions, i.e., of increased and reduced risk. As no statistical significance was reached to support the protective role of ACEIs and ARBs, the authors associated their data with three studies with the same design carried out in China, two of a small sample size and the study of Zhang et al.[29], enrolling 1,128 patients, and developed a meta-analysis. The meta-analysis involved 1,006 hypertensive patients on ACEI/ARBs and 3,478 controls, finding a statistically significant death risk reduction in the group on the medications (RR, 0.65; CI 95 p = 0.02)[24].

The authors' hypothesis for the mechanism underlying risk reduction was based on animal models and on the hypothesis of biphasic action: in the acute phase, deregulation of ACE2 activity in the lungs and facilitation of neutrophilic infiltration, increase in AngII and activation of local RAS; followed by higher ACE2 levels and activation of the RAS protective axis[24]. They emphasized the observational studies limitations in providing sound inferences and the importance of waiting for randomized clinical trials.

In the editorial of the European Heart Journal in June 2020, Ruilope et al. of the University of Madrid[31] emphasized the importance of RAS blockers in hypertensive patients but also in those with diabetes and chronic kidney disease (risk conditions prevalent in in-patients with COVID-19) to maintain blood pressure levels and protect target-organs. They refer to studies with the same analysis and to guidelines drawn by the scientific societies in Cardiology and Hypertension, rapidly made available to the scientific community and society, arguing against the potential risk suggested by Fang et al.[14] and suggesting maintenance of the medications[31]. The authors[31] also emphasized the need to design studies to investigate the potential beneficial effect of RASIs as potential drugs for the specific treatment of COVID-19. A further advantage of using RASIs in the treatment of severe patients with COVID-19 would be their anti-thrombotic properties. Thus, ACEIs and ARBs would improve the prognostic of patients with COVID-19 based on different mechanisms, even in the absence of arterial hypertension[31]. Such therapeutic potential of RASIs with the use of recombinant ECA2 suggested in the Ramirez-Sagredo review[22], has been studied in the biomedical engineering field, with successful *in vitro* neutralization of the SARS-CoV-2[32,33].

Progress was made regarding the harmful or protective effects of the medications. Besides the retrospective observational studies, four cohort studies were conducted, two in Italy[34,35], one in China[36], and one in England [37]. The paper by Felice et al.[34], published on June 8, 2020 (submitted on May 7) in the American Journal of Hypertension, followed 133 hypertensive patients diagnosed with COVID-19 admitted to the emergency department, found a statistically significant difference in patients on RASIs as compared to other anti-hypertensive treatments, with lower admission rates to semi-intensive/ intensive care units. The mortality risk was also lower, albeit not reaching statistical significance[34].

The Cannata et al.[35] study was submitted on May 13, 2020, accepted on May 15 and published on June 15, in the European Heart Journal, as a correspondence. Among the 397 evaluated patients, 44 were on ACEI/ARBs at hospital admission; two-thirds had discontinued the use and those that maintained the medication presented a lower mortality risk for COVID-19. The authors recommended that the treatment should be maintained. The Chinese study[36] was published in the Annals of Translational Medicine Journal, submitted on March 27, and accepted for publication three days later. It enrolled 50 patients with confirmed COVID-19 diagnosis, grouped into patients on ACEI/ARBs (n=20) and in no use of medication for ASH (n=30). All patients kept the medications and there was no significant difference between the groups. The English study[37] was submitted in May 2020 and accepted for publication in July 2020, as a preprint in the Heart Journal and as a journal paper in September of the same year. The authors analyzed a total of 19,486 patients with COVID-19 and found a lower risk for severe disease, highlighting ethnicity as a significant variable to evaluate the outcome, suggesting further analysis of the influence of this variable on the effect of ACEI/ ARBs in the susceptibility to the disease.

A single clinical trial addressed the topic and was published in July 2020 in the Journal of the American College of Cardiology as an open paper by Spanish researchers[38]. The study was an arm of a randomized clinical trial underway (RAS blockade benefits in clinical evolution and ventricular

remodeling after transcatheter implantation of an aortic valve) to evaluate the use of Ramipril in the COVID-19 risk in this group of high-risk patients. One hundred and two patients were enrolled in the study (50 in the Ramipril arm and 52 in the control group). Mean age was high, the subjects were predominantly male and eleven patients (10.8%) developed COVID-19 (six in the control group and five in the Ramipril arm). No difference in oxygen demand or death risk was observed between the groups in this small sample. The authors recommended that the medication should be maintained.

Finally, on March 31, 2021, one year after the issue had been raised, a systematic review and meta-analysis paper on the association between the use of RASIs and clinical outcomes in hypertensive patients with COVID-19 was published in the Jama Open Net, putting an end to the controversy, generating definitive evidence favorable to the use of RAS medications in hypertensive patients with COVID-19[39]. Inclusion criteria were: COVID-19 diagnosis by laboratory or radiological tests and clinical outcome evaluated in adults on ACEIs or ARBs. The meta-analysis included 52 studies, 40 of which were cohort studies, six series of cases, four case-control studies, a randomized clinical trial, and a transversal study. Of the 101,949 patients, 26% were on ACE inhibitors or ARBs. The data showed a significant reduction in both mortality risk (adjusted OR 0.57; CI 95%, 0.43-0.76, p <0.001) and progress to severe condition (adjusted OR 0.68; CI 95%, 0.53-0.66, p <0.001). The benefit of the use of these medications was also proven in a comparison between hypertensive patients on ACEIs/ARBs versus other medications, concerning both mortality (adjusted OR 0.51; CI 95%, 0.32-0.84, p =0.008) and occurrence of a severe adverse event (adjusted OR 0.55; CI 95%, 0.36-0.85, p = 0.007).

One year after the controversial declaration and the publication of almost 1,800 registers in the PubMed and Embase databases[39], the role of ACEIs and ARBs in hypertensive patients with COVID-19 was established. The evidence was produced mainly from retrospective and observational studies conducted in China, Europe (especially Italy and England) and, to a lesser extent, in North America. It should be noted that knowledge production followed the geographic track of the pandemics concentrated in the regions of higher economic and social development.

The last guideline by the Brazilian regulatory bodies dealing with the use of ACEIs/ARBs in the treatment of hypertensive patients with COVID-19 dates back to May 2020[41]. Published by SCTIE, it was collaboratively designed, grounded on the principles of evidence-based medicine. The document analyzes the available evidence as insufficient and conflicting, and presents the position of the American, European, and Brazilian societies of Cardiology (the latter endorsed by the Brazilian Department of Health) in favor of the maintenance of the treatment, considering that withdrawal of the medication would be precipitated, given the poor evidence available by then, a recommendation that should be strengthened by more robust studies. The guidelines recommend the maintenance of the treatment in hypertensive patients as well as in cardiovascular or diabetic patients already on such medications.

Concluding: reflections on the trajectory

COVID-19 is a systemic disease. The cardiovascular system plays an important role in the etiology and pathophysiology of the disease, and it is implicated, via RAS, in the clinical progression of the condition. Initially implied as a risk factor for severe disease and death, given the proven COVID-19 aggravation in hypertensive patients, when the role of ECA-2 was found to be the entry path for cell invasion by the virus, the cardiovascular system became acknowledged as a mediator of the infection and, therefore, a potential target for treatment.

The high prevalence of ASH and the consequent use of RASIs raised hypotheses that such medicines could probably play a role in the aggravation of the COVID-19 infection. What was supposed to be nothing but an expert opinion, a hypothesis not confirmed by scientific studies, and, therefore, the poorest evidence in the Evidence-Based Medicine classic pyramid was quickly spread in the media, in the speed that characterizes the technical-scientific-informational milieu, boosted by the pandemics. What was supposed to be a hypothesis to be investigated cast medical and lay doubts on the use of such medications and generated orientations for withdrawal, despite the recognized protective role of ACEIs and ABRs in target-organ injuries, especially in patients with

diabetes and kidney failure, comorbidities known to aggravate the COVID-19 clinical progress.

Rapidly, the scientific community was mobilized. Previous experimental studies on physiology and animal models conducted to investigate the role of RAS in other viral infections, including those causing SARS, were reassessed and combined in integrative analyses, reiterating RAS complexity, the dynamic balance of its components and the importance of its alternative axes, particularly those mediated by ACE2. RAS function, not only for hemodynamic balance but, equally, for immune modulation, activated by contact with the S-protein of the SARS-CoV-2, demonstrated the complex interaction between the virus and the body as well as the balance among the different human systems: respiratory, circulatory, immunological and, renal.

The high ECA2 concentration in the lung, heart and kidneys, and AngII catalysis into Ang1-7, considering that the former is vasoconstrictive, pro-fibrotic, pro-inflammatory, and the latter is vasodilator and protective[13] was used by the hypertension experts' societies and by the regulatory bodies as an argument for the treatment to be maintained for hypertensive patients with COVID-19[16]. Regulatory agencies and normative bodies corroborated such guidelines[41] while expecting more robust evidence from studies in progress that were rapidly evaluated and published in open platforms.

Simultaneously, studies in animal models evaluated RAS response to cell invasion by the SARS-CoV-2, observing an initial drop in ACE2 concentration, with a resulting unbalance between ACE and ACE2 and a rise in AngII concentration, followed by a down-regulation of RAS and an increased ECA2 production[22].

The physiological studies pointed to the protective role of ACEIs and ARBs in hypertensive patients with COVID-19, given the increased ACE2 concentration caused by such drugs[28]. Clinical, observational, retrospective, and cohort studies and one small randomized clinical trial, an arm of a larger study, followed. The studies initially enrolled a small number of participants, and maintenance of RAS-modulating drugs seemed to have a protective effect; however, the studies failed to reach statistical significance. About one year after the hypothesis was cast, finally, a meta-analysis[39] demonstrated the protective effect of RASIs concerning both the severe progression of the disease and mortality risk in COVID-19 hypertensive patients.

We thus conclude that, despite the circulation velocity of the information disclosed in scientific journals as hypotheses that acquired a recommendation character among the scientific community and the lay media, knowledge of the influence of RAS and the inhibitors of such systems (ACEIs and ARBs) evolved complying with the rules of the Evidence-Based Medicine. Hypotheses disclosed with no support from epidemiological studies triggered expert opinions grounded on previous studies; reviewed literature, case series, observational studies, clinical trials, and, finally, meta-analysis. In the end, the ACEIs and ARBs effect proved to be beneficial in COVID-19 hypertensive patients, given its effect on increased ECA2 and resulting protective immune modulation. Thus, in severe cases of the disease, ECA2 concentration is low since it is the target for SARS-CoV-2 to enter the cells, and ACEIs and ARBs medications activate the ECA2 axis of RAS, rebalancing its body concentration and promoting the protective effect of its by-products, Ang1-7 and Ang1-9. There are currently clinical trials underway to evaluate the therapeutic use of recombinant ECA2 to prevent severe COVID-19 manifestations.

Fast-track publications allowed for the construction and integration of knowledge of the basic fields (immunology and physiology) of pharmaceutical science, medicine, and epidemiology. Papers were published in scientific journals of basic and clinical fields of knowledge. Such evidence was analyzed with scrutiny, precaution, and discernment by experts' associations and regulatory bodies, resulting in guidelines that informed and oriented clinical management, protecting the patients from adverse events, whether caused by the disease or aggravated by the treatment (or, in this case, due to treatment withdrawal). Social media followed the debate, while experts' recommendations were also made available to the public. The want of Clinical Guidelines updates for COVID-19 management, issued by the SCTIE, as well as a new positioning from experts' societies presenting robust evidence and recommending the maintenance of RASIs treatment in COVID-19 hypertensive and diabetic patients, drew our attention.

The relevance of proper scientific communication in pandemic times of high demand marked scientific production, and fast circulation of information and knowledge is evident. This includes a clear presentation of the limitations of the research by the authors; disclosure of the relevance of evidence, retraction, whenever necessary, update of articles in open access databases and, finally, the role of experts' societies and regulatory bodies in critical and evidence-based analysis, as well as its translation into clinical guidelines and communication for the lay press. In Brazil, the institutional framework structured for the evaluation of new technologies in public healthcare since the implantation of the SUS must be complied with and strengthened, for it has played an important role in conveying trustworthy information and, therefore, promoting the safety of both patients and professionals.

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Vianna, P.V.C - substantial contribution to the study outline; coordination and writing the preliminary version; revision and approval of the final version; responsible for the exactness and integrity of the entire study.

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