Renin-angiotensin-system inhibition in the context of corona virus disease-19: experimental evidence, observational studies, and clinical implications

Filippos Triposkiadis[1,2] · Randall C. Starling[3] · Andrew Xanthopoulos[1] · Javed Butler[4] · Harisios Boudoulas[5]

Abstract

Coronavirus disease 2019 (COVID-19) is due to severe acute respiratory syndrome coronavirus (SARS-CoV)-2 which binds and enters the host cells through the angiotensin-converting enzyme (ACE)2. While the potential for benefit with the use of renin-angiotensin-aldosterone system inhibitors (RAASi) and the risks from stopping them is more evident, potential harm by RAASi may also be caused by the increase in the activity of the ACE2 receptor, the inefficient counter regulatory axis in the lungs in which the proinflammatory prolyloligopeptidase (POP) is the main enzyme responsible for the conversion of deleterious angiotensin (ANG) II to protective ANG [1–7] and the proinflammatory properties of ACE2(+) cells infected with SARS-CoV-2. Acknowledging the proven RAASi benefit in patients with several diseases such as hypertension, heart failure, coronary disease, and diabetic kidney disease in the non-COVID-19 era, it is a reasonable strategy in this period of uncertainty to use these agents judiciously with careful consideration and to avoid the use of RAASi in select patients whenever possible, until definitive evidence becomes available.

Keywords COVID-19 · Angiotensin · Proinflammatory prolyloligopeptidase · Hypertension · Heart failure

"Prudence is the footprint of Wisdom."
— Amos Bronson Alcott

Coronavirus disease 2019 (COVID-19) is due to severe acute respiratory syndrome coronavirus (SARS-CoV)-2 which binds and enters the host cells through the angiotensin-converting enzyme (ACE)2. Therapy with renin-angiotensin-aldosterone system (RAAS) inhibitors (ACE inhibitors [ACEi], angiotensin [ANG] II receptor blockers [ARB], and mineralocorticoid receptor antagonists [MRA]) may increase ACE2 [1]. The concern, therefore, has been raised that a potential increase in ACE2 by these agents may facilitate development and increase severity of COVID-19. In this brief review, we contend that a potential harmful effect of RAAS inhibitors cannot be excluded in the COVID-19 era and thus, caution required when prescribing these agents.

Lung renin angiotensin system

The traditional view is that some of renin-angiotensin system intermediate products may be processed in alternative ways by ACE2, establishing a second axis through ACE2/ANG [1–7]/Mas receptor which counteracts the effects of the classical axis [2]. However, recent evidence suggests that prolyloligopeptidase (POP) is the main enzyme responsible for the conversion of deleterious ANG II to protective ANG [1–7] in the circulation and lungs, whereas ACE2 contributes to ANG [1–7] formation in the kidney [3]. In addition, POP is an important player in neutrophilic inflammation [4]. Regarding Mas, further studies need to clarify its relationship with ANG [1–7], which may depend on the specific cell types

✉ Filippos Triposkiadis
ftriposkiadis@gmail.com

1 Department of Cardiology, Larissa University General Hospital, PO Box 1425, 411 10 Larissa, Greece

2 University of Thessaly, Volos, Greece

3 Kaufman Center for Heart Failure and Recovery, Heart, Vascular, and Thoracic Institute, Cleveland Clinic, Cleveland, OH, USA

4 Department of Medicine, University of Mississippi, Jackson, MS, USA

5 Department of Medicine/Cardiovascular Medicine, The Ohio State University, Columbus, OH, USA

and their expression of other G protein-coupled receptors [5]. Thus, it is questionable whether an efficient ACE2/ANG [1–7]/Mas axis is operative in the lungs.

ACE2 and coronavirus entry

The major entry of SARS-CoV-2 is via the respiratory system where it readily affects differentiated cells that express more ACE2 [6]. The type II transmembrane serine proteases TMPRSS2 and ADAM17 (a disintegrin and metalloproteinase) promote SARS-CoV entry by ACE2 cleavage, promotes viral uptake, and SARS-S cleavage, resulting in activation of the viral S protein, which in turn fuses with cell membrane [7]. The attachment of the viruses to cell surface ACE2 protects them from immune surveillance mechanisms and provides the virus access to the host cell system, an environment not just to sustain and proliferate, but also to mutate and modify host evasion mechanisms. The precise relationship, however, between ACE2 levels and activity, viral infectivity, and severity of infection, is incompletely understood.

ACE2 and lung inflammatory injury

Prior to COVID-19 pandemic, it was suggested that ACE2 dysregulation is implicated in acute inflammatory lung injury (ILI) by inducing an imbalance in the RAS. It was proposed that in acute ILI: (i) a decrease in pulmonary ACE2 and an increase in ANG II levels occur; (ii) supplementation with ACE2 or inhibition of ANG II improves outcomes; and (iii) a lack or decrease of pulmonary ACE2 aggravates viral-induced ILI [8]. However, these findings are not applicable to COVID-19 because in pre COVID-19 studies, ACE2 was not involved in the pathogenesis of ILI [9–12]. Thus, the protective effect of ACE2 observed in non-SARS-CoV models of ILI could be deleterious in ILI related to COVID-19 where ACE2 serves as the receptor for viral entry [13]. The expression of ACE2, SARS-CoV spike (S) protein, and some proinflammatory cytokines (PICs) in autopsy tissues from patients who died of SARS was studied with immunohistochemistry (IHC) and in situ hybridization (ISH) assays [13]. SARS-CoV S protein and its RNA were only detected in ACE2(+) cells in the lungs and other organs, indicating that ACE2-expressing cells are the primary targets for SARS-CoV infection in vivo in humans. High levels of PICs were expressed in the SARS-CoV-infected ACE2(+) cells, but not in the uninfected cells suggesting that cells infected by SARS-CoV produce elevated levels of PICs which may cause immuno-mediated damage to the lungs resulting in ILI [13]. Similar were the findings in a recent study [14] which used gene set enrichment analysis (GSEA) and showed that the high expression of ACE2 is related to innate immune responses, adaptive immune responses, B cell regulation, and cytokine secretion, as well as an enhanced cytokine-induced inflammatory response. Based on these findings, it has been postulated that the immune system dysfunction involved in the high expression of ACE2 may be related to the development of the hyperinflammatory response in COVID-19 [14]. Consistent with these lung inflammatory changes, a persistent increase in inflammatory markers, such as c-reactive protein, d-dimer, ferritin, interleukin-6, is associated with major complications and increased mortality in COVID-19 [15]. Moreover, obesity, which is associated with chronic inflammation and high expression of ACE2, significantly increases the risk for severe COVID-19 even in younger age groups [16].

Effect of RAAS inhibitors on ACE

RAAS inhibitors (RAASi) with the possible exception of aliskiren (a direct inhibitor of renin), which is infrequently used, tend to increase tissue ACE2 activity [17–19]. However, professional scientific societies recommend the unrestricted prescription of RAASi during the COVID-19 pandemic. In a recent statement of the European Medicinal Agencies (EMA), it is emphasized (10 June 2020 EMA/284513/2020): "Recent observational studies of angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs, also called sartans) have not shown an effect of these medicines on the risk of becoming infected with severe acute respiratory syndrome coronavirus 2 (the virus causing COVID-19) and do not indicate a negative impact on the outcome for patients with COVID-19 disease. EMA therefore reiterates its previous advice that patients should continue to use ACE inhibitors or ARBs as advised by their doctors".

Table 1 provides a summary of all the references on which the EMA statement is based. It is obvious that (1) all studies, both positive and negative, are retrospective and observational (OSs); (2) some studies have a low sample size and other are preprints; (3) importantly, not all studies support the safety of RAASi; and (4) some studies supporting the safety of RAASi emphasize that caution is required in the interpretation of the findings. Thus, the recommendations of the EMA like those of the other scientific societies are based mostly on speculation and not on solid evidence.

Research in the COVID-19 era: the lack of randomized studies

In cases of epidemics when answers are urgently required, the quality of research is usually diminished when many teams of investigators are involved in the same field [20]. In this setting, even senior investigators may not follow the established rules and deviation of the rules may lead in unintentional errors and occasionally in catastrophic results. Further,

Table 1 References cited in the European Medicinal Agencies statement (June 10, 2020)

Study	Aims	Population	Conclusion	Comments
1. Bean D, et al. doi: 10.13140/RG.2.2.34883.14889/1.	Exploration of whether ACEi increase the risk of severe COVID-19 infection.	Inpatients with COVID-19 ($n = 205$).	No evidence for ACEi increasing severity of COVID-19. Possible trend towards beneficial effect need to be explored.	Preprint Small sample size
2. de Abajo F, et al. doi: 10.1016/S0140-6736(20)31030-8.	Epidemiological exploration of possibility that RAASi predispose to severe COVID-19.	1139 hospitalized cases with COVID-19 and 11,390 controls.	RAASi do not increase risk of COVID-19 requiring hospital admission. This finding should be confirmed.	No information on in-hospital RAASi treatment.
3. Felice C, et al. doi: 10.1093/ajh/hpaa096.	Association between chronic use of ACEi or ARB and COVID-19 outcomes in hypertensives.	133 COVID-19 hypertensives admitted with acute respiratory symptoms and/or fever.	RAASi do not negatively affect clinical course of COVID-19 in hypertensives. Finding should be confirmed.	Small sample size
4. Gao C, et al. doi: 10.1093/eurheartj/ehaa433.	Association between treatment of hypertension and mortality of patients with COVID-19.	2877 hospitalized COVID-19 patients.	No harm of RAASi in patients infected with COVID-19. Results should be considered as exploratory and interpreted cautiously.	Remaining questions: (i) which medication should be given to untreated hypertensives (CCBs or RAASi); (ii) could such medications mitigate the risk; and (iii) will RAASi affect risk of infection when equally exposed to the virus?
5. Gnavi R, et al. doi: 10.1093/cid/ciaa634.	Association between RAASi and COVID-19 in hypertensives (HY) and patients with circulatory diseases/diabetes (CDD).	316 HY and 171 CDD cases of COVID-19 infection matched with 1580 and 855 controls.	No reason to modify antihypertensive therapy. Study limited to explore whether RAAS therapy increases the risk of SARS-CoV-2 infection	Small sample size
6. Guo T, et al. doi: 10.1001/jamacardio.2020.1017.	Association of underlying CVD and myocardial injury with fatal outcomes in COVID-19.	187 patients with COVID-19.	Myocardial injury associated with fatal outcome of COVID-19. Prognosis of patients with CVD but without myocardial injury relatively favorable.	Small sample size Significantly increased TnT levels in patients with ACEi/ARB use history.
7. Jung S-Y, et al. doi: 10.1093/cid/ciaa624/5842160.	Associations between prior use of RAASi and clinical outcomes among Korean patients with COVID-19.	5179 COVID-19 cases.	Prior use of RAASi not independently associated with mortality in COVID-19. Controversy regarding the role of RAAS blockade in COVID-19 calls for urgent multicenter trials.	Unadjusted in-hospital mortality for 33 RAASi users 9% and 51 nonusers 3% ($p < 0.001$).
8. Li J, Wang X, et al. doi: 10.1001/jamacardio.2020.1624.	Investigation of whether hypertensives taking ACEi/ARB have increased severity of illness or risk of mortality during hospitalization for COVID-19.	1178 hospitalized patients with COVID-19.	ACEi/ARB not associated with the severity or mortality of COVID-19 in hospitalized hypertensive patients.	Small number of patients taking ACEIs/ARBs. Uncertain whether the ACEi/ARB treatment was maintained throughout hospitalization.
9. Mancia G, et al. Renin–Angiotensin: 10.1056/NEJMoa2006923.	Association between the use of ARBs/ACEi and risk of COVID-19.	6272 patients COVID-19 patients matched to 30,759 controls.	More frequent use of ACEi/ARB in patients with COVID-19 than controls attributed to higher prevalence of cardiovascular disease. ACEi/ARB did not affect the risk of COVID-19.	Information on drug use limited to prescriptions, and actual drug consumption by the case patients and controls was not assessed.
10. Mehra MR, et al. doi: 10.1056/NEJMoa2007621.	-	-	-	Retracted doi: 10.1056/NEJMc2021225.

Table 1 (continued)

Study	Aims	Population	Conclusion	Comments
11. Mehta N, et al. doi: 10.1001/jamacardio.2020.1855.	Role of ACEi and ARB in the setting of COVID- 19.	18,472 patients tested for COVID-19.	No association between ACEi or ARB use and COVID-19 test positivity. Further study in larger numbers of hospitalized patients receiving ACEi-ARB therapy is needed.	Among patients with positive test and overlap propensity score weighing, 54% taking ACEi (vs 39% not taking ACEi) were admitted to hospital; 24% taking ACEi (vs 15% not taking ACEIs) were admitted to ICU; and 14% taking ACEi (vs 11% not taking ACEi) required mechanical ventilation. Similarly, 53% taking ARB (vs 41% not taking ARB) were admitted to hospital; 20% taking ARB (vs 18% not taking ARB) were admitted to ICU; and 14% taking ARB (vs 12% not taking ARB) required mechanical ventilation.
12. Meng, J, et al. doi: 10.1080/22221751.2020.1746200.	Association between ACEi/ARB and clinical outcomes in COVID-19 patients with hypertension.	417 hospitalized patients with COVID-19.	ACEi/ARB improve clinical outcomes of COVID-19 patients with hypertension.	Small sample size
13. Rentsch CT, et al. doi: 10.1101/2020.04.09.20059964.	Association between demographic and clinical characteristics and testing positive for COVID-19, and among COVID-19+ subsequent hospitalization and intensive care.	2,026,227 Veterans aged 54–75 years and active in care, 585/3789 (15.4%) tested COVID-19+.	Racial differences in testing positive for COVID-19 underestimate of general population. Risk of hospitalization and intensive care better characterized by laboratory measures and vital signs.	Preprint History of ACEi/ARB use associated with increased risk of ICU admission.
14. Reynolds HR, et al. doi: 10.1056/NEJMoa2008975.	Association between treatment with ACEi, ARB, BBs, CCBs, or thiazides and likelihood of a) positive or negative COVID-19 testing, and b) severe illness among patients who tested positive.	12,594 patients tested for Covid-19 [(46.8%) positive; 1002 (17.0%) severe illness].	No substantial increase in likelihood of a positive COVID-19 test or risk of severe COVID-19 among patients who tested positive in association with antihypertensive medications.	Possible overestimation of the proportion of cases with severe COVID-19. The electronic health records used may not reflect actual drug exposure.
15. Richardson S, et al. doi: 10.1001/jama.2020.6775.	Clinical characteristics and outcomes of hospitalized patients with COVID-19.	Case series of patients ($n = 5700$) with COVID-19 admitted to hospital.	This study provides characteristics and early outcomes of sequentially hospitalized patients with confirmed COVID-19.	Unadjusted mortality rates for hypertensives not taking an ACEi/ARB, taking an ACEi, and taking an ARB were 26.7%, 32.7%, and 30.6%, respectively.
16. Rossi PG, et al. doi: 10.1101/2020.04.13.20063545.	Age- and sex-specific prevalence of COVID-19 and its prognostic factors.	2653 symptomatic patients who tested positive for SARS-CoV.	Deeper understanding of causal chain from infection, disease onset, and immune response to outcomes.	Preprint Association between ACEi and hospitalization, likely due to residual confounding.
17. Tedeschi S, et al. doi: 10.1093/cid/ciaa492.	Investigation of whether treatment with RASi, has an impact on in-hospital mortality in hypertensives hospitalized for COVID-19.	311 hypertensives hospitalized for COVID-19.	Use of RASi not associated with outcome.	Letter to the editor Small sample size
18. Yang G, et al. doi: 10.1101/2020.03.31.20038935.	Correlation of ARB/ACEi usage with the pathogenesis of COVID-19.	126 hypertensive COVID-19 patients.	Findings support use of ARB/ACEi in hypertensive COVID-19 patients.	Preprint Small sample size

Table 1 (continued)

Study	Aims	Population	Conclusion	Comments
19. Zeng Z, et al. doi: 10.1101/2020.04.06.20054825	Investigation of whether hypertensives are more likely to be infected with SARS-COV-2 than the general population and whether there is a difference in severity of COVID-19 pneumonia in patients who have taken ACEi/ARB.	274 hospitalized hypertensives with clinically confirmed COVID-19.	Hypertensives with COVID-19 who had taken ACEi/ARB drugs at increased risk to develop severe pneumonia.	Preprint Small sample size
20. Zhang P, et al. doi: 10.1161/CIRCRESAH-A.120.317134.	Association between in-hospital use of ACEi/ARB and all-cause mortality in hypertensive COVID-19 patients.	1128 hospitalized hypertensives with COVID-19.	Unlikely that in-hospital use of ACEi/ARB was associated with an increased mortality risk. Potential for residual confounders not considered.	Traditional Chinese medicine given in 91% of ACEi/ARB group and 86% of non-ACEi/ARB group.

ACEi angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *BBs* beta-blockers, *RAASi* renin angiotensin aldosterone system inhibitors, *RASi* renin angiotensin system inhibitors, *CCBs* calcium channel blockers, *CVD* cardiovascular disease, *TnT* troponin T

members of scientific societies are under pressure and feel that they have an obligation to provide answers, even when such answers are not available.

Answering the question whether RAASi are safe in the COVID-19 context is crucial. The current prevailing view is that medical practices should be based on well-designed randomized controlled trials (RCTs). This is the best way to show a benefit or at least no harm in hard outcomes (mortality or morbidity), and current standards of care should be systematically subjected to such testing [21]. However, some questions about therapy cannot wait for RCTs to be conducted (e.g., RAASi safety in the COVID-19 context) and scientific societies feel that they have an obligation to make recommendations based on observational studies (OSs).

OSs, however, do not provide the final answer. Based on OSs, one cannot be certain that the recommendations are accurate and to assess if one drug is better or safer than another. Importantly, harm related to therapy cannot be excluded even after application of multiple adjustment techniques [22]. The conclusions of these studies, therefore, should not be taken as a surrogate for appropriate randomized data to guide the management with RAASi in the COVID-19 context [22].

Clinical implications

"ΩΦΕΛΕΕΙΝ Η ΜΗ ΒΛΑΠΤΕΙΝ" (if you cannot help at least do not harm)-Hippocrates

When it comes to one's medical worldview, there is no neutral position. Every clinician makes the choice daily. For most of us, our decisions are capricious, uneven, and arbitrary based upon our personal experiences and beliefs [21]. For interventions we spurn, we proudly assert that "there is no evidence." For others that we favor, we stress that "there are no negative studies" and rely on "anecdotal experience" and/ or results from registries and not randomized trials. For other interventions with promising rationale and negative empirical trials, we argue that null data are flawed [23].

Over the past four decades, results from well-done RCTs have repeatedly contradicted practices supported by clinical observation [24]. A typical paradigm was hormone replacement therapy in post-menopausal women. In the Women's Health Initiative (WHI, $n = 151,870$), the results of OSs and RCTs differed for the association of hormone therapy with outcome after adjusting for confounding factors and stratifying on factors that were hypothesized to modulate the effects of hormone therapy or that empirically modulated the effects of hormone therapy [25]. Likewise, beta-blockade therapy in patients with heart failure (HF) and preserved ejection fraction (HFpEF) reduced mortality in 15 OSs ($n = 26,211$), whereas it did not decrease mortality in two RCTs ($n = 888$) [26]. As a result, in the guidelines, beta-blockers are not recommended for the treatment of HFpEF. These are just few examples that OSs studies proved wrong. Thus, OSs cannot replace RCTs, even after application of multiple adjustment techniques.

In our current practice when it comes to prescribe a RAASi in the COVID-19 context, we base our decision on the following premises: (a) COVID-19 is a pandemic responsible for millions of infections and hundreds of

thousands deaths worldwide; (b) COVID-19 is due to SARS-CoV-2 which binds and enters host cells through the ACE2 receptor; (c) the protective ACE2/ANG [1–7]/ Mas axis may not be efficiently operative in the lungs; (d) RAASi may increase the tissue expression of ACE2; (e) lethal complications of COVID-19 are more common in diseases frequently treated with RAASi such as hypertension, other cardiovascular disease, and diabetes; (f) confounding cannot be corrected even after application of multiple adjustment techniques; (g) RAASi had proved lifesaving in the pre COVID-19 era; (h) RCTs testing the efficacy and safety of RAASi in the COVID-19 era are lacking; and (i) considering that RCTs are lacking we must follow the trail to the next best external evidence and work from there [27].

Based on the above, we believe that in the current period of uncertainty, the decision to prescribe RAASi should be individualized and based on evidence originating from physiology, pathophysiologic mechanisms, observational studies OSs, and clinical judgment. In this regard, the strategy that we follow is outlined below:

(A) Patients in whom RAASi proved beneficial in the pre-COVID-19 era but are currently not indispensable (Fig. 1). Effective agents which potentially do not affect RAAS should be considered [28, 29]. Guideline-recommended alternatives depend on the underlying disease and include beta-blockers, which reduce plasma concentrations of ANG II (the ACE2 substrate) by reducing renin release from the kidneys as well as cleavage of ANG I to ANG II as well as calcium channel blockers, which are neutral concerning ANG II availability. Regarding diuretics, which are RAAS stimulators, torsemide is a highly effective diuretic agent that lowers blood pressure [30] and has favorable effects on neurohormones, electrolytes, cardiac remodeling, but has been predominantly used in patients with HF [31]. There is no doubt that switching from a RAASi to another antihypertensive therapy in stable ambulatory patients may occasionally be challenging. However, this challenge should be taken in the era of this lethal COVID-19 pandemic.

(B) Patients in whom RAASi proved beneficial in the pre-COVID-19 era but are currently indispensable (Fig. 1). RAAS inhibitors should be prescribed and in patients already treated with these agents they should not be discontinued [28, 29]. Sodium-glucose cotransporter 2 inhibitors (SGLT2i), a new drug class approved for treatment of diabetes, have been shown to significantly reduce atherosclerotic events, hospitalization for HF, cardiovascular and total mortality, and progression of chronic kidney disease (CKD) even in patients without diabetes [32]. Increasing experimental and clinical data
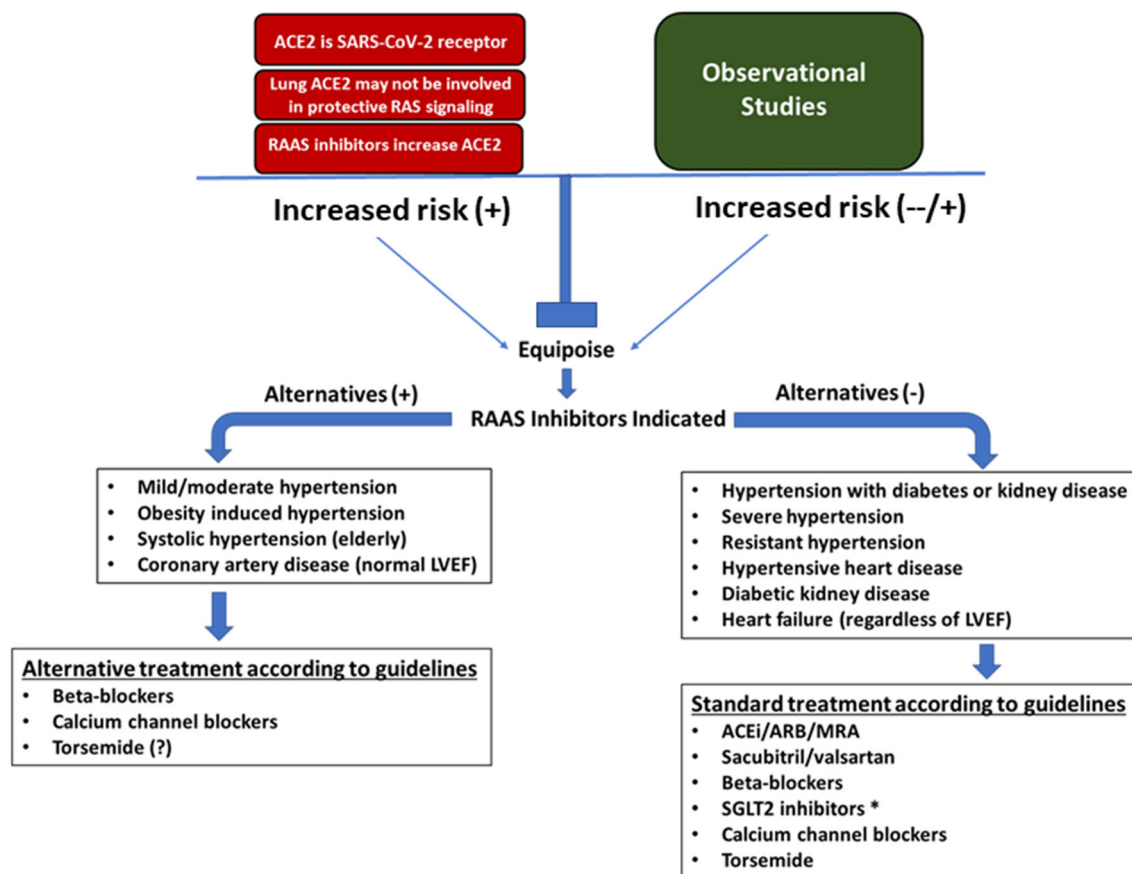
demonstrated a reduction in neurohormonal activity with these agents, including in key target organs such as the heart and the kidneys [32].

Undoubtedly, further experimental and clinical data are required to clarify the role of RAAS modulation in COVID-19. The important issue that the outcome of a viral infection may be related to therapy provided for another underlying disease should be taken into consideration not only for COVID-19 but for other future viral or non-viral infections as well. In the meantime, it is important to caution that the strategy that we follow is the result of obligatory decision making in a period that solid data are lacking and new ones emerge daily regarding mechanisms, clinical characteristics, treatment options, and outcomes for COVID-19. Steadfast use of ACEi/ARB based on current guidelines should be strongly encouraged when there are no alternatives. Deviation from these practices until solid evidence becomes available should be avoided.

Conclusion

Evidence regarding the efficacy and safety of RAASi in the COVID-19 context is based on OSs, which have provided useful information in the past but have also led to errors even after application of multiple adjustment techniques. While the potential for benefit with the use of RAASi and the risks from stopping them is more evident, potential harm by RAASi may also be caused by the increase in the activity of the ACE2 receptor which the SARS-CoV-2 binds and enters into the host, the doubtful protective effects of the ACE2/ANG [1–7]/Mas axis in the lungs, and the proinflammatory properties of ACE2(+) cells infected with SARS-CoV-2. Acknowledging the proven RAASi benefit in patients with several diseases such as hypertension, heart failure, coronary disease, and diabetic kidney disease in the non-COVID-19 era, it is a reasonable strategy in this period of uncertainty to use these agents judiciously with careful consideration to avoid the use of RAASi in select patients whenever possible, until definitive evidence becomes available. Shared decision making with patient and caregivers is important in this. Admittedly, this strategy, like all the other recommendations on this issue, is not based on solid evidence but is intended to be individualized and, in this regard, differs from the "one size fits all" approach. It is obvious that in a complex biological system where multiple factors interact, one cannot incorporate all these factors into the guidelines and/or algorithms. In this case, sound clinical judgment and common sense should be used by the clinician for the individual patient. There is no substitute for that.

Fig. 1 Rational and algorithm for the use of renin-angiotensin-aldosterone system (RAAS) inhibitors in the coronavirus disease 2019 (COVID-19) era. It should be noted that this strategy, like all the other recommendations on this issue, is not based on solid evidence due to the lack of the relevant randomized control trials. However, it is an individualized approach and, in this regard, better than the "one size fits all" approaches. (+): present; (—/+): possibly absent; (−): absent; RAS, renin-angiotensin system; LVEF: left ventricular ejection fraction; ACEi: angiotensin converting enzyme inhibitors; ARB: angiotensin receptor blockers; MRA: mineralocorticoid receptor antagonist; SGLT2, sodium glucose cotransporter 2; *, not yet in guidelines but effectiveness documented in randomized control trials

Future perspective

Until now, studies evaluating the pharmacological properties of the different drugs focused on their pharmacokinetic and pharmacodynamic effects. The possibility that a viral infection may alter drug effects and consequently the final disease outcome was not taken into consideration. This is a new area of research in which pharmacologists, virologists, epidemiologists, and clinicians should be involved.

Compliance with ethical standards

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