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Editorial article

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RENIN-ANGIOTENSIN SYSTEM INHIBITORS IN MANAGEMENT OF HYPERTENSION DURING THE COVID-19 PANDEMIC

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COVID-19, which is caused by the single-stranded RNA severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), has introduced significant therapeutic dilemmas in several areas. One of these is concern regarding the use of renin-angiotensin system (RAS) inhibitors. Dysfunction of the RAS has been observed in COVID-19 patients, but whether RAS inhibitors, such as angiotensin -converting enzyme inhibitors (ACEIs) and angiotensin II type-1 receptor blockers (ARBs), are associated with improved or worse clinical outcomes, remains unclear. RAS inhibitors are currently widely used in the treatment of hypertension. Emerging data suggest an increased association and a heightened mortality in patients of COVID-19 with co-morbidities such as hypertension, coronary heart disease, and diabetes mellitus, particularly in the elderly. Therefore, several recently published research papers have focused on the management of hypertension during the COVID-19 pandemic, as this co-morbidity was found to be the most common in patients with coronavirus infections. SARS-CoV-2 viral surface protein is known to attach angiotensin converting enzyme-2 (ACE-2) on the cell membrane to facilitate viral entry into the cytoplasm. While the SARS-CoV-2 viral load remains the highest in upper respiratory tract of COVID-19 patients, it has also been reported in multiple sites in COVID-19, and patients not infrequently require ICU admission. However, despite the theoretical concerns of possible increased ACE2 expression by RAS blockade, there is no evidence that RAS inhibitors are harmful during COVID-19 infection, and indeed they have been shown to be beneficial in some animal studies. In this review we summarise the pathophysiology of the interaction between RAS, ACEIs/ARBs inhibitors and COVID-19, and conclude, on the basis of current data, that RAS blockade should be maintained during the current coronavirus pandemic.

Key words: *Covid-19, angiotensin converting enzyme-2, angiotensin, aldosterone, hypertension, renin*

COVID-19 AND HYPERTENSION

An outbreak caused by a newly-recognised severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first reported in Wuhan, China, in December 2019. It soon spread across the globe (1, 2). The clinical spectrum of this coronavirus disease, COVID-19, ranges from asymptomatic to a severe condition in up to 17% of cases, not infrequently leading to admission to the Intensive Care Unit (ICU), with a significant mortality (2-4).

COVID-19 disease is caused by the single-stranded RNA coronavirus SARS-CoV-2. It is generally believed that the lung is the major target organ for SARS-CoV-2; however, viral RNA has been detected in numerous different clinical samples and tissues (including conjunctival swabs, blood samples, gastric juice, faeces, anal swabs and urine) in critically-ill patients (3).

Emerging data suggest an increased association and a heightened mortality in patients of COVID-19 with various co-morbidities (5). Hypertension, coronary heart disease, and diabetes mellitus, particularly in the elderly, increase susceptibility to SARS-CoV-2 infection (6, 7). Patients with previous cardiovascular and metabolic diseases may face a greater risk of developing a severe form of COVID-19 requiring ITU admission, and these co-morbidities can greatly affect the prognosis of the viral infection (5-8). Due to increasing evidence demonstrating a possible direct metabolic link to the viral disease process, early and thorough metabolic control for all patients affected by COVID-19 has been recommended (9). Simultaneously, attention has also focused on viral infection-related heart damage in the course of disease and its treatment (8).

However, the disease COVID-19 has introduced significant therapeutic dilemmas. Most importantly, the interaction of the SARS-CoV-2 with angiotensin converting enzyme-2 (ACE-2), and the interaction with the renin-angiotensin-aldosterone system, has led to particular concern regarding the use of renin-angiotensin system (RAS) inhibitors in COVID-19 patients. This has led to uncertainty amongst both healthcare professionals as well as patients. In particular, should people currently taking RAS inhibitors continue doing so, and/or should they stop if they become infected? Furthermore, the question remains as to

whether these inhibitors may in fact play a role in treating COVID-19 (10).

COVID-19 AND RAS/RAS INHIBITORS

The RAS is an important system of vasoactive peptides in human physiology. The renin-angiotensin system includes two key angiotensin converting enzymes (ACE-1 and ACE-2). These two enzymes control the balance of peptides in the angiotensin family, including angiotensin I, angiotensin II, angiotensin-(1-9), and angiotensin-(1-7) (*Fig. 1*) (10). This balance of these vasoactive peptides has profound effects on several organ systems and is altered by both ACE inhibitors (which block the action of ACE-1) and ARBs (which block the action of angiotensin II at AT1 receptors) (*Fig. 1*) (10). However, ACE inhibitors do not inhibit ACE2 because ACE and ACE-2 are quite different enzymes (6). ACE-2 is an enzyme that physiologically counters RAS activation. However, it also functions as a receptor for both SARS viruses (*Figs. 1* and *2*) (6, 11, 12). ACE-2 is found on epithelial cells in the respiratory and gastrointestinal tracts (10): in its full-length form it is a membrane-bound enzyme, whereas its shorter (soluble) form circulates in blood at very low levels (6). Furthermore, ACE-2 and the serine protease TMPRSS2 are both essential for viral infectivity. SARS-CoV-2 has a viral envelope studded with spike glycoproteins composed of two subunits (S1 and S2). Subunit S1 binds to ACE-2 on the cell surface; subunit S2 fuses with the cell membrane. TMPRSS2 then promotes cellular entry of SARS-CoV-2 (12). This in turn leads to loss of the membrane-bound ACE-2 and eventuates in loss of its regulatory control of the RAS. In effect, the classic RAS is up-regulated. Binding of SARS-CoV-2 with ACE-2 leads to their internalisation and to ACE-2 shedding. Lower availability of ACE-2 results in a lower rate of ANGII degradation and excessive stimulation of AT1R, which facilitates acute respiratory disease syndrome (ARDS) and myocardial injury. Excessive ANGII is also metabolised to ANGIV, which binds to AT4R and promotes thrombosis (*Figs. 2* and *3*) (5, 6, 13-17).

Dysfunction of the RAS has been observed in COVID-19 patients, and it has been speculated that this is one of the pathogenetic mechanisms of the disease. Anti-hypertensive drugs are one of the most commonly used pharmacologic agents in the world, especially in the elderly, and RAS inhibitors specifically (13).

HYPERTENSION AND COVID-19

Hypertension was reported as the most frequent co-existing condition in COVID-19 patients in China, with an initial estimated prevalence of 15% (1, 18). However, in the recent systematic review of the currently-available Chinese studies including in total 2,209 COVID-19 patients, hypertension was present in nearly 21% (5). In the observational study from New York University (NYU), 5,894 patients were positive for the presence of the virus (46.8% of 12,594 enrolled patients, who were identified in the NYU Langone Health electronic health records as having a COVID-19 test result recorded between March 1st and April 15th 2020): 1002 of these COVID-19 positive patients (17.0%) had severe illness. A history of hypertension was present in 4,357 of all enrolled patients (34.6%), of whom 2,573 (59.1%) had a positive test, while 634 of these patients (24.6%) had severe illness (4).

The frequency with which COVID-19 patients are hypertensive is not entirely surprising, nor does it necessarily support a causal relationship between hypertension and COVID-19 or its severity, as hypertension is particularly frequent in the

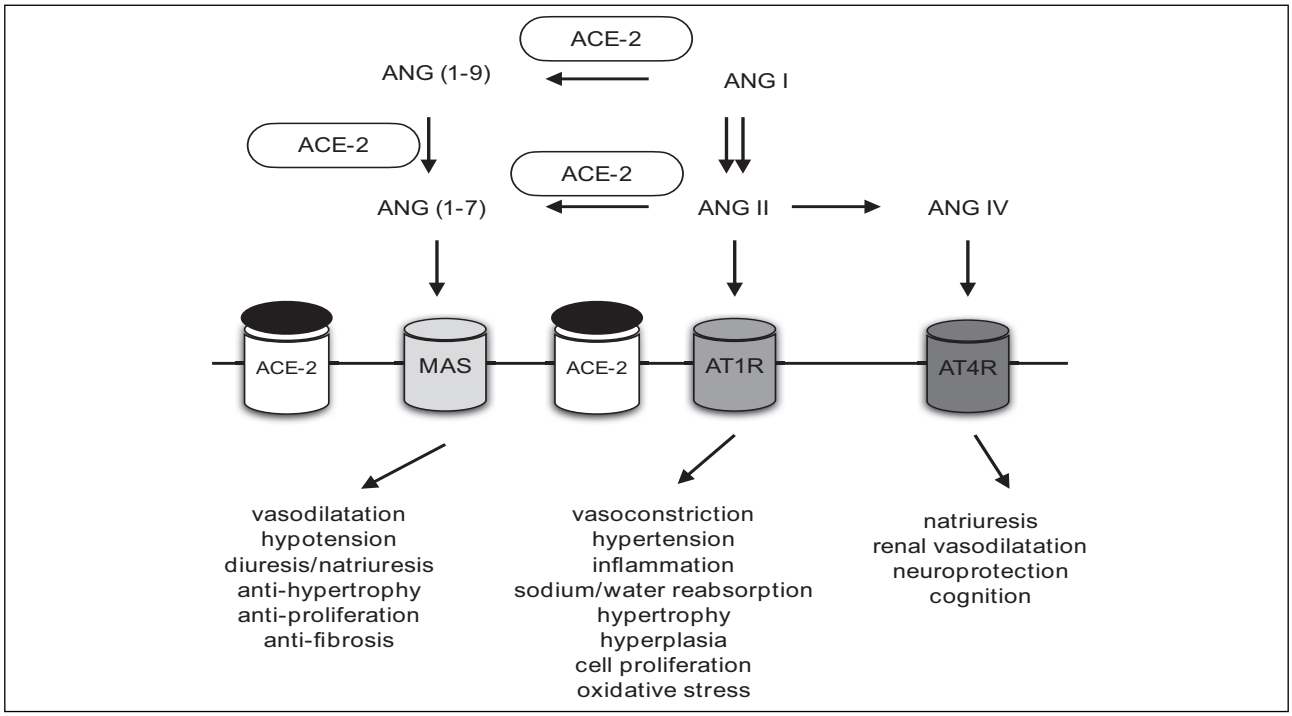

Fig. 1. ANGII binding to AT1R elevates blood pressure and promotes inflammation. ACE2 inactivates ANGII by converting it to ang-(1-7) and negatively regulates the renin-angiotensin system, promoting vasodilatation and hypotension.
Abbreviations: ACE-, angiotensin converting enzyme-2; Ang-(1-7), angiotensin-(1-7); Ang-(1-9), angiotensin-(1-9); ANG I, angiotensin I; ANG II, angiotensin II; ANG IV, angiotensin IV; AT1R, angiotensin II type 1 receptor; AT4R, angiotensin II type 4 receptor; MAS, an abbreviation of the last name (Massey) of the person who donated the human tumor from which the MAS gene was derived (5, 6, 13-17).

elderly; older people appear to be at particular risk of being infected with the SARS-CoV-2 virus, and additionally they experience severe forms and complications of COVID-19 (19). Furthermore, in other infective illnesses, hypertension (as a coexisting disease) has been a key prognostic determinant (20), and this also appears to be the case with COVID-19 (5, 21).

Lippi *et al.*, in a pooled analysis of the current scientific literature, suggested that hypertension may be associated with an up to 2.5-fold higher risk of severe and fatal COVID-19, especially among older individuals (22). It is unclear, though, whether uncontrolled blood pressure is a risk factor for acquiring COVID-19, or whether controlled blood pressure among patients with hypertension is or is not less of a risk factor. Having said that, several organisations have recently stressed the fact that blood pressure control remains an important consideration in order to reduce disease burden, even if it has no effect on initial susceptibility to the SARS-CoV-2 viral infection (23).

Several recently-published reviews have addressed the issue of hypertension in COVID-19, the number increasing daily (5, 7, 19, 24). The concerns about the use of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II type 1 receptor blockers (ARBs) in COVID-19 patients is under intensive discussion due to their use in the treatment of hypertension (14, 25, 26). Healthcare professionals and patients ask if ACEIs/ARBs should be discontinued prophylactically, or just in the context of suspected or severe COVID-19 cases (7, 14, 19, 24-26).

Polymorphisms of the ACE-2 gene have been identified; however, there is no evidence that they affect susceptibility to or severity of SARS-CoV-2 infection (27). A recent study found differential ACE-2 gene expression in human lung tissue with no racial/gender differences, but a higher gene expression in lungs of smokers compared to non-smokers, which could explain the higher risk of infection in smokers (28).

Downregulation of ACE-2 was observed in animal models of lung injury induced by SARS-CoV (29). Recombinant ACE-2 improved pulmonary blood flow and oxygenation in animals with lung injury, indicating that ACE-2 may be the main determinant of lung injury caused by SARS-CoV-2. However, there is a lack of human data except a small study in 10 patients with acute respiratory distress syndrome which showed that recombinant ACE-2 was well tolerated and led to an increase in angiotensin (1-7) (summarised by Singh *et al.* (5)).

ACE-1 inhibitors and ARBs could in theory be harmful in COVID-19 disease, since any consequential increased ACE-2 activity might potentially increase viral entry into cells (*Fig. 3*). Both ACE inhibitors and ARBs were also found to substantially increase ACE-2 activity in cardiac myocytes (30). This results in concerns as if RAS inhibitors increase ACE-2 activity (taking into account variations in ACE2 expression), this could in part be responsible for disease virulence in the ongoing COVID-19 pandemic (7, 31, 32).

However, increased ACE-2 activity could also promote conversion of angiotensin II to angiotensin-(1-7), a peptide with potentially protective anti-inflammatory properties (33). Even if that effect was probably be small, it is unclear whether increasing anti-inflammatory activity is harmful or beneficial in COVID-19 (10, 34).

There is evidence from animal studies that ARBs may upregulate membrane-bound ACE-2, whereas ACE inhibitors may not. The current data, however, are often conflicting and vary between different ARBs and different tissues (*e.g.*, heart versus kidney). Even if the reported up-regulation of tissue ACE-2 by ARBs in animal studies could be extrapolated to humans, this would not necessarily establish sufficiency to facilitate SARS-CoV-2 entry, and increased ACE-2 expression by pre-existing ARBs treatment could potentially be protective in the course of SARS-CoV-2 infection (6).

COVID-19 AND HYPERTENSION MANAGEMENT

The growing literature on the management of hypertension in COVID-19 disease consists of almost wholly observational and retrospective analyses. While understanding underlying mechanisms can influence drug treatment in many ways, most

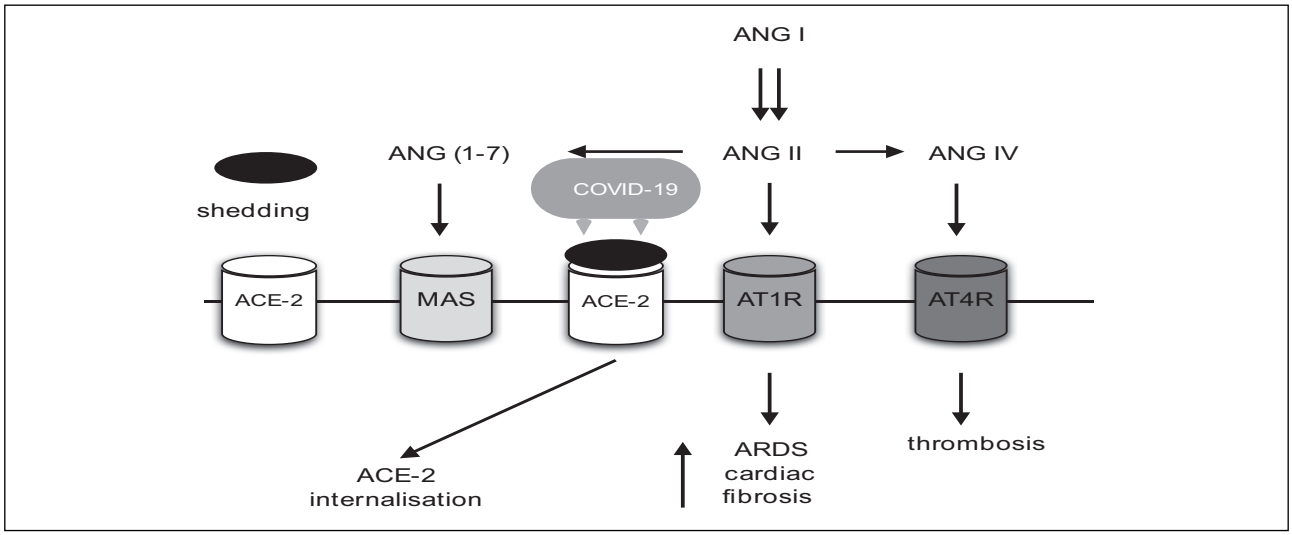

Fig. 2. COVID-19 disease. Binding of SARS-CoV-2 with ACE2 leads to their internalisation and to ACE2 shedding. Lower availability of ACE2 results in a lower rate of ANGII degradation and excessive stimulation of AT1R, which facilitates ARDS and myocardial injury. Excessive ANGII is also metabolized to ANGIV, which binds to AT4R and promotes thrombosis.
Abbreviations: ACE-2, angiotensin converting enzyme-2; Ang-(1-7), angiotensin-(1-7); ANG I, angiotensin I; ANG II, angiotensin II; ANG IV, angiotensin IV; ARDS, acute respiratory distress syndrome; AT1R, angiotensin II type 1 receptor; AT4R, angiotensin II type 4 receptor; MAS, an abbreviation of the last name (Massey) of the person who donated the human tumor from which the MAS gene was derived (5, 6, 13-17).

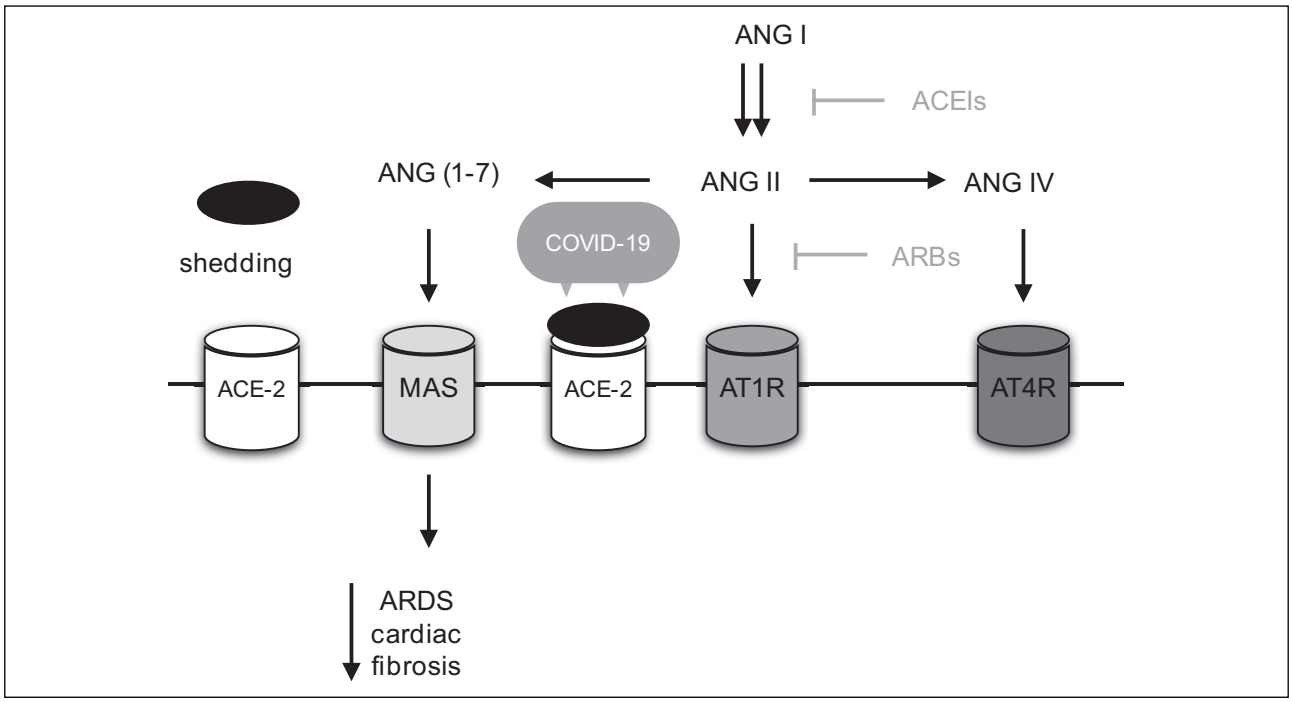

Fig. 3. SARS-CoV-2 infection and ACEIs/ARBs treatment. ACEIs and ARBs upregulate ACE2, and more ACE2 remains after viral binding. ANGII is still degraded by ACE2 in its beneficial metabolite Ang-(1-7), and AT1R and AT4R are less stimulated. ANGII binding on AT1R prevention with ARB and ANGII synthesis decrease with ACE lead to less AT1R stimulation and persistent interaction with ACE2, avoiding ACE2 internalisation.
Abbreviations: ACE-2, angiotensin converting enzyme-2; ACEIs, angiotensin converting enzyme inhibitors; Ang-(1-7), angiotensin-(1-7); ANG I, angiotensin I; ANG II, angiotensin II; ANG IV, angiotensin IV; ARBs, angiotensin receptor blockers; ARDS, acute respiratory distress syndrome; AT1R, angiotensin II type 1 receptor; AT4R, angiotensin II type 4 receptor; MAS, an abbreviation of the last name (Massey) of the person who donated the human tumor from which the MAS gene was derived (5, 6, 13-17).

specialists have agreed that it would be unwise to base any final decisions of hypertension treatment on an untested mechanistic hypothesis (6, 10).

Fang *et al.* suggested that patients with cardiac diseases, hypertension, or diabetes who are treated with putative ACE2-increasing drugs may be at higher risk for severe COVID-19 infection and, therefore, ACE-2-modulating medications such as ACE inhibitors or ARBs should probably be avoided. They suggested that as calcium channel blockers do not increase ACE-2 expression or activity, they could be a suitable alternative treatment in these patients (7).

Vaduganathan *et al.* proposed an alternative hypothesis to the above statement, suggesting that ACE-2 may be beneficial rather than harmful in patients with COVID-19-induced lung injury (14). This is due to the fact that increasing ACE-2 was found to be protective in animal models of acute lung injury, and that pre-treatment with ACE inhibitors, ARBs, or beta- blockers may reduce the extent of experimentally-induced lung injury and improve outcomes, an effect mediated by inhibition of the RAS (14, 35, 36). They therefore suggest the alternative view that these medications could theoretically be beneficial, reducing the risk of severe disease among patients with COVID-19 (14). They explicitly raised the concern that there is clear potential for harm related to the withdrawal of RAS inhibitors in patients in otherwise stable condition and that may actually be harmful in certain high-risk patients with known or suspected COVID-19. COVID-19 disease is particularly severe in patients with underlying cardiovascular diseases, and in many of these patients, active myocardial injury, myocardial stress and cardiomyopathy develop during the course of illness. RAS inhibitors have established benefits in protecting the kidney and myocardium, and their withdrawal may risk clinical decompensation in high-risk patients (14).

In an observational analysis conducted by Reynolds *et al.* (4), the authors assessed the relation between previous treatment with ACEIs, ARBs, beta-blockers, calcium-channel blockers or thiazide diuretics, and the likelihood of a positive or negative result on COVID-19 testing, as well as the likelihood of severe illness among patients who tested positive. In their analysis, severe illness was defined as an ICU admission, mechanical ventilation, or death. They compared outcomes in patients who had been treated with these medications and in untreated patients, overall and in those with hypertension, after propensity-score matching for receipt of each medication class. In that study, there was *no* association between any single medication class and an increased likelihood of a positive test. Furthermore, none of the medications examined was associated with a substantial increase in the risk of severe illness among patients who tested positive. The authors therefore concluded that they found no substantial increase in the likelihood of a positive test for COVID-19 or in the risk of severe COVID-19 among patients who tested positive in association with five common classes of anti-hypertensive medications, not only ACEIs/ARBs (4).

Singh *et al.* evaluated the outcome in hypertensive patients with COVID-19 and its relation to the use of RAS blockers. Their literature review suggested that while special attention is definitely required in patients with COVID-19 with associated co-morbidities including hypertension, diabetes and established cardiovascular disease, COVID-19 patients should not routinely stop these drugs at this point in time (following the recommendations of various world organisations) (5). Current

guidance is to continue taking RAS blockers (14, 26), noting the possible harmful effects of discontinuation (37).

Two relatively small-scale studies from China focused on the association between cardiac medications and COVID-19 (13, 38). Meng *et al.* enrolled 417 COVID-19 patients, of whom 51 suffered hypertension (12.23%). In that subgroup, 42 patients were treated with anti-hypertensive therapies (82.4.%). The authors evaluated the effect of RAS inhibitors and observed that patients receiving ACEIs or ARB therapy had in fact a lower rate of severe disease and a trend toward a lower level of IL-6 in peripheral blood. In addition, ACEI or ARB therapy increased CD3+ and CD8+ T-lymphocyte cell counts in peripheral blood and decreased the peak viral load compared to other anti-hypertensive drugs. This study supports the hypothesis that ACEIs or ARBs may potentially improve the clinical outcomes of COVID-19 patients with hypertension (13). In a multi-site database study that included 78 patients with hypertension, there was no association between previous treatment with any cardiovascular medication class and severe COVID-19. In that cohort, among the elderly (defined as aged > 65 years) COVID-19 patients with hypertension, the risk of severe COVID-19 disease was significantly decreased in patients who took ARBs prior to hospitalisation, compared to patients who took no drugs (OR = 0.343, 95% CI 0.128 – 0.916, P = 0.025). The meta-analysis showed that ARB use has positive effects associated with less morbidity and mortality of pneumonia. The authors therefore concluded that COVID-19 patients with hypertension who are aged > 65 years and are taking ARBs anti-hypertension drugs may be less likely to develop severe lung disease compared to patients who take no anti-hypertension drugs (13, 38).

Some authors have argued that the balance of potential benefits and harms from continuing ACE inhibitor or ARB therapy during an acute infection depends on the reason for prescribing. It seems that many people taking these drugs long-term for mild hypertension may, in fact, show a benefit over years, rather than weeks or months (10). During the COVID-19 epidemic, the people most likely to be infected include household contacts of infected people and healthcare workers. These individuals might choose to adopt the precautionary principle, deferring long-term cardiovascular benefit to reduce a theoretical short-term risk from continuing treatment while they are infected (10). However, they would still recommend that patients who may deteriorate rapidly if treatment with ACE inhibitors or ARBs is stopped, including those with heart failure or poorly-controlled hypertension, should continue to take them, even during active infection. Most patients, however, will be able to take their medications as usual during the pandemic, only considering withholding treatment if they get a severe infection (10).

Nevertheless, the majority of current studies tend to suggest a beneficial effect of drugs aimed at the RAS in patients with hypertension who develop COVID-19, despite the theoretical concerns of increased ACE-2 expression by RAS blockade. There is as yet no evidence that hypertension is related to outcomes of COVID-19, or that ACE inhibitors or ARBs use is harmful. Use of these agents should be maintained for the control of blood pressure, and they should not be discontinued, at least on the basis of current evidence at this time (6, 19). Nevertheless, ACE inhibitors and ARBs should not be used to treat COVID-19 without convincing evidence of clinical efficacy from randomised clinical trials or data mining studies (10, 34). While we await better clinical evidence, we support the careful yet pragmatic recommendations to help doctors advise patients with COVID-19 on appropriate treatment (7, 10, 19, 23-26, 37, 39).

In conclusion, while the evidence is generally conflicting on the use of ACE inhibitors or ARBs in treating COVID-19, on balance the evidence is that they are probably beneficial and unlikely to be harmful. For patients already taking these drugs, the European Society of Cardiology recommended treatment continuation in the light of the fact that there is no clinical or scientific evidence to suggest that treatment with ACEI or ARBs should be discontinued because of the COVID-19 infection (39). Similarly, the American College of Cardiology advises that patients should continue taking these medications for heart failure, hypertension, or ischaemic heart disease, and that if COVID-19 occurs, individualised treatment decisions should be made according to each patient's haemodynamic status and clinical presentation (7, 10, 14, 19, 23-26, 37, 39).

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