Hypertension, Covid-19 and use of ACEIs/ARBs: Current Evidence and Perspectives

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Abstract- The pneumonia like disease caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), named as coronavirus disease 2019 (Covid-19), continues to be a global public health issue even today. The disease first reported in Wuhan, China in December 2019, earned a pandemic status within couple of months as it spread to various parts of the globe, infecting a substantial world population and exhibiting high mortality rate. However, many studies indicated that despite being a global health issue the impact was not homogenous across the globe, few countries suffered more as compared to others. Further, a large number of reported deaths worldwide, were attributed to comorbid conditions. Subsequently, many research studies investigated the issue and suggested several plausible risk factors ranging from air quality, to biological attributes like age, sex and certain comorbidities, that predispose the population to SARS-CoV-2 infection or enhance the severity of Covid-19 outcomes in the patients. As the pathophysiology of the disease gradually unfolded, highlighting the damage inflicted to multiple organs, it also drew researchers' attention to hypertension, one of the frequently observed comorbidity in Covid-19 patients that developed severe form of the disease. Angiotensin-converting enzyme 2 (ACE2), a vital key for the virus entry into the cell, performs crucial role in several physiological functions, including vasodilatation via renin-angiotensin system (RAS). The apparent relationship between hypertension, severity of Covid-19, ACE2 and its antihypertensive role via RAS, led to several research studies, set to find out the possible linkage between hypertension and Covid-19. This also generated debate over use of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) for treatment of Covid-19. This study is an attempt to provide a critical review on the relationship between hypertension and Covid-19 and the possible clinical outcomes of using ACEI and ARBs for treatment in Covid-19 patients.

Index Terms- ACE2, ACEIs, ARBs, Covid-19, Hypertension, RAS

I. INTRODUCTION

Coronavirus disease 2019 (Covid-19) pandemic caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has affected 373,229,380 people and claimed 5,658,702 lives worldwide, to date [1]. The disease was first reported in Wuhan, China, on 31, December,2019 and on 11 March 2020, the World Health Organization (WHO) declared it a pandemic [2], subsequent to its accelerated spread to various parts of the world. As the world reeled under the Covid-19 pandemic, many studies reported poor prognosis and high mortality rate of Covid-19 patients with underlying health issues [3,4,5] and suggested a potential correlation between comorbidities and vulnerability of patients to severe complications of SARS-Cov-2 infection. It was observed that though Covid-19 disease primarily affects the lungs resulting in pneumonia and severe acute respiratory distress syndrome (ARDS), in severe cases it inflicted damage to multiple organs, especially the cardiovascular system and deaths were mainly due to ARDS, renal and cardiac failure [6].The novel coronavirus SARS-CoV-2 employs Angiotensin Converting Enzyme -2 (ACE2) [7], a modulator of the renin angiotensin system (RAS), to infiltrate the cells and inflicts damage to multiple organs. The RAS, exerts physiological control over cardiovascular system via a hormonal cascade and is critically important for maintaining blood pressure. The association of SARS-CoV-2 with ACE2 and prevalence of hypertension as one of the leading health issue amongst severely ill and deceased Covid-19 patients [8,9,10,11], led to speculations that hypertension could be a plausible player potentiating susceptibility to infection and aggravating the clinical outcomes of Covid-19. Concerns were also raised over administration of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) in patients as these tend to upregulate expression of ACE2 - the receptor mediating cellular entry of SARS-Cov-2 [12]. This study is an attempt to critically review the relationship between hypertension and Covid-19 and comprehend the possible clinical outcomes of using RAS modifiers in treatment of patients.

II. RAS

The renin angiotensin system (RAS) is an intricate and highly regulated cascade of hormones and receptors. It plays a pivotal role in physiological control of blood pressure regulation via regulating body fluid volume and maintaining systemic vascular resistance [13], entailing multiple organ systems. Interestingly, the system is also involved in several pathological processes

including vasoconstriction and hypertension [13,14,15]. The RAS signal transduction system comprises of a classical RAS pathway and a protective RAS/ counter- regulatory RAS pathway (Figure 1). Classical renin-angiotensin system (Classical RAS) pathway is responsible for generation of the crucial and the main effector molecule of RAS - Angiotensin II (Ang II), a peptide hormone from the substrate angiotensinogen (Agt) through sequential cleavage by proteases; renin- converting Agt into Angiotensin I (Ang I) and angiotensin converting enzyme (ACE) –catalyzing formation of Ang II from Ang I [13,14].
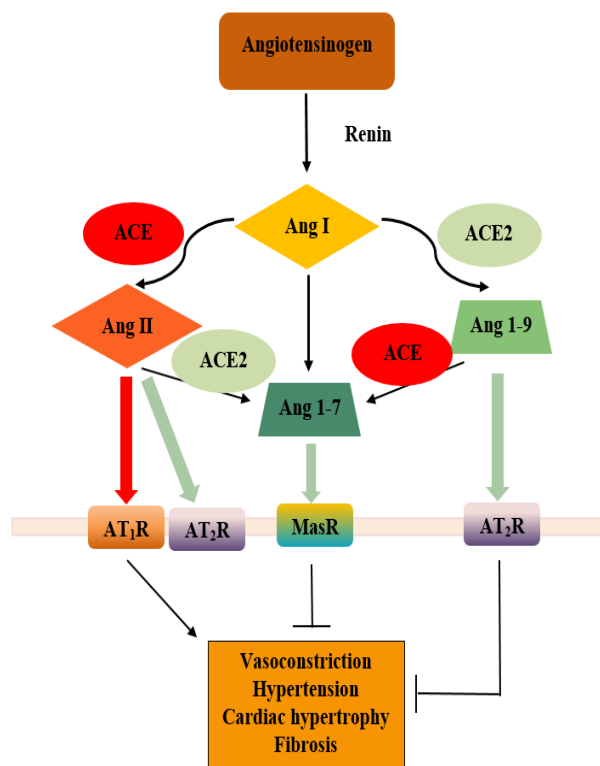

Figure 1 Classical and counter-regulatory renin- angiotensin system (RAS)
ACE, angiotensin-converting enzyme; ACE2, angiotensin-converting enzyme 2; Ang 1-7, angiotensin 1-7; Ang II, angiotensin II; AT1R, type 1 angiotensin II receptor; MasR, Mas receptor; AT2R, type 2 angiotensin II receptor

The cellular effects of classical RAS are mediated via Ang II and the two specific angiotensin receptors it binds with, called Ang II Type 1 (AT1R) and Ang II Type2 (AT2R) receptors. In classical RAS, Ang II mainly acts by binding to AT1R and promotes vasoconstriction and salt and fluid retention, consequently leading to elevated blood pressure. Overstimulation of classical RAS is responsible for many detrimental pathological processes. This represents the "classical arm" of RAS pathway. Further, in the presence of angiotensin converting enzyme 2 (ACE2, a homologue of ACE), Ang I, can also form Ang (1–9) and Ang II can be converted to Ang (1–7) by ACE [16], constituting the protective RAS pathway. Ang (1–7) mainly exerts the biological effects through Mas receptor (MasR) and Ang (1-9) binds to AT2R, resulting in vasodilation and promoting anti-proliferative and anti-inflammatory effects [16]. This arm of the RAS pathway

known as "protective arm", is actually counter-regulatory in nature and balance the effects exerted by classical arm of the RAS [14,15]. The ACE2, therefore, is at the center of counter-regulatory RAS system, playing critical role, both in promotion and protection against pathological conditions, including hypertension- a comorbid condition reported in many Covid-19 patients. Role of ACE2 in vasodilation and its interaction with SARS-Cov-2, an essential step for cellular entry of the virus makes the idea of hypertension having a link with Covid-19 very attractive.

III. RAS AND COVID-19

Studies have confirmed the role of ACE2 in novel coronavirus entry into cell, which also serves as the central component of protective arm of RAS. To investigate the association between RAS and Covid-19 it's important to understand the expression and function of ACE2 under normal and Covid-19 infection conditions. As SARS-CoV-2 exploits ACE2 to invade cells, the resulting internalization of ACE2 leads to an acquired deficiency of this cell surface receptor, theoretically translating into suppression of protective arm of RAS, justifying the various clinical pathological conditions observed in Covid-19 cases. The acquired ACE2 deficiency can also lead to overstimulation of classical RAS, as the level of Ang II - the main effector molecule of RAS, surges due to reduced conversion into Ang (1-7), resulting into vasoconstriction, hypertension and inflicting serve injury to multiple organs in Covid-19 patients. Studies based on animal model and human have reported an elevated ACE/ACE2 ratio in cardiovascular disease and hypertension, resulting from enhanced ACE2 downregulation [17,18,19,20]. In rat models, ACE2 deficiency lead to increased levels of Ang II, exacerbating the hypertension [19,20] and cardiac impairment [17]. ACE2 gene expression and/ ACE2 protein was found to be downregulated in case of human hypertensive patients as compared to normotensive ones [20]. The suppression of protective arm and activation of classical arm of RAS can explain the link between RAS and observed pathophysiology of Covid-19.

IV. HYPERTENSION AND COVID-19

There is a growing body of evidence indicating hypertension as one of the major risk factor associated with Covid-19 infection and severe consequences in patients. A retrospective cohort study in Wuhan, reported hypertension as the most prevalent (30%) comorbidity observed in adult Covid-19 patients with underlying health issues [8]. In case of severe Covid-19 patients 23.7% had hypertension while the prevalence rate was reported to be 58.3% in another study [21,22]. The observed high prevalence rate of hypertension amongst Covid-19 patients, turning it into the most common comorbidity is justifiable as elderly are prone to infection and develop a severe form of the disease and chances of hypertension increase with advancement of age, that explains the observed linkage between Covid-19 cases and hypertension. The observed association raised concerns - whether individuals with hypertension are at higher risk of acquiring SARS-CoV-2 infection and developing severe complications or not [23] and lead to several research studies investigating the issue. Studies have suggested increased risk of getting the infection and

developing a severe disease in patients with cardiovascular disease (CVD) including hypertension [24]. Hypertension was found to be associated with poor prognosis and severe outcomes in many Covid-19 cases [6,25,26] and the reason could be ACE2 involvement in both RAS and Covid-19. In a study using rodent models, marked increase in plasma Ang II levels was reported in ACE2 deficient mice as compared to control when Ang II was infused and exhibited enhanced susceptibility to Ang-II induced hypertension while no abnormalities were observed in cardiac structure and functioning [27]. Absence of expected cardiac abnormalities emerging from increased Ang II in ACE2 deficient mice models, indicates that effect of ACE2 on heart involves a more complex mechanism than what it looks [27]. Angiotensin-converting enzyme 2 (ACE2) is highly expressed in lungs and heart making cardiovascular system the next target of SARS-Cov-2, after lungs. ACE2 plays a vital role in cardiovascular system functioning and maintaining the blood pressure, as negative regulator of RAS and suppression of the protective arm in hypertensive individuals can exacerbate the complications in case of Covid-19 infection. One plausible explanation for increased susceptibility and chances of severe outcomes of Covid-19 in patients with hypertension can be increased shedding of ACE2 due to overexpression of metalloproteinase ADAM17 also known as TNF-α-converting enzyme (TACE) resulting from increased levels of Ang II, a vasoconstrictor and pro-inflammatory molecule [28]. Downregulation of ACE2 resulting from SARS-CoV-2 mediated internalization of ACE2 would further upregulate ADAM17, exacerbating the RAS imbalance, leading to aggravated disease condition. Studies have established that SARS-CoV induced ADAM17 mediated shedding of ACE2 ectodomain can facilitate viral entry into cell though the precise mechanism is yet to be understood [18,29]. As SARS-CoV and SARS-CoV-2 belong to the same family and both use ACE2 as receptor to enter the cell there is a possibility that SARS-CoV-2 also takes advantage of ADAM17 mediated ACE2 shedding for increased viral entry. SARS-Cov-2 virus in one hand leads to acquired deficiency of membrane bound ACE2 (mACE2) due to internalization, that may further elevate the blood pressure in hypertensive Covid-19 patients, on the other hand it induces ACE2 shedding leading to increased levels of soluble ACE2 (sACE2) that retains the catalytic activity. The consequent surge in Ang II due to reduced levels of mACE2 further enhances ACE2 shedding as it upregulates the ADAM17 that normally cleaves the mACE2 and releases it as sACE2 [30]. The function of sACE2 remains elusive but elevated levels of sACE2 has been found associated with cytokine storm in patients with severe disease, suggesting a possible link between sACE2 and aggressive inflammation, adding to disease severity in Covid-19 cases. Augmented proinflammatory cytokines like IL-1b, IL-6, IFN-γ, IL-8, and TNF-α induced by SARS-CoV-2 give rise to an acute inflammatory response (cytokine storm) [31,32] and has been associated with exacerbation of ARDS and extensive tissue damage leading to multi-organ failure and mortality, in Covid-19 patients [33,34]. Therefore, increased levels of sACE2 in Covid-19 patients with CVD including hypertension could be an indicator for development of severe form of disease [24,35]. Further, downregulation of ACE2 has been found to induce lung injury via increased binding of AngII with AT1R [19]. In a small cohort study of Covid-19 patients in

China, elevated plasma Ang II levels were reported to be linearly linked with viral load and lung injury [36]. SARS-CoV-2 infection exacerbates downregulation of ACE2 in hypertensive patients that leads to plethora of adverse effects, manifested in multiple ways. Targeting ACE and angiotensin II receptor via ACE inhibitors (ACEIs) and Angiotensin receptor blockers (ARBs) respectively, could be an effective therapy for management of Covid-19 patients but it also raises concern over safety and potential outcomes of antihypertension therapy involving these pharmacological classes of drugs, in hypertensive patients as these drugs tend to upregulate ACE2 in animal models [37,38,39] , the receptor for SARS-Co-V-2 and that might translate into increased susceptibility to infection.

V.   ACEI AND ARBs FOR TREATMENT IN COVID-19 PATIENTS

The protective arm of RAS exerts its effect by counter balancing classical RAS system and provides protection against various pathological disease conditions especially related to pulmonary and cardiovascular system and is anti-inflammatory in nature. In human physiology ACE2 enzyme plays a critical role via RAS [16,19,20,30,40]. Altered ACE2 expression may lead to pathological conditions and also enhances susceptibility to infection and severity of Covid-19. SARS-CoV-2 invasion, induces downregulation of ACE2 that can exacerbate the preexisting ACE2 deficiency in subjects with certain comorbid conditions like hypertension. Further, SARS-CoV-2 disrupts the ACE/ACE2 ratio that facilitates rapid progression of infection into ARDS to multiple organ failure, leading to death. Upregulation of ACE2, through RAS blockers such as ACEIs and ARBs can modulate Ang II levels and turns these two classes of drugs into promising candidates for treatment of Covid-19 patients [41,42]. Studies based on animal models have indicated that ACEIs and ARBs can upregulate the ACE2[39]. A pathobiology based model of Covid-19 also suggested that ACEIs and ARBs can prove effective therapeutics by elevating expression of ACE2 [43]. Enhanced expression of ACE2 also means increased viral entry points thus leading to speculations that these drugs could have detrimental effects in Covid-19 patients. The argument though a speculation only raised potential outcome concerns and is probably the reason that despite of well-established role of ACE2 as vasodilator and providing protection against tissue injuries triggered by Coronavirus invasion, use of ACEIs and ARBS in treatment of hypertensive Covid-19 patients remains controversial as ACE2 upregulation can potentiate increased susceptibility to infection [12,44]. The speculation led to number of studies investigating the issue and several researchers reported no positive correlation between these two classes of drugs and associated risk of getting the infection and developing a severe disease in Covid-19 patients [45,46,47] and thus could not provide any evidence in favour of the hypothesis. Analysis of a study based on Italian population post multivariable adjustment found no significant association between ACEIs/ARBs used alone or in combination with other antihypertensive drugs and increased risk of infection or development of a severe form of Covid-19 [46]. In a similar

population-based investigation carried out in Spain involving 1139 COVID-19 patients and 11,390 matched controls, examined the use of various antihypertensive drugs and found no association of ACEIs/ARBs and increased risk of infection or with hospitalization [48]. In another population based study conducted in South Korea to examine the association between RAS inhibitors including ACEIs/ARBs and risk and severity of Covid-19 infection, 950 out of 16,281 hypertensive subjects tested positive for Covid-19 and increased risk of hospitalization was absent in those who received ACEIs or ARBs treatment [49]. A meta-analysis of these three population based case-control studies comprising 882 Covid-19 patients that were using ACEIs/ARBs and 6144 respective population-based matched controls failed to find any significant association between ACEI/ARB and all-cause mortality/severe disease [50]. In another meta-analysis, involving 3936 hypertensive patients tested positive for Covid-19, no correlation was found between ACEI/ARB treatment and severity of disease. However, the study reported a reduced mortality [51]. Another study encompassing 19,000 Covid-19 cases, found no association between use of ACEIs/ARBs and increased risk of infection, severity or mortality, however a reduced risk of mortality was reported [52]. Similar protective effects of ACEIs and ARBs were reported in a retrospective cohort study, comprising of hypertensive patients with no other known comorbidity, that compared the three antihypertensive drug classes- ACEIs, ARBs and calcium channel blockers (CCBs), for the risk of hospitalization in Covid-19 patients [53]. In a recent detailed review also no negative impact of ACEIs/ARBs could be established regarding increased susceptibility and exacerbation of Covid-19 infection [54], though authors cautioned that more clinical trials are required to establish safety or protective role of these two classes of antihypertensive drugs.

VI. CONCLUSION

Hypertension is one of the most prevalent comorbidity in Covid-19 patients across the globe and many studies have suggested a positive correlation between hypertension and increased risk and severity of Covid-19. All the studies presented in the present review serve as an evidence and suggest that hypertension, resulting from a dysfunctional RAS, can be a decisive factor in outcome of Covid-19, however increased susceptibility to infection could not be substantiated by these studies and requires further evidence. Further, as the individual responses between patients vary to a great extent, hypertension alone cannot be considered as the single disease phenotype and other host attributes also need to be taken into consideration while predicting the Covid-19 disease outcome. The finding of this review can be helpful in preliminary screening of patients at higher risk of poor prognosis and serious clinical outcomes of Covid-19. It can also help hypertensive Covid-19 patients to be cautious and monitor the disease prognosis closely as SARS-CoV-2 infection can transform from ARDS to multiple organ failure and mortality in a relatively short span of time. Based on the studies reported, it is also concluded that use of ACEIs and ARBs in hypertensive Covid-19 subjects does not increase the risk of infection, severity of disease and mortality, however the risk of mortality is reduced. Therefore, ACEI/ARB use should not be discontinued in hypertensive patients tested positive for Covid-19.

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