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The advantageous effects of ACE-inhibitors and Angiotensin-receptor blockers on COVID-19 patients

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Abstract
COVID-19 is an infectious respiratory disease which is caused by novel Coronavirus-2019 (SARSCoV-2). SARS-CoV-2 uses ACE2-a member of renin-angiotensin system- as receptor in host cells. Recently, use of ACEI and ARB drugs rose question among patients and medical staffs after reports showed that hypertension, diabetes, cardiovascular and kidney diseases in which usage of these drugs are more common, are the comorbid and risk factors in COVID-19 patients. COVID-19 patients show reduced ACE2 and induced Angiotensin-2 levels. While ACE2 which is upregulated by ACEI and ARBs, expresses protective effect in the lung, heart, intestinal and kidney injures. Recently published meta-analysis and cohort retrospective studies show beneficial effects of ACEI/ARB drugs on COVID-19 patients. In this review we briefly discussed the effects of ACEI/ARB on COVID-19 patients with considering comorbid diseases.

Keywords: COVID-19, SARS-CoV-2, ACE-inhibitors, Angiotensin receptor blockers, ACE2

Introduction
Late 2019 appeared novel coronavirus (SARS-CoV-2) causes infectious respiratory disease (COVID-19). Many of the symptoms such as acute respiratory syndrome, are similar to the SARS which is caused by severe acute respiratory syndrome coronavirus (SARS-CoV) (Yushun Wan, 2020). The pandemic of COVDI-19 led to 1,937,268 morbidity and 120,600 deaths worldwide up to 14th April 2020. SARS-CoV-19 uses ACE2-a member of renin angiotensin system-as receptor for fusion and entry to the host cell. The controversial thoughts regarding to the beneficial or worse effect of ACEI or ARBs rose when that have been reported which hypertension, cardiovascular disease, diabetes and kidney diseases, in which it is more likely to use ACEI and ARBs, are among the most comorbid and risk factors for COVID-19. Several articles published in this regard and discussed that patients using ACEI and ARBs are at high risk of COVID-19 morbidity and mortality. Recently, some retrospective cohort studies and meta-analysis have been published that show ACEI and ARBs do not worsening the severity of COVID-19 patients, even they have beneficial effects.

Main Text
Late 2019 appeared novel coronavirus (SARS-CoV-2) causes infectious respiratory disease (COVID-19). Many of the symptoms caused by 2019-nCoV, are similar to those caused by severe acute respiratory syndrome coronavirus (SARS-CoV) (Yushun Wan, 2020) [50]. The pandemic of COVDI-19 led to 1,937,268 morbidity and 120,600 deaths worldwide up to 14th April 2020. SARSCoV-2 contains four structural proteins: spike (s), envelope (E), membrane (M), and nucleocapsid (N) proteins. Spike-protein facilitates viral attachment, fusion and entry to the host cells. S1 subunit of the receptor-binding domain (RBD) of spike protein facilitates binding of viral to the receptor and then, S2-subunit facilitates the fusion of viral with the host cell membrane. Similar to the SARS-CoV, SARSCoV-2 also recognize Angiotensin Converting Enzyme (ACE2) as a host-cell receptor and binds with more affinity than SARS-CoV (Wanbo Tai, 2020; Yushun Wan, 2020; Alexandra C. Walls, 2020; Wrapp, 2020) [40, 50, 1, 42] which leads to endocytosis of the virus and loss of ACE2 (Kuba K, 2005) [26]. This binding does not interfere with catalytic activity of the ACE2 at molecular site. SARS-CoV-2 has high transmissibility which suggests presence of a co-receptor as there was co-receptor, the lectin L-SIGN, for SARS-CoV (Jeffers, 2004) [8] or involvement of other factors in infection of respiratory tract ACE2 expressing cells (Lukassen, 2020) [28]. Wanbo Tai and colleagues found that blocking of human ACE2 (hACE2) receptors by

Recombinant RBD proteins could prevent SARS-CoV-2 entry to the hACE2-expressing cell. They also have shown that cross-neutralizing of SARS-CoV-2 pseudovirus infection by SARS-CoV receptor binding domain-specific polyclonal antibodies could be a potential to develop vaccines for prevention of both SARS-CoV-2 and SARS-CoV infections (Wanbo Tai, 2020) [40].

Angiotensin converting enzyme-1 (kininase II) increases the blood pressure by two mechanism: first, converts angiotensin-1 to angiotensin-2-a vasoconstrictor and stimulator of aldosterone secretion, second, inactivating the Bradykinin-a vasodilator and stimulator of prostaglandin synthesis (Katzung, Basic & Clinical Pharmacology, ed 9th,, 2004) [23]. ACE2, membrane-associated carboxypeptidase, is another member of renin-angiotensin system (RAS) which converts Angiotensin-2 to a vasodilator heptapeptide Angiotensin (1-7), and Angiotensin-1 to an inactive nonapeptide Angiotensin (1-9), hence, playing role as an effective endogenous ACE inhibitor (Chun Xi Liu, 2011) [4]. ACE2 is expressing in several tissues such as heart, blood vessels, kidney tubules, testis, and the luminal surface of the small intestine (Crackower M.A., 2002; Penninger, 2006; Yanqing Ding, 2004; I Hamming, 2007; Zhang, 2020; Gu, 2005) [6, 32, 46, 16, 51, 13] this is why pathology due to SARSCoV-2 can be seen in other organs than lungs also (Wu, 2020).

Acute respiratory distress syndrome (ARDS) is one of the most severe symptoms in SARS and COVID-19 patients. In human, ACE2 is expressed primarily in alveolar epithelial type-2 cells of the lungs (Zhao, 2020). These cells serve as surfactant producer to reduce surface tension in the lungs and prevent collapsing (Dobbs, 1989) [9]. Vanessa Monteil et al., reported that clinical-grade human recombinant soluble ACE2 (hrsACE2) was able to reduce viral growth in Vero E6 cells by a factor of 1,000-5,000, as well as can inhibit blood vessel organoids and kidney organoids infection at the early stage of infection (Vanessa Monteil, 2020) [38]. hrsACE2 significantly blocks cell-expressed ACE2 (Wanbo Tai, 2020) [40]. The viral load is positively linked to the severity of the lung disease, and linearly is associated with Ang-2 plasma level (Y. Liu, 2020) [45]. Side of ACE2's function as a receptor for SARS-CoV and SARS-CoV-2, it is also protecting lungs from injury (Zhang, 2020) [51]. These findings show important role of ACE2 in lung injury in COVID-19 patients. Several studies which are reviewed by Keiji Kuba and colleagues showed the protective effect of ACE2, ACEI and angiotensin receptor-1 blockers (ARBs) in lung injury such as ARDS. While overproduction of ACE, Ang-2 and Angiotensin-2 receptor-2 (ATR2) have worsening effect on lung injury (Keiji Kuba, 2006) [24]. Studies show that ace2 knockout mice were resistant to SARS infection and the virus titers in lung tissues were 10^5-fold lower than wild-type infected mice. Mice treated with SARS-spike proteins showed induced level of Ang-2, and ATR1 blockers partially reversed ARDS symptoms. They have shown that RAS including ACE2 could play important role in controlling the severity of acute lung diseases after disease process initiated. ACE2 expressing was downregulated in lungs of wild-type SARS-infected mice (Kuba K, 2005) [26] and Ang-2 level was in plasma (Y. Liu, 2020). Increased Ang-2 level signaling through ATR-type 1a in SARS patients promote disease pathogenesis, induce pulmonary edemas and impair respiratory function (Y. Liu, 2020) [45]. Losartan, an ARB drugs, improve acute lung failure in SARS mouse model (Kuba K, 2005) [26].

Diabetes and kidney disease are among the most comorbid which increase the risk of death in COVID-19 patients (Wie-jie Guan, 2020; Fei Zhou, 2020) [41, 12]. Renin-Angiotensin System, especially renal renin-angiotensin system has important role in the pathogenesis of diabetic nephropathy. Proteinuria and progressive renal insufficiency are two clinical characteristics of diabetic nephropathy. ACE-inhibitors (ACEI) and antagonists of Ang-2 receptor-1 are used as standard therapy for renoprotection in diabetic kidney disease (Chun Xi Liu, 2011) [4]. The higher ACE2 expression in the normal kidneys (Donoghue M, 2000) [10] and reduced ACE2 expression in diabetic rats (Douglas J.G., 1987) [11] and human kidney disease (Heather N.Reich, 2008) suggests ACE2's important role in diabetic nephrology, and in antiproteinuric efficacy of RAS inhibition (Chris Tikellis, 2008) [3]. Chun Xi findings show ACE2 overexpression and ACE-inhibitors had similar affects as renoprotective (Chun Xi Liu, 2011) [4]. Captopril, one of ACE-inhibitors, increases ACE2 expression and applies its protective effect on osteoporosis through overexpression of ACE2 and local activation of ACE2/Ang1-7/Mas signaling cascade (Hatem M. Abuohashish, 2017) [14]. Several strains of hypertension show reduced ACE2 mRNA level (Crackower MA, 2002) [6] and ACEIs induce Ang (1-7) (Dilek Iusuf, 2008) which suggest overexpression of ACE2 following ACEI treatment.

Some COVID-19 patients develop gastro-intestinal abnormality and diarrhea, nausea and vomiting can be seen in average 7-9 % of patients. Hypoalbuminemia is also among the most common laboratory abnormalities in COVID-19 patients (Mao-liang Huang, 2010; Rajab Mardani, 2020) [29, 35]. As albumin is a negative-phase reactant protein (Mechael L. Bioshop, 2010) [30], reduction could be due to infection, low amino acid absorption or liver disfunction. Anyway, ACE2 could be involved in all cases. ACE2 expresses in intestine cells as well. Increased ACE2 expression in intestine, enhances the absorption of peptides and amino acids through overexpression of their transporters. ACEI and ARBs induce ACE2 expression in intestine which in turn reduce susceptibility to intestine inflammation (Vuille-Dit-Bille, et al., 2015) [15]. ACEIs up-regulate ACE2 both *in vivo* and *in vitro* under the liver injury condition, which can be beneficial in treatment of liver fibrosis. ACE2-Ang1-7-Max axis in liver may shift the renin-angiotensin system away from pro-fibrotic responses towards antifibrotic responses (Mao-liang Huang, 2010) [29]. ACEIs through ACE2-axis and amino acid transporter induction may increase absorption of some drugs such beta-lactam antibiotics, valacyclovir, vigabatrin and 5-aminolevulinic acid (Vuille-Dit-Bille, et al., 2015) [39]. Still there is no such an evidence, but maybe ACEI improve absorption of antiviral drugs using in COVID-19 patients right now.

Heart disease is among the most comorbid in COVID-19 patients which in turn increase the risk to death (Fei Zhou, 2020; Jing Yang, 2020; Rajab Mardani, 2020; Wie-jie Guan, 2020) [12, 35, 20, 41]. ACE2 also plays role in regulation of structure and function of the heart. Sine ace2 knockout mice exhibited decreased cardiac contractility in the same time elevated circulating and cardiac Ang-2. Ace2 knockout mice also exhibited elevated hypoxia-induced gene expression which leads to endothelial dysfunction, vasocontraction and

cardiac hypoperfusion (Crackower MA, 2002) [6]. ACE2-deficient hearts have increased ROS, matrix metalloproteinases levels and gelatinase activity (Kassiri Z, 2009). ACE2 appears to be a negative regulator of ACE in the heart (U. Danilczyk, 2004) [37]. ACE2 is overexpressed in heart failure to counterbalance ACE and Ang-2 induction via producing Ang1-7, which ameliorate the development of ischemia-induced heart failure, can suggest the protective effect of ACE2 in heart failure (Andrew B Goulter, 2004). Many studies suggests ACEI and ARBs induce ACE2 gene expression and enhance Ang(1-7) level in heart, while decrease angiotensin-2-receptor 1 (Igase M, 2011; Zong WN, 2011) [17, 53] which leads to their cardio-protective effects (Simo es e Silva Ana Cristina, 2016) [36].

Although, some other studies showed the opposites. Studies show that long-term ACE2 overexpression or Angiotensin1-7 injection can accelerate myocardial fibrosis or diabetic nephropathy (Rachel Masson, 2009; Ying Shao, 2008) [34, 47]. There is also a meta-analysis shows that ACEI/ARBs are not inducing ACE2 expression in human (Krishna Sriram, 2020) [25].

The controversial thoughts regarding to the beneficial or worse effect of ACEI or ARBs rose when that have been reported which hypertension, cardiovascular disease, diabetes and kidney diseases, in which it is more likely to use ACEI and ARBs, are among the most comorbid and risk factors for COVID-19. A study on 1099 COVID-19 patients in China, reported that percentage of hypertension, CVD, diabetes and kidney disease were higher in severe cases in compare to non-severe cases (Wie-jie Guan, 2020) [41]. In other published article, from 191 COVID-19 patients, 30% had hypertension, 19% diabetes and 8% coronary heart disease. While, these numbers were very different between non-survivors and survivors. For example, 48% against 23%, 31% against 14% and 24% against 1% for hypertension, diabetes and coronary heart disease respectively. IL-6 level was 11.0 pg/ml in non-survivors while it was 6.3 pg/ml in survivors (Fei Zhou, 2020) [12]. Similarly, a meta-analysis of eight studies including 46,248 patients with laboratory confirmed covid-19 indicated that those with the most severe disease were more likely to have hypertension, respiratory disease and cardiovascular disease (Jing Yang, 2020) [20].

ACE2 is the receptor for SARS-CoV-19. Theoretically, increase in receptor may increase virus entry to the host cells and viral load. Several viruses such as SARS, human coronavirus-NL63, and SARS-CoV-2 which use ACE2 as receptors are less common to infect children (Ping-Ing Lee, 2020). This predicting less ACE2 expression in children then adults, while studies on rats, and upregulation of ACE2 by estrogens and androgens (Jiawei Chen, 2020) [19] show opposite result (Xie Xudong, 2006) [44]. Although, ACE2 is also expressing in upper respiratory system, but the symptoms and severity of the disease caused by SARS-CoV-2 are much dependent to lower respiratory system. It may suggest the presence of co-receptor and/or other factors which are not much activated in children, needs more investigation. From other hand, ACEI and ARBs are increasing ACE2 expression which is receptor for SARS-CoV-19. Thus, may can suggest that patients using ACEI or ARBs are more prone to be infected by SARS-CoV-19. Still there is no any research-based evidence to show correlations of ACEI and ARBs to COVID-19 morbidity. Hence, some studies investigated accordingly.

Meta-analysis of COVID-19 patients having hypertension and using one of from 5 types of anti-hypertensive drugs (ACIE, ARBs, Ca-channel blockers, thiazide or beta-blockers) showed no statically difference in disease severity compared to COVID-19 patients taken no drugs by all ages. While, their study showed COVID-19 patients over the age of 65 who took ARB drugs prior to the admission in hospital had reduced risk of severity and this effect remained positive in protecting from severe respiratory failure upon SARS-CoV-2 infection. ARBs were also found to be associated with a reduced mortality rate for pneumonia (Yingxia Liu., 2020b) [49]. Another retrospective study reported that ACEI and ARBs had no statistical significant effect in the outcomes of 112 COVID-19 patients with combined cardiovascular diseases (Peng Y.D., 2020) [31], which shows that ACEI and ARBs are not worsening COVID-19 patients condition. A retrospective study in Shenzhen Third Peoples' Hospital, China, on 42 hypertensive COVID-19 patients (age 55.8- 69 years) showed that the median number of days from the onset of symptoms to hospital admission was 2.0 and 3.0 in the non-ACEI/ARB and the ACEI/ARB groups respectively. Meanwhile, this number was 16.5 and 20.0 days from symptom onset to hospital discharge in the non-ACEI/ARB and the ACEI/ARB groups respectively. Severe patients were 48% with one death in non-ACEI/ARB group, and 23% with no death in ACEI/ARB group. Similarly, IL-6 level was also lower in ACEI/ARB group. The absolute numbers of CD3+ and CD8+ T-cells were significantly higher in the ACEI/ARB group than that in the non-ACEI/ARB group. But No significant changes have been seen in CD4+ T-cell counts between these two groups. Although the viral load was same between the two groups at hospital admission, but ACEI/ARB group had significantly lower viral load peak during hospitalization (Juan Meng, 2020). A cohort study of 205 acute inpatients with COVID-19 at Princess Royal University Hospital and King's Collage Hospital, London, UK, showed treatment with ACE-inhibitors was not associated with an increased risk of rapidly deteriorating severe disease (Daniel M Bean, 2020) [7]. While, they have not observed ARBs effects due to low samples.

After several publication warning about use of ACEI and ARBs in COVID-19 patients, on March 12th, 2020, the European Society of Hypertension (ESH) stated no different use of RAS blockers in COVID-19 patients due to lack of evidence-based data. Similarly, on March 16th, 2020, the International society of Hypertension stated that there is still no clinical data in human to show beneficial or worsening effects of ACEI or ARBS in term of susceptibility to COVID-19 infection or outcomes of those infected.

Conclusion

SARS and SARS-2 viruses use ACE2, a member of renin-angiotensin system, as their receptor to enter the host cells which decrease ACE2 level in host cells, and induce Ang-2 level. ACE2 has protective effects on lung, heart, intestine, kidney and liver. ACEI and ARBs increase ACE2 expression though which implementing their therapeutic effects.

The only perception concerning use of ACEI and ARBs is the higher severity and mortality rates among COVID-19 patients having comorbid such hypertension, cardiovascular diseases, diabetes and kidney failure who most are likely

using ACE or ARBs. While, studies showed ACEI and ARBs improve lung injury, heart injury and nephrotic diseases through induction of ACE2 expression. Some recently published articles also show beneficial effect of ACEI and ARB drugs in COVID-19 patients. Hence, usage of ACEI and ARBs, more likely ARBS-also suggested by Liu Y (Y. Liu, 2020)- could be beneficial for those who are infected to SARS-CoV-19 and showing sign of lung disease. Further studies are recommended to show their affects and also compare the effects between ACEI and ARBs in COVID-19 patients.

List of Abbreviation

ACEI: Angiotensin Converting Enzyme Inhibitor
ARB: Angiotensing-2-receptor-1 Blocker
ACE2: Angiotensin Converting Enzyme 2
ARDS: Acute Respiratory Distress Syndrome
COVID-19: Coronavirus disease-19
SARS-CoV: Severe acute respiratory syndrome coronavirus
SARS-CoV-2: Severe acute respiratory syndrome coronavirus-2
RBD: receptor-binding domain
S-protein: Spike protein

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