JMedSci

Journal of the Medical Sciences
(Berkala Ilmu Kedokteran)

Volume 52, Number 3 (SI), 2020; 67-76
http://dx.doi.org/10.19106/JMedSciSI005203202006

Controversy of angiotensin receptor blockers (ARBs) and angiotensin converting enzyme inhibitors (ACEIs) prescription for hypertension patients in coronavirus disease 2019 (COVID-19) pandemic

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Submited: 2020-04-21
Accepted : 2020-05-08

ABSTRACT

Coronavirus disease 2019 (COVID-19) pandemic has made all the world in a mess. Novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causing COVID-19 infects human cells through angiotensin-converting enzyme 2 receptors (ACE receptors). Angiotensin-converting enzyme 2 (ACE) is upregulated in diabetes and cardiovascular diseases including hypertension. Hypertension patients commonly consume angiotensin receptor blockers (ARBs) and/or angiotensin-converting enzyme inhibitors (ACEIs) which could increase ACE receptors. It was suspected that the ARBs or ACEIs administration may worsen the clinical outcome for the hypertension patients with COVID-19. However, no clinical trial had significantly revealed how appropriate management and prescription of ARBs and ACEIs for the hypertension patients with COVID-19. The use of ARBs and ACEIs for these patients is still controversy. Studies concerning the side effect of single or combination use of ARBs and ACEIs in the hypertension patients with COVID-19 as well as specific morbidity and mortality are needed. This review was aimed to provide understanding concerning the appropriate management and prescription of ARBs and ACEIs for hypertension patients with COVID-19.

Keywords:
COVID-19;
ACE inhibitor;
ARBs;
hypertension;
management;

ABSTRAK

Pandemi penyakit coronavirus 2019 (COVID-19) telah membuat dunia dalam kekacauan. *Severe acute respiratory syndrome coronavirus* 2 (SARS-CoV-2) baru penyebab COVID-19 menginfeksi sel manusia melalaui reseptor *angiotensin-converting enzyme 2* (reseptor ACE). *Angiotensin-converting enzyme 2* (ACE) mengalami peningkatan pada penyakit diabetes dan kardiovaskular termasuk hipertensi. Penderita hipertensi biasanya mengkonsumsi penghambat reseptor angiotensin (*angiotensin receptor blockers*/ARBs) dan/atau penghambat enzim konversi angiotensin (*angiotensin-converting enzyme inhibitors*/ACEIs) yang dapat meningkatkan reseptor ACE. Diduga pemberian ARBs atau ACEIs kemungkinan memperburuk kondisi klinik pada penderita hipertensi yang disertai COVID-19. Namun demikian tidak ada uji klinik yang secara nyata mengungkap bagaimana peresepan dan pengelolaan ARBs dan ACEIs yang tepat untuk penderita hipertensi yang disertai COVID-19. Penggunaan ARBs dan ACEI pada pasien tersebut masih kontroversi. Penelitian mengenai efek samping baik pada pemberian tunggal maupun kombinasi ARBs dan ACEIs pada penderita hipertensi yang disertai COVID-19 serta morbiditas dan mortalitasnya diperlukan. Kajian ini bertujuan memberikan pemahaman mengenai peresepan dan pengelolaan yang untuk terapi ARBSs dan ACEIs pada penderita hipertensi yang disertai COVID-19.

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INTRODUCTION

An outbreak of coronavirus disease 2019 (COVID-19) pandemic has made all of the world in a mess. All of our daily live changes dramatically. Social distancing, physical distancing, work from home, and lockdown are familiar daily terms nowadays. From the December 2019 until this paper is written, corona virus pandemic has been intriguing all the world researchers to study and learn in depth about this virus.[1]

Coronaviruses (CoVs) comprise of a large family of positive single strand enveloped RNA viruses with diameter approximately 120nm.[2-4] Severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle-East respiratory syndrome coronavirus (MERS-CoV) had previously caused fatal outbreaks in a short time. The current concern is about pandemic by the highly contagious novel SARS-CoV called SARS-CoV-2. This virus causes a new disease called coronavirus disease 2019 (COVID-19). It has been spreading rapidly because it is underdiagnosed and underestimated at the first time it appeared.[1] The COVID-19 cases usually got worsened on frail subjects with age over sixty, comorbidities such as diabetes, cardiovascular disease, hypertension, and chronic obstructive pulmonary disease.[1,2] Therefore, stratifying patients based on the risk of suffering severe clinical presentation while treating them is a good strategy in coping with COVID-19.[1]

Viral infection actually is common disease in human life. The range of infection might be mild, moderate, or severe. However, the COVID-19 has some special clinical features. This virus can be manifested as mild, moderate, to severe cases. Spreading speed is very fast and communal. The COVID-19 has made all the world anxious. The number of people with positive test has been increasing from time to time.[1]

Hypertension is one of the most common comorbid condition found in COVID-19 patients. It is also usually found in COVID-19 patients who suffered from acute respiratory distress syndrome (ARDS) and acute lung injury. The SARS-CoV-2 uses angiotensin-converting enzyme 2 receptors (ACE receptors) in the lung to infect the cells. Therefore, there are some questions regarding risk and benefit of taking angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs). These two kinds of antihypertension are the most common prescribed for controlling hypertension and they are presumed to interfere ACE receptor. This paper reviewed controversy of ARBs and ACEIs prescription for hypertension patients in COVID-19 pandemic.[5]

DISCUSSION

Epidemiology

The COVID-19 has been challenging all the medical and paramedical staff in the world. Until April 15th2020, there have been 8 top countries in the world with the most positive cases confirmed. They are United States (602,989 cases), Spain (172,541 cases), Italy (162,488 cases), France (131,361 cases), Germany (131,359 cases), United Kingdom (94,845 cases), China (83,306 cases), and Iran (74,877 cases). There are total 1,981,239 positive cases confirmed, with 126,681 deaths and 185 countries affected worldwide.[6] Meanwhile, there were 10,118 positive cases in Indonesia until the end of April 2020.[7]

Pathogenesis of human coronaviruses

Severe acute respiratory syndrome coronavirus (SARS-CoV) belongs to the large subfamily coronavirinae (CoVs). There are two groups of corona viruses, i.e. low pathogenic and highly pathogenic groups. Low pathogenic group consists of four coronaviruses (HCoVs, namely

HCoV 229E, NL63, OC43, and HKU1). This group causes non- severe acute respiratory syndrome (SARS)-like CoVs. It causes mild endemic disease. However, there are three highly pathogenic, novel zoonotic CoVs. They are the SARS-CoV-1 in 2002, the MERS-CoV in 2012; and novel SARS-CoV-2 in December 2019. The SARS-CoV-2 that cause COVID-19 was first known after analyzing clinical samples from patients with pneumonia in Wuhan, China. Now, COVID-19 has become pandemic as stated by WHO.[4]

The COVID-19 has high transmission rate. It spread from human to human. Various clinical features are available.[8] COVID-19 news are widely spread due to social media blasts. Rapid spread of COVID-19 transmission news cause isolation, quarantine, travel restriction, economic collapse, and many unemployment nowadays.[9] The clinical presentation of COVID-19 is similar to upper respiratory tract as general. The difference is COVID-19 might get worse in people with comorbidities (hypertension, diabetes mellitus, cardiac disease, kidney disease, and chronic pulmonary diseases), elderly patients, and immunosuppression patients. Those people are susceptible populations.[3,8] COVID-19 has become pandemic very quickly in a short time due to super spreaders. Super spreaders mean asymptomatic infected COVID-19 patients that transmitted the infection to other people. This made the high transmission rate of COVID-19.[10,11]

Fatality rate

The average fatality rate caused by COVID-19 is about 3.4% in the world. It is less than SARS and MERS.[12] COVID-19 lethality is rising with age. This virus infects children and elderly more severely. Asymptomatic patient can transmit to other people as well. This condition made the pandemic harder to be controlled. We really have to avoid tremendous transmission speed. This only can be achieved if everyone obeys some rules such as social distancing, work from home, clean lifestyle, and washing hands thoroughly. Otherwise, doctors, paramedics, and society will be in great danger because the healthcare staff and systems canot cope with the speed of transmission anymore. Moreover, effective antiviral drugs and vaccines have not been found.[1]

Managing hypertension patients in COVID-19 pandemic

Proper management should be carried out in managing hypertension patients in COVID-19 pandemic. Each patient should receive proper medicine. Actually, there is no specific treatment other than usual hypertension regimen for COVID-19 patients with hypertension comorbidity. Hypertension patients, with COVID-19, is predicted to have increased mortality risks. There might be adverse effects of ACE-1 inhibitors, such as captopril, ramipril, and enalapril or ARBs. ARBs is also called angiotensin receptor antagonists. ARBs consists of valsartan, telmisartan, olmesartan, and candesartan, etc.[2]

SARS-CoV-2 uses ACE receptors to infect human cells. The ACE receptor role is as co receptor for viral entry for COVID-19.[3] This receptor is expressed in human airway epithelial cells (especially in lung, in type II alveolar cells), gastrointestinal system, heart and kidney.[3,13-15]

Minimizing ACE receptor activity might reduce the competency SARS-CoV-2 to infect cells. Nevertheless, ACE-1 inhibitor can not inhibit ACE. In contrary, ACE-1 inhibition enhance angiotensin I and angiotensin level in circulation. Increased angiotensin I level could upregulate ACE receptor. In animal models, ACE-1 inhibitor and ARBs might upregulate ACE receptors in heart. However, there is no consistent data in

human trial yet.[2,16]

The possible risk of ARBs and or ACEIs use in COVID-19 patients

Angiotensin-converting enzyme2 is upregulated in diabetes and cardiovascular patients who consumed ARBs and ACEIs. Increasing of ACE receptor expression will make these patients in jeopardy. These specific patients will be more susceptible compared to other patients without diabetes and cardiovascular disease nor consuming any of ARBs and ACEIs.[2] Moreover, it is believed that the patient will tend to suffer from more severe disease progression rather than general population. This condition raised controversy among patients, physicians and experts, whether the medications should be continued or not. Meanwhile, the evidence base for this situation is very limited.[17] Both patients and doctors are uncertain about what to do with the dosage ACEIs and ARBs. Changes of antihypertensive need visit to physician. Meanwhile visiting physician means increasing risk for COVID-19. Medication type and dosage changes need time to take effect. Uncontrolled blood pressure will further increase risk of COVID-19.[3] Therefore, the vicious circle continues as it seen on FIGURE 1.

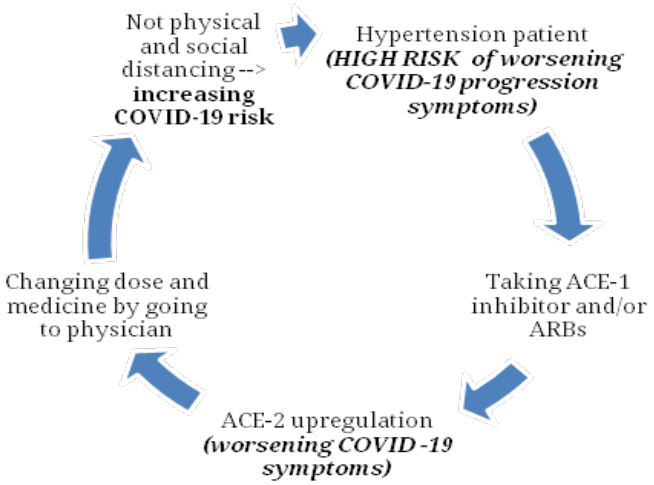

FIGURE 1. Changing prescription and dosage of usual antihypertension during COVID-19 pandemic might worsen patients' condition and putting them into jeopardy

There is growing concern that consuming ACEIs and ARBs might increase ACE receptor expression. Patient will be more susceptible to viral host cell entry. Studies in animal models revealed there was increased ACE receptor expression in brain, heart, and urine after medication with ARBs. In contrary, there was lack evidence about changes in serum or pulmonary ACE levels. Therefore, further study is needed to explain this problem.[3]

The ACEIs and ARBs act by blocking renin-angiotensin-aldosterone system (RAAS). These two antihypertensive drugs usually are consumed by hypertension and heart diseases patients. It is started at low dose and then gradually increased to reach the target dose. The most common side effect of ACEI is cough. Renal insufficiency and hyperkalemia might happen when the dose is increased. ACEI has neurohormonal modulatory effects, such as antiinflammatory, vasodilator, antithrombotic, plaque-stabilizing, and antiproliferative effects. ARBs are often chosen as alternative for patients who can not tolerate ACEI cough side

effect. Indication of ACEI and ARBs are hypertension, heart failure, and diabetes mellitus. Contraindication are hyperkalemia, pregnancy, severe aortic stenosis, and angioedema.[18]

In addition, due to social media blow up every single thing about COVID-19, hypertension patients who are currently taking ACEI or ARB become very concerned. Some of them even stopped taking their medicine by themselves without doctor consultation. They are unsure about the ACEI or ARB treatment efficacy anymore. Afraid of being infected by COVID-19 is much greater than their wishes to control the high blood pressure and cardiovascular complications. Nevertheless, there is no sufficient evidence base to support the safety and harmful effect of taking ACEI and ARB in COVID-19 pandemic situation.[17]

The possible benefit of ARB and or ACEI use in COVID-19 patient to minimizeacute lung injury or acute respiratory distress syndrome (ARDS)

Hypertension is associated with overactive renin angiotensin system. Acute lung injury andacute respiratory distress syndrome (ARDS) during COVID-19 are assumed to be activated through renin angiotensin system dysregulation.[19] If renin angiotensin system is blocked, COVID-19 infection might be subsided. ACEI and ARBs might increase ACE and make COVID-19 infection worsened. However, ACE-2 has lung protection effect in some studies.[16]

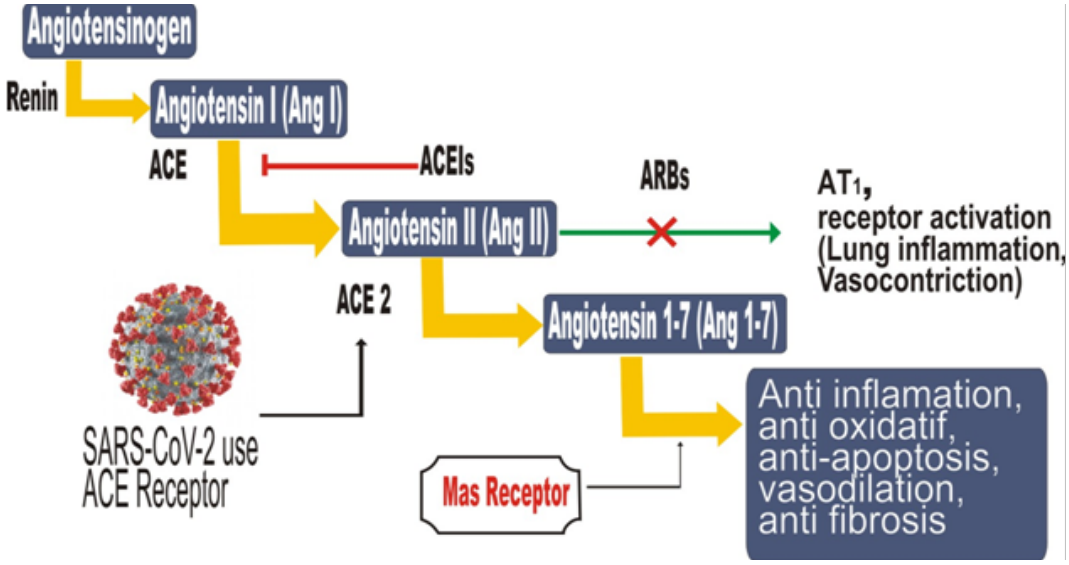

FIGURE 2. Renin angiotensin system and ACE mechanism of action related to COVID-19

FIGURE 2 shows that renin angiotensin system has specific pathway. Angiotensinogen is converted into angiotensin I (Ang I) by renin and then it is converted into angiotensin II (Ang II) by ACE. Angiotensin is converted into angiotensin 1-7 by ACE 2. The Ang II activates type 1 angiotensin 2 receptor (AT_1R) lead to vasoconstriction, lung edema, oxidative effects, inflammation, and fibrosis. Meanwhile, angiotensin 1-7 [Ang-(1-7)] have anti inflammation, antiapoptosis, and antifibrosis effect.[16,19]

COVID-19 uses ACE receptor to infect cells so there will be down regulation of ACE receptor. When ACE receptor is down regulated, renin angiotensin aldosterone system will be hyperactivated.[20] ACEIs inhibit alteration of Ang I into Ang II, whereas ARBs inhibit binding of Ang II with AT_1receptor. ACEIs and ARBs use might upregulate expression of ACE

receptor in animal studies.[21,22] Both ACEIs and ARBs inhibit ACE mechanism of action, so ACE will be abundant in circulation. Moreover, ACE in circulation is assumed to have protective effect towards lung, especially ARDS. However, decreased ACE activity will increase Ang II lead to AT_1 receptor activation that yield ARDS.[16] Therefore, ACE/Ang-(1-7)/ Mas receptor axis is antagonist with ACE/ Ang II/Ang I axis.[19]

A study conducted in rats showed that selective blockade of Ang II increased cardiac ACE gene expression and activity. Combination losartan and lisinopril elevated cardiac ACE activity. Ang I antagonists antihypertensive effect might be related to increasing Ang II metabolism by ACE.[21] ACEIs can not inhibit ACE2 activity, although they regulates ACE mRNA. However, in animal studies revealed that increasing cardiac ACE2 mRNA might increase cardiac ACE activity when animals were given losartan (ARBs) or combination of losartan and lisinopril (ACEIs).ACE activity is not inhibited by ACEIs.[21]

COVID-19 tends to get worsen in patients with hypertension, diabetes, and cardiovascular disease. These conditions are related to low ACE level. COVID-19 uses ACE receptor. Therefore, ACE activity will be further diminished in the COVID-19 patients with hypertension.[19] In other words, ACE is down regulated and Ang II is accumulated.[15] ACE/Ang II/Ang I axis will be dominant. This condition causes vasoconstriction, inflammation, oxidative stress, organ damage, and high risk of pulmonary inflammation, which will be ended with acute lung injury or ARDS.[19]

Fang *et al.*[23] reported that ARBs and ACEIs prescription cause COVID-19 patients at a higher risk for severe infection due to upregulation of ACE. However, increasing ACE concentration in circulation might bind SARS-CoV-2, thus lung infection might be minimized. In addition, ACEIs and ARBs might increase Ang-(1-7) as lung protection due to anti-inflammatory, antiapoptosis, and antifibrosis properties. There is controversy about discontinuation of ACEIs or ARBs. It was suggested that renin angiotensin system blockade might decrease COVID-19 progression. Although studies in animals suggesting protective effects of COVID-19 against lung complications for COVID-19 infected patients, no human studies have established those protective effects yet.[23] ARBs could upregulate ACE expression. It might be beneficial in post-infarction ventricular remodeling and left ventricular function in a rat study of congestive heart failure. ARBs also prevented neointimal hyperplasia rat arteries. Olmesartan might reverse cardiac hypertrophy and impaired ventricular contractility in rats.[22]

Ongoing study regarding the use or ACEI or and ARB in COVID-9

There has been three COVID-19 clinical trials regarding hypertension and ACEIs usage listed in the International Clinical Trials Registry Platform, on the WHO's website ICTRP. Those three ongoing trials are 1) Clinical characteristics difference between the hypertension patients with and without ACEI treatment when suffered with 2019-nCoV infection in China" (registered on 12 February 2020); 2) Recombinant human angiotensin-converting enzyme 2 (rhACE2) as a treatment for patients with COVID-19 (registered on 21 February 2020) and 3) Clinical study for the effects of ACEI/ARBs on the infection of novel coronavirus pneumonia (CoVID-19) (registered on 2 March 2020).[2]

ACEI is presumed to directly inhibit ACE. In fact, the function of ACE 2 is as enzyme; i.e. carboxypeptidase. It is not inhibited by ACEIs. ACE essential role is counterbalance the effect of ACE. ACE produces Ang II from Ang I. ACE yields angiotensin from Ang II after binding to

Mas receptor. Vasodilatation will take place as the result. The vasodilatation effect in the pathogenesis of COVID-19 is vague. It was only revealed in animal studies. ACE2 and angiotensin was protective in different lung injury studies.[24]

Preclinical data revealed that ACE2 expression might alleviate lung injury due to COVID-19. However, there is no clinical evidence base to support ACE2 as an effective treatment for viral-induced lung injury. Only a preliminary trial of 10 patients was conducted to show efficacy of ACE2 infusion in ARDS. This trial result is not significant and strong enough to prove that ACEIs or ARBs might decrease severity of pulmonary injury by COVID-19.[3] Zhang *et al.*,[20] reported a retrospective, multi-center study, which involved 1128 COVID-19 patients with hypertension in China. Only 188 of them taking ACEI/ARB (median age 64). ACEI/ARB group had lower mortality rate compared with non ACEI/ARB group (3.7% vs. 9.8%; p = 0.01).

The concern that ACEIs and ARBs affect the severity and mortality of COVID-19 is 2-fold.[3] Wu *et al.*,[26] reported that there is increase mortality and morbidity for COVID-19 patients with hypertension in China. The death hazard ratio was 1.70, meanwhile the hazard ratio for ARDSwas 1.82 in total of 201 COVID-19 patients. Furthermore, Zhou *et al.*[25] reported that the hazard ratio is 3.05 for in-hospital mortality in 191 hypertension patients with COVID-19. However, none of those studies were adjusted for confounding variables. Therefore, the association is not strong enough to conclude whether the number of hazard ratio is related to hypertension pathogenesis, treatment, or other comorbidities. The possible confounding variable was antihypertensive medicine, i.e. ACEIs and ARBs.[25,26] In Indonesia, the first death case of COVID-19 is 53 years old patient, foreign citizen, with severe preexisting condition such as diabetes, hypertension, hyperthyroidism, and chronic obstructive lung disease.[27] On March 13th 2020, European Society of Cardiology Council on Hypertension on ACE-Inhibitors and Angiotensin Receptor Blockers stated that there was no significant and sufficient evidence regarding harmful effects of ACEI and ARB in COVID-19 pandemic. The Council on Hypertension recommends that both physicians and patients should continue treatment with usual antihypertensive therapy. No significant clinical trial revealed that ACEIs or ARBs should be discontinued due to COVID-19.[17]

The similar statement was followed by some professional association. On March 17th 2020, American Heart Association, the Heart Failure Society of America, and the American College of Cardiology declared a joint statement. They suggested patients to continue ACEIs and ARBs as usual.[3] American College of Cardiology has stated that for COVID-19 patients with cardiovascular disease, treatment should be taken individualized based on each patient condition.[2] There was also joint statement from the Indonesian Cardiovascular Doctor Association, Indonesian Internist Association, Indonesian Anesthesiologist and Intensive Care Association, Indonesian Pediatrician Association, and Indonesian Pulmonologist Association. They wrote one protocol book for COVID-19. It was said that ACEIs and ARBs should be continued as previous because there is no significant evidence base regarding benefit nor harms using those drugs in COVID-19 patients with hypertension. Eventhough ACE is the ACE homolog, the ACE activity is not inhibited by ACEI. In addition, animal pilot study revealed that ACEIs and ARBs had protective effects for severe lung injury due to viral pneumonia.[28] This is important guidance for Indonesian physicians. They should not hesitate anymore in prescribing ACEIs and ARBs as usual for their hypertension patients

because there are not any harms in prescribing those drugs in COVID-19 patients with hypertension.

There is no interaction between ACEIs, ARBs, and chloroquine. Some reports indicated chloroquine might be efficient against COVID-19. Chloroquine is regularly used as malaria prevention and treatment. In COVID-19 cases, chloroquine is expected to be used as treatment and prophylaxis for vulnerable patients such as elderly and having comorbidities.[29-31]

CONCLUSION

No clinical trial has significantly revealed how appropriate management for hypertension patients with COVID-19 infection. Researchers need to find the side effect of using ACEIs, ARBs, or the combination in the COVID-19 patients with hypertension. Specific morbidity and mortality rate should be counted also. This is the research gap need to be well answered. While waiting for the significant clinical trial result come, hypertension patients should continue using ACEI, ARB, or both according to previous prescription of their physicians. This is supported by European Society of Cardiology Council on Hypertension, American Heart Association, the Heart Failure Society of America, and the American College of Cardiology statement about continue using ACEIs and ARBs because there is no significant clinical trial result until recently. There was also joint statement from the Indonesian Cardiovascular Doctor Association, Indonesian Internist Association, Indonesian Anesthesiologist and Intensive Care Association, Indonesian Pediatrician Association, and Indonesian Pulmonologist Association. They wrote one protocol book for COVID-19. It was said that ACEI and ARB should be continued as previous. This is important guidance for Indonesian physicians. They should not hesitate anymore in prescribing ACEI and ARB as usual for their hypertension patients because there aren't any harms in prescribing those drugs in COVID-19 patients with hypertension.

ACKNOWLEDGEMENTS

Author declares that there is no conflict of interest in the preparation of the manuscript.

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