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COMMENT

Mitigating secondary disaster triggered by fear of COVID-19: the role of professional medical societies

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As of August 2023, coronavirus disease 2019 (COVID-19) had become one of the largest threats in human history, with over 760 million infections and approximately 7 million deaths. (https://www.who.int/emergencies/diseases/novel-coronavirus-2019) In the early stages of the COVID-19 pandemic, "fear" took precedence over "mature discourse" among people, and media coverage further exacerbated the situation.

The initial outbreak of a mysterious respiratory illness occurred in Wuhan, China, in late 2019. The disease was initially referred to as "pneumonia of unknown etiology." The Chinese authorities identified a new type of coronavirus, which was isolated on 7 January 2020. The genetic analysis revealed significant similarities between the genomes of the new type of coronavirus and the severe acute respiratory syndrome coronavirus (SARS-CoV) which emerged in 2002 in Guangdong province, China, suggesting that they are closely related viruses. Concurrently, the name of the new virus was designated as "SARS-CoV-2" to indicate its association with the SARS-CoV. In 2000, angiotensin-converting enzyme 2 (ACE2) was initially identified, which is a homolog of the ACE receptor [1]. In 2003, it was reported that ACE2 is a major entry receptor for SARS-CoV [2], and ACE2 expression on cell lines correlates with susceptibility to SARS-CoV S-driven infection [3]. In general, cell entry receptors are the key factors which determine the tropism and influence the severity of infection. Furthermore, several studies have reported that renin angiotensin aldosterone system (RAAS) inhibitors such as ACE inhibitors and angiotensin II type-1 receptor blockers (ARBs) may up-regulate the expression of ACE2 [4, 5]. Therefore, concerns arose that RAAS inhibitors might increase ACE2 expression, potentially exacerbating the infectivity and severity of SARS-CoV infections. Amidst such historical context, the causative virus of the current pandemic that plunged the world into fear has been identified as SARS-CoV-2. The possibility of SARS-CoV-2 binding to ACE2 similar to the SARS-CoV was suggested. In light of this, concerns have resurfaced that patients receiving RAAS inhibitors may be more susceptible to infection with SARS-CoV-2 and become more severely ill when such an infection occurs. In February and March 2020, early reports from China and Italy indicated a higher prevalence of hypertensive patients among individuals with COVID-19 [6, 7]. (https://www.epicentro.iss.it/coronavirus/bollettino/Report-COVID-2019_20_marzo_eng.pdf) The presence of hypertension was suggested to be associated with a higher mortality rate in COVID-19. This further fueled concerns that hypertension and antihypertensive medications might potentially contribute to an increased infectivity and mortality rate in cases of COVID-19. On March 11, 2020, the World Health Organization (WHO) declared the COVID-19 outbreak a global pandemic, subsequently triggering a state of emergency worldwide. On the very same day, Professor Michael Roth and colleagues commented in a prominent medical journal, "We suggest that patients with cardiac diseases, hypertension, or diabetes, who are treated with ACE2-increasing drugs, are at higher risk for severe COVID-19 infection [8]". Although this is only a hypothesis, the theoretical risk has been emphasized by the media and websites, such as "medications for hypertension and diabetes could raise the risk of deadly coronavirus symptoms" on March 13th and "perhaps 4X more likely to die of COVID-19 if take ACE inhibitors" on March 22nd. (https://www.dailymail.co.uk/news/article-8108735/Medicines-high-blood-pressure-diabetes-worsen-coronavirus-symptoms.html, https://vitamindwiki.com/

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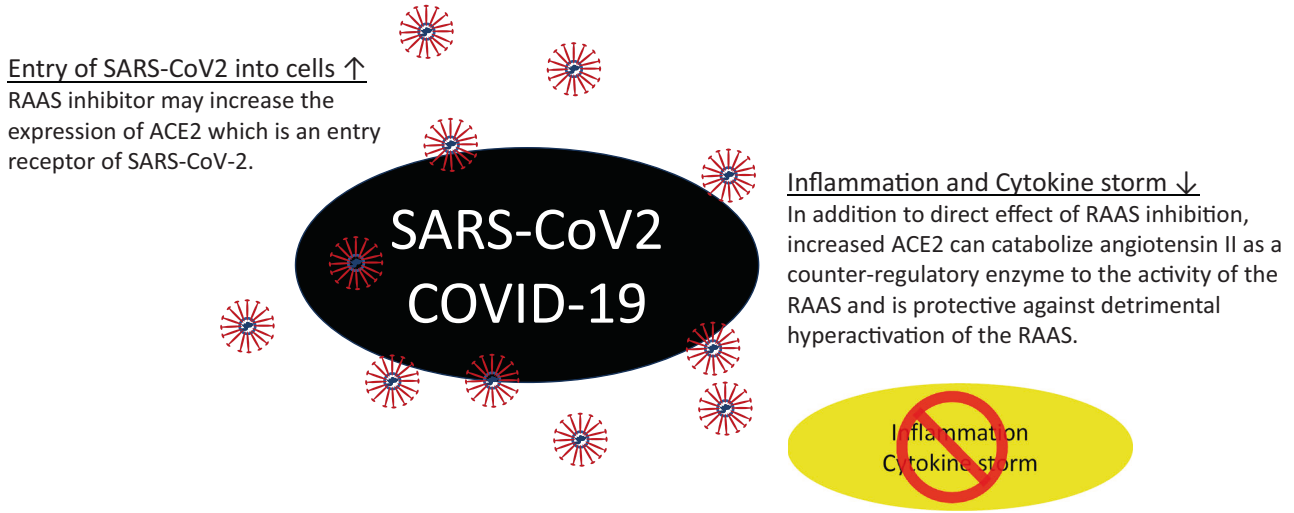

Fig. 1 Suspected two different effects of RAAS inhibitors in COVID-19. ACE2 angiotensin-converting enzyme 2, COVID-19 coronavirus disease 2019, RAAS renin angiotensin aldosterone system, and SARS-CoV2 the severe acute respiratory syndrome coronavirus 2

Perhaps+4X+more+likely+to+die+of+COVID-19+if+take+ACE+inhibitors+%28reduce+blood+pressure%29+-+March+2020) Due to these premature reportings, both patients and clinical practitioners have become hesitant about continuing the use of RAAS inhibitors.

In response to these, medical societies promptly reacted. On March 13th, the European Society of Cardiology criticized the speculation regarding the safety of ACE inhibitor or ARB treatment in relation to COVID-19, stating, "This speculation about the safety of ACE inhibitor or ARB treatment in relation to COVID-19 does not have a sound scientific basis or evidence to support it." (https://www.escardio.org/Councils/Council-on-Hypertension-(CHT)/News/position-statement-of-the-esc-council-on-hypertension-on-ace-inhibitors-and-ang) The Council on Hypertension strongly recommended that physicians and patients continue their usual anti-hypertensive therapy. Around the same time, the International Society of Hypertension and the Japanese Society of Hypertension also issued similar statements. (https://ish-world.com/a-statement-from-the-international-society-of-hypertension-on-covid-19/, http://www.jpnsh.jp/topics/669.html) Subsequently, numerous observational and interventional studies have been conducted, which provided important data in humans on the safety of RAAS inhibitors in relation to COVID-19. The New England Journal of Medicine (NEJM), a leading medical journal, published three papers, one of which was later retracted, stating that the RAAS inhibitors do not worsen the prognosis of COVID-19 [9, 10]. The editors of NEJM criticized the media and websites, and declare that patients should not discontinue ACE inhibitor or ARB therapy out of a concern that they are at increased risk for infection, severe illness, or death during the COVID-19 pandemic [11].

The safety became assured, and furthermore, discussions began to revolve around the potential benefits of RAAS inhibitors in relation to COVID-19 [12, 13]. Since before, a protective role for ACE2 in acute respiratory distress syndrome (ARDS) has been proposed. In the pathophysiology of COVID-19, ACE2 and the RAAS play important roles through the downregulation of ACE2 expression by the SARS-CoV-2 spike protein. Infection with SARS-CoV-2 triggers the activation of the local RAAS while simultaneously reducing the expression of membrane-bound ACE2 in the lungs, which contributes to heightened inflammation and the development of ARDS [14]. ACE2 acts both as the entry receptor for SARS-CoV-2 and as a counterregulatory enzyme against RAAS activity. This counterregulation prevents excessive inflammatory cytokine release, which is responsible for the development of detrimental ARDS. Therefore, RAAS inhibitors may have two different effects in COVID-19 (Fig. 1). Several randomized trials which have compared discontinuation and continuation of RAAS inhibitors during COVID-19, and the evidence from the randomized withdrawal trials supports that existing treatment with an RAAS inhibitor should not be stopped in non-critically ill patients with COVID-19 if prescribed for a preexistent indication [14]. While the safety of continuing ACE inhibitors or ARBs has been confirmed, there are still many uncertainties regarding the potential benefits of ACE inhibitors or ARBs. Further research findings are eagerly awaited to clarify this aspect.

The present study by Miura et al. demonstrates that there was no suggestion that the prescribing of ACE inhibitors and ARBs was affected by the COVID-19 pandemic [15]. During the late 2019 through early 2020 period, a highly fatal novel coronavirus infection spread rapidly worldwide. Due to the unknown fear, people fell into a state of panic,

and as a result, various pieces of information were circulating, leading to further confusion. The debate over the usage of ACE inhibitors and ARBs also fell into this confusion. However, medical societies, including the Japan Hypertension Society, strongly advocated for accurate information, which helped bring the confusion under control. While professional medical societies serve various functions such as research and education, the current case demonstrated an accomplishment in fulfilling a crucial role of effectively conveying accurate information. This achievement is evident in the results of the current study.

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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