ISSN No:-2456-2165

The COVID-19 Code – Cracked – WHO can Save The World (?)!

The missing link – between COVID-19 entry, injury, inflammation, immune response and clinical presentation, deterioration, and death – discovered – WHO can save the world from this pandemic (?)!

Dr. Velmurugan Kuppuswamy MRCP (London UK)
Consultant Cardiologist & Director
Department of Cardiology
Aarogya Hospitals Mogappair West
Chennai Tamil Nadu India

Dr. Deepa Nagarajan M. D
Assistant Professor of Medicine
Division of Hospital Medicine
Emory Johns Creek Hospital
Emory University School of Medicine
James B. Williams Medical Education Building
100 Woodruff Circle
Atlanta, GA 30322

Dr. Suhasini Balasubramaniam FRCR (UK)
Professor & Head of Department
Department of Radiodiagnosis
Government Medical College
Omandurar Government Estate,
Chennai Tamil Nadu India

Dr. Rajarajeswari Velmurugan MRCGP (London UK)
Consultant Family Physician & Director
Aarogya Hospitals
Mogappair West
Chennai Tamil Nadu India

Dr. Safi Kottililkutty MBBS
Consultant PhysicianQueens Medical center Nottingham
University Hospitals NHS trust
Derby Road, Lenton, Nottingham, NG7 2UH
United Kingdom

Dr. (Lt. Commander) Devashish Tarra, MBBS, Indian Navy
(Ex) Honorary Physician
Department of Medicine
Aarogya Hospitals Mogappair West
Chennai Tamil Nadu India

Abstract:- The first step in COVID-19 pathogenesis is the viral spike protein priming by Trans Membrane Peptide Receptor Serine S2 (TMPRSS2). TMPRSS2 promotes viral entry, cell to cell transmission, evasion of host immune response, and Angiotensin-Converting Enzyme 2 (ACE2) downregulation. Androgen through Androgen Receptor (AR) increases TMPRSS2 gene expression. Blocking AR may prevent viral entry and other TMPRSS2 mediated actions.

ACE2 acts as an entry point for COVID-19 and as the counter regulator in Renin-Angiotensin-Aldosterone System (RAAS). RAAS maintains homeostasis of blood pressure, salt and water, inflammation, and immune response – through its two arms called "killer" and "protective pathways." The balance between these two pathways determines life or death in disease states. ACE2 converts Angiotensin II to Angiotensin (1-7), which through Mas receptors mediates anti-inflammatory, immune-modulatory, and anti-fibrotic actions.

Angiotensin II also acts on Angiotensin type 2 Receptor (AT2R) to produce similar actions, called a "protective pathway." Further, Angiotensin II acts through its primary Angiotensin type 1 Receptor (AT1R), causing inflammatory, cytokine storm, and pro-fibrotic response – called "Killer pathway." In COVID, down-regulated ACE2 leads to unabated Angiotensin II/AT1R – "Killer pathway" – actions producing a vicious cycle of "hyper-inflammatory state," resulting in ALI, ARDS, and death. AT1R activation further stimulates the secretion of aldosterone, which through Mineralocorticoid Receptor (MR), augments AT1R mediated 'killer pathway". None of the COVID guideline drugs modulate this pathogenic mechanism. We examine the first time in history the scientific rationale for combined AR/AT1R/MR blockade for COVID-19 treatment and prevention.

ISSN No:-2456-2165

Summary box

What is already known about this subject?

- There is a controversy that ARBs and ACEi must be discontinued during the pandemic as they may increaseCOVID-19 infection and severity by up-regulating the ACE2 viral entry receptor.
- This speculation has been rested with emerging evidence and various global scientific societies coming forward in support of ARBs and ACEi and soliciting their continued clinical use during the pandemic.

What are the new findings?

- Androgen, RAAS, and its two pathways determine viral entry, cell to cell transmission, inflammation, immune response, and clinical manifestation such as acute lung injury (ALI), adult respiratory distress syndrome (ARDS), and death or recovery.
- The upregulation of ACE2 receptors is beneficial, and its downregulation is deleterious.
- Collectively blocking androgen, angiotensin II and aldosterone may stop viral entry into the human cell and may reverseALI, ARDS, and promote recovery.

What are the essential recommendations for policy and practice?

- ARBs and Spironolactone (anti-androgenic and anti-aldosterone) should be included in the WHO guidelines for treatment and prevention of the COVID-19 pandemic. Further, there is an imminent need for an RCT evaluating the prognostic and preventive benefits of the above drugs in the COVID-19 pandemic.

I. INTRODUCTION

"Corona virus crisis may get worse and worse and worse" – warns WHO.

"Let me be blunt, too many countries are headed in the wrong direction, and the virus remains public enemy number one" –

WHO Director-General Dr. Tedros Adhanom Ghebreyesus.

Reuters, July 14, 2020, 06.55 am.[1]

The Covid-19 pandemic cripples the world. Over 34 million people infected, more than 1 million dead since November 2019, and still counting[2]. More than 213 countries affected,with country-specific lockdownsbringing the globaleconomy to a grinding halt. Businesses worldwide have shut down, throwing millionsinto unemployment andthe ensuing hunger and poverty compounding deaths and disabilities. The world has not seen anything of this scale or seriousness since World War II.

Further, there are no vaccines, no specific treatments, and noextended time to develop new drugs to counter the viral pandemic – Its war – and our best option is to seek salvation in existing drugs. At the same time, we await development, human trials, mass production, and clinical application of either vaccine or drugs (or both) – which at the least is a couple of years away. Numerous drugs have been repurposed and experimented in clinical set-up and research trials for COVID patients – namely hydroxychloroquine (HCQ), dexamethasone, methylprednisolone, anti-virals, antibiotics, and vitamins amidst others. Recently the world health organization (WHO) on the 4Th of July 2020 pre-terminated the HCQ, lopinavir, and ritonavir treatment arms of COVID-19 trial following lack of benefits.[3]

The world seems lost for directions in handling this pandemic and is looking up to its scientific community in desperation – for education, understanding, awareness, and ultimately for a solution to treat this viral disease and prevent it. We explored the pathophysiological mechanisms underlying COVID-19 and human interactions to identify potential therapeutic targets, which existing drugs may exploit. Medicines that may have a plausibility to prevent viral infection and potentially reverse pathogenesis.

For the first time in published literature, we propose a new multi-prong therapeutic intervention for COVID -19 with repurposed drugs – that are freely available, widely used, cheap, and safe – based on a fresh understanding of well-established pathophysiological mechanisms and published preclinical and clinical studies. We believe that the novel therapeutic intervention can reverse viral disease in infected patients and prevent COVID-19 infection in healthy individuals.

II.UNDERSTANDING THE ANDROGEN-RENIN-ANGIOTENSIN-ALDOSTERONE-COVID AXIS: RECEPTORS, ENZYMES, AND "KILLER VERSUS PROTECTIVE" PATHWAYS.

Androgen Receptor: The first step in the virus entering the human cell is called the priming – which involves cleaving the viral spike (S) protein. Trans Membrane Peptide Receptor Serine S2 (TMPRSS2)enzymecleaves the "S" protein and facilitates viral entry into the human cell.[4]Curiously,*TMPRSS2* gene expression is promoted through Androgen Receptor (AR)and increases upon exposure to androgens.[5]TMPRSS2 promotes viral entry, cell to cell transmission, evasion of host immune response, and Angiotensin-Converting Enzyme 2 (ACE2)downregulation – and the myriad of itsconsequences.[6]Androgen receptors are potential therapeutic targets to block: firstly viral entry, secondly cell-to-cell transmission, thirdly the evasion of host immune response, and finally ACE2 down-regulation. **(Figures 1).**

Angiotensin-Converting Enzyme 2, AT1, AT2, and Mas Receptor: The cascade of RAAS regulatory and counter-regulatory mechanism is mediated through four primary receptors, namely (Figure 4):ACE2, Angiotensin type 1 (AT1R), Angiotensin type 2 (AT2R) and the Mas receptor. ACE2isa type I transmembrane metallo-carboxypeptidase present on the surface of vascular endothelial and epithelial cells of the renal tubules, lung, and gastrointestinal tract.[7]The membrane-bound ACE2 receptor serves as the

entry point for COVID-19. Conversely, it supports an anti-inflammatory pathway that protects against the misplaced and misdirected host inflammatory and immune response, triggered by the virus – that is counterproductiveif left unchecked.[8,9]

Covid-19 has a 10 to 20 fold higher affinityfor ACE2 receptor on type 2 alveolar epithelial cells than SARS-CoV.[10]ACE2 is homologous to Angiotensin-converting enzyme (ACE)[11], a crucial component of the Renin-Angiotensin-Aldosterone System (RAAS) that converts Angiotensin I to Angiotensin II (Ang II).[12] The effects of Ang II are mediated through the type 1 Angiotensin receptor (AT1R)[13]—the so-called "Killer pathway." **(Figure 2)**

Activation of this pathway causes vasoconstriction and increases renal reabsorption of sodium and water—all serving to increase the blood pressure. ACE-Ang II- AT1R also induces oxidative stress through immune-mediated cytokine storm, fibrosis, and inflammation in various tissues, especially the heart, lungs, and kidneys.[14] In the lung, the immune-mediated effects of ACE-Ang II lead to widespread tissue injury, inflammation, and fibrosis, resulting in increased vascular permeability, acute lung injury (ALI), adult respiratory distress syndrome (ARDS)[15], heightened platelet aggregationand hypercoagulable state**(Figure 2)**.[16]Conversely, Ang II also acts through AT2R activation to decrease platelet aggregation, promote insulin action, and decrease blood pressure through vasodilation.[17]

This counterbalancing mechanism—the "Protective pathway"—is driven by ACE2, a vital component of the counter-regulatory pathway.[18] ACE2 breaks down Ang II into Ang (1-7), which acts through the Mas receptor (found in the alveolar type 2 epithelial cells, cardiovascular and renal tissue) promoting renal sodium and water excretion and vasodilation to decrease blood pressure modestly.[19] Importantly, the Ang (1-7) has an anti-inflammatory effect through nitric oxide production, thereby opposing the pro-inflammatory cascade triggered by Ang II through AT1R.[20]

The majority of organ and tissue systems in the human body co-express the structural components of both "Killer Pathway" and "Protective Pathway. [21] The balance between these two pathways in response to external stimulus determines the extent of tissue injury across organ systems. When extrapolated for COVID-19, data from SARS-CoV shows that ALI characteristic of the severe COVID-19 disease is the result of the "Killer Pathway" left unchecked by the counter-regulatory protective mechanism.[22] Central to this imbalance is the downregulation of the ACE2 receptor.[23]

ACE2 expression is down-regulated by several conditions: aging, excessive Ang II, various disease states, and SARS-CoV-2 viral entry intohuman cells.[24] COVID down-regulatesACE2 receptor: by converting it into its soluble form in serum; by internalizing within the cell (endocytosis), [25]and moreover, by elevating circulating Ang II.Ang II through its action on AT1R triggers a self-perpetuating cycle whereby Ang II downregulatesACE2 up-regulates ACEI, whichfurther increase Ang II levels in local tissues[26] – perpetuating in a vicious cycle leading to a "hyper inflammatory state[27]**(Figure3).**

In-vitro human airway epithelial studies show that a low ACE2 expression is associated with increased COVID infection severity.[28] Animal studies have demonstrated that loss of ACE2 in knock-out (KO) mice caused increased inflammation, oedema and impaired oxygenation compared to wild-type (WT) mice after acid-induced lung injury.[29] However, when these KO mice were pre-treated with AT1R inhibitors before acid-induced ARDS, they had significantly lower lung injury.[30] In other experimental animal models of ARDS, wild-type (WT) and ACE2 knock-out (KO) mice treated with catalytically active recombinant ACE2 protein could escape lung failure.[31] Ang (1-7) administration protected against the lung injury, whereas blocking the Mas receptor reversed this action.[32]

Further, the COVID-19 spike protein-ACE2 attachment enhances circulating Ang II levels. It down-regulates ACE2 expression, both of which push the physiological balance in favour of the "Killer Pathway"[33]**(Figure 3).**On the other hand, AT1R blockade by Angiotensin Receptor Blockers (ARBs) up-regulates ACE2 and protects against lung injury by increased conversion of Ang II to Ang (1-7) diverting the RAAS effects from [ACE/Ang II/AT1R]-mediated "Killer Pathway" to [ACE2/Ang II/Ang (1-7)/AT2R/Mas receptor]-mediated "Protective Pathway"[34](**Figure 4).**The ARB Losartan attenuates the severity of acute lung injury in SARS-CoV infection in both the pre-treatment and post-infection (rescue) models.[35] Thus, it is readily evident that innovative pharmaceutical therapies that activate the ACE2/Ang (1-7)/Mas receptor pathway hold significant promise in treating COVID-mediated lung injury. Further, activation of the AT1R by Ang II stimulates the secretion of aldosterone which through its action on AR augments "killer pathway" induced hyper-inflammation by its effect through the Mineralocorticoid Receptor (MR)(**Figure 4)**

Mineralocorticoid Receptor: Angiotensin II induces aldosterone's release from the adrenal cortex, promoting vascular damage via MR activation.[36] Aldosterone also exerts multiple actions on immune cells, which expressMR.[37]Dysregulated RAAS signaling with enhanced aldosterone-mediated MR activation could represent an important link between COVID-19/ACE2 interaction and inflammatory lung injury, suggesting an interesting therapeutic potential for RAAS inhibitors and in particular MR antagonists[38]**(Figure 4).**

III. CONTROVERSIES AND MISUNDERSTANDINGS SURROUNDING RAAS BLOCKADE IN COVID-19 INFECTION: UP-REGULATED ACE2 ENHANCES COVID ENTRY – DOES IT?

At the outset of the pandemic, concerns emerged that ACE inhibitors and ARBs could theoretically increase the risk and severityof COVID-19 owing to their role in enhanced ACE2 receptor expression.[39] Consequently, summoning their discontinuation in clinical use in hypertensive and cardiovascular patients. This simple deduction unsupported by experimental data may be questionable and deleterious. Further, such a hypothesis may lead to higher rates of cardiovascular deaths in COVID-19 patients.[40]

The findings of a recent meta-analysis essentially put an end to this continuing controversy.[41] The study evaluated over 10,000 patients and provided robust evidence on the absence of risk, from RAAS inhibitors treatment in COVID-19 patients during the pandemic – endorsing several scientific societies' views.[42,43,] On the contrary, emerging evidence ensued in postulation for the protective role of ARBs against disease progression and mortality inthe COVID-19[44]– given the recently found protective action of the ACE2-Angiotensin (Ang) 1-7-Mas axis on the lung. RAAS blockers augment thisprotective processby reducing Ang II-AT1R stimulation, increasing Ang II substrate, and up-regulationof ACE2, and leading to a larger increase in Ang 1-7. [45]Therefore it is clear from ensuing evidence that the up-regulation of the ACE2 receptor is beneficial (contrary to recently triggered controversy), and down-regulation is deleterious in the general population and particularly in COVID-19 patients**(Figure 2).**

Serendipitously, recent research suggests that therapy with RAAS Inhibitors decreases mortality in COVID-19 patients with hypertension.[46]Devoid this controversy, RAAS blockers would have already found clinical use in this pandemic. In the light of repurposed drugs on guidelines – playingno role inmodulating androgen-RAAS-COVID axis –showing minimal benefits,RAAS blockers may have saved thousands of lives and prevented millions of hospitalization in the last nine months – an opportunitymissed – but better late than never.

IV.NOVEL THERAPEUTIC INTERVENTIONS FOR COVID-19: PLEOTROPISM OF SPIRONOLACTONE AND ARBS.

Theonly available optionin the middle of a pandemic to treat COVID-19 is repurposingexisting drugs – that modulate androgen and RAAS and its two countering pathways. While waiting for trials, mass production of drugs or vaccine and their clinical applications could be time-consuming and detrimental.

An ideal repurposed drug in fighting the pandemic should possess the following five characteristics:

1. Safe, widely available, extensively used and cheap
2. Cardio-pulmonary protective profile
3. Block killer pathway
4. Facilitate the protective pathway
5. Plausibly prevent viral entry and infection.

Drugs that can block the viral entry – Spironolactone: The modest anti-androgenic effects of Spironolactone on AR may prevent the initial priming of COVID-19 "S" protein by TMPRSS2.[47] It may further block TMPRSS2 induced: cleaving of ACE2, cell to cell transmission, and ACE2 down-regulation[48] – thatimpairs the counter-regulation of the angiotensinII/AT1 mediated killer pathway**(Figure 1).** The androgen receptor regulates both ACE2 and TMPRSS2.[49]Many androgen blockers are currently in clinical use, but Spironolactone might well be best in the pandemic because of its concomitant cardio-pulmonary benefits. Spironolactone has an excellent safety profile and is and widely available as 25mg or 50 mg preparations.(**Figure 4)**

Drugs that block the killer pathway and facilitate recovery pathway:ACEis, ARBs, and Spironolactone: An autopsy analysis of a group of patients who succumbed with severe COVID-19 during this pandemic showed hyper-inflammation and cytokine storm syndrome leading to ARDS and death.[50]Astudy by Liu et al[51]demonstrated that patients with COVID-19 pneumonia had significantly higher serum angiotensin II levels than healthy subjects.Further angiotensin II levels were linearly associated with viral load and lung injury. Recent evidence suggests that ACEIs/ARBs may be beneficial in patients with ALI or ARDS.[52]A meta-analysis of ACEIs and ARB's trials showed a reduced risk of pneumonia and pneumonia-related mortality in the treatment group than the control.[53]

In a Korean study with 132 patients with ARDS, patients taking ACEIs/ARBs showed better survival than controls, although severallimitations could have influenced the results.[54]Understanding the pathophysiology of SARS-CoV-2 infection and pleiotropic effects of ACEIs/ARBs suggests that these agents may have a potential role in managing select patients with severe COVID-19.[55] Although ACEi decreases Ang II levels and the harmful effect through AT1 receptor – at clinical doses, ACEi only partially affects this conversion, as 40% of Ang II formation occurs outside the ACE pathway.[56]Evidence suggests that ARBs fair better than ACEi.[57]

ARBs increase Ang II levels in all organs, except in the kidney.[58] The consequence of this increase are two – one is the up-regulation of ACE2 and two, a redirection of Ang II activity through anti-inflammatory and vasodilatory ACE2/ AT 2R/Mas receptor– the protective pathway.[59]Further ACE2, compared to ACE, regulates both Ang II and Ang (1–7) local levels to a higher degree.[60]Emerging evidence highlight that ARBs have a higher potential to rebalance RAAS pathways compared to ACEifavourably.[61] Animal models of ALI, including a model of SARS-CoV infection, suggest that ARBs may mitigate COVID-19 by attenuating Ang II-mediated ALI by blocking AT1R.[62]

The free circulating forms of ACE2 may inactivate COVID-19 by stopping its coupling to membrane ACE-2 receptor (competitive receptor site)and consequent entry into pulmonary endothelial cells.[63, 64]Opening up a therapeutic avenue for soluble ACE2 as a potential intervention to stop viral entry. Spironolactone – a potassium-sparing diuretics and an antihypertensive drug acting on RAAS, increases the circulating form of ACE-2 expression in plasma three to fivefold.[65]Spironolactone also increases levels of ACE2 messenger RNA in humans [66]– it is in widespread use for cardiovascular and hyper-androgenic conditions.[67]Use of Spironolactone along with ARBs and resultant elevated ACE2 expression may prevent the consequences of organ damagein patients with Covid-19 infection through inhibition of angiotensin II and its direct effects mediated by MR and AT1R. [68, 69] **(Figure 4).**

As a result of varying severity during the pandemic, patients with overactive RAAS may differ in their response to therapy. The timing of initiation of treatment is crucial in COVID-19 infection.RAAS modulation may have significantly beneficial effects early on in the disease process, and this underscores the exigency for immediate recommendations of these drugs in WHO, International, and National guidelines.To pave the way for their imminent clinical use in selected patients with COVID-19 infections and high-risk healthy individuals such as healthcare workers and primary and secondary COVID patients' contacts.

V. CONCLUSION

Current therapeutic interventions in COVID-19beyond supportive care include repurposed drugs– all showing minimal promise. Effective treatments are, therefore, vital to handle the surge of COVID-19 infections, which at present, is rampaging across the globe.Any intervention promptlypushed to the warfront may potentially alter the course of this pandemic and may save the world.

Androgen and RAAS drive and remain the backbone of the pathogenesis of COVID-19 infection and its clinical presentations.Unfortunately, no single drug modulating this pathogenesis has found a place in the WHO, International, or National guidelines. While few trials evaluate some of these drugs individually, there are no trials in the present process, evaluating the combination of Androgen – AT1R – and Aldosterone blockade. However, imperative waiting for their design, conduction, and results will waste valuable time atthis acute crisis of already devastating pandemic.

We have put forth a sound scientific rationale for the medical-scientific community to consider and recommend the drugs – that directly act on reversing viral pathogenic mechanisms – for early treatment and prevention ofCOVID-19 and in parallel randomized control trial (RCT).The rationale for using Androgen and RAAS blockersis built on a robust understanding of COVID-19pathophysiology, in which the existing repurposed drugs on the guidelines lack.We urge the WHO scientific committee to take “Suo Motto” cognizance of the case in points and include ARBs[70] (Telmisartan, losartan, etc.) and AR-MR blocker (Spironolactone) in their guidelines. We conclude with the following recommendations for the management of COVID-19 and an RCT.

RECOMMENDATIONS FOR PREVENTION AND TREATMENT OF COVID-19 INFECTION AND AN RCT

1. Use AR-MR blocker spironolactone at 25 mg/day single dose in healthy subjects with no contradictions, to prevent full-blown viral infection. We reckon that this may block the viral entry, cell to cell transmission, evasion of host immune response, and downregulation of the ACE2.**(Figure 4)**
2. In the first instance, it could be tried in high-risk healthy subjects such as all healthcare workers, primary, and secondary contacts ofCOVID patients.
3. Use 20mg of Telmisartan and25 mg of Spironolactonetwice a day in COVID patients and up-titrate the dose as required to its approved maximum daily dose,while monitoring clinical response, blood pressure, renal function, and electrolytes.
4. ARB and AR-MR blocker is best initiated at an early stage of infection toreverse and stop the Androgen-RAAS-COVID pathogenesis and the resultant hyper-inflammatory state that may lead to ALI, ARDS, MSOF, and death.**(Figure 4)**
5. As a priority, it may be offered to COVID patients in the age group between 30 – 55 years who supposedly have high androgen drive.Further, it may be initiated in allCOVID patients with comorbidities such as diabetes mellitus, hypertension, cardiovascular and pulmonary pathologies.
6. There is an imminent need for an RCT to evaluate the preventive and prognostic benefits of combined blockade of androgen and RAAS with Spironolactone and ARB in COVID-19 patients and healthy subjects.

"Entire pandemic is about the balance between the RAAS "killer and protective pathway," the solution is in blocking the former and facilitating the later, Spironolactone and Telmisartan are best suited for that task."
Dr VC Kuppuswamy et al.

REFERENCES

[1]. https://in.reuters.com/article/us-health-coronavirus-who-idINKCN24E1ZK
[2]. https://covid19.who.int/
[3]. https://www.who.int/news-room/detail/04-07-2020-who-discontinues-hydroxychloroquine-and-lopinavir-ritonavir-treatment-arms-for-covid-19
[4]. Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. Cell 2020;1–19

[5]. Mikkonen L, Pihlajamaa P, Sahu B, Zhang F-P, Jänne OA. Androgen receptor and androgen-dependent gene expression in the lung. Molecular and Cellular Endocrinology 2010;317(1-2):14–24
[6]. Jian Shang, Yushun Wan, Chuming Luo, Gang Ye, Qi bin Geng, Ashley Auerbach, Fang Li. Cell entry mechanisms of SARS-CoV-2 Proceedings of the National Academy of Sciences May 2020, 117 (21) 11727-11734; DOI: 10.1073/pnas.2003138117
[7]. Montopoli et al., Androgen-deprivation therapies forprostate cancer and riskof infection by SARS-CoV-2: a population-based study ANNALS OF ONCOLOGY, HTTPS://DOI.ORG/10.1016/J.ANNONC.2020.04.479
[8]. Zhang, H., Penninger, J.M., Li, Y. et al. Angiotensin-converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor: molecular mechanisms and potential therapeutic target. Intensive Care Med 46, 586–590 (2020). https://doi.org/10.1007/s00134-020-05985-9
[9]. Imai, Y., Kuba, K., Rao, S. *et al.* Angiotensin-converting enzyme 2 protects from severe acute lung failure. *Nature* 436, 112–116 (2005). https://doi.org/10.1038/nature03712
[10]. Shang, J., Ye, G., Shi, K. et al. Structural basis of receptor recognition by SARS-CoV2. Nature 581, 221–224 (2020). https://doi.org/10.1038/s41586-020-2179-y
[11]. Rice GI, Thomas DA, Grant PJ, Turner AJ, Hooper NM. Evaluation of angiotensin-converting enzyme (ACE), its homolog ACE2, and neprilysin in angiotensin peptide metabolism. Biochem J 2004; 383:45-51.
[12]. J Godbout K Parsons T Baronas E Hsieh F 2002 Hydrolysis of biological peptides by human angiotensin-converting enzyme-related carboxypeptidase VCHP Kaushik, VDLGJ Tang - Journal of Biological Chemistry
[13]. M. de Gasparo, K. J. Catt, T. Inagami, J. W. Wright, and Th. Unger. International Union of Pharmacology. XXIII. The Angiotensin II Receptors. Pharmacological Reviews September 1, 2000, 52 (3) 415-472;
[14]. Antonio Colantuoni et al. MINI REVIEW ARTICLE COVID-19 Sepsis and Microcirculation Dysfunction Front. Physiol., June 26, 2020, | https://doi.org/10.3389/fphys.2020.00747
[15]. Moccia, F., Gerbino, A., Lionetti, V., Miragoli, M., Munaron, M. L., Pagliaro, P., et al. (2020). COVID-19-associated cardiovascular morbidity in older adults: a position paper from the Italian Society of Cardiovascular Researches. GeroScience 20, 1–29. doi: 10.1007/s11357-020-00198-w
[16]. Leisman, D. E., Deutschman, C., and Legrand, M. (2020). Facing COVID-19 in the ICU; vascular dysfunction, thrombosis, and dysregulated inflammation. Intensive Care Med. 28:1–4. doi: 10.1007/s00134-020-06059-6
[17]. Leisman, D. E., Deutschman, C., and Legrand, M. (2020). Facing COVID-19 in the ICU; vascular dysfunction, thrombosis, and dysregulated inflammation. *Intensive Care Med*. 28:1–4. doi: 10.1007/s00134-020-06059-6
[18]. Unger TM, Steckelings UM, Santos RAS. The Protective Arm of the Renin-Angiotensin System: Functional Aspects and Therapeutic Implications. Elsevier Academic Press: Amsterdam, 2015
[19]. Robert M. Carey, AT2 Receptors: Potential Therapeutic Targets for Hypertension, American Journal of Hypertension, Volume 30, Issue 4, April 01, 2017, Pages 339 347 https://doi.org/10.1093/ajh/hpw121
[20]. Daniel Henrion, Nathalie Kubis, and Bernard I. Lévy. Physiological and Pathophysiological Functions of the AT2 Subtype Receptor of Angiotensin II, Hypertension Volume 38, Issue 5
[21]. " Inagami T. Molecular biology and signaling of angiotensin receptors: an overview. Journal of the American Society of Nephrology: JASN. 1999 Jan; 10 Suppl 11:S2-7.
[22]. D'Ardes D, Boccatonda A, Rossi I, Guagnano MT, Santilli F, Cipollone F, et al. COVID-19 and RAS: unravelling an unclear relationship. Int J Mol Sci 2020; 21(8):3003.
[23]. Imai Y, Kuba K, Rao S, Huan Y, et al. Angiotensin-converting enzyme 2 protects from severe acute lung failure. Nature, 2005, *436*, 112–116.
[24]. Ciulla, M.M. SARS-CoV-2 down-regulation of ACE2 and pleiotropic effects of ACEIs/ARBs. *Hypertens Res* (2020). https://doi.org/10.1038/s41440-020-0488-z
[25]. Y. Li, W. Zhou, L. Yang, R. You. Physiological and pathological regulation of ACE2, the SARS-CoV-2 receptor. Pharmacol Res, 14 (April (157)) (2020), Article 104833
[26]. Mahmoud Gheblawi, Kaiming Wang, Anissa Viveiros, et al. Quynh Nguyen, Jiu-Chang Zhong, Anthony J. Turner, Mohan K. Raizada, Maria B. Grant, Gavin Y. Oudit. Angiotensin-Converting Enzyme 2: SARS-CoV-2 Receptor and Regulator of the Renin-Angiotensin System. https://doi.org/10.1161/CIRCRESAHA.120.317015 Circulation Research. 2020;126:1456–1474
[27]. " Vijay Koka, Xiao Ru Huang, Arthur C.K. Chung, Wansheng Wang, Luan D. Truong, and Hui Yao Lan Angiotensin II Up-Regulates Angiotensin I-converting Enzyme (ACE), but Down-Regulates ACE2 via the AT1-ERK/p38 MAP Kinase Pathway. Am J Pathol. 2008 May; 172(5): 1174 1183. doi: 10.2353/ajpath.2008.070762 PMCID: PMC2329828 PMID: 18403595
[28]. Jia HP, Look DC, Shi L, *et al.* ACE2 receptor expression and severe acute respiratory syndrome coronavirus infection depend on differentiation of human airway epithelia. *J Virol* 2005; 79:14614–14621

[29]. ImaiY,KubaK,RaoS,*etal.*Angiotensin-convertingenzyme2protectsfromsevereacutelungfailure .*Nature* 2005; 436: 112–116
[30]. ImaiY,KubaK,RaoS,*etal.*Angiotensin-convertingenzyme2protectsfromsevereacutelungfailure .*Nature* 2005; 436: 112–116
[31]. Sun ML, Yang JM, Sun YP, et al. [Inhibitors of RAS might be a good choice for COVID-19 pneumonia]. Zhonghua Jie He He Hu Xi Za Zhi 2020; 43: 219–222
[32]. Klein, Nadine DVM1; Gembardt et al. Angiotensin-(1–7) Protects From Experimental Acute Lung Injury, Critical Care Medicine: November 2013 - Volume 41 - Issue 11 - p e334-e343 doi: 10.1097/CCM.0b013e31828a6688
[33]. Deshotels MR, Xia H, Sriramula S, *et al.* Angiotensin II mediates angiotensin-converting enzyme type 2 internalization and degradation through an angiotensin II type I receptor-dependent mechanism. *Hypertension* 2014; 64:1368–1375
[34]. Juan Meng, Guohui Xiao, Juanjuan Zhang, Xing He, Min Ou, Jing Bi, Rongqing Yang, Wencheng Di, Zhaoqin Wang, Zigang Li, Hong Gao, Lei Liu & Guoliang Zhang (2020) Renin-angiotensin system inhibitors improve the clinical outcomes of COVID-19 patients with hypertension, Emerging Microbes & Infections, 9:1, 757-760, DOI: 10.1080/22221751.2020.1746200
[35]. Zeinalian, M., Salari-Jazi, A., Jannesari, A., & Khanahmad, H. (2020). A potential protective role of losartan against coronavirus-induced lung damage. Infection Control & Hospital Epidemiology, 41(6), 752-753. doi:10.1017/ice.2020.80
[36]. Biwer LA, Wallingford MC, Jaffe IZ. Vascular mineralocorticoid receptor: an evolutionary mediator of wound healing turned harmful by our modern lifestyle. Am J Hypertens. 2019;32:123–34
[37]. Belden Z, Deiuliis JA, Dobre M, Rajagopalan S. The role of the mineralocorticoid receptor in inflammation focuses on kidney and vasculature. Am J Nephrol. 2017; 46:298–314.
[38]. KubaK,ImaiY,RaoS,GaoH,GuoF, GuanB,HuanY,YangP,ZhangY, DengW,etal.Acrucialroleofangiotensin-convertingenzyme2(ACE2) inSARScoronavirus-inducedlunginjury.*NatMed*.2005;11:875-879.doi: 10.1038/nm1267
[39]. FangL,KarakiulakisG,RothM.Arepatientswithhypertension and diabetesmellitusatincreasedriskforCOVID-19infection? *Lancet Respir Med* 2020; 8: e21.
[40]. Kuster GM, Osswald S. Switching antihypertensive therapy in times of COVID-19: why we should wait for the evidence. Eur Heart J 2020;41:1857.
[41]. Flacco ME, Acuti Martellucci C, Bravi F, et al. Treatment with ACE inhibitors or ARBs and risk of severe/lethal COVID-19: a meta-analysis. Heart, Published Online First: July 01, 2020. doi: 10.1136/heartjnl-2020-317336
[42]. European Society of Cardiology. Position statement of the ESC Council on hypertension on ACE inhibitors and angiotensin receptor blockers, 2020. Available:https://www.escardio.org/Councils/Council-on-Hypertension-(CHT)/News/position-statement-of-the-esc-council-on-hypertension-on-ace-inhibitors-and-ang
[43]. American Heart Association. Patients taking ACE-i and Arbs who contract COVID-19 should continue treatment, unless otherwise advised by their physician, 2020. Available:https://newsroom.heart.org/news/patients-taking-ace-i-and-arbs-who-contract-covid-19-should-continue-treatment-unless-otherwise-advised-by-their physician?utm_campaign=sciencenews19-20&utm_source=science-news&utm_medium=phd-link&utm_content=phd03-17-20
[44]. Association of Inpatient Use of Angiotensin-Converting Enzyme Inhibitors. Angiotensin II Receptor Blockers With Mortality Among Patients With Hypertension Hospitalized With COVID-19, Peng Zhang et al. Circulation Research. Volume: 126, Issue: 12, Pages: 1671-1681, DOI: (10.1161/CIRCRESAHA.120.317134)
[45]. Bavishi C, Maddox TM, Messerli FH. Coronavirus disease 2019 (COVID-19) infection and renin-angiotensin system blockers. JAMA Cardiol,2020. doi:10.1001/ jamacardio.2020.1282
[46]. Association of Inpatient Use of Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers With Mortality Among Patients With Hypertension Hospitalized With COVID-19, Peng Zhang et al. Circulation Research. Volume: 126, Issue: 12, Pages: 1671-1681, DOI: (10.1161/CIRCRESAHA.120.317134)
[47]. Wambier, C.G., Goren, A., Vaño-Galván, S., Ramos, P.M., Ossimetha, A., Nau, G., Herrera, S. and McCoy, J. (2020), Androgen sensitivity gateway to COVID -19 disease severity. Drug Dev Res. doi:10.1002/ddr.21688
[48]. Wambier, C.G., Goren, A., Vaño-Galván, S., Ramos, P.M., Ossimetha, A., Nau, G., Herrera, S. and McCoy, J. (2020), Androgen sensitivity gateway to COVID -19 disease severity. Drug Dev Res. doi:10.1002/ddr.21688
[49]. Adeline Heurich, Heike Hofmann Winkler, Stefanie Gierer, et al. TMPRSS2 and ADAM17 Cleave ACE2 Differentially and Only Proteolysis by TMPRSS2 Augments Entry Driven by the Severe Acute Respiratory Syndrome Coronavirus Spike Protein Journal of Virology Dec 2013, 88 (2) 1293-1307; DOI: 10.1128/JVI.02202-13
[50]. Chen Tao, Wu Di, Chen Huilong, Yan Weiming, Yang Danlei, Chen Guang, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study BMJ 2020; 368:m1091

[51]. Junyi Guo MD, Zheng Huang MD, Li Lin MD, Ph.D. linlee271227@163.com , and Jiagao Coronavirus Disease 2019 (COVID-19) and Cardiovascular Disease: A Viewpoint on the Potential Influence of Angiotensin-Converting Enzyme Inhibitors/Angiotensin Receptor Blockers on Onset and Severity of Severe Acute Respiratory Syndrome Coronavirus 2 Infection
[52]. Bavishi C, Maddox TM, Messerli FH. Coronavirus Disease 2019 (COVID-19) Infection and Renin-Angiotensin System Blockers. *JAMA Cardiol.* 2020;5(7):745–747. doi:10.1001/jamacardio.2020.1282
[53]. Caldeira Daniel, Alarcão Joana, Vaz-Carneiro António, Costa João. Risk of pneumonia associated with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers: a systematic review and meta-analysis BMJ 2012; 345:e4260
[54]. Kim J, Choi SM, Lee J, et al.Effect of Renin-Angiotensin System Blockade in Patients with Acute Respiratory Distress Syndrome: A Retrospective Case-Control Study. Korean J Crit Care Med 2017; 32: 154–163. doi:10.4266/kjccm.2016.00976
[55]. Caldeira D, Alarcão J, Vaz-Carneiro A, Costa J. Risk of pneumonia associated with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers: systematic review and meta-analysis. *BMJ*. 2012;345: e4260. doi:10.1136/bmj.e4260
[56]. Hollenberg NK, Fisher ND, Price DA. Pathways for angiotensin II generation in intact human tissue: evidence from the renin system's comparative pharmacological interruption. Hypertension 1998; 32: 387–392. doi:10.1161/01.HYP.32.3.387
[57]. Ferrario CM, Jessup J, Chappell MC, et al. effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockers on cardiac angiotensin-converting enzyme 2. Circulation 2005; 111: 2605–2610.
[58]. Campbell DJ. Endogenous angiotensin II levels and the mechanism of action of angiotensin-converting enzyme inhibitors and angiotensin receptor type 1 antagonists. Clin Exp Pharmacol Physiol Suppl 1996; 3: S125–S131. doi:10.1111/j.1440-1681.1996.tb03073.
[59]. Turner AJ. ACE2 cell biology, regulation, and physiological functions. In: Unger T, Steckelings UM, dos Santos RAS, eds. The Protective Arm of the Renin-Angiotensin System (RAS). Boston, Academic Press, 2015; pp. 185–189.
[60]. Tikellis C, Thomas MC. Angiotensin-converting enzyme 2 (ACE2) is a crucial modulator of the renin-angiotensin system in health and disease. Int J Pept 2012; 2012: 256294.
[61]. Tikellis C, Thomas MC. Angiotensin-converting enzyme 2 (ACE2) is a key modulator of the renin-angiotensin system in health and disease. Int J Pept 2012; 2012: 256294.
[62]. Wosten-van Asperen RM, Lutter R, Specht PA, et al. Acute respiratory distress syndrome leads to a reduced ratio of ACE/ACE2 activities and is prevented by angiotensin-(1-7) or an angiotensin II receptor antagonist. J Pathol 2011; 225: 618–627.
[63]. Batlle D, Wysocki J, Satchell K. Soluble angiotensin-converting enzyme 2: a potential approach for coronavirus infection therapy? *Clin Sci (Lond)* 134: 543–545, 2020. doi:10.1042/CS20200163.
[64]. Wysocki J, Ye M, Rodriguez E, González-Pacheco FR, Barrios C, Evora K, Schuster M, Loibner H, Brosnihan KB, Ferrario CM, Penninger JM, Batlle D. Targeting the degradation of angiotensin II with recombinant angiotensin-converting enzyme 2: prevention of angiotensin II-dependent hypertension. *Hypertension* 55: 90–98, 2010. doi:10.1161/HYPERTENSIONAHA.109.1384
[65]. Keidar S, Gamliel-Lazarovich A, Kaplan M, Pavlotzky E, Hamoud S, Hayek T, Karry R, Abbasi Z. Mineralocorticoid receptor blocker increases angiotensin-converting enzyme 2 activity in congestive heart failure patients. *Circ Res* 97: 946–953, 2005. doi:10.1161/01.RES.0000187500.24964.7A
[66]. Shlomo Keidar, Aviva Gamliel-Lazarovich, Marielle Kaplan, et al. Mineralocorticoid Receptor Blocker Increases Angiotensin-Converting Enzyme 2 Activity in Congestive Heart Failure Patients. Originally published22 Sep 2005https://doi.org/10.1161/01.RES.0000187500.24964.7ACirculation Research. 2005;97:946–953
[67]. https://www.mayoclinic.org/drugs-supplements/spironolactone-oral-route/description/drg-20071534
[68]. Sato A, Saruta T, Funder JW. Combination therapy with aldosterone blockade and renin-angiotensin inhibitors confers organ protection. Hypertens Res 2006;29:211-216
[69]. Liaudet, L., Szabo, C. Blocking mineralocorticoid receptor with Spironolactone may have a wide range of therapeutic actions in severe COVID-19 disease. *Crit Care* 24, 318 (2020). https://doi.org/10.1186/s13054-020-03055-6.
[70]. Vaduganathan M, Vardeny O, Michel T, McMurray JJV, Pfeffer MA, Solomon SD. Renin-angiotensin-aldosterone system inhibitors in patients with Covid-19. N Engl J Med 2020; 382:1653-1659.

ISSN No:-2456-2165

Figures 1. The Role of Male Sex Hormone – Androgen – in Covid-19 Infection

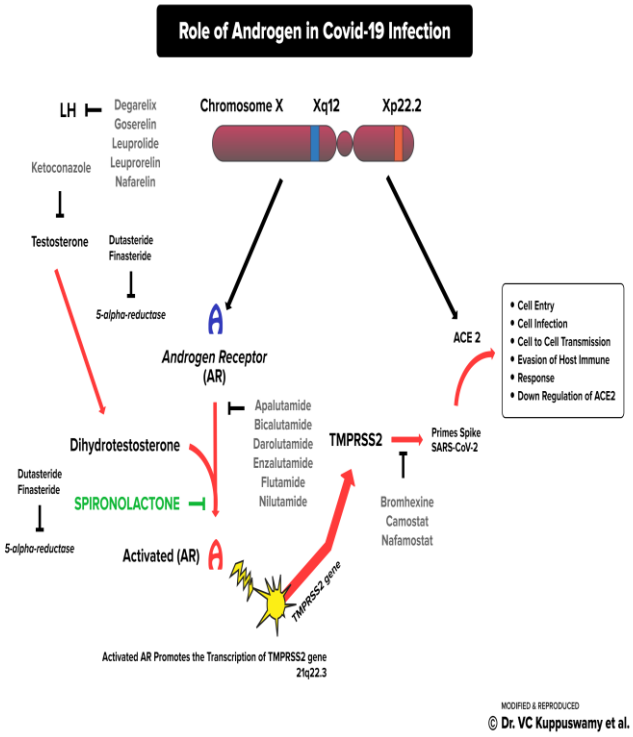

Figure 1: Role of Androgen in COVID-19 infection. Red arrows highlight the steps that are targeted by androgen blockers. The first step in COVID-19 pathogenesis is cleaving (priming) of viral spike protein by Trans Membrane Peptide Receptor Serine S2 (TMPRSS2). TMPRSS2 promotes viral entry, cell to cell transmission, evasion of host immune response, and Angiotensin-Converting Enzyme 2 (ACE2) downregulation. TMPRSS2 gene expression is encouraged through the Androgen Receptor (AR) and increases upon exposure to androgens. Blocking AR may prevent viral entry and other TMPRSS2 mediated actions. Androgen receptor inhibitor Spironolactone blocks androgen-mediated TMPRSS2 gene transcription and its ensuing effects.

Figure 2: The RAAS and Balance Between Killer and Protective Pathway In COVID-19 Infection

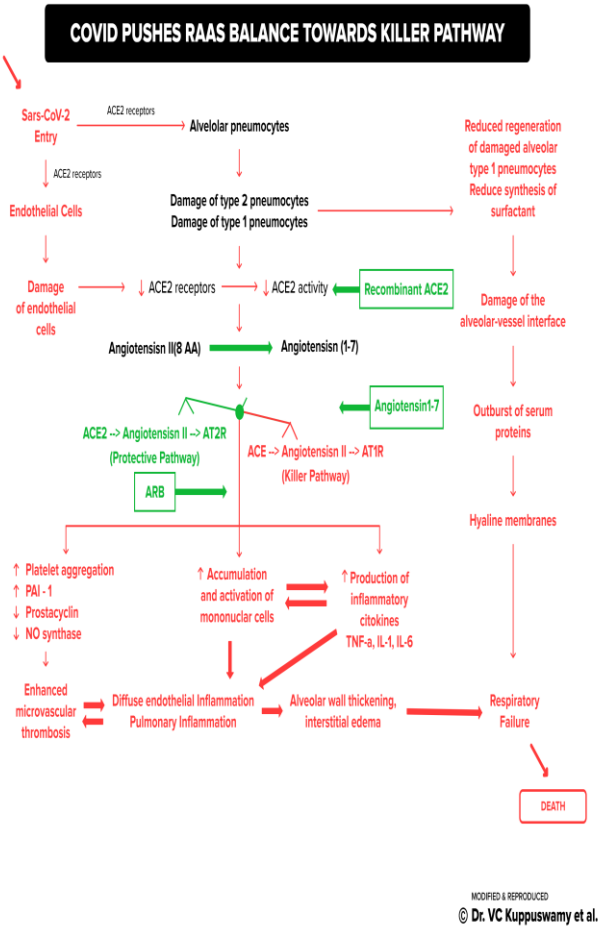

Figure 2: Central role of the imbalance between "killer" (ACE→Angiotensin II→AT1) and "protective"pathway (ACE2→Angiotensin1-7→Mas receptor) axis in the setting of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Green arrows denote the potential targets of treatments. IL indicates interleukin; PAI, plasminogen activator inhibitor; and TNF, tumour necrosis factor.

Figure 3: COVID -19 induced Angiotensin II Vicious Cycle and Hyper Inflammatory State

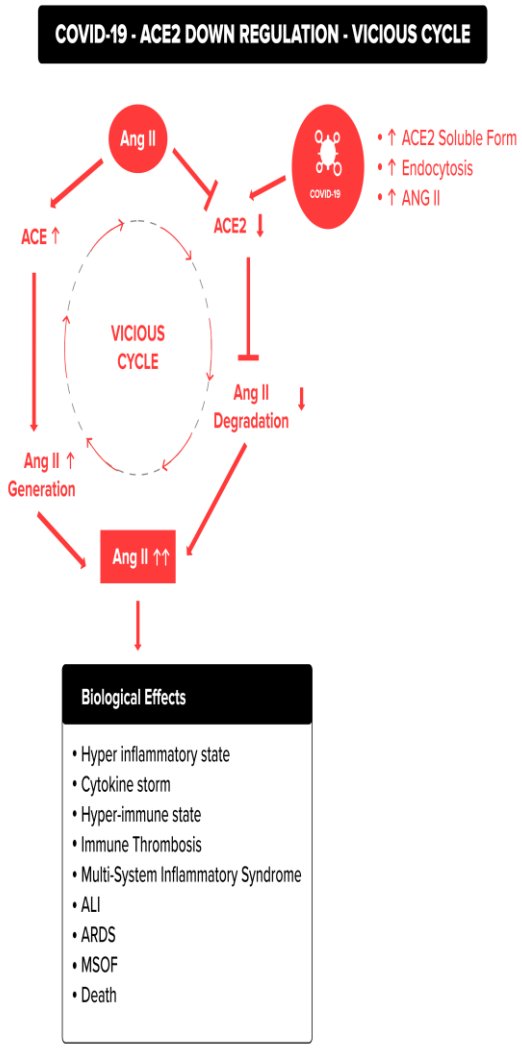

Figure 3: Scheme for physiological and pathological Ang II auto-regulatory feedback loop leading to its biological effects. Ang II signals through the AT1 receptor to up-regulate the ACEI-dependent Ang II generating pathway and down-regulate the ACE2-mediated Ang II degradation pathway, ultimately leading to the elevation of Ang II levels and hypertension. In COVID-19, down-regulated ACE2 leads to unabated Angiotensin II/AT1R action producing a further downregulation of ACE2 and up-regulation of ACEI, leading to a vicious cycle of "hyper inflammatory state" resulting in ALI, ARDS, and death.

Figure 4: Novel Therapeutic Interventions Blocking AR-MR-The Killer Pathway and Facilitating The Protective Pathway

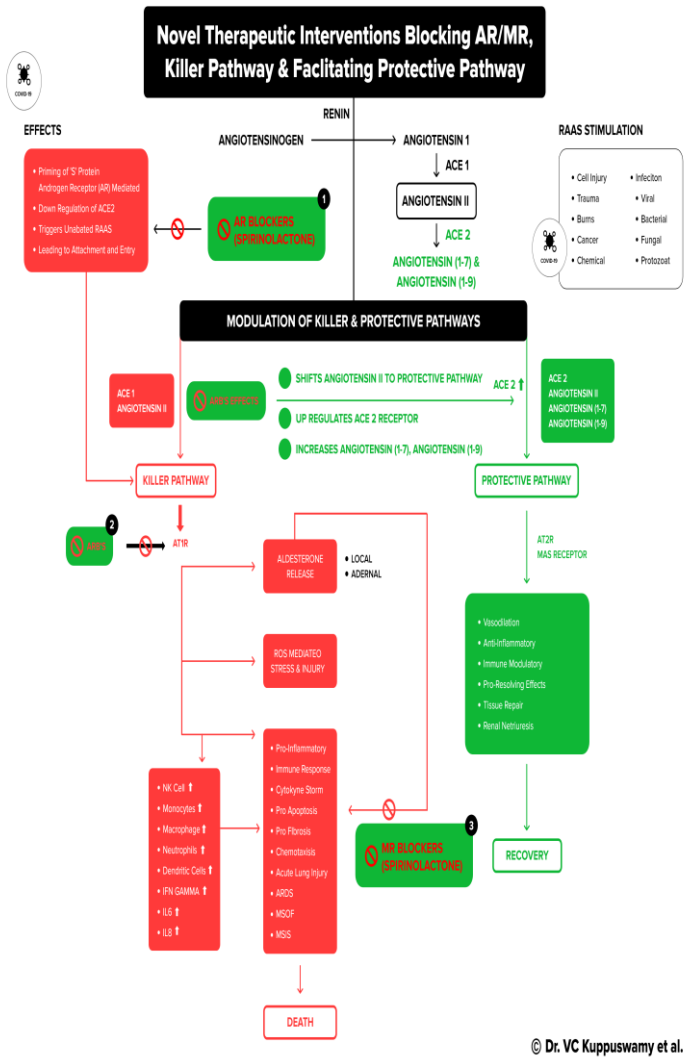

Figure 4: Use of AR-blocker spironolactone may block the viral entry, cell to cell transmission, evasion of host immune response, and downregulation of the ACE2. ARB and MR blocker Spironolactone initiated at an early stage of infection may reverse and stop the RAAS - COVID pathogenesis and the resultant hyper-inflammatory state that may lead to ALI, ARDS, MSOF and death