Disclosure potential conflict of interest

voor bijeenkomst mogelijk relevante relatie:	bedrijfsnaam:
onderzoeksgeld	Alnylam Pharmaceuticals (angiotensinogeen siRNA)

Erasmus MC
University Medical Center Rotterdam

Nationaal Hypertensie Congres
Zeist, 18 juni 2021

Hypertensie en COVID-19

A.H. Jan Danser

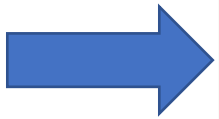
Afdeling Interne Geneeskunde,

Erasmus MC, **Rotterdam**

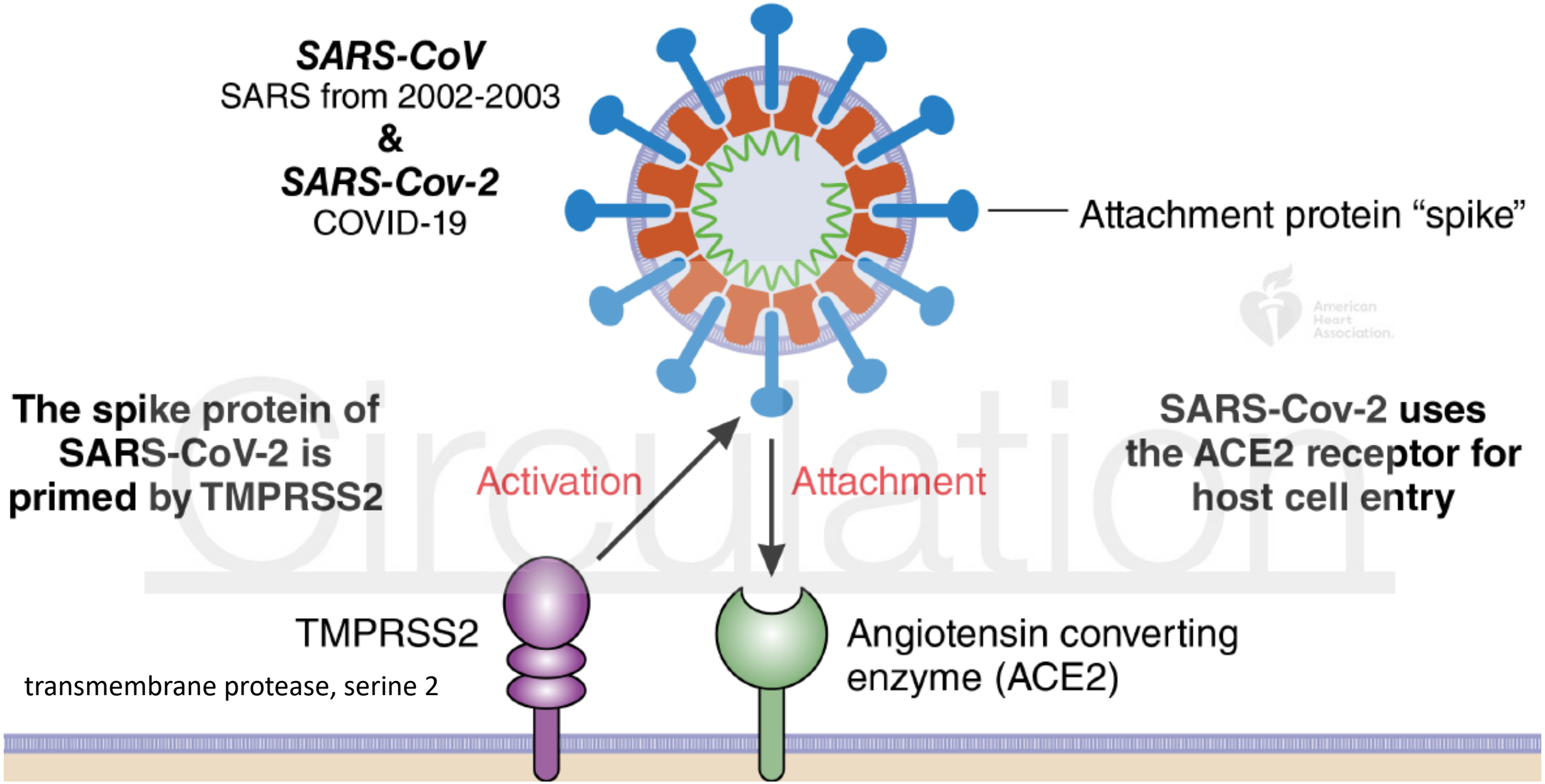
JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus–Infected Pneumonia in Wuhan, China

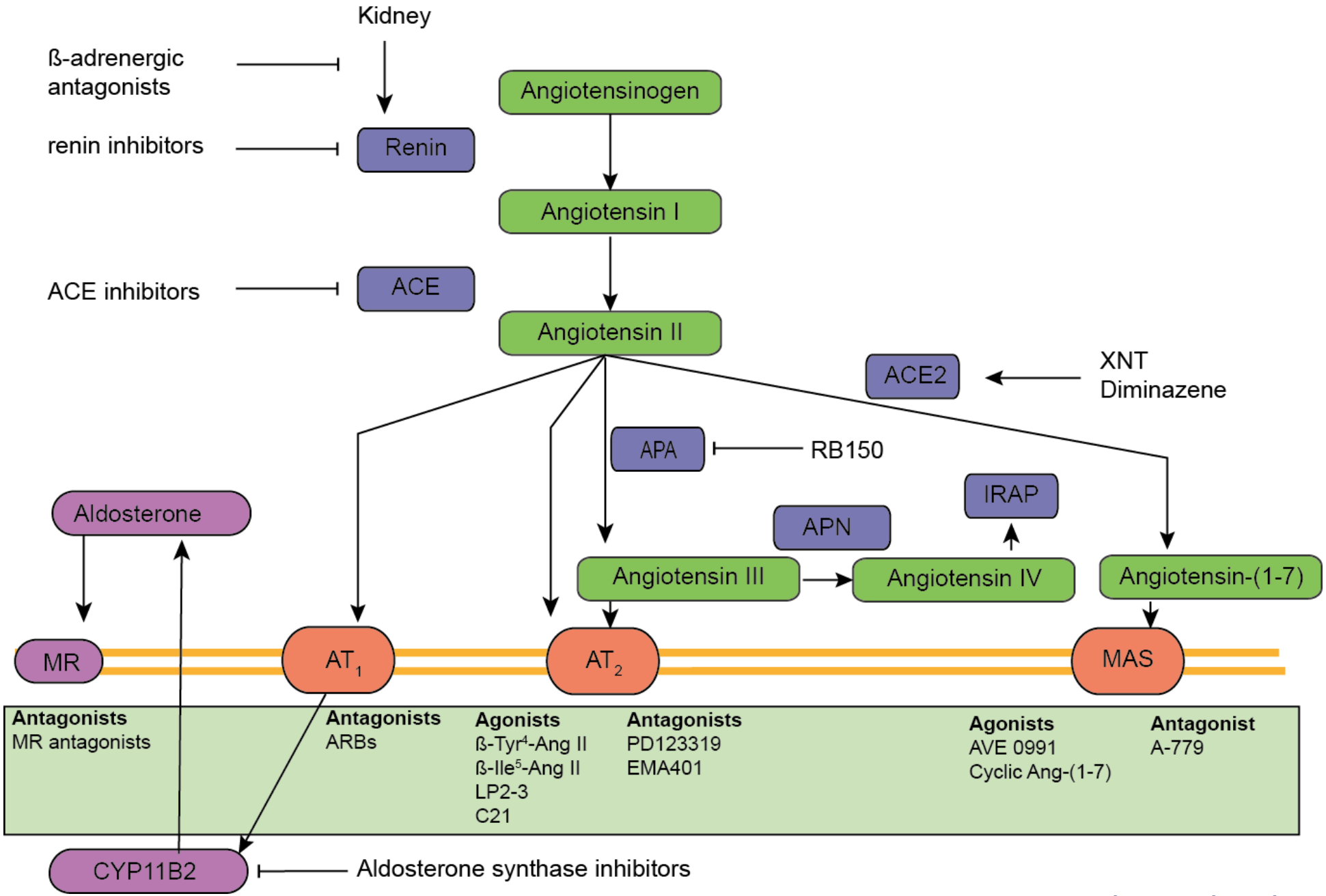
Dawei Wang, MD; Bo Hu, MD; Chang Hu, MD; Fangfang Zhu, MD; Xing Liu, MD; Jing Zhang, MD; Binbin Wang, MD; Hui Xiang, MD; Zhenshun Cheng, MD; Yong Xiong, MD; Yan Zhao, MD; Yirong Li, MD; Xinghuan Wang, MD; Zhiyong Peng, MD



Comorbidities	64 (46.4)	26 (72.2)	38 (37.3)	<.001
Hypertension	43 (31.2)	21 (58.3)	22 (21.6)	<.001
Cardiovascular disease	20 (14.5)	9 (25.0)	11 (10.8)	.04
Diabetes	14 (10.1)	8 (22.2)	6 (5.9)	.009
Malignancy	10 (7.2)	4 (11.1)	6 (5.9)	.29
Cerebrovascular disease	7 (5.1)	6 (16.7)	1 (1.0)	.001
COPD	4 (2.9)	3 (8.3)	1 (1.0)	.054



Hoffmann et al., *Cell* 2020 & Clerkin et al., *Circulation* 2020



te Riet et al., *Circ Res* 2015

Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection?

The most distinctive comorbidities of 32 non-survivors from a group of 52 intensive care unit patients with novel coronavirus disease 2019 (COVID-19) in the study by Xiaobo Yang and colleagues[1] were cerebrovascular diseases (22%)

inhibitors and ARBs, which results in an upregulation of ACE2.[5] ACE2 can also be increased by thiazolidinediones and ibuprofen. These data suggest that ACE2 expression is increased in diabetes and treatment with ACE inhibitors and ARBs increases ACE2 expression. Consequently, the increased expression of ACE2 would facilitate infection with COVID-19. We therefore hypothesise that diabetes and hypertension treatment with ACE2-stimulating drugs increases the risk of developing severe and fatal COVID-19.

suitable alternative treatment in these patients.

We declare no competing interests.

*Lei Fang, George Karakiulakis, *Michael Roth*

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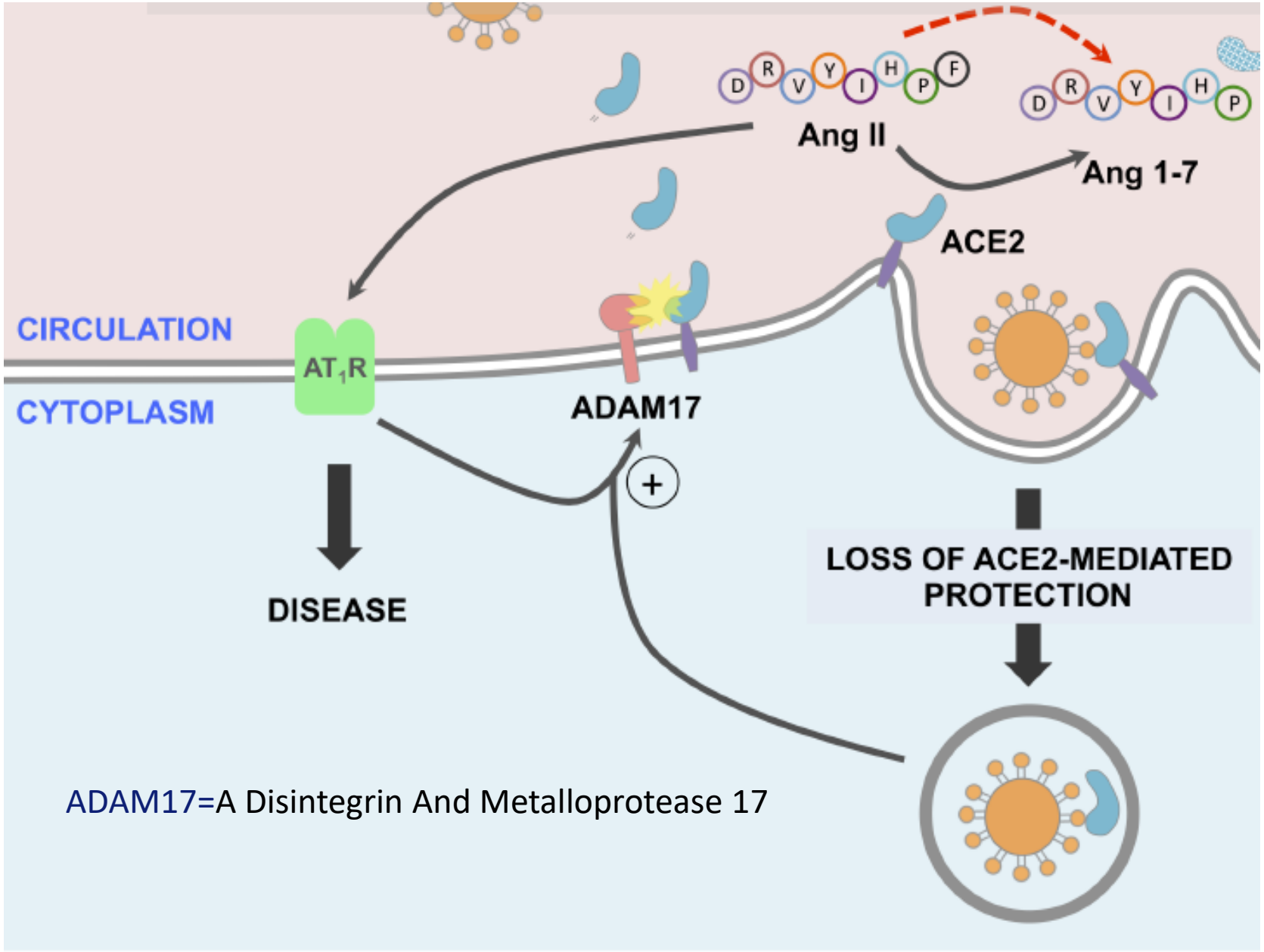
Pulmonary Cell Research and Pneumology, Department of Biomedicine and Internal Medicine, University Hospital Basel, CH-4031 Basel, Switzerland (LF, MR); and Department of Pharmacology, School of Medicine, Aristotle University of Thessaloniki, Thessaloniki, Greece (GK)

1 Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational

Lancet Respir Med 2020

Published Online March 11, 2020 https://doi.org/10.1016/PII

eerste punt van verwarring: remmen ACE remmers ACE2?
antwoord: NEE, ACE (''ACE1'') en ACE2 zijn 2 verschillende enzymen



ADAM17=A Disintegrin And Metalloprotease 17

Wang et al., *Circulation* 2020

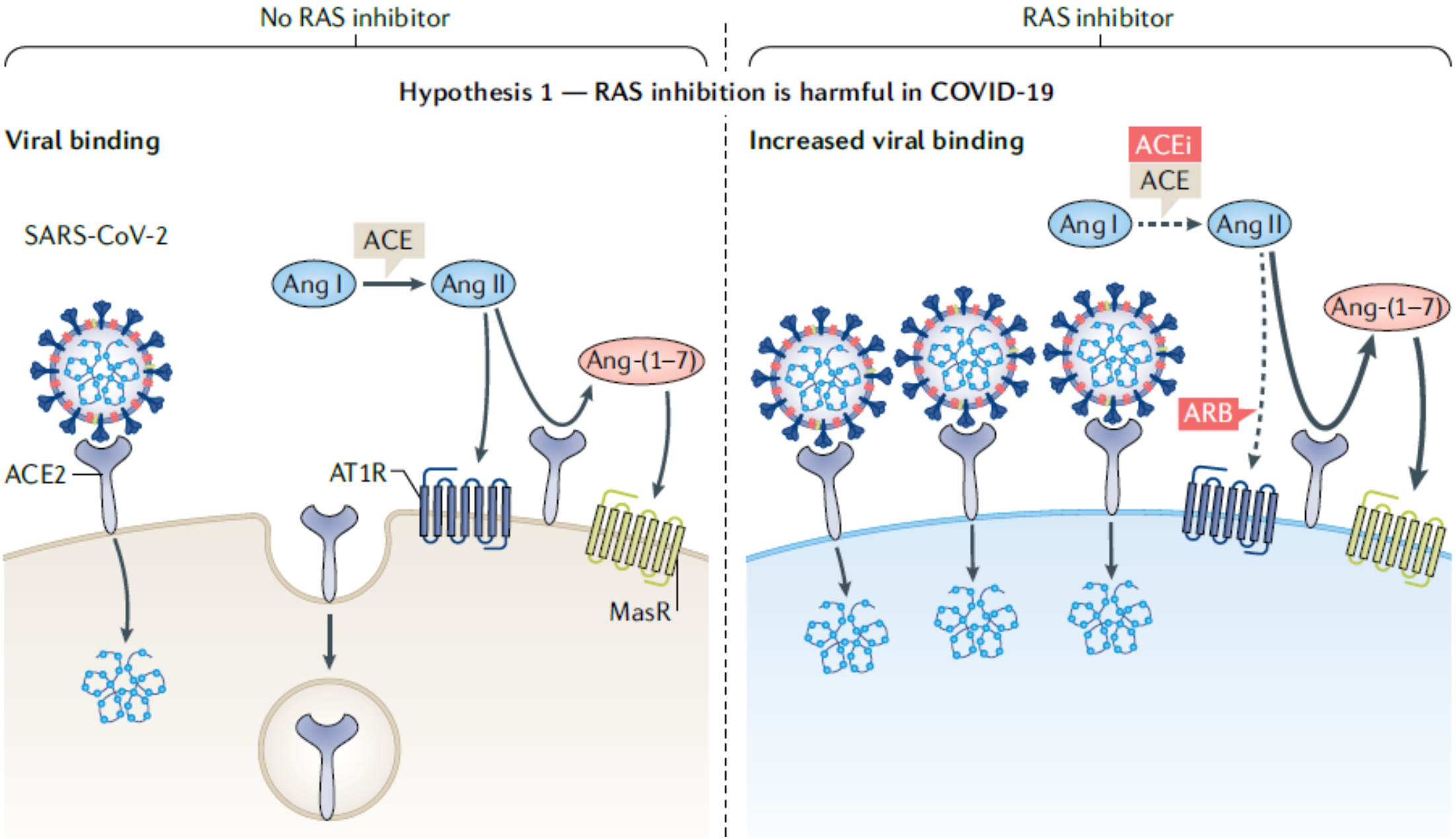
Effects of angiotensin II

1. ADAM17 upregulation:
   cell-membrane ACE2 ↓
   soluble ACE2 ↑

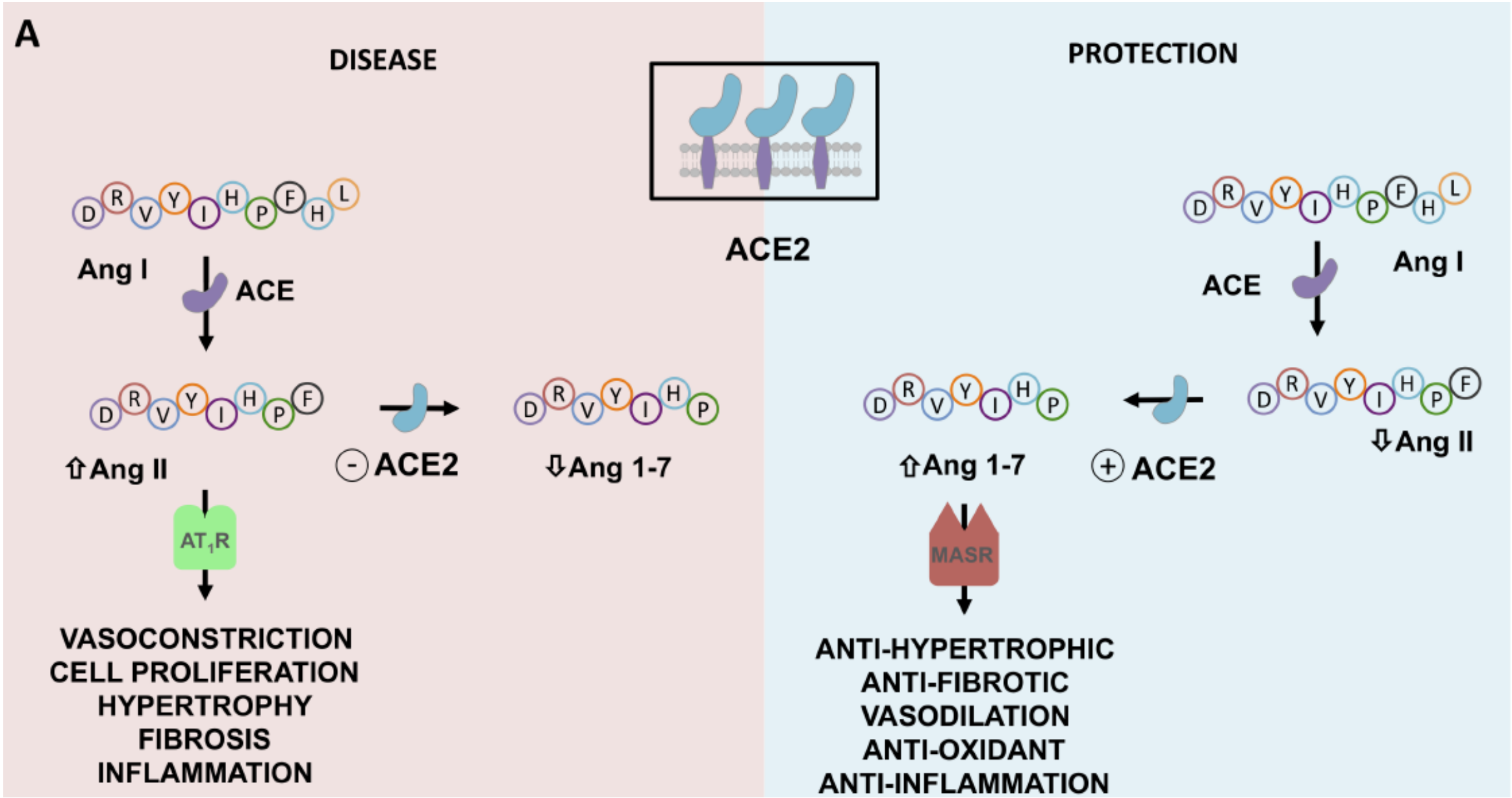
(Xu et al., *Circ Res* 2017)

2. ACE2 internalization:
   cell-membrane ACE2 ↓

(Deshotels et al., *Hypertension* 2014)

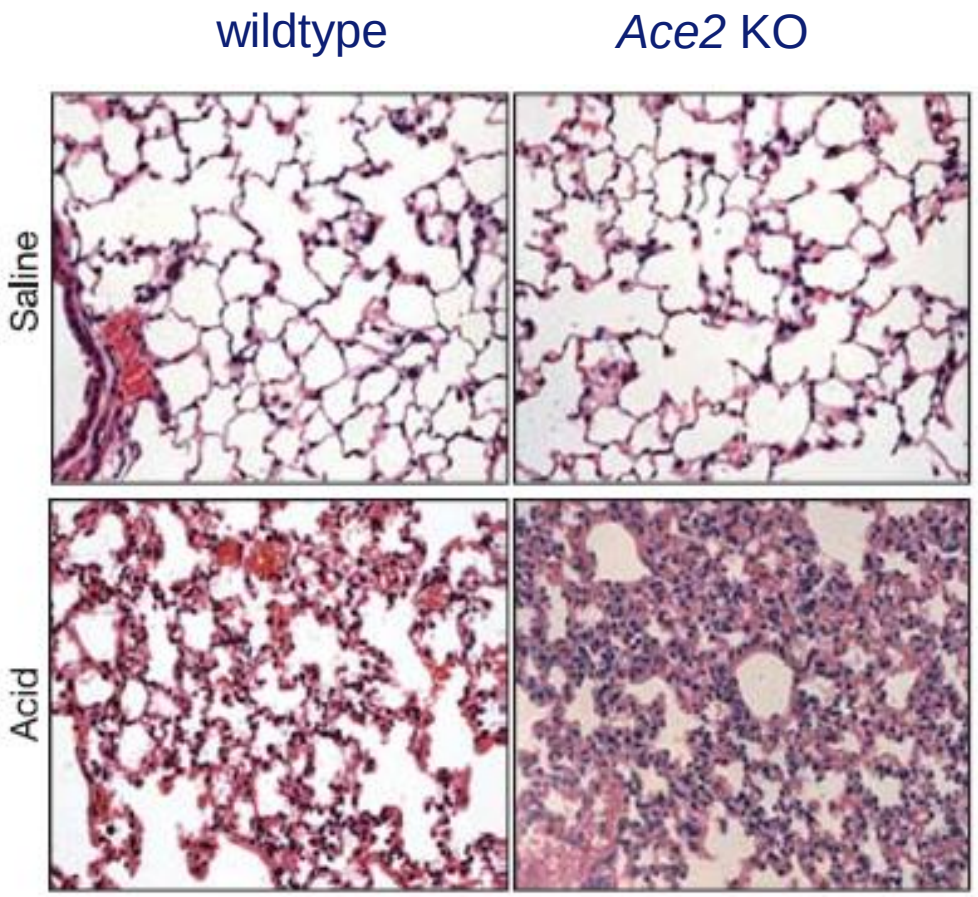


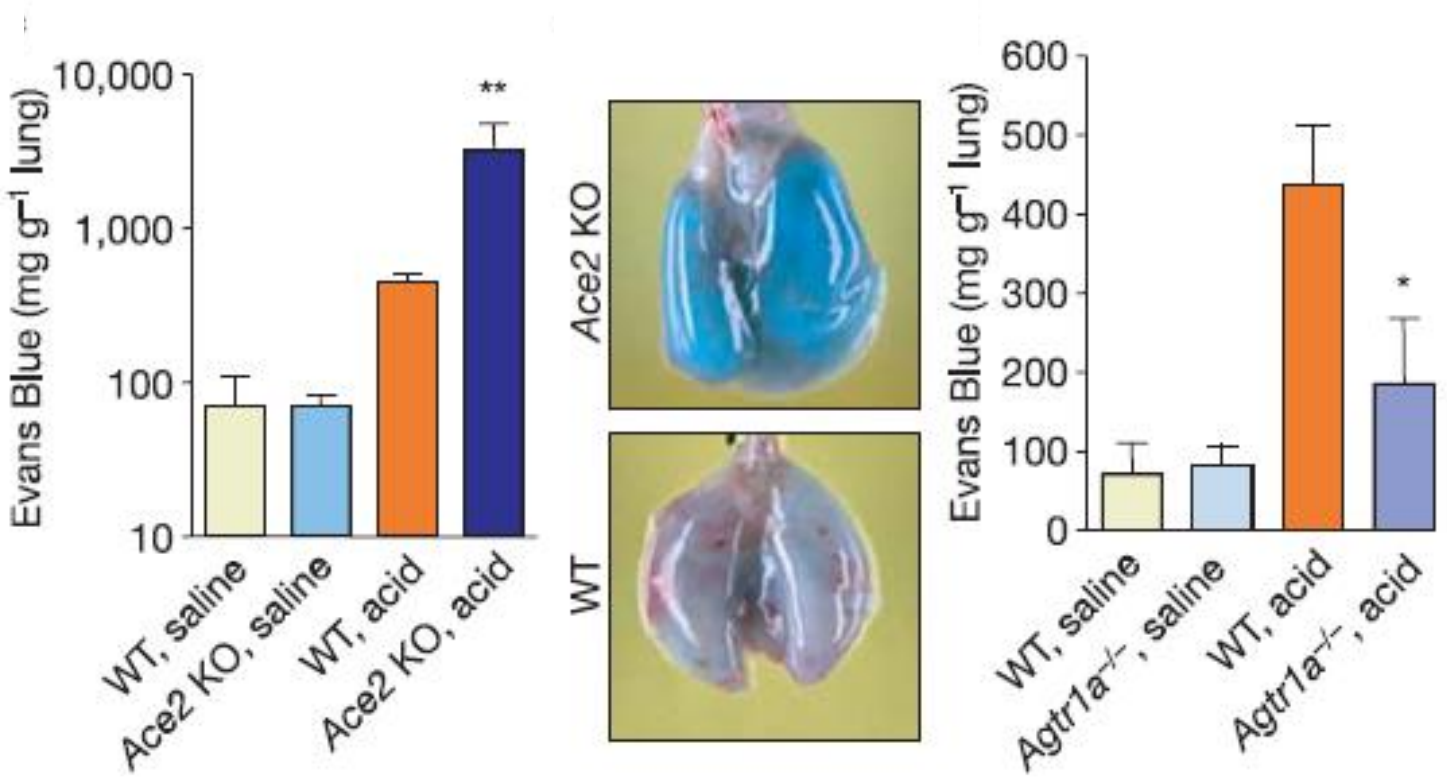
South et al., *Nat Rev Nephrol* 2020



Wang et al., *Circulation* 2020

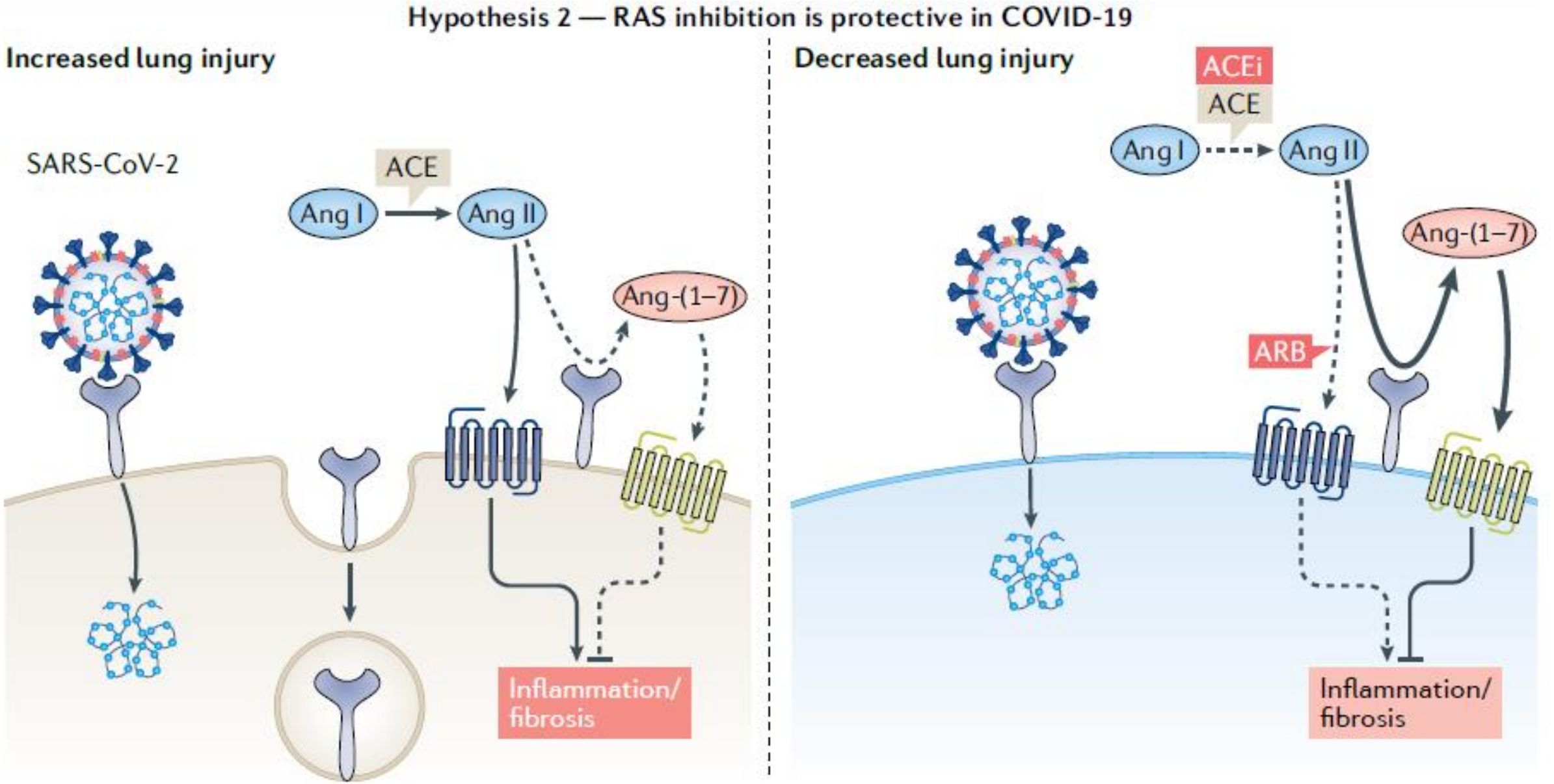
ACE2 and Acute Respiratory Distress Syndrome





model: acid aspiration in mice, resulting in inflammatory cell infiltration and lung oedema;
Evans Blue uptake represents pulmonary permeability

Imai et al., *Nature* 2005



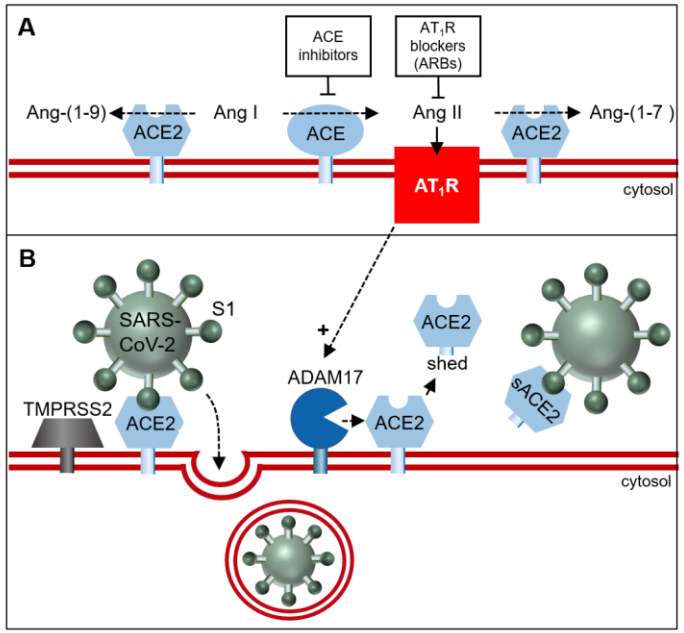
South et al., *Nat Rev Nephrol* 2020

Review

Renin-Angiotensin System Blockers and the COVID-19 Pandemic

At Present There Is No Evidence to Abandon Renin-Angiotensin System Blockers

A.H. Jan Danser, Murray Epstein, Daniel Batlle



Abstract—During the spread of the severe acute respiratory syndrome coronavirus-2, some reports of data still emerging and in need of full analysis indicate that certain groups of patients are at risk of COVID-19. This includes patients with hypertension, heart disease, diabetes mellitus, and clearly the elderly. Many of those patients are treated with renin-angiotensin system blockers. Because the ACE2 (angiotensin-converting enzyme 2) protein is the receptor that facilitates coronavirus entry into cells, the notion has been popularized that treatment with renin-angiotensin system blockers might increase the risk of developing a severe and fatal severe acute respiratory syndrome coronavirus-2 infection. The present article discusses this concept. ACE2 in its full-length form is a membrane-bound enzyme, whereas its shorter (soluble) form circulates in blood at very low levels. As a mono-carboxypeptidase, ACE2 contributes to the degradation of several substrates including angiotensins I and II. ACE (angiotensin-converting enzyme) inhibitors do not inhibit ACE2 because ACE and ACE2 are different enzymes. Although angiotensin II type 1 receptor blockers have been shown to upregulate ACE2 in experimental animals, the evidence is not always consistent and differs among the diverse angiotensin II type 1 receptor blockers and differing organs. Moreover, there are no data to support the notion that ACE inhibitor or angiotensin II type 1 receptor blocker administration facilitates coronavirus entry by increasing ACE2 expression in either animals or humans. Indeed, animal data support elevated ACE2 expression as conferring potential protective pulmonary and cardiovascular effects. In summary, based on the currently available evidence, treatment with renin-angiotensin system blockers should not be discontinued because of concerns with coronavirus infection.

Key Words: ACE inhibitor ■ angiotensin receptor blocker ■ coronavirus ■ COVID-19 ■ severe acute respiratory syndrome

Hypertension
75: 1382-1385, 2020

Circulation Research

ORIGINAL RESEARCH

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,* Lihua Zhu,* Jingjing Cai,* Fang Lei,* Juan-Juan Qin,* Jing Xie, Ye-Mao Liu, Yan-Ci Zhao, Xuewei Huang, Lijin Lin, Meng Xia, Ming-Ming Chen, Xu Cheng, Xiao Zhang, Deliang Guo, Yuanyuan Peng, Yan-Xiao Ji, Jing Chen, Zhi-Gang She, Yibin Wang, Qingbo Xu, Renfu Tan, Haitao Wang, Jun Lin, Pengcheng Luo, Shouzhi Fu, Hongbin Cai, Ping Ye, Bing Xiao, Weiming Mao, Liming Liu, Youqin Yan, Mingyu Liu, Manhua Chen, Xiao-Jing Zhang, Xinghuan Wang, Rhian M. Touyz, Jiahong Xia, Bing-Hong Zhang, Xiaodong Huang, Yufeng Yuan, Loomba Rohit, Peter P. Liu, Hongliang Li

…unlikely that ACEi/ARB use associates with increased mortality risk….

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Renin–Angiotensin–Aldosterone System Blockers and the Risk of Covid-19

Giuseppe Mancia, M.D., Federico Rea, Ph.D., Monica Ludergnani, M.Sc., Giovanni Apolone, M.D., and Giovanni Corrao, Ph.D.

Renin–angiotensin system blockers and susceptibility to COVID-19: an international, open science, cohort analysis

Daniel R Morales, Mitchell M Conover, Seng Chan You, Nicole Pratt, Kristin Kostka, Talita Duarte-Salles, Sergio Fernández-Bertolín, Maria Aragón, Scott L DuVall, Kristine Lynch, Thomas Falconer, Kees van Bochove, Cynthia Sung, Michael E Matheny, Christophe G Lambert, Fredrik Nyberg, Thamir M Alshammari, Andrew E Williams, Rae Woong Park, James Weaver, Anthony G Sena, Martijn J Schuemie, Peter R Rijnbeek, Ross D Williams, Jennifer C E Lane, Albert Prats-Uribe, Lin Zhang, Carlos Areia, Harlan M Krumholz, Daniel Prieto-Alhambra, Patrick B Ryan, George Hripcsak, Marc A Suchard

Lancet Digit Health 2020

ESC European Society of Cardiology

European Journal of Heart Failure (2020)
doi:10.1002/ejhf.2060

RESEARCH ARTICL

Association between renin–angiotensin–aldosterone system inhibitor use and COVID-19 hospitalization and death: a 1.4 million patient nationwide registry analysis

Gianluigi Savarese[1,2]*, Lina Benson[1], Johan Sundström[3], and Lars H. Lund[1,2]

Continuation versus discontinuation of renin–angiotensin system inhibitors in patients admitted to hospital with COVID-19: a prospective, randomised, open-label trial

Jordana B Cohen, Thomas C Hanff, Preethi William, Nancy Sweitzer, Nelson R Rosado-Santander, Carola Medina, Juan E Rodriguez-Mori, Nicolás Renna, Tara I Chang, Vicente Corrales-Medina, Jaime F Andrade-Villanueva, Alejandro Barbagelata, Roberto Cristodulo-Cortez, Omar A Díaz-Cucho, Jonas Spaak, Carlos E Alfonso, Renzo Valdivia-Vega, Mirko Villavicencio-Carranza, Ricardo J Ayala-García, Carlos A Castro-Callirgos, Luz A González-Hernández, Eduardo F Bernales-Salas, Johanna C Coacalla-Guerra, Cynthia D Salinas-Herrera, Liliana Nicolosi, Mauro Basconcel, James B Byrd, Tiffany Sharkoski, Luis E Bendezú-Huasasquiche, Jesse Chittams, Daniel L Edmonston, Charles R Vasquez, Julio A Chirinos

Lancet Respir Med 2021

Hypertension

COVID-19

Antihypertensive Drugs and COVID-19 Risk

A Cohort Study of 2 Million Hypertensive Patients

Laura Semenzato,* Jérémie Botton,* Jérôme Drouin, Bérangère Baricault, Clémentine Vabre, François Cuenot, Laetitia Penso, Philippe Herlemont, Emilie Sbidian, Alain Weill, Rosemary Dray-Spira, Mahmoud Zureik

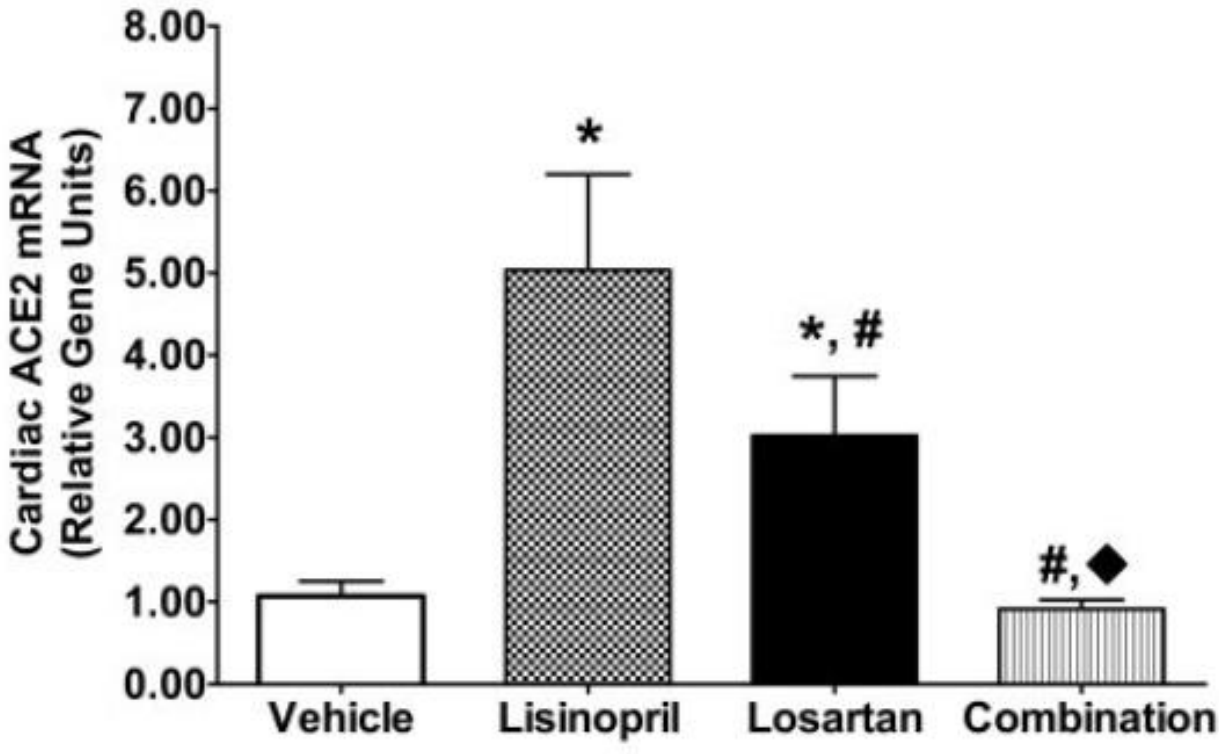
JAMA | Original Investigation

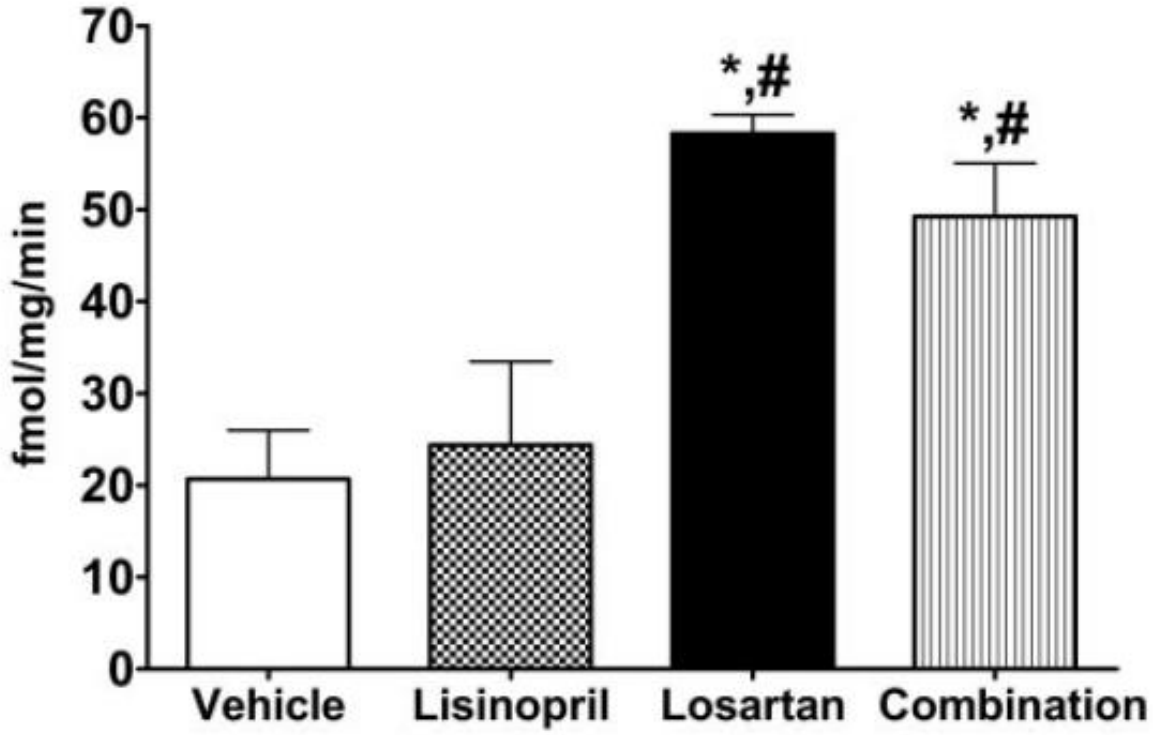
Effect of Discontinuing vs Continuing Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers on Days Alive and Out of the Hospital in Patients Admitted With COVID-19

A Randomized Clinical Trial

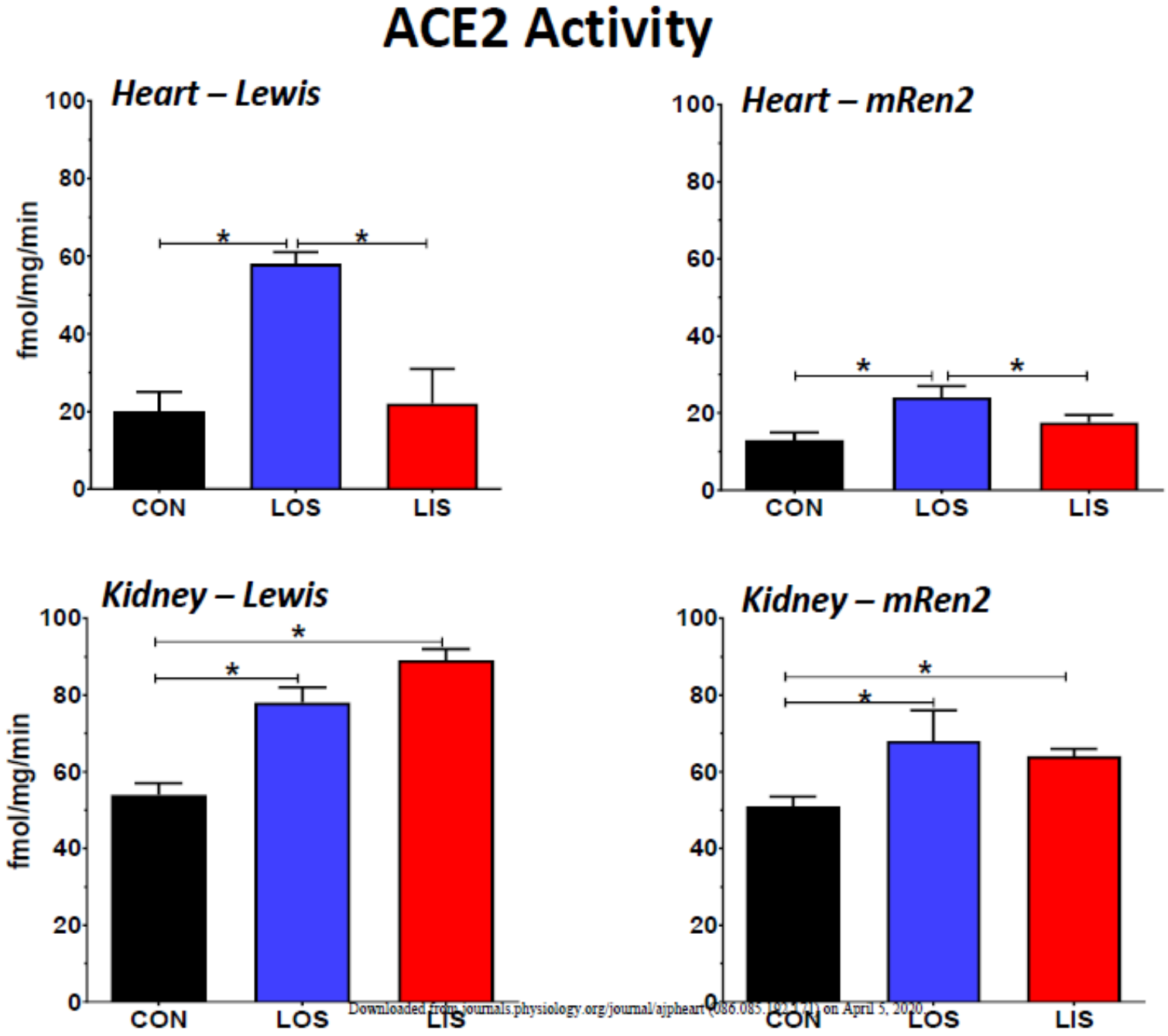
Renato D. Lopes, MD, PhD; Ariane V. S. Macedo, MD, MSc; Pedro G. M. de Barros E Silva, MD, PhD; Renata J. Moll-Bernardes, MD, PhD; Tiago M. dos Santos, MSc; Lilian Mazza, RT; André Feldman, MD, PhD; Guilherme D'Andréa Saba Arruda, MD; Denílson C. de Albuquerque, MD, PhD; Angelina S. Camiletti, RN, MSc; Andréa S. de Sousa, MD, PhD; Thiago C. de Paula, MD; Karla G. D. Giusti, MD; Rafael A. M. Domiciano, MD; Márcia M. Noya-Rabelo, MD, MHS, PhD; Alan M. Hamilton, MD; Vitor A. Loures, MD; Rodrigo M. Dionísio, MD; Thyago A. B. Furquim, MD; Fábio A. De Luca, MD, MBA, PhD; Ítalo B. dos Santos Sousa, MD; Bruno S. Bandeira, MD; Cleverson N. Zukowski, MD, PhD; Ricardo G. G. de Oliveira, MD; Noara B. Ribeiro, MD; Jeffer L. de Moraes, MD; João L. F. Petriz, MD, MHS, PhD; Adriana M. Pimentel, MD, PhD; Jacqueline S. Miranda, MD; Bárbara E. de Jesus Abufaiad, MD; C. Michael Gibson, MD; Christopher B. Granger, MD; John H. Alexander, MD, MHS; Olga F. de Souza, MD, PhD; for the BRACE CORONA Investigators

Discrepancy between ACE2 upregulation after ACEi, ARB or ACEi+ARB treatment in normotensive Lewis rats





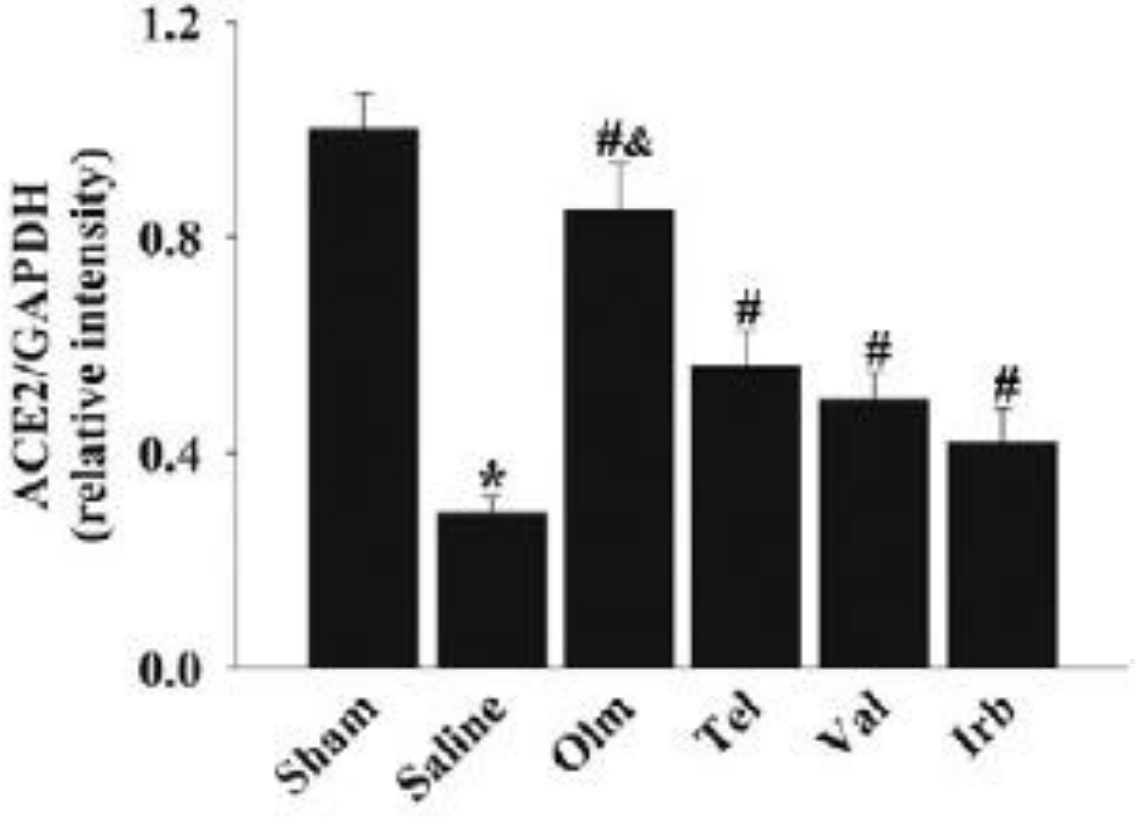
Ferrario et al., *Circulation* 2005

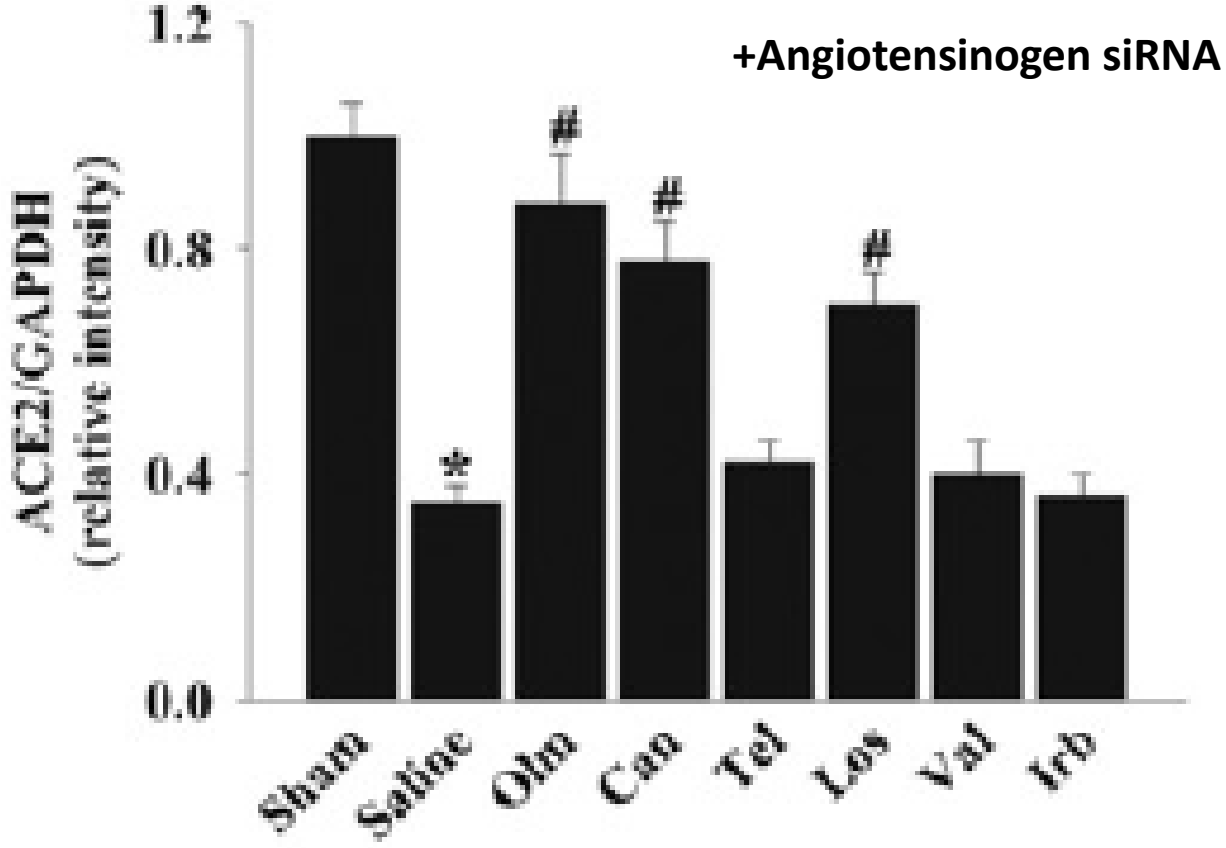


ACE2 upregulation differs per model and organ…

South et al.,
Am J Physiol Heart 2020

Different ACE2 effects with different ARBs, and effects even occur in the absence of angiotensin II





pressure overload model: transverse aortic constriction in mice

Olmesartan, Telmisartan, Valsartan, Irbesartan, Candesartan, Losartan

Wang et al.,
J Mol Cell Cardiol 2016

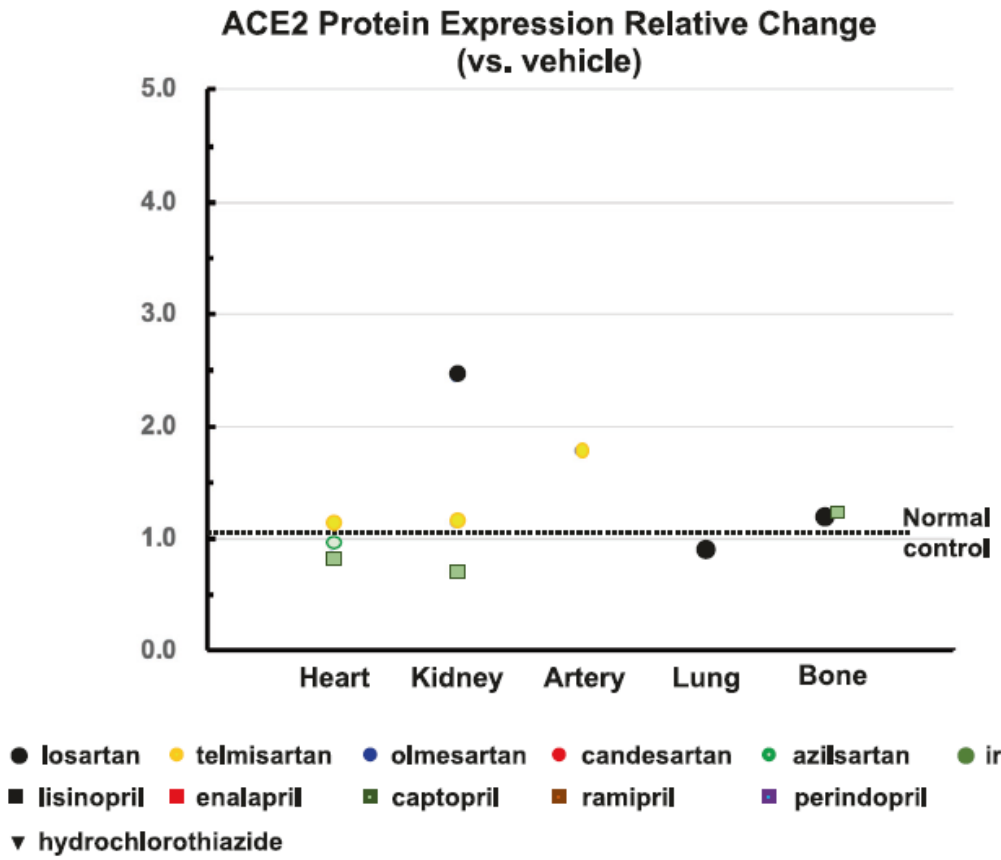
Hypertension Research
https://doi.org/10.1038/s41440-021-00641-1

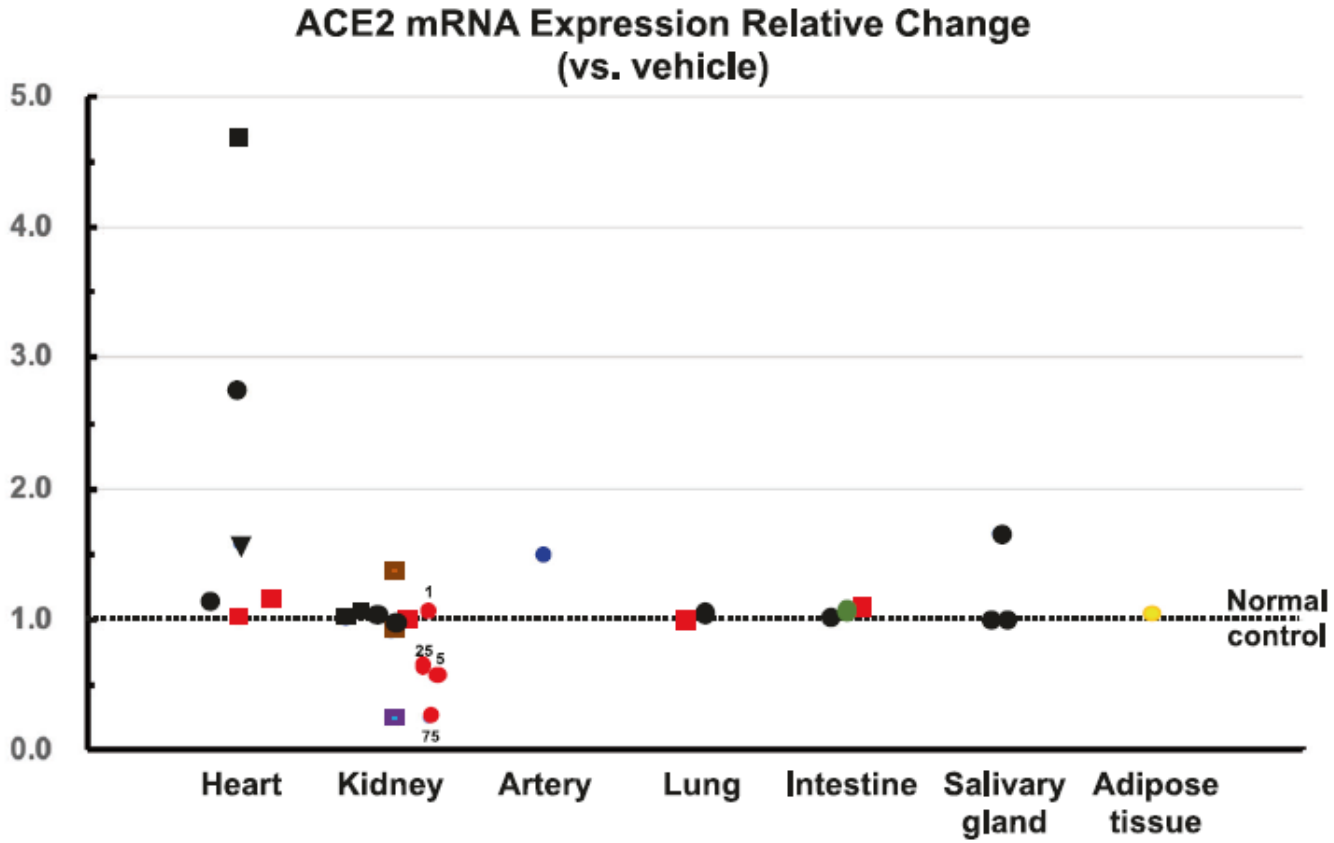
ARTICLE

Overexpression of angiotensin-converting enzyme 2 by renin-angiotensin system inhibitors. Truth or myth? A systematic review of animal studies

Hisashi Kai[1] · Mamiko Kai[2] · Hiroshi Niiyama[1] · Norihito Okina[1] · Motoki Sasaki[1] · Takanobu Maeda[1] · Atsushi Katoh[1]

Received: 13 December 2020 / Revised: 24 January 2021 / Accepted: 3 February 2021



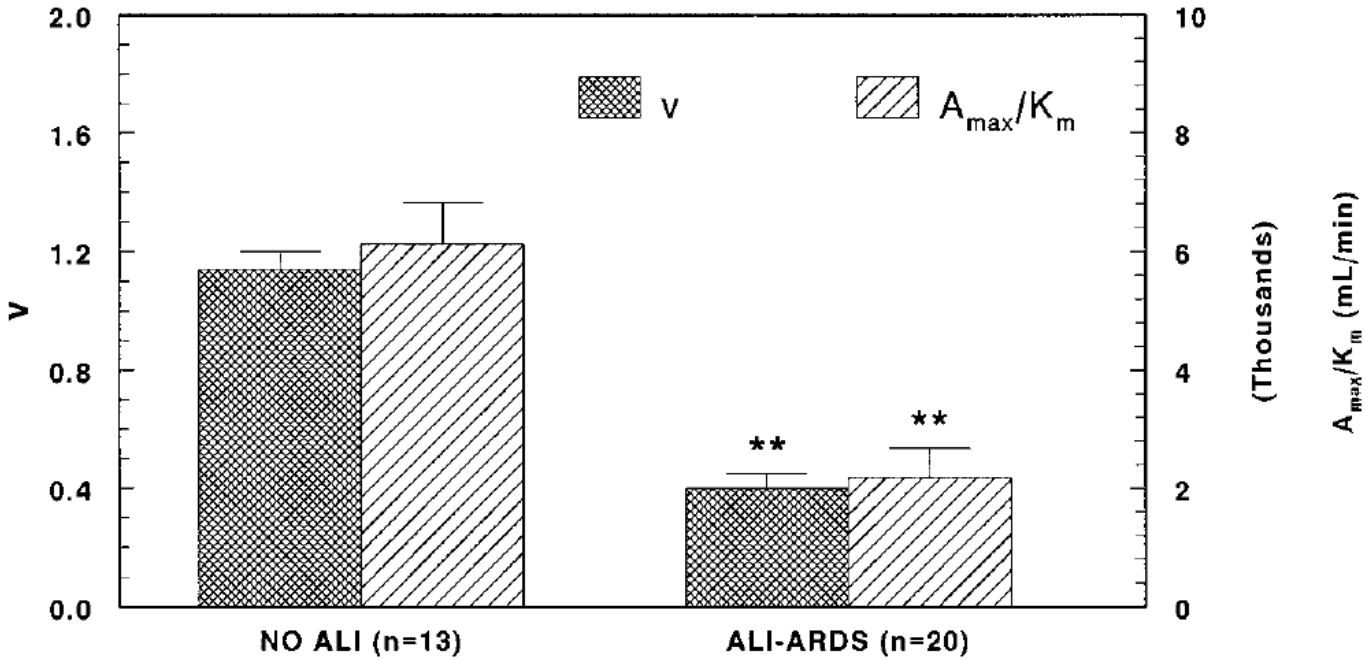


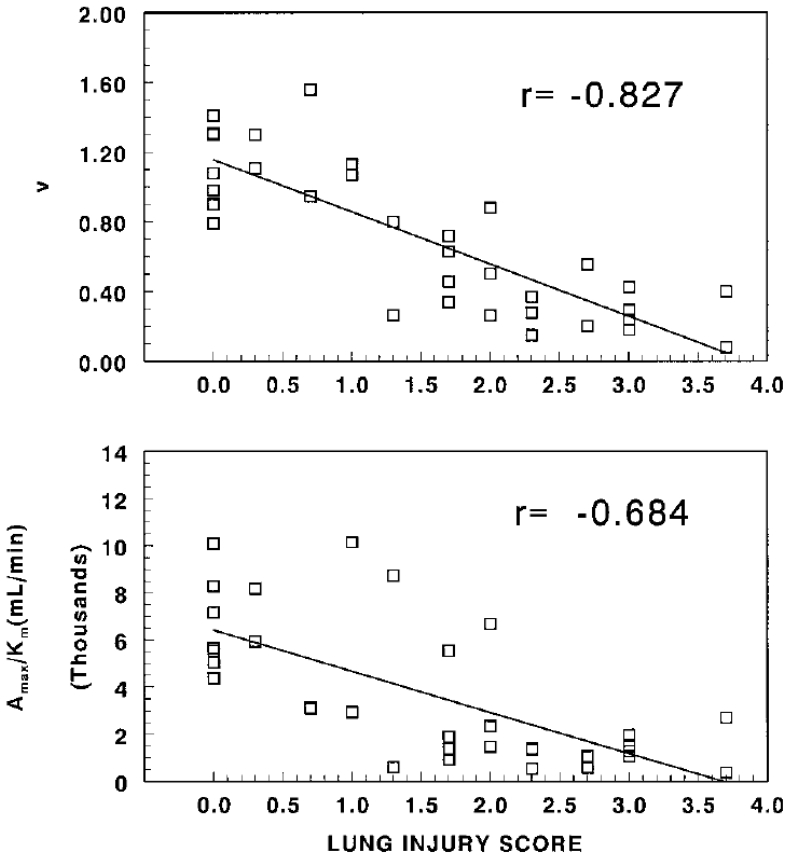
….ACE2 overexpression seems to be a rare rather than common consequence of RAS inhibitor treatment in healthy animals and disease conditions…..

Pulmonary Capillary Endothelium-Bound Angiotensin-Converting Enzyme Activity in Acute Lung Injury

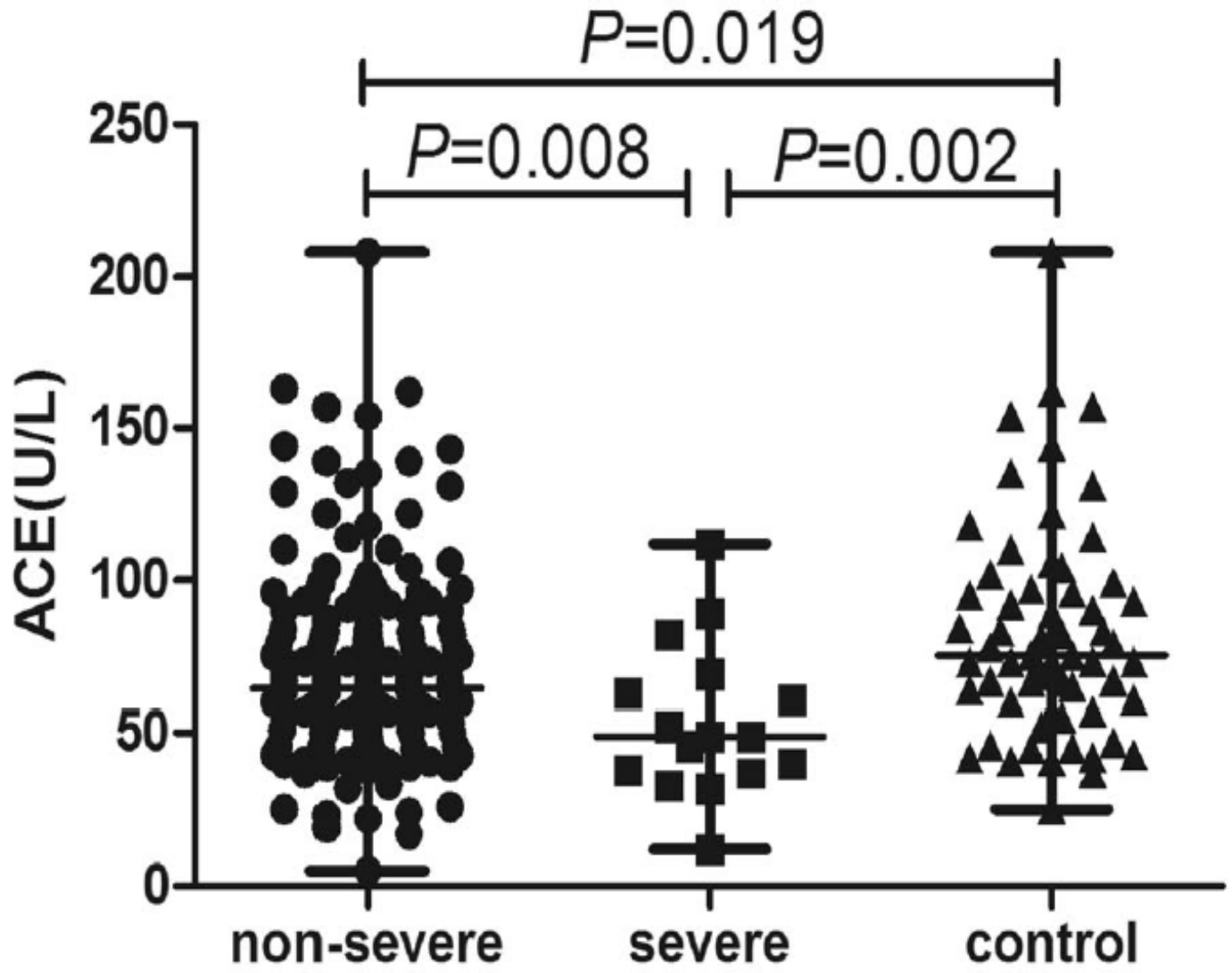
Stylianos E. Orfanos, MD, PhD; Apostolos Armaganidis, MD; Constantinos Glynos, MD; Ekaterini Psevdi, MD; Panagiotis Kaltsas, MD; Paulina Sarafidou, MD; John D. Catravas, PhD; Urania G. Dafni, ScD; David Langleben, MD; Charis Roussos, MD, PhD

(*Circulation*. 2000;102:2011-2018.)



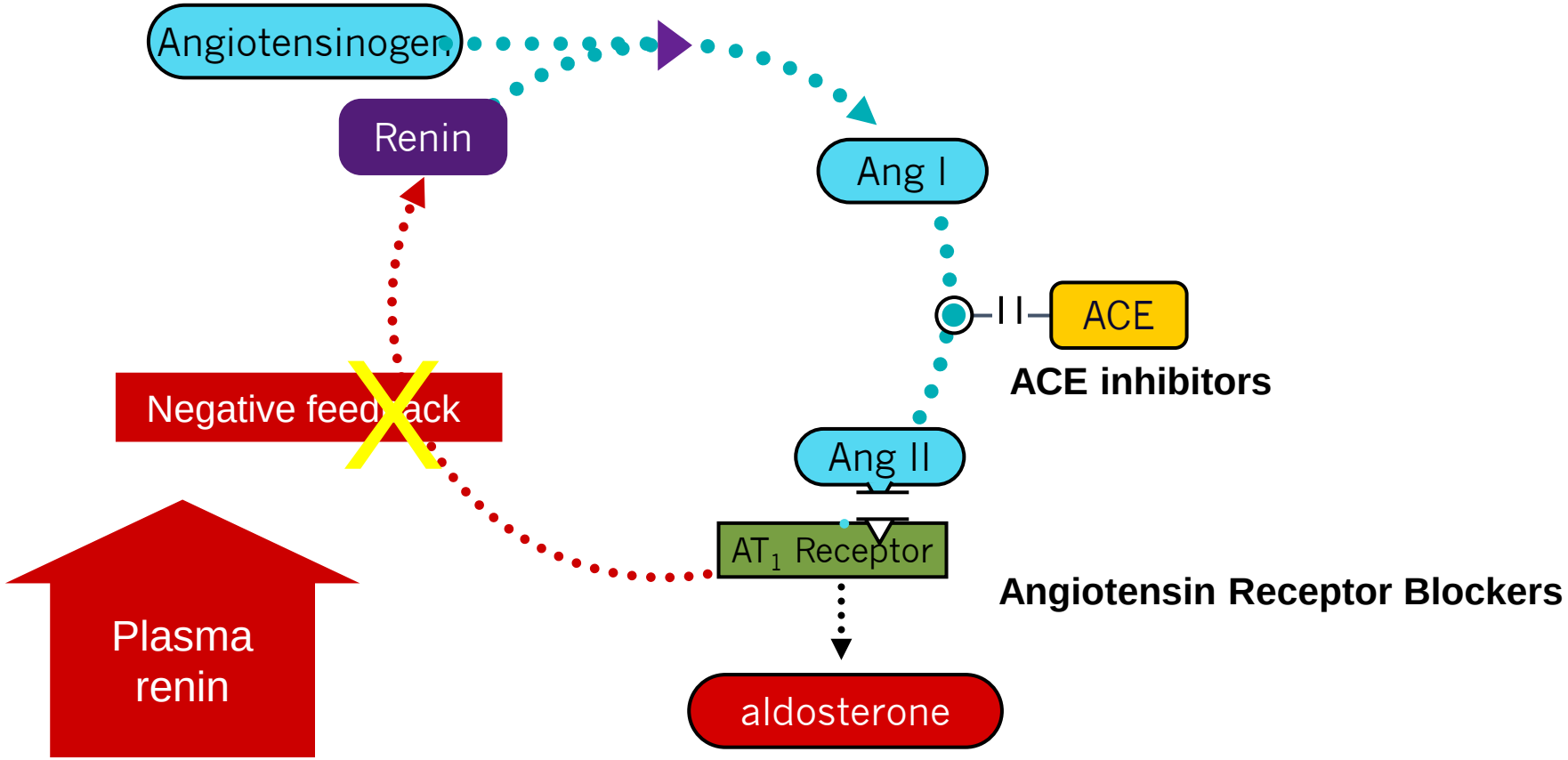


COVID-19 onderdrukt ACE!



Zhu et al.,
***BMC Infectious Diseases* 2020**

Renine-angiotensine systeem (RAS) blokkers en de negatieve feedback loop



ACE remming: aldosteron daalt, renine stijgt

Take home messages

- hypertensie, net als bijv. ouderdom en diabetes, vergroot de kans op ernstige gevolgen van COVID-19
- het corona virus dringt via de receptor ACE2 het lichaam binnen, en ACE2 is toevallig ook één van de vele enzymen die angiotensine kunnen afbreken
- de oorspronkelijke gedachte dat RAS blokkers ACE2 verhogen is bij nader inzien onjuist
- ACE remmers remmen ACE (ook wel ACE1 genoemd), NIET ACE2
- RAS blokkers kunnen veilig gebruikt worden tijdens COVID-19 en bieden ook dan hun gebruikelijke bescherming bij cardiovasculaire patiënten
- COVID-19 kan mogelijk leiden tot ACE onderdrukking (gevolg van endotheelschade?) en zodoende leidt COVID-19 ‘’vanzelf’’ tot een situatie die lijkt op RAS blokkade, waarbij renine stijgt en aldosterone daalt