# In God we trust


## Renin-angiotensin and kallikrein systems in COVID-19

Presented by:

**Sepideh Zununi Vahed**

Assistant Professor of Medical Biotechnology

Kidney Research Center, Tabriz University of Medical Sciences

# SARS-CoV-2

- Over the past 20 years, several outbreaks of coronaviruses (CoVs) have received worldwide attention since they were responsible for the SARS (severe acute respiratory syndrome coronavirus) in China (2002-2003) and the MERS-CoV (Middle East respiratory syndrome) in Saudi Arabia (2012).

- At this time, the world is worried about the novel CoV (SARS-CoV-2) that initially was recognized in China in late 2019.

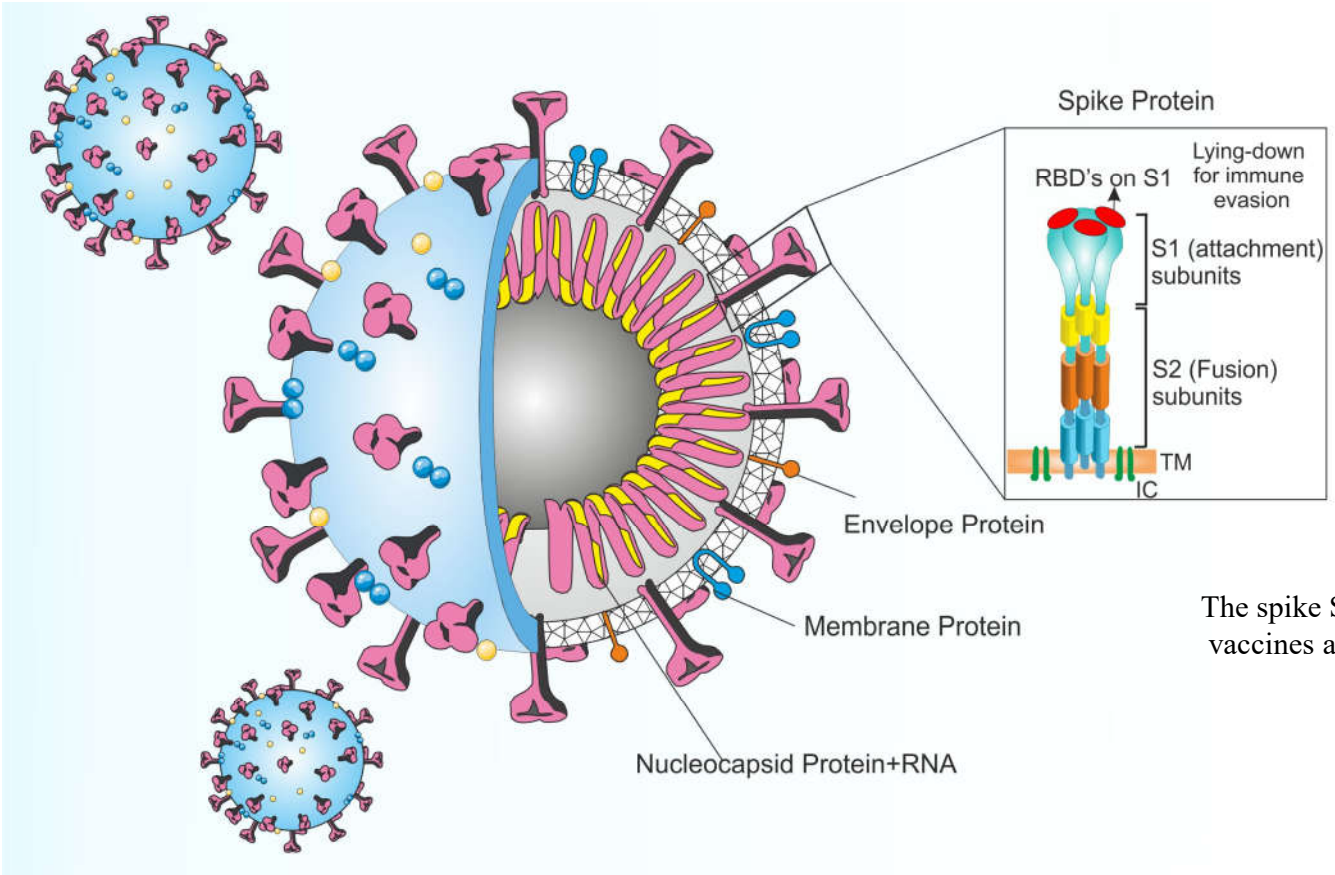
- The novel coronavirus (SARS-CoV-2) is rapidly growing around world and has turned into a life-threatening pandemic disease (COVID-19).

- The pathophysiology of COVID-19 is complex with the involvement of a diversity of systems and can evolve to death.

- Among the various systems involved in the disease, the renin-angiotensin (RAS) and kallikrein-kinin (KKS) systems stand out.

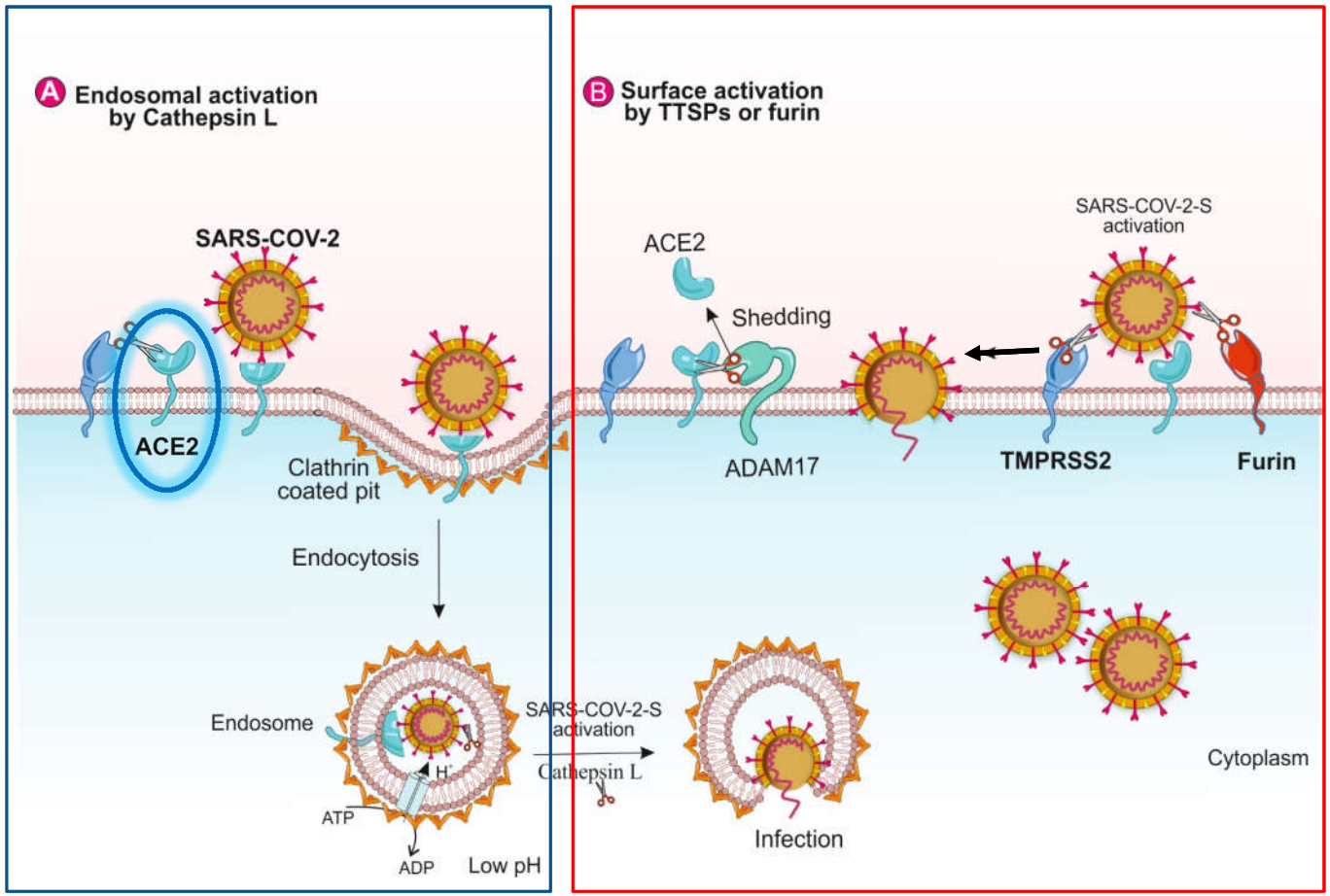
- Here we described RAS and KKS in COVID-19 suggesting their importance in the evolution of the disease.

# SARS-COV-2

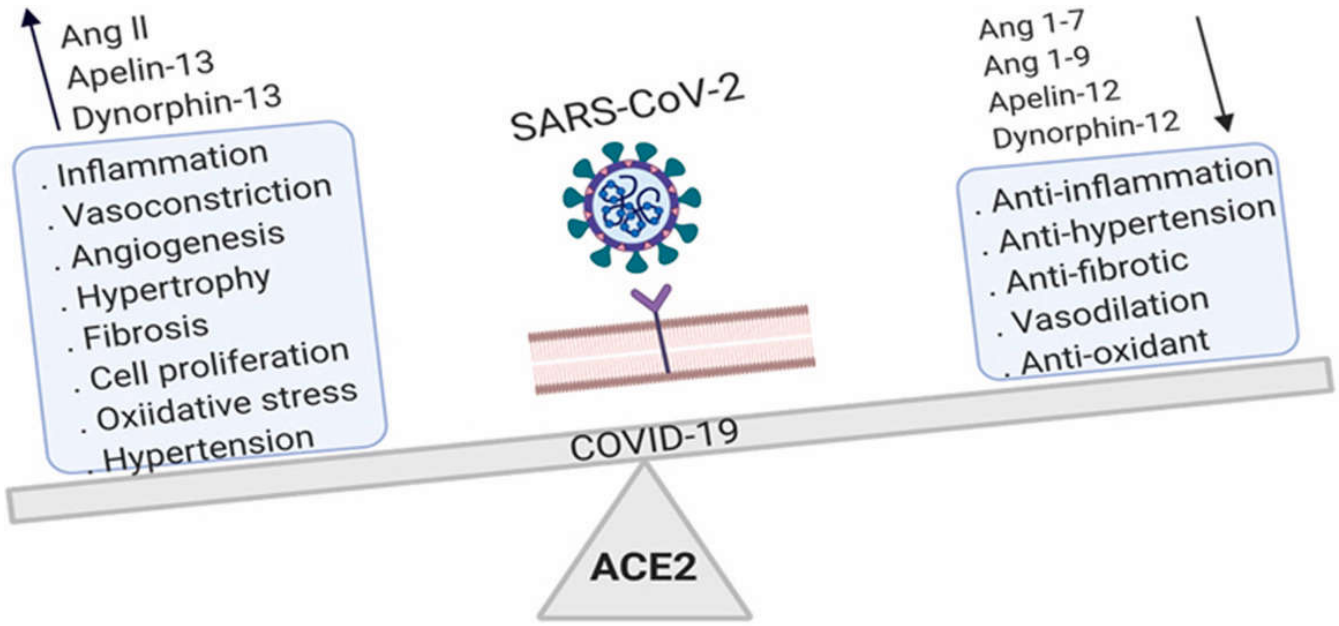



The spike S is the common target for vaccines and neutralizing antibodies

# ACE2: from a vasoactive peptide to the gatekeeper of a global pandemic

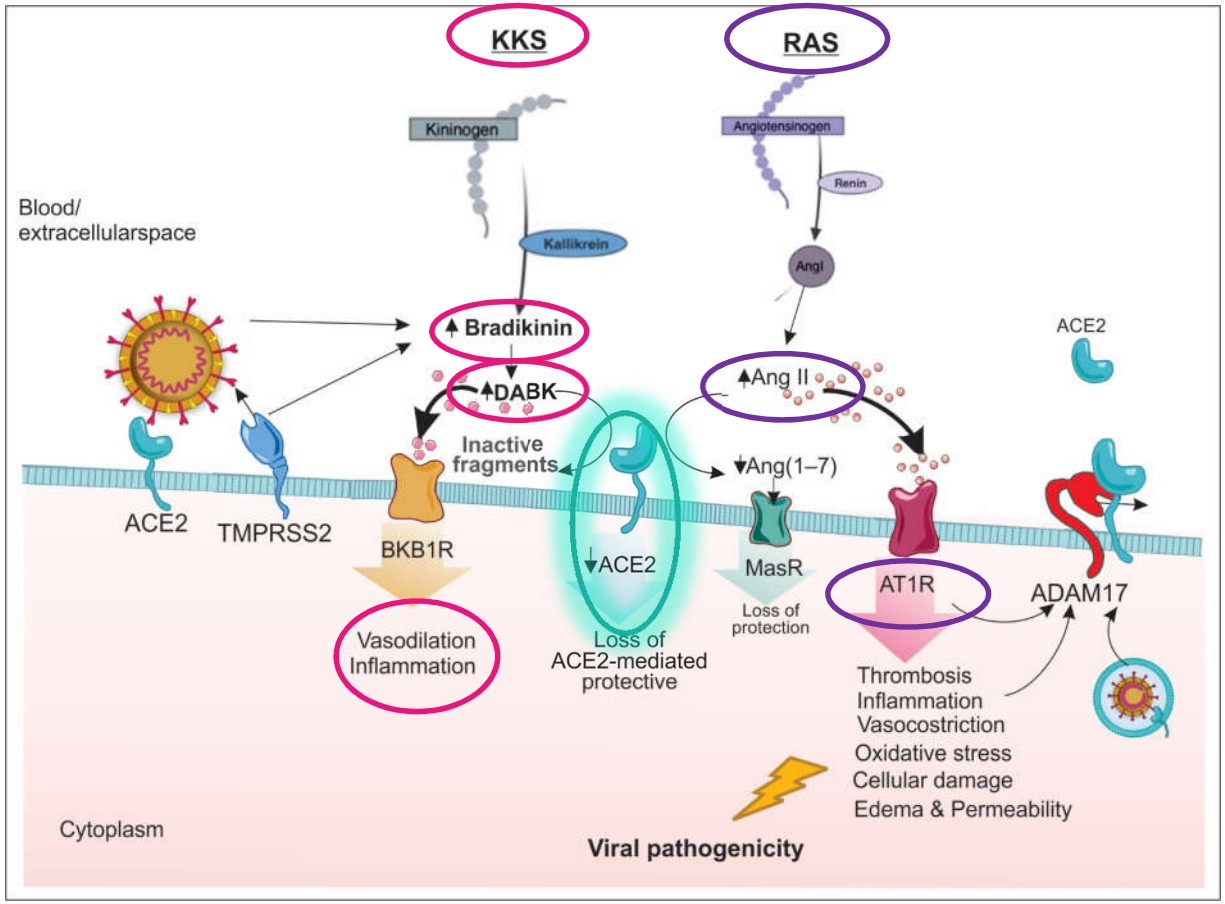


## Dysregulation of ACE-2 upon the entry of SARS-CoV exacerbates the severity of COVID-19

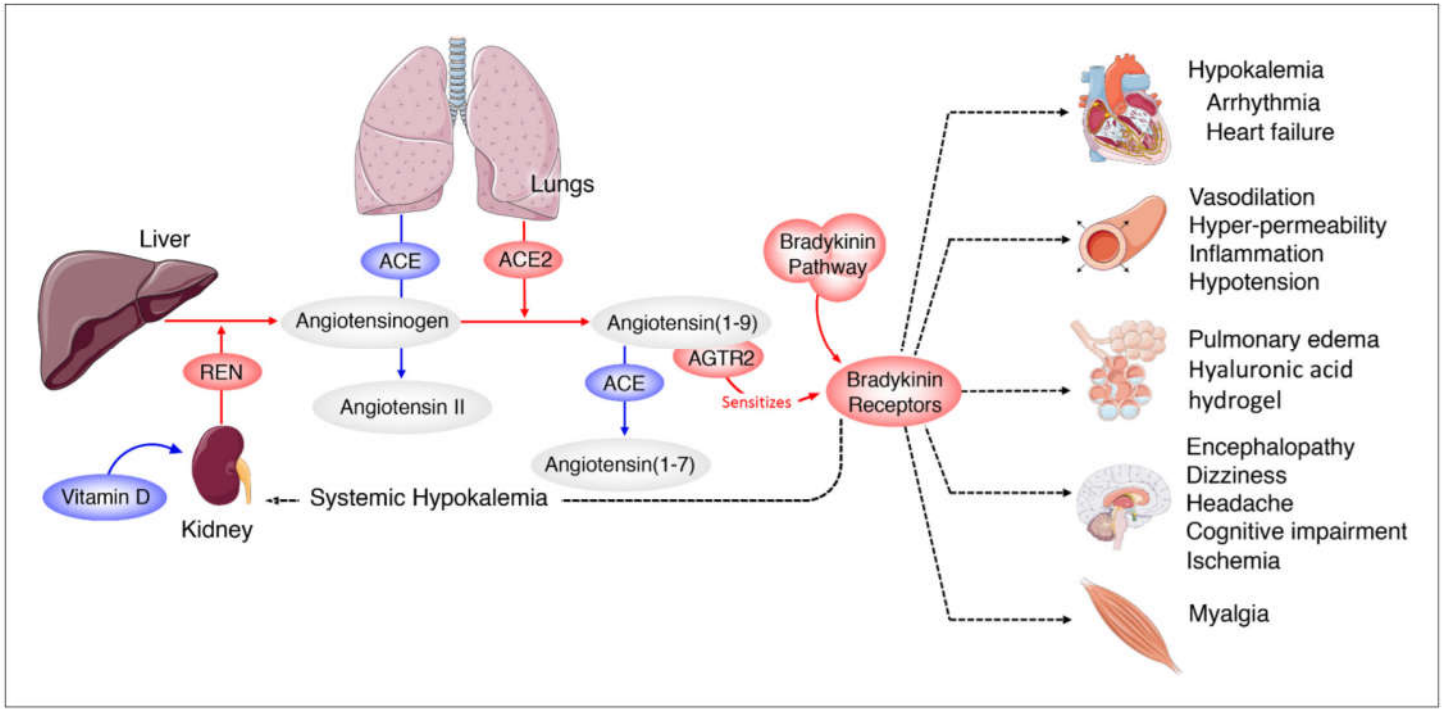



✓ While the most publicized contribution of the RAAS to SARS-CoV-2 infection has been ACE2, bradykinin may be an important extension of this system to consider

The interconnection of the RAS and KKS is done by **angiotensin-converting enzymes** present in both systems.



# Systemic-level effects of critically imbalanced RAS and BK pathways

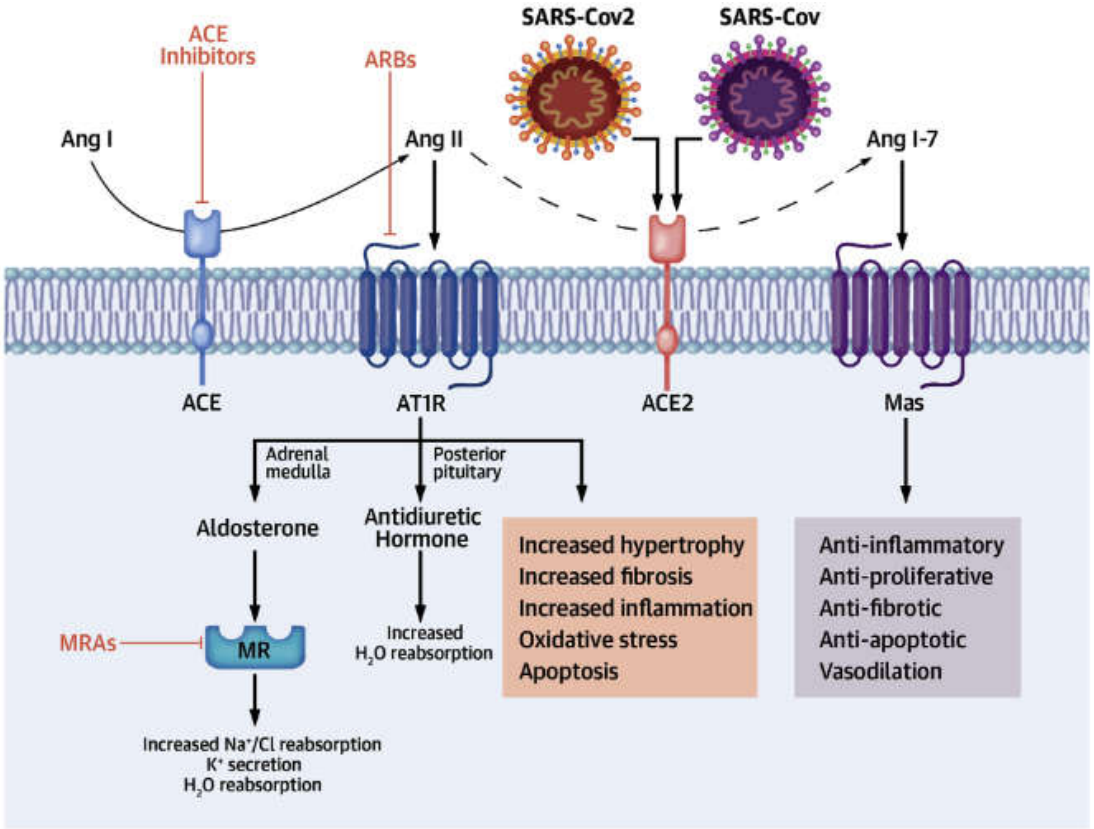



A mechanistic model and therapeutic interventions for COVID-19 involving a RAS-mediated bradykinin storm, Elife 9 (2020). https://doi.org/10.7554/eLife.59177.

# ACEIs & ARBs

Upregulate ACE2 expression in animal studies.

It is reasonable to hypothesize that hypertensive patients taking these drugs may have a higher risk of COVID-19 infection.



Italy, 6272 cases infected with SARS-CoV-2: There was no evidence that ACE inhibitors or ARBs affected the risk of COVID-19

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.

ABSTRACT

**BACKGROUND**

A potential association between the use of angiotensin-receptor blockers (ARBs) and angiotensin-converting–enzyme (ACE) inhibitors and the risk of coronavirus disease 2019 (Covid-19) has not been well studied.

**METHODS**

We carried out a population-based case–control study in the Lombardy region of Italy. A total of 6272 case patients in whom infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was confirmed between February 21 and March 11, 2020, were matched to 30,759 beneficiaries of the Regional Health Service (controls) according to sex, age, and municipality of residence. Information about the use of selected drugs and patients' clinical profiles was obtained from regional databases of health care use. Odds ratios and 95% confidence intervals for associations between drugs and infection, with adjustment for confounders, were estimated by means of logistic regression.

From the University of Milano–Bicocca (G.M.), the National Center of Healthcare Research and Pharmacoepidemiology (F.R., G.C.) and the Unit of Biostatistics, Epidemiology, and Public Health, Department of Statistics and Quantitative Methods (F.R., G.C.), University of Milano–Bicocca, Azienda Regionale per l'Innovazione e gli Acquisti (M.L.), and Fondazione IRCCS Istituto Nazionale dei Tumori (G.A.), Milan, and Policlinico di Monza, Monza (G.M.) — all in Italy. Address reprint requests to Dr. Corrao at the Department of Statistics and Quantitative Methods, Università degli Studi di Milano–Bicocca, Via Bicocca degli Arcimboldi, 8, Edificio U7, 20126 Milan, Italy, or at giovanni.corrao@unimib.it.

## Studies in humans of the relationship between ACEI/ARB use and ACE2 protein expression

| Source | Details of study | Effect of ACEI/ ARB on ACE2 |
|---|---|---|
| Mizuiri *et al.*[47] | Urinary ACE2 protein levels were measured in 190 patients with chronic kidney disease and 36 healthy subjects | No significant difference in urinary ACE2 was observed in response to treatment with ACEI and ARB |
| Furuhashi *et al.*[24] | Urinary ACE2 protein concentration was assayed in 617 subjects, including 101 subjects who did not use any medication and 100 hypertensives treated with various drugs | Enalapril, losartan, valsartan, candesartan, valsartan, and telmisartan had no effect. Olmesartan increased urinary ACE2. |
| Liang *et al.*[23] | Urinary ACE2 protein concentration was assessed in 132 patients with type-2 diabetes and 34 healthy volunteers | Patients with hypertension had an ~ 40% decrease in urinary ACE2 if treated with inhibitors of renin-angiotensin signaling, compared with hypertensive patients not taking such medications |
| Mariana *et al.*[48] | Urinary ACE2 protein levels were measured via ELISA in 75 patients with type-2 diabetes | Use of ARBs or ACEIs had no effect on urinary ACE2 levels |
| Epelman *et al.*[49] | Plasma ACE2 activity was assayed from 228 patients with heart failure | No association was found between ACEI/ARB use and ACE2 levels |
| Soro-Paavonen *et al.*[22] | Serum ACE2 activity was measured in 859 patients with type-1 diabetes and 99 healthy control subjects | ACE2 was increased ~ 10 to 20% (higher in women) in patients with diabetes using ACEIs. No association was found between ARB usage and ACE2 levels. |
| Ortiz-Perez *et al.*[50] | Serum ACE2 activity was assayed in 95 patients with ST-elevation myocardial infarction and 22 control subjects | No association was found between ACEI use and ACE2 levels. ARB usage was not discussed. |
| Anguiano *et al.*[25] | Plasma ACE2 activity was measured in $n = 568$ control subjects, $n = 1458$ with stage 3–5 chronic kidney disease, and $n = 546$ patients on dialysis. Multivariate regression analysis was performed to identify which factors influenced ACE2. | ACEI use had no effect on ACE2 in any group. ARB use did not predict ACE2 activity in control or stage 3–5 patients; in patients on dialysis ARB use had a small effect raising ACE2 activity. |


Evidence from human (19,000 COVID-19 cases) and animal studies imply that administration of ACEIs/ARBs:

- does not increase ACE2 expression and the risk of complications from COVID-19.
- does not increase SARSCoV-2 virus infectivity and/or severity.
- Patients being treated with ACEIs and ARBs should continue their use for approved indications.

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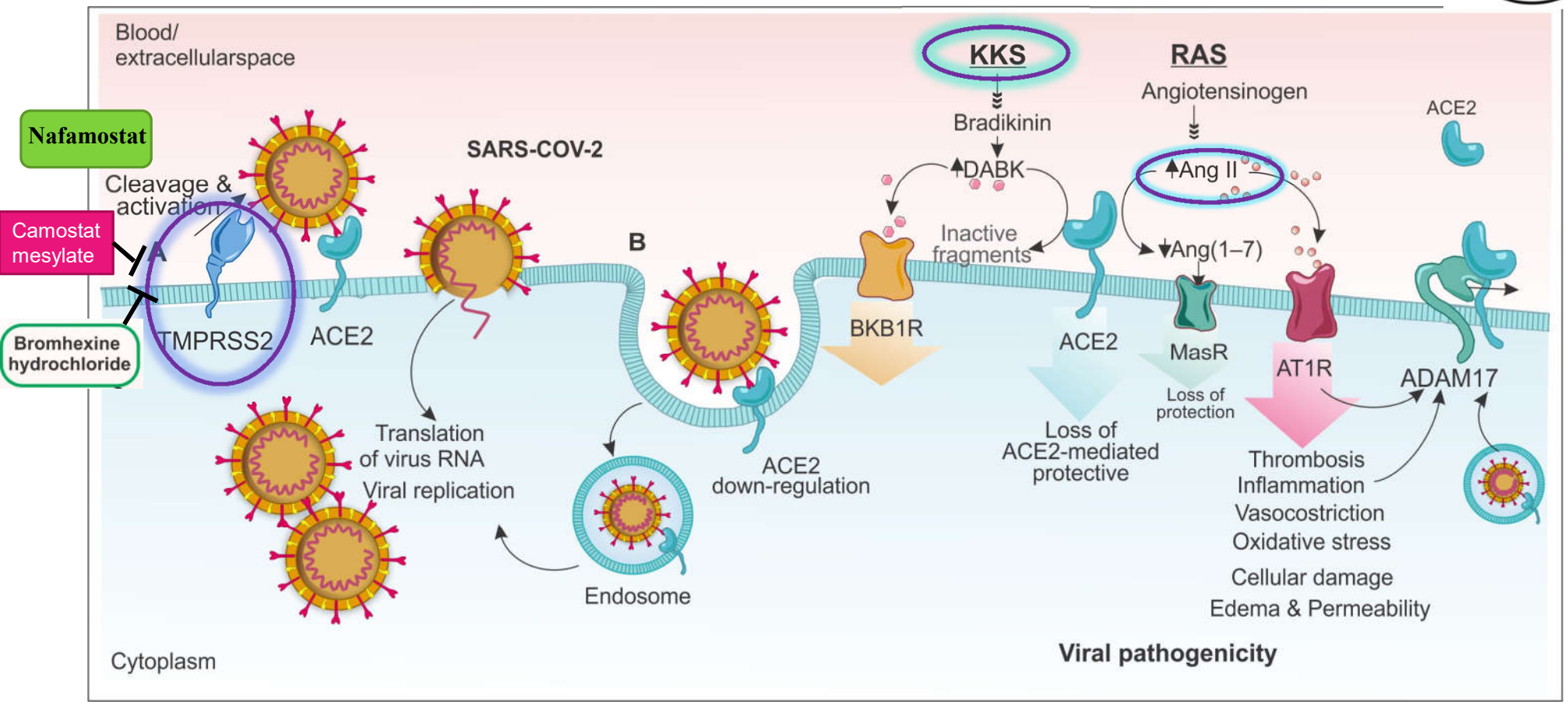
# Today, there exists no therapy to treat SARS-COV-2 infection





Blood/
extracellularspace
Nafamostat
Camostat mesylate
Bromhexine hydrochloride
Cleavage & activation
A
TMPRSS2
ACE2
SARS-COV-2
Translation of virus RNA
Viral replication
B
Endosome
ACE2 down-regulation
KKS
Bradikinin
DABK
Inactive fragments
BKB1R
RAS
Angiotensinogen
Ang II
Ang(1–7)
ACE2
MasR
Loss of protection
Loss of ACE2-mediated protective
AT1R
ADAM17
ACE2
Thrombosis
Inflammation
Vasocostriction
Oxidative stress
Cellular damage
Edema & Permeability
Cytoplasm
Viral pathogenicity

# COVID-19: an angiotensin/kinins systemic disease

Dysfunction of the RAS and KAS by SARSCoV2 is mainly due to:

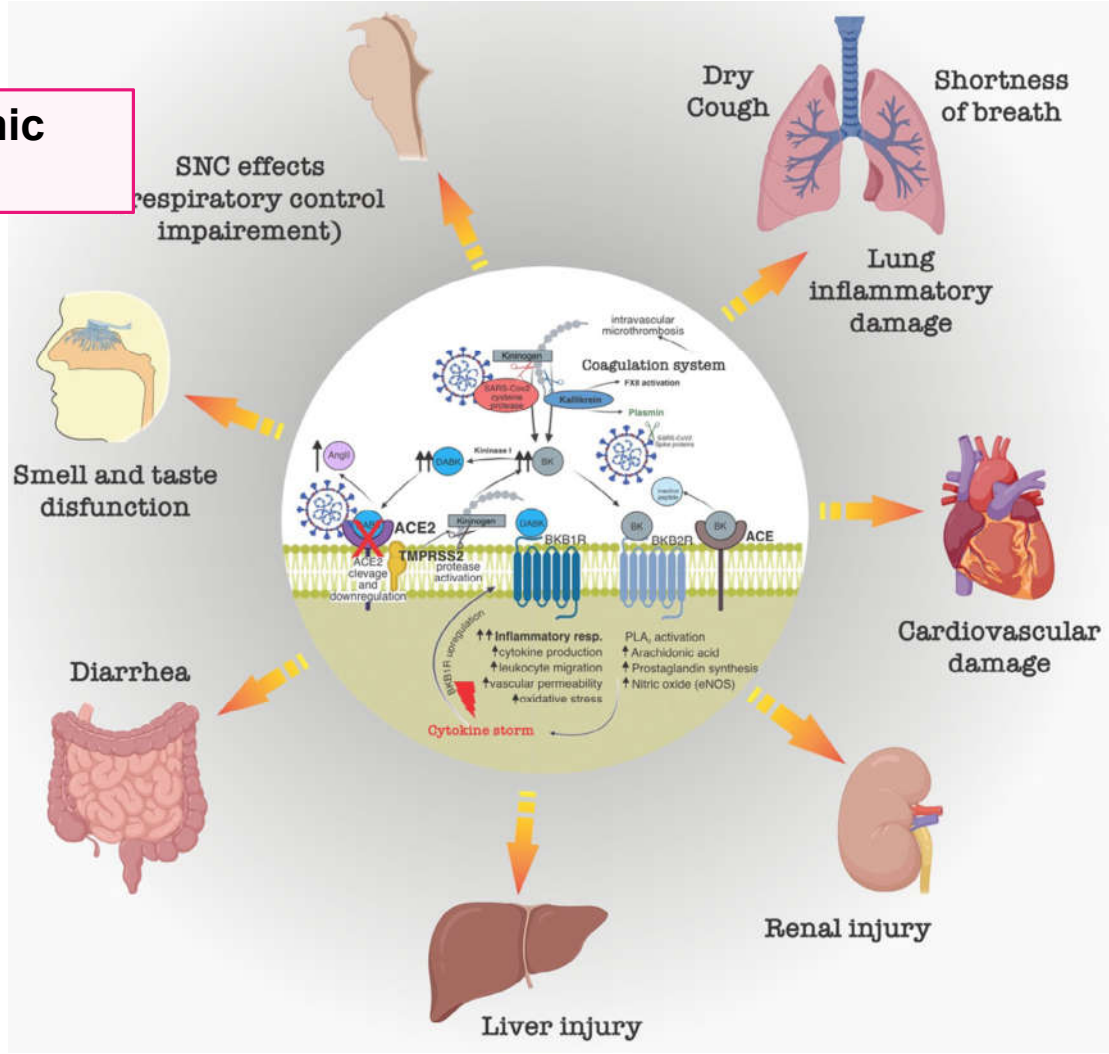
- downregulation of ACE2,
- activation of the kinin cascade
- increased angiotensin II (AngII),
- increased bradykinin (BK) and des-Arg9BK (DABK),

**leads to pathological repercussions in the most diverse organs**.

**Symptoms are caused by**:

- Inflammation
- oxidative stress and
- intravascular microthrombi

❑ Cytokine storm and intravascular microthrombi may be late events related to COVID-19 mortality.

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