COVID-19 and RAAS Inhibitors

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Disclosures

Grant Support/Drugs

- Daiichi-Sankyo

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- V-Wave Medical - Svelte

Consulting/Advisory Boards

- Medtronic - Edwards Lifesciences
- Boston Scientific - Abbott Vascular

COVID-19 and RAAS Inhibitors

- Background-- Why RAAS inhibitors?
- What have we learned so far?
- Ongoing studies
- Summary/Current recommendations

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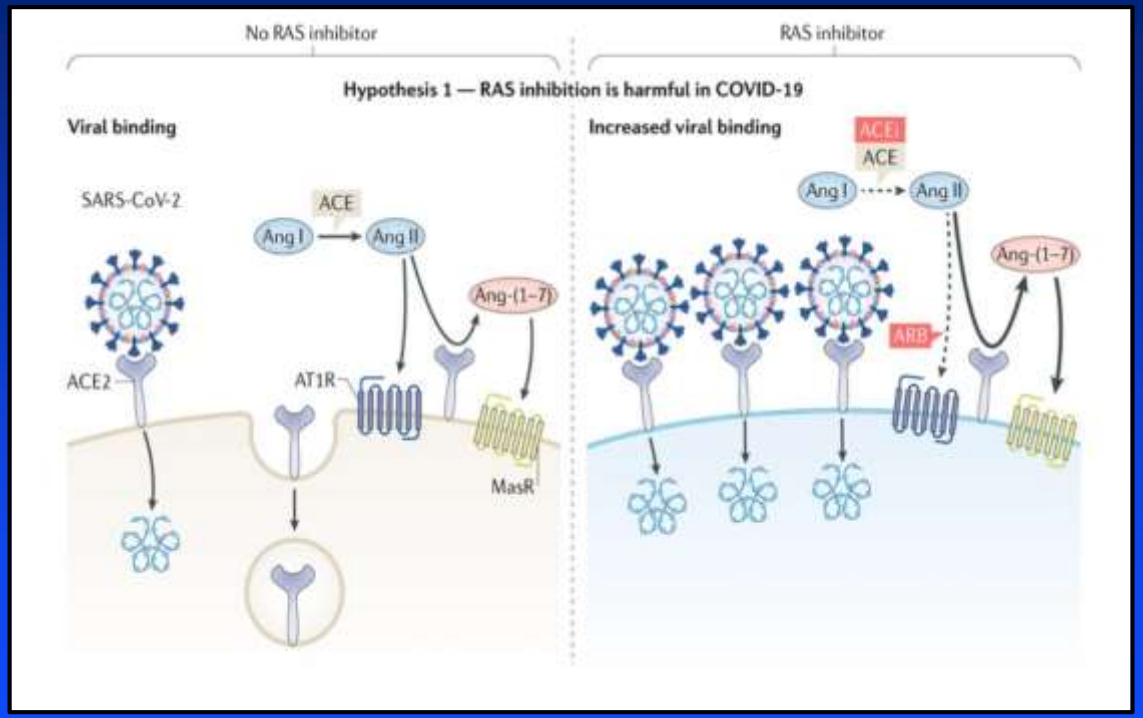
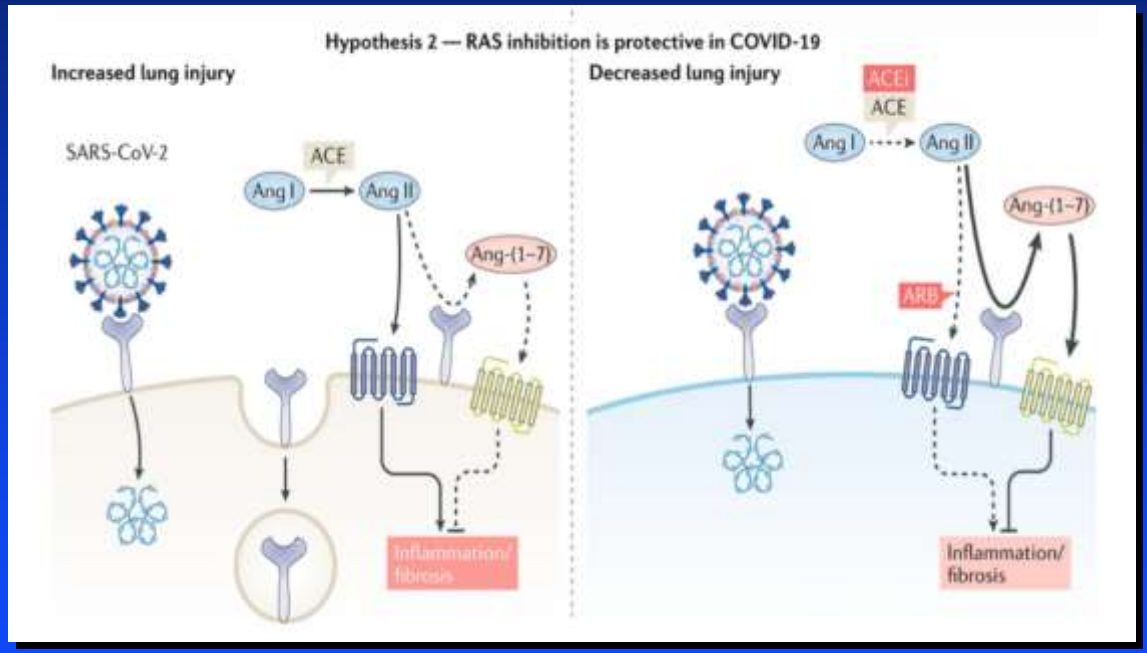
Preclinical Evidence -1



- Animal models demonstrate that exposure to ACEi and ARBs leads to upregulation of ACE2 receptor
- ? Could treatment with ACEi/ARBs lead to increased rates of infection and viral load in humans

Preclinical Evidence- 2



- ACE leads to increased production of angiogtensin-II, which amplifies local inflammation
- ? Could treatment with ACEi/ARBs lead to decreased lung inflammation/injury and improve prognosis in COVID-19?

RAAS and COVID-19: Early Concerns

- SARS-CoV-2 enters human cells via binding of “spike protein” on viral surface to membrane-bound ACE2 receptor, which is abundant on respiratory epithelial cells
- Initial data from China and Italy suggested that patients with hypertension were more likely to develop severe manifestations of COVID-19

Taken together, these 2 findings raised concerns that treatment with ACEIs and ARBs might increase the risk of COVID-19 after viral exposure

The Mercury News Blood-pressure drugs are in the crosshairs of...

Blood-pressure drugs are in the crosshairs of COVID-19 research

Medicines taken by 6.6million people with high blood pressure and diabetes could raise the risk of deadly coronavirus symptoms, scientists claim

- ACE inhibitors and angiotensin receptor blockers may lead to worse illness
- Patients should not stop taking their medication unless their doctor says so
- The pills increase amounts of an enzyme the coronavirus uses to infect the body
- Experts said patients with high blood pressure or diabetes should be monitored

NEWS HEALTH & MEDICINE

Why some heart patients may be especially vulnerable to COVID-19

People with hypertension and cardiovascular disease risk severe bouts of the disease

Patients with high blood pressure have twice the risk of dying from coronavirus, study finds

By Maggie Fox, CNN Jun 4, 2020 0

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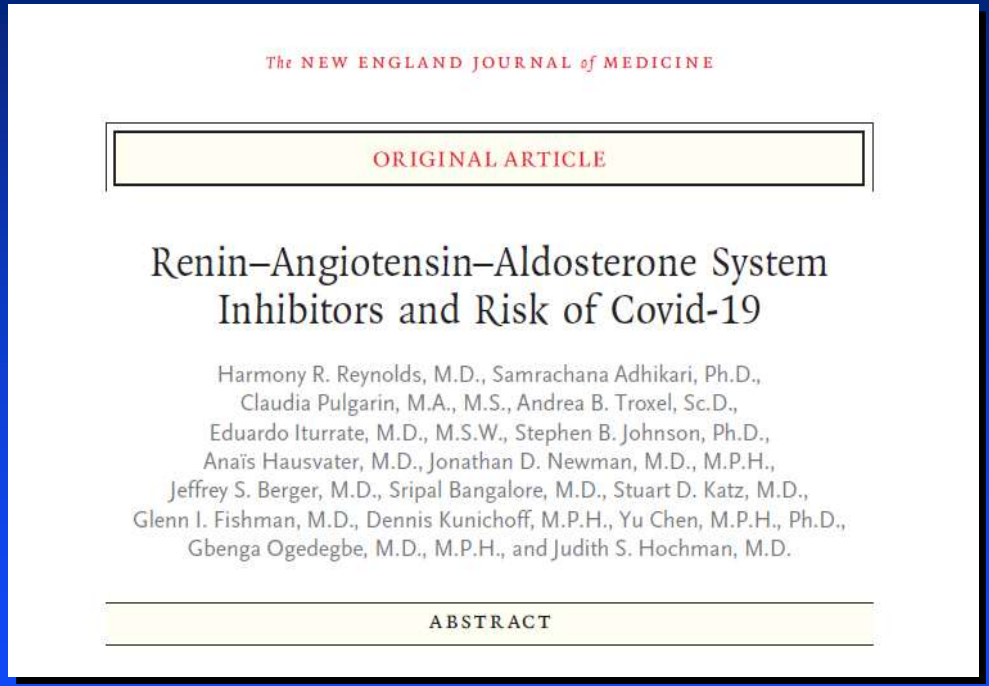
Clinical Evidence- Italy



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Renin–Angiotensin–Aldosterone System Inhibitors and Risk of Covid-19

Harmony R. Reynolds, M.D., Samrachana Adhikari, Ph.D., Claudia Pulgarin, M.A., M.S., Andrea B. Troxel, Sc.D., Eduardo Iturrate, M.D., M.S.W., Stephen B. Johnson, Ph.D., Anaïs Hausvater, M.D., Jonathan D. Newman, M.D., M.P.H., Jeffrey S. Berger, M.D., Sripal Bangalore, M.D., Stuart D. Katz, M.D., Glenn I. Fishman, M.D., Dennis Kunichoff, M.P.H., Yu Chen, M.P.H., Ph.D., Gbenga Ogedegbe, M.D., M.P.H., and Judith S. Hochman, M.D.

ABSTRACT

Case Control Study

- 6272 COVID+ cases from Lombardy Region compared with 30,759 non-COVID controls matched for age, sex, and municipality
- Conditional logistic regression used to examine association between ACEi/ARB prescription and incidence of COVID-19

Mancia G, et al. N Engl J Med 2020;382:2431-40

Association between ACE/ARB and Incidence of COVID-19

Drug Class	Unadjusted OR	Adjusted OR
ACE inhibitors	1.16 (1.08-1.24)	0.96 (0.87-1.07)
ARBs	1.20 (1.12-1.29)	0.95 (0.86-1.05)
Ca++ channel blockers	1.28 (1.18-1.38)	1.03 (0.95-1.12)
Beta blockers	1.42 (1.33-1.51)	0.99 (0.91-1.08)
Thiazide diuretics	1.09 (1.01-1.17)	1.03 (0.86-1.23)
Mineralocorticoid antagonists	1.59 (1.37-1.85)	0.90 (0.75-1.07)

Mancia G, et al. N Engl J Med 2020;382:2431-40

Clinical Evidence- NYU

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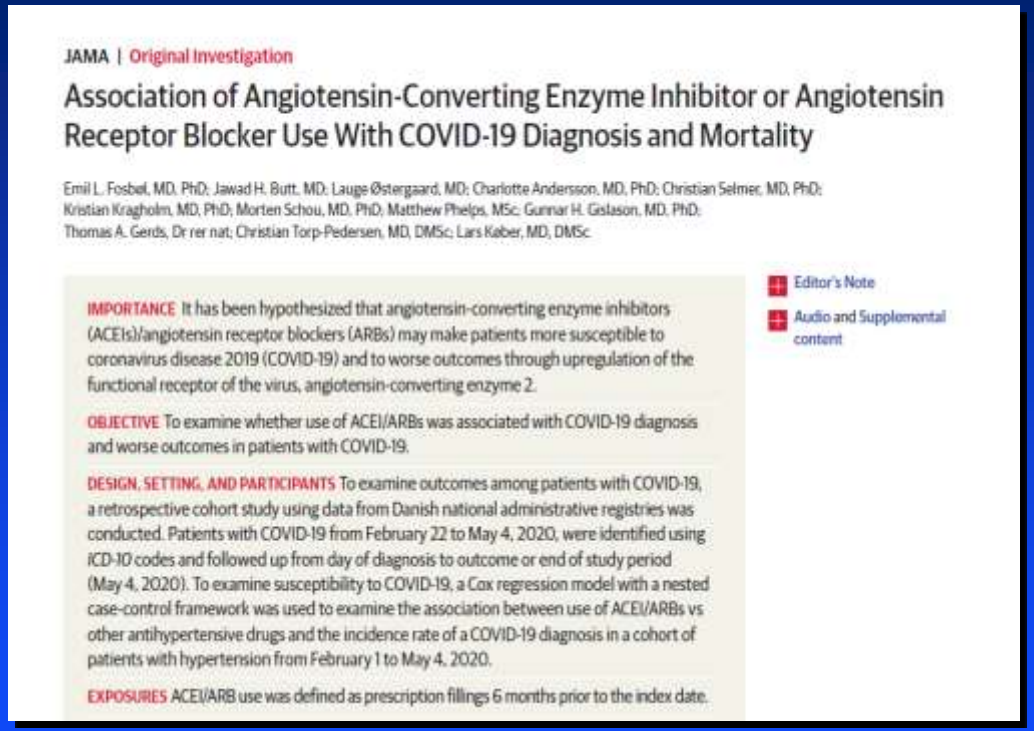
ABSTRACT

- 12,594 patients tested for COVID-19 in NYU health system
- Propensity matching used to compare patients receiving different classes of antihypertensive medications vs. matched hypertensive patients
- Key Findings
  - No association between ACE-I or ARBs and likelihood of COVID-19+
  - No association between medication classes and incidence of severe disease among COVID-19+ pts

Reynolds HR, et al. N Engl J Med 2020; 382:2441-8

Clinical Evidence- Denmark



JAMA | Original Investigation

Association of Angiotensin-Converting Enzyme Inhibitor or Angiotensin Receptor Blocker Use With COVID-19 Diagnosis and Mortality

Emil L. Fosbøl, MD, PhD; Jawad H. Butt, MD; Lauge Østergaard, MD; Charlotte Andersson, MD, PhD; Christian Selmer, MD, PhD; Kristian Kragholm, MD, PhD; Morten Schou, MD, PhD; Matthew Phelps, MSc; Gunnar H. Gislason, MD, PhD; Thomas A. Gerds, Dr rer nat; Christian Torp-Pedersen, MD, DMSc; Lars Køber, MD, DMSc

Editor's Note

Audio and Supplemental content

IMPORTANCE It has been hypothesized that angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin receptor blockers (ARBs) may make patients more susceptible to coronavirus disease 2019 (COVID-19) and to worse outcomes through upregulation of the functional receptor of the virus, angiotensin-converting enzyme 2.

OBJECTIVE To examine whether use of ACEI/ARBs was associated with COVID-19 diagnosis and worse outcomes in patients with COVID-19.

DESIGN, SETTING, AND PARTICIPANTS To examine outcomes among patients with COVID-19, a retrospective cohort study using data from Danish national administrative registries was conducted. Patients with COVID-19 from February 22 to May 4, 2020, were identified using *ICD-10* codes and followed up from day of diagnosis to outcome or end of study period (May 4, 2020). To examine susceptibility to COVID-19, a Cox regression model with a nested case-control framework was used to examine the association between use of ACEI/ARBs vs other antihypertensive drugs and the incidence rate of a COVID-19 diagnosis in a cohort of patients with hypertension from February 1 to May 4, 2020.

EXPOSURES ACEI/ARB use was defined as prescription fillings 6 months prior to the index date.

- Data from Danish national administrative registries used to link prescription records with diagnostic codes
- Nested case-control design used to assess association between medication class and incidence of COVID-19
- Cohort design used to assess association between outpt medication use and prognosis (death) among pts with COVID-19

Fosbol EL, et al. JAMA 2020; doi:10.1001/jama.2020.11301

ACEI/ARB vs. COVID-19 Incidence

Table 5. Susceptibility Analysis Using Nested Case-Control Design for ACEI/ARB Use and Adjusted Associated Incidence Rate of COVID-19 Among Patients With Hypertension[a]

	Hazard ratio (95% CI)	*P* value
Associated incidence rate of COVID-19		
ACEI/ARB use vs use of other antihypertensives	1.05 (0.80-1.36)	.67
ACEI use vs use of other antihypertensives	0.85 (0.70-1.01)	.08
ARB use vs use of other antihypertensives	1.15 (0.96-1.37)	.11
ACEI/ARB use vs use of CCB	1.23 (0.89-1.70)	.21

- No evidence of association between prescription of ACEI/ARB in previous 6 months and COVID-19 diagnosis
- Siimilar results for ACEI and ARB, separately, and when compared with Ca++ blocker

Fosbol EL, et al. JAMA 2020; doi:10.1001/jama.2020.11301

ACEI/ARB vs. COVID-19 Prognosis

Table 2. Hazard Ratios for ACEI/ARB Use vs No Use and Death, Composite of death or severe dz

	No. (%)		Unadjusted model		Fully adjusted model[a]	
	ACEI/ARB users (n = 895)	ACEI/ARB nonusers (n = 3585)	Hazard ratio (95% CI)	*P*	Hazard ratio (95% CI)	*P* value
Primary outcome						
Mortality	181 (20.2)	297 (8.3)	2.65 (2.18-3.23)	<.001	0.83 (0.67-1.03)	.09
Secondary outcomes						
Mortality or severe COVID-19	292 (32.6)	526 (14.7)	2.49 (2.15-2.88)	<.001	1.04 (0.89-1.23)	.61
Severe COVID-19	203 (22.6)	373 (10.4)	2.34 (1.97-2.77)	<.001	1.15 (0.95-1.41)	.15

Fosbol EL, et al. JAMA 2020; doi:10.1001/jama.2020.11301

Clinical Evidence- Surgisphere

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cardiovascular Disease, Drug Therapy, and Mortality in Covid-19

Mandeep R. Mehra, M.D., Sapan S. Desai, M.S., Ph.D., SreyRam Kuy, M.D., M.H.S., Timothy D. Henry, M.D., and Amit N. Patel, M.D.

ABSTRACT

BACKGROUND

Coronavirus disease 2019 (Covid-19) may disproportionately affect people with cardiovascular disease. Concern has been aroused regarding a potential harmful effect of angiotensin-converting–enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARBs) in this clinical context.

"Because all the authors were not granted access to the raw data and the raw data could not be made available to a third-party auditor, we are unable to validate the primary data sources underlying our article, we therefore request that the article be retracted."

- Mehra MR, et al (June 4, 2020)

Mehra MR, et al. N Engl J Med (May 1, 2020)

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- Background-- Why RAAS inhibitors?
- What have we learned so far?
- Ongoing studies
- Summary/Current recommendations

Limitations of Current Data

- Some mortality studies have significant informative censoring due to patients who remained in hospital at the time of data harvest
- Exposure defined as pre-procedure ACEI/ARB prescription→ cannot assess impact of continued treatment during COVID-19 on prognosis
- Retrospective, observational studies→ possible residual confounding

Ongoing and Planned RCTs of ACEI/ARB in COVID-19

Study Identifier Estimated completion date	Target N Country	Population	Interventions	Primary Outcome
Prevention in patients not known to have COVID-19				
NCT04330300 (CORONACION) March 2021	3414 Ireland	Age ≥60 receiving ACEI/ARB for hypertension prior to enrolment, without known COVID-19	Switch from chronic ACEI/ARB to alternative agent (thiazide-like, calcium-channel	Time to death, need for intubation in intensive care unit, or hospitalization for non-invasive ents who develop n 12
Confirmed COVID-19 - C				
NCT04329195 (ACORES-2) May 2020	554 Fran			vement on WHO scale† or whever comes first) up to
NCT04338009 (REPLACE COVID) December 2020	152 United States	Hospitalized for confirmed COVID-19, receiving ACEI/ARB prior to enrolment Key exclusions: Heart failure with reduced ejection fraction; ARNI use prior to enrolment; BP >180/110 mm Hg	Discontinue ACEI/ARB during hospitalization (resumed on discharge) Comparator: Continue ACEI/ARB throughout hospitalization (open-label)	Composite global rank score based on time to death; number of days requiring mechanical ventilation or ECMO; number of days supported by renal replacement therapy or vasopressors/ inotropes; modified SOFA score
NCT04351581 (RASCOVID-19) December 2020	215 Denm			spital by day 14
NCT04364893 (BRACE-CORONA) December 2020	500 Brazil	Key exclusions: taking sacubitril-valsartan for heart failure; hospitalization for heart failure in the last 12 months; taking ≥3 antihypertensive medications; clinical indication to stop ACEI/ARB	(open-label)	out of the hospital from
NCT04353596 (ACEI-COVID) May 2022	208 Austria and Germany	Confirmed COVID-19, managed in hospital or as outpatient, receiving ACEI/ARB prior to enrolment for coronary artery disease, diabetes, heart failure, or hypertension	Stop chronic ACEI/ARB Comparator: Continue ACEI/ARB (open-label)	SOFA score and death at 30 days

5 trials of ACEI/ARB continuation vs. discontinuation in patients hospitalized for COVID-19

1 trial of ACEI/ARB continuation vs. discontinuation in patients with HTN but without known COVID-19

Ongoing and Planned RCTs of ACEI/ARB in COVID-19

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NCT04353596 (ACEI-COVID) May 2022	208 Austria and Germany	Confirmed COVID-19, ma receiving ACEI/ARB prior diabetes, heart failure, or		

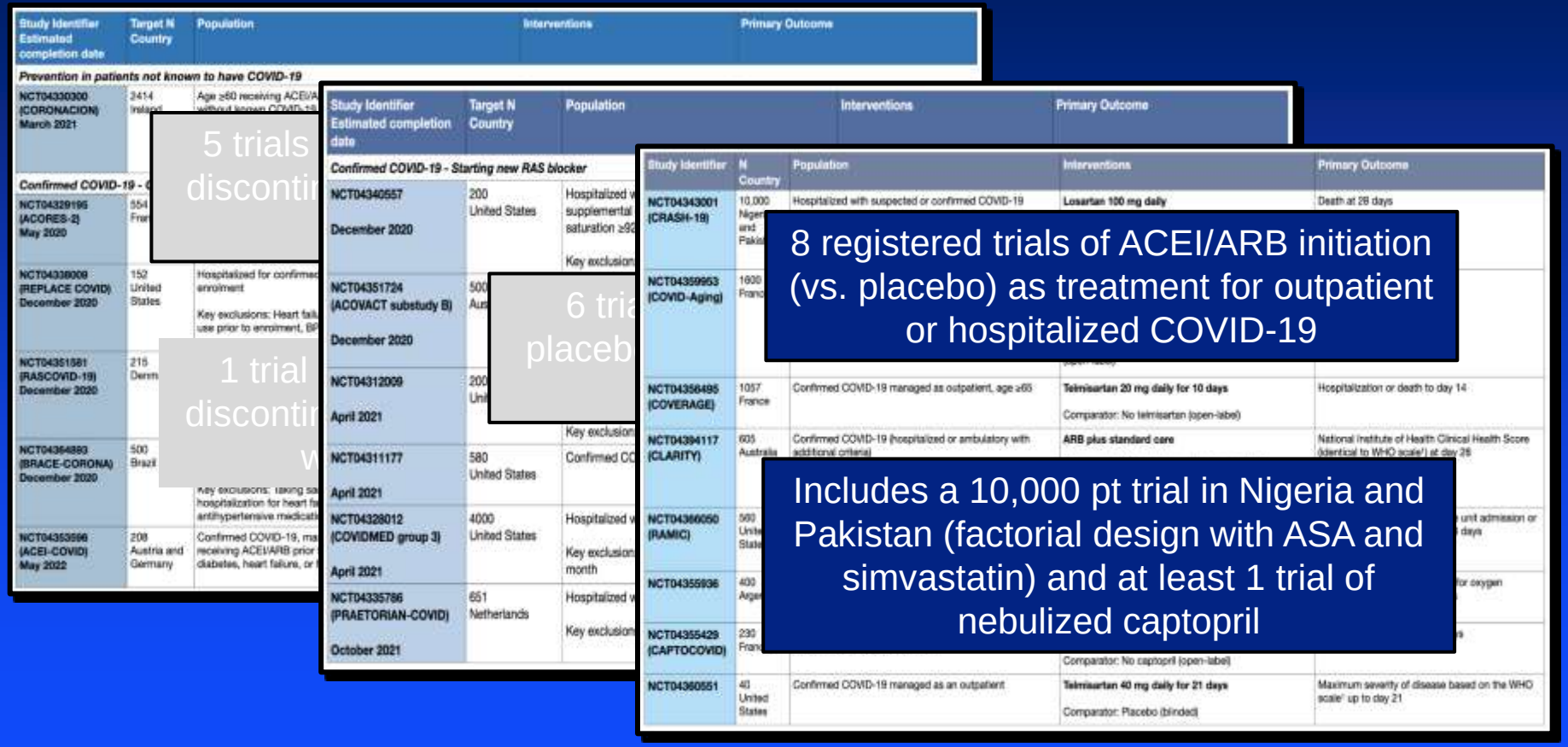
5 trials discontin

1 trial discontin w

Study Identifier Estimated completion date	Target N Country	Population	Interventions	Primary Outcome
Confirmed COVID-19 - Starting new RAS blocker				
NCT04340557 December 2020	200 United States	Hospitalized with confirmed COVID-19 requiring supplemental oxygen ≥2 L/min to maintain oxygen saturation ≥92% Key exclusion: Receiving ACEI/ARB prior to admission	**Losartan 12.5 mg twice daily for up to 10 days** Comparator: No losartan (open-label)	Mechanical ventilation up to day 45
NCT04351724 (ACOVACT substudy B) December 2020	500 Aus			ment >48 hours on 29
NCT04312009 April 2021	200 Unit	Key exclusion: Receiving ACEI/ARB		: fraction of inspired rs
NCT04311177 April 2021	580 United States	Confirmed COVID-19 managed as an outpatient	**Losartan 25 mg daily** Comparator: Placebo (blinded)	Hospitalization within 15 days
NCT04328012 (COVIDMED group 3) April 2021	4000 United States	Hospitalized with confirmed COVID-19 Key exclusion: Already receiving ACEI/ARB within 1 month	**Losartan 25 mg daily for 5-14 days** Comparator: Matching placebo for 14 days (blinded)	National Institute of Allergy and Infectious Diseases COVID-19 ordinal severity scale at day 60
NCT04335786 (PRAETORIAN-COVID) October 2021	651 Netherlands	Hospitalized with confirmed COVID-19 Key exclusions: Currently receiving ACEI/ARB/ARNI	**Valsartan up to 160 mg twice daily for up to 14 days** Comparator: Placebo (blinded)	Intensive care unit admission, mechanical ventilation or death within 14 days

6 trials of ACEI/ARB initiation (vs. placebo) as treatment for outpatient or hospitalized COVID-19

Ongoing and Planned RCTs of ACEI/ARB in COVID-19



COVID-19 and RAAS Inhibitors

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Summary

- Although there are animal data suggesting that treatment with RAAS inhibitors may increase susceptibility to SARS-CoV2, the relevance of these findings to humans is unknown
- Early data suggesting an association between ACEI/ARB use and rates of COVID-19 infection were highly confounded by age and comorbid conditions
- Data from observational studies to date are consistent– demonstrating no significant association between ACEI/ARB use and either susceptibility to COVID-19 infection or prognosis once infected

Recommendations

The HFSA, ACC, and AHA recommend continuation of RAAS antagonists for those patients who are currently prescribed such agents for indications for which these agents are known to be beneficial, such as heart failure, hypertension, or ischemic heart disease. In the event patients with cardiovascular disease are diagnosed with COVID-19, individualized treatment decisions should be made according to each patient's hemodynamic status and clinical presentation

The Surgisphere Saga:
A drama in 4 acts

The Surgisphere Saga

- Over the course of 6 weeks, “Surgisphere” published 3 major observational studies on therapies for COVID-19
  - NEJM 5/1/20 (n=8000): ACEI and ARBs are not harmful in pts with COVID-19
  - Lancet 5/22/20 (n=96,000): Hydroxychloroquine and Chlorquine are associated with ~40% increase in mortality among hospitalized pts with COVID-19 and a 2-4x increase in ventricular arrhythmias
  - SSRN preprint (n=1400): Ivermectin associated with 80% reduction in mortality among hospitalized pts with COVID-19
- These studies led to suspension of several RCTs of HCQ and widespread adoption of ivermectin in several S. American countries

The Surgisphere Saga- 2

Although no concerns were raised with publication of the *NEJM* paper, the *Lancet* HCQ paper was highly scrutinized almost immediately…

- 609 pts enrolled in Australia at a time when this represented virtually all the cases in the country→ Correction→ one hospital originally assigned to Australia was actually in Asia (??)
- Detailed racial data reported from all continents and all patients (even though this is not permitted by many EU countries)
- 4402 pts enrolled in Africa (~25% of all cases at the time)→ not credible per other researchers
- “The collection and analysis of data in the registry have been deemed unneecessary” (By whom?)

Additional Concerns– Implausible Data

Table S3. Summary Data by Continent

Variable	North America	South America	Europe	Africa	Asia	Australia
N	63,315	3,577	16,574	4,402	7,555	609
Age (years)	54.4 +/- 17.8	53.6 +/- 17.1	52.7 +/- 17.0	53.9 +/- 16.9	51.9 +/- 17.2	55.8 +/- 17.7
BMI (kg/m^2)	28.1 +/- 5.3	26.4 +/- 5.4	28.1 +/- 5.3	23.8 +/- 5.4	24.8 +/- 5.3	28.1 +/- 5.4
Female sex	29,288 (46.3)	1,678 (46.9)	7,730 (46.6)	1,981 (45.0)	3,486 (46.1)	263 (43.2)
Coronary artery disease	7,850 (12.4)	485 (13.6)	2,169 (13.1)	614 (13.9)	980 (13.0)	39 (6.4)
Congestive heart failure	1,639 (2.6)	73 (2.0)	366 (2.2)	105 (2.4)	179 (2.4)	6 (1.0)
History of arrhythmia	2,293 (3.6)	118 (3.3)	543 (3.3)	146 (3.3)	256 (3.4)	25 (4.1)
Diabetes mellitus	8,654 (13.7)	521 (14.6)	2,360 (14.2)	570 (12.9)	1,069 (14.1)	86 (14.1)
Hypertension	17,159 (27.1)	954 (26.7)	4,368 (26.4)	1,140 (25.9)	2,010 (26.6)	179 (29.4)
qSOFA < 1	52,301 (82.6)	2,958 (82.7)	13,682 (82.6)	3,670 (83.4)	6,267 (83.0)	490 (80.5)
SPO_2 < 94%	6,191 (9.8)	345 (9.6)	1,576 (9.5)	439 (10.0)	701 (9.3)	65 (10.7)

The Surgisphere Saga- 3

Additional concerns began to surface about Surgisphere, itself…

- *Based on LinkedIn searches, the company seemed to have at most 5-10 employees, none of whom had any experience in data analytics*
- *The marketing manager was also a Las Vegas showgirl and adult content model*
- *The company claimed to have data analytic contracts with 600+ hospitals worldwide, but not one hospital ever stepped forward to acknowledge the existence of a contract*

The Surgisphere Saga- The Final Chapter

- May 28/31– Open letters from >200 members of scientific community to EIC of *Lancet* and *NEJM* recommending thorough investigation
- June 2/3-- *Lancet* and *NEJM* issue “Expression of Concern” regarding data integrity of the HCQ and ACEI/ARB papers
- June 4– Retraction of both papers within hours of each other