# COVID-19 and the CVS

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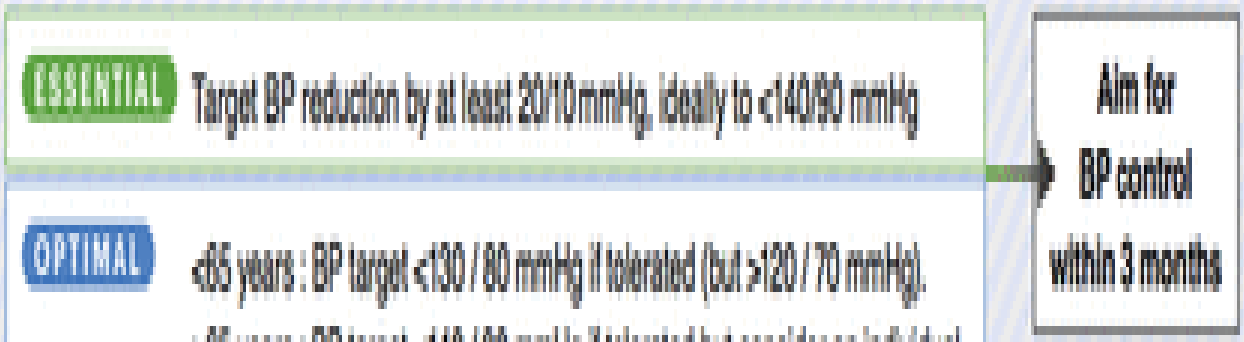
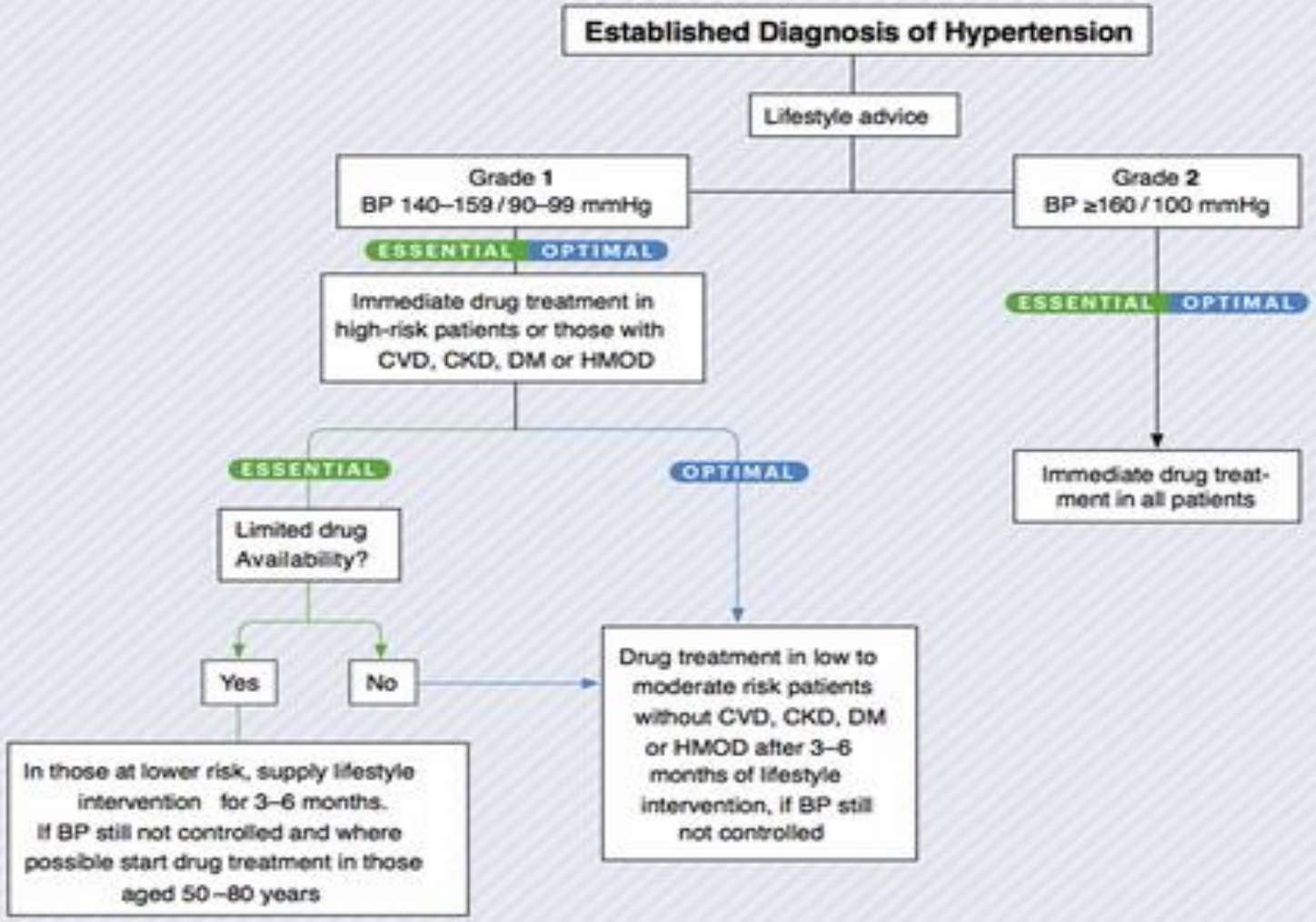
# ISH Global Hypertension Practice Guidelines: 2020

- Evidence based, reviewed by experts in high and low/middle income countries
- Applicable in low and high resource settings
- Concise, simplified, easy to use
- No industry influence


ESSENTIAL
Target BP reduction by at least 20/10 mmHg, ideally to <140/90 mmHg
OPTIMAL
<65 years : BP target <130 / 80 mmHg if tolerated (but >120 / 70 mmHg).
≥65 years : BP target <140 / 80 mmHg if tolerated but consider an individualised BP target in the context of frailty, independence and likely tolerability of treatment.
Aim for BP control within 3 months


Established Diagnosis of Hypertension
Lifestyle advice
Grade 1
BP 140–159 / 90–99 mmHg
Grade 2
BP ≥160 / 100 mmHg
ESSENTIAL
OPTIMAL
ESSENTIAL
OPTIMAL
Immediate drug treatment in high-risk patients or those with CVD, CKD, DM or HMOD
Immediate drug treatment in all patients
ESSENTIAL
OPTIMAL
Limited drug Availability?
Yes
No
Drug treatment in low to moderate risk patients without CVD, CKD, DM or HMOD after 3–6 months of lifestyle intervention, if BP still not controlled
In those at lower risk, supply lifestyle intervention for 3–6 months. If BP still not controlled and where possible start drug treatment in those aged 50–80 years

# Hypertension in Blacks

- TOD at a younger age
- Greater resistant hypertension
- Greater nocturnal hypertension
- Greater renal disease
- Greater stroke incidence
- Greater cardiac  failure

# Hypertension in Blacks

- Supressed renin-angiotensin system
- Altered renal sodium handling
- Increased cardiovascular reactivity
- Early vascular aging

**ESSENTIAL**

- Use whatever drugs are available with as many of the ideal characteristics (see ***Table 9***) as possible.
- Use free combinations if SPCs are not available or unaffordable
- Use thiazide diuretics if thiazide-like diuretics are not available
- Use alternative to DHP-CCBs if these are not available or not tolerated (i.e. Non-DHP-CCBs: diltiazem or verapamil).

**OPTIMAL**

| | | |
|---|---|---|
| **Ideally Single Pill Combination Therapy (SPC)** | **Step 1** Dual low-dose# combination | **A + C** [a,b,c] |
| | **Step 2** Dual full-dose combination | **A + C** [a,b] |
| | **Step 3** Triple combination | **A + C + D** |
| | **Step 4** (Resistant Hypertension) Triple Combination + Spironolactone or other drug* | **A + C +D Add Spironolactone (12.5 – 50 mg o.d.)**[d] |

**ESSENTIAL** **OPTIMAL**

Consider beta-blockers at any treatment step when there is a specific indication for their use, e.g. heart failure, angina, post-MI, atrial fibrillation, or younger women with, or planning pregnancy.

**a)** Consider monotherapy in low risk grade 1 hypertension or in very old (≥80 yrs) or frailer patients.
**b)** Consider A + D in post-stroke, very elderly, incipient HF or CCB intolerance.
**c)** Consider A + C or C + D in black patients.
**d)** Caution with spironolactone or other potassium sparing diuretics when estimated GFR <45 ml/min/1.73m² or $K^+$ >4.5 mmol/L.

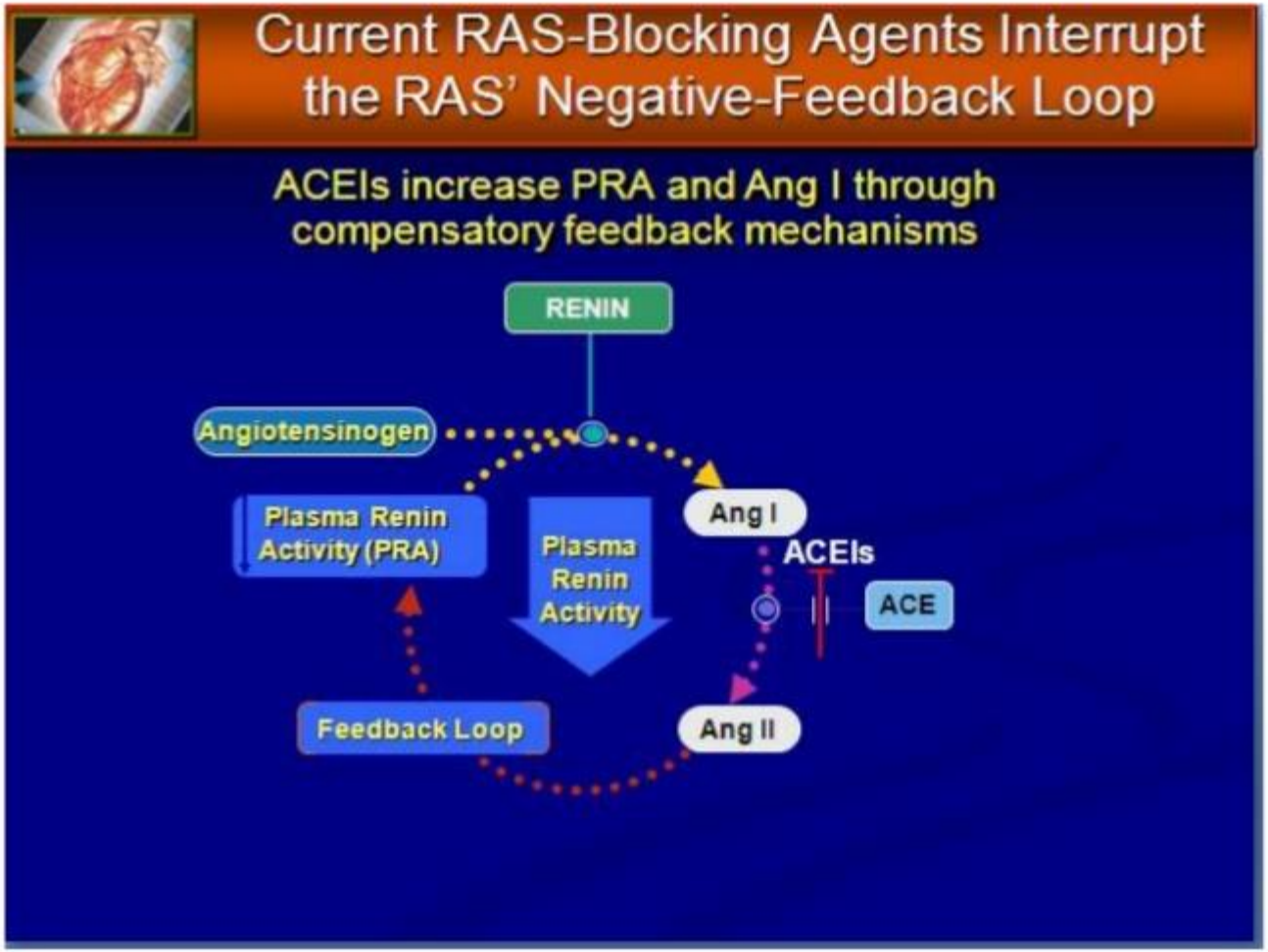
**A** = ACE-Inhibitor or ARB (Angiotensin Receptor Blocker)
**C** = DHP-CCB (Dihydropyridine -Calcium Channel Blocker)
**D** = Thiazide-like diuretic

**Supportive references:** A + C,[69,70] Spironolactone,[71] Alpha-blocker,[72] C + D[73].

* Alternatives include: Amiloride, doxazosin, eplerenone, clonidine or beta-blocker.

# low-dose generally refers to half of the maximum recommended dose

RCT-based benefits between ACE-I's and ARB's were not always identical in different patient populations. Choice between the two classes of RAS-Blockers will depend on patient characteristics, availability, costs and tolerability.


Current RAS-Blocking Agents Interrupt the RAS' Negative-Feedback Loop
ACEIs increase PRA and Ang I through compensatory feedback mechanisms
RENIN
Angiotensinogen
Plasma Renin Activity (PRA)
Plasma Renin Activity
Ang I
ACEIs
ACE
Feedback Loop
Ang II

# ACE 2

- Discovered 22 years ago
- Analagous to ACE
- Membrane bound
- Cleaved from membrane, become smaller, start circulating
- Monocarboxypeptidase,cleaving one amino acid from angiotensin11
- Cleaves one amino acid from angiotensin 1, also

# Cell surface receptors of RAS

- AT1: Angiotensin II type 1 receptor
  - Angiotensin II, Angiotensin III
  - Vasoconstriction, stimulation of aldosterone release and sympathetic nerve activity, promotion of cell growth, matrix deposition, inflammation
- AT2: Angiotensin II type 2 receptor
  - Angiotensin II
  - Antagonism of the effects of AT1, promotion of apoptosis, protection of neural tissue, possible synergism with AT1 in promoting inflammation

Renin-angiotensin system and cardiovascular risk Lancet 2007; 369: 1208–19

# The $AT_2$ Receptor

- gene - a single copy on the X chrmosome.
- highly expressed in fetal mesenchymal tissues
- clearly detectable in the adult kidney, heart, and blood vessels.
- mediate vasodilation by stimulating the production of BK, NO, and cGMP

- Activation of the $AT_2$ receptor mediates at least some of the beneficial effects of $AT_1$ receptor blockade via a BK/NO/cGMP pathway.

- This paradigm opens the door for potential synergistic therapeutic effects of $AT_2$ receptor agonists in combination with $AT_1$ receptor blockers.

# Angiotensin-Converting Enzyme-2

- In the year 2000, ACE 2 a zinc metalloprotease was discovered
- gene mapped to the X chromosome in humans
- ACE 2 may be a candidate gene in hypertension.

ACE 2

Predominantly in endothelium of coronary and renal vasculature

ACE2 counterbalances the enzymatic actions of ACE1

Does not convert A1 to A11

Activity not affected by Ace Inhibitors

# ACE 2

- Found in epithelial cells, upper & lower respiratory tract, alveolar cells

- Afford lung protection, in contrast to A11/AT1 receptor activity
- Animal studies: upregulation in ACE2 , after treatment with RAS blockers

# ACE 2 Role

- Imai et al Cell Mol Life 2007
- Supe S et al  Br J Pharmacol 2016
- It plays a protective role against pulmonary inflammation
- Cheng et al  J Med Virol 2020….”AT1 receptor blockade and ensuing ACE2 increased activity may protect against lung involvement”

# ACE 2 viral-coupling

- Lesser ACE2
- Lesser A11 degradation
- A11 rises, more vessel permeability ,more injury
- More aldosterone so more potassium loss
- Murray E et al  Cardiovasc Res 2020

## Angiotensin 1 -9 (Ang1-9) & Ang1-7

- Ang 1-9
  - reduces
  - incre
  - St
    r
  -
- Ang
  effec
  G prot
  receptor

### ACE 2

- Novel enzyme similar to ACE, called angiotensin-converting enzyme 2 (ACE2)
- Removes the COOH-terminal amino acid phenylalanine and has 400-fold less affinity to Ang I than to Ang II
- ACE2 can cleave des-Arg(9)-bradykinin
- **Insensitive to ACE inhibitors**

# Sequelae: low A11, A1-7

- Kassiri Z et al  Circ Heart Fail 2009
- Above results in poor maladaptive LV remodelling post MI (A1-7  has vasodilatory, antiinflammatory, antioxidant properties)

# Angiotensin (1–7)

- IN 1988 major biologically active peptide product of the RAS
- ANG I by neutral-endopeptidase (NEP) 24.11 or prolyl-endopeptidase (PEP)
  ANG II via PEP or prolyl-carboxypeptidase
- NEP 24.11 plays a major role in both circulating and tissue ANG (1–7) formation
- cleaved to biologically inactive fragments by aminopeptidases or ACE.

- Ang III and IV- in tissue with high levels of aminopeptidases A and N, such as brain and kidney tissue.

- Ang III - in CNS , play an important role in tonic blood pressure maintenance and in hypertension.

- Ang IV [(3-8)] is a hexapeptide . Some report that Ang IV is a vasorelaxative agent and this effect is contributed to activation of endothelial NOS
- others: Cooperative effect of Ang IV on angiotensin II type 1 (AT1)-receptor signaling

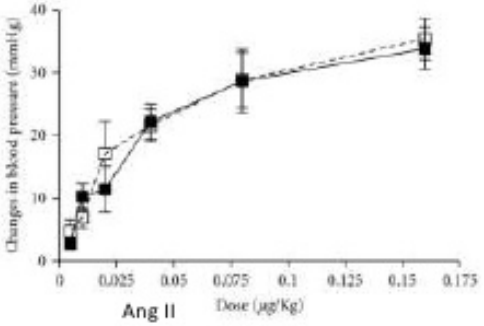
- The type 4 (AT4) receptors- mediate the release of plasminogen activator inhibitor 1 by Ang II and by the N-terminal truncated peptides (Ang III and Ang IV).

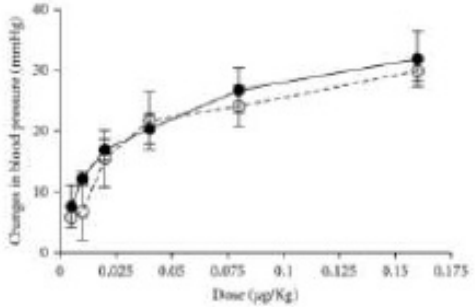
- The AT4 receptor appears to be involved in memory acquisition and recall.

- but the function of the type 3 (AT3) receptors is unknown.

# Cardiac ACE2/Ang-(1–7)/Mas Axis

- Protective role of ACE2 in the heart
- Vascular endothelial cells( including kidney, lung & small intestine), cardiomyocytes, fibroblasts & myofibroblasts
- ACEi, ARBs, and aldosterone receptor blockers, increase ACE2 activity/ expression
- **Ang-(1–7) causes vasodilation in forearm circulation of normotensive subjects and patients with essential hypertension** but **no significant effect in the same vascular territory in ACEi-treated patients**
- **Activation of Endogenous ACE2 (XNT) causes a dose-dependent hypotensive effect in normotensive and hypertensive rats but no significant effect in response to the administration of Ang II or Losartan**




With XNT

Without XNT

**International Journal of Hypertension**
**Volume 2012 (2012),** Article ID 147825, 13 pages
doi:10.1155/2012/147825

# Chemical transporter kinetics

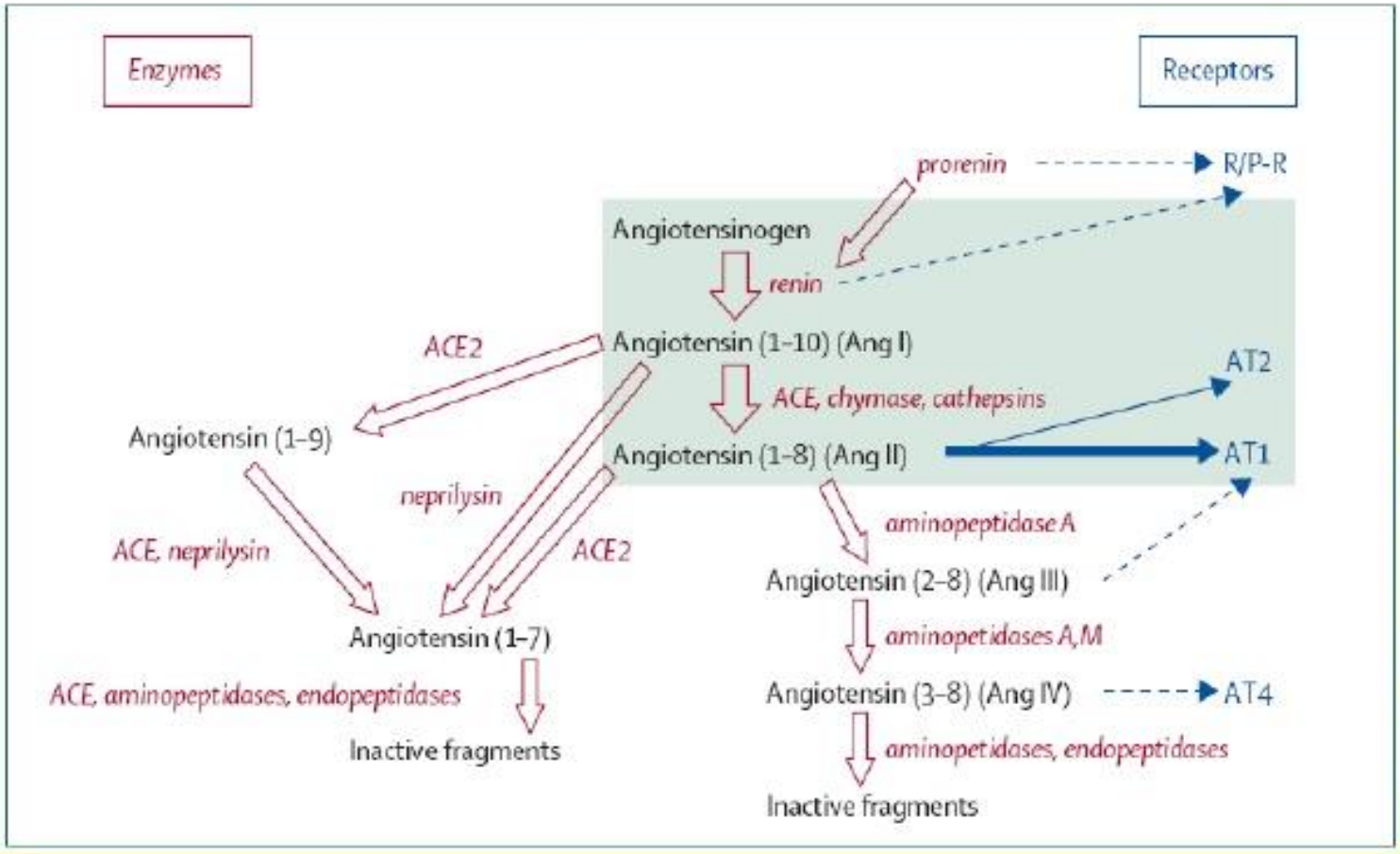
- Transporter
- Substrate
- Substrate concentration

# Mechanism of Atherosclerosis

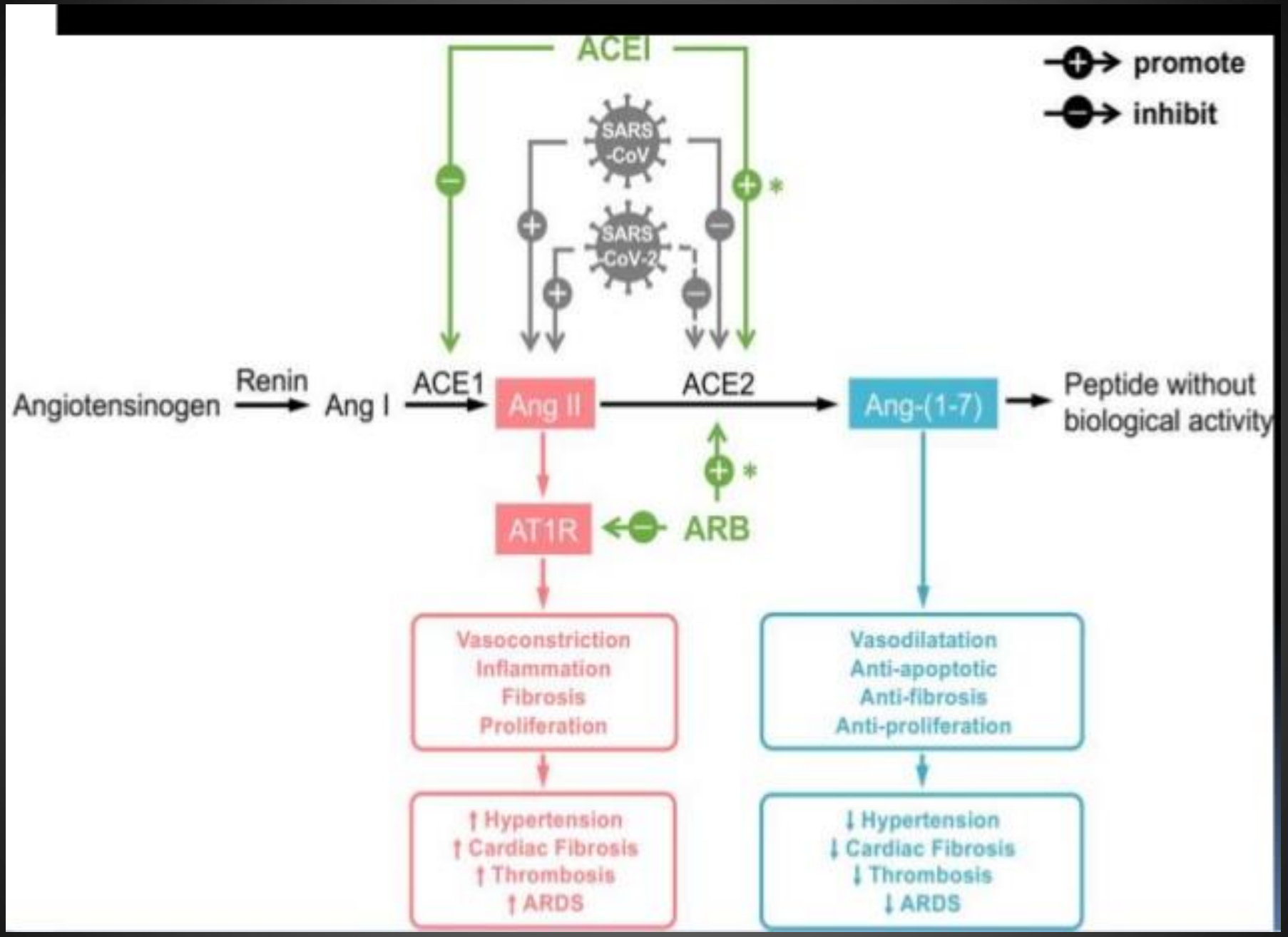
- Vascular inflammation, generation of reactive oxygen species, and alterations of endothelial function
- Renin-angiotensin system: **AT1 receptors** is major effecter
- Production of pro-inflammatory cytokines: **interleukin 1, tumor necrosis factor α, and interleukin 6**.
- The concentration of circulating cytokines is associated with an adverse outcome in patients with coronary atherosclerosis.

- Plaque rupture has been connected with activation of matrix metalloproteinases (MMP) in the fibrous cap of the atherosclerotic lesion and there is evidence that angiotensin II is implicated in matrix metalloproteinases activation, both through direct actions and through induction of interleukin 6.

# Renin Angiotensin System (RAS) overview




Renin-angiotensin system and cardiovascular risk Lancet 2007; 369: 1208–19


promote
inhibit
ACEI
SARS -CoV
SARS CoV-2
Angiotensinogen
Renin
Ang I
ACE1
Ang II
ACE2
Ang-(1-7)
Peptide without biological activity
AT1R
ARB
Vasoconstriction
Inflammation
Fibrosis
Proliferation
Vasodilatation
Anti-apoptotic
Anti-fibrosis
Anti-proliferation
↑ Hypertension
↑ Cardiac Fibrosis
↑ Thrombosis
↑ ARDS
↓ Hypertension
↓ Cardiac Fibrosis
↓ Thrombosis
↓ ARDS

# RAAS- ACE -COVID

**ACE2 is a key counterregulatory enzyme that degrades angiotensin II to angiotensin-(1–7), thereby attenuating its effects on vasoconstriction, sodium retention, and fibrosis**

- Despite substantial structural homology between ACE and ACE2, their enzyme active sites are distinct
- ACE inhibitors in clinical use do not directly affect ACE2 activity
- SARS-CoV-2 appears to subsequently downregulate ACE2 expression
- Unabated angiotensin II activity may be in part responsible for organ injury in Covid-19

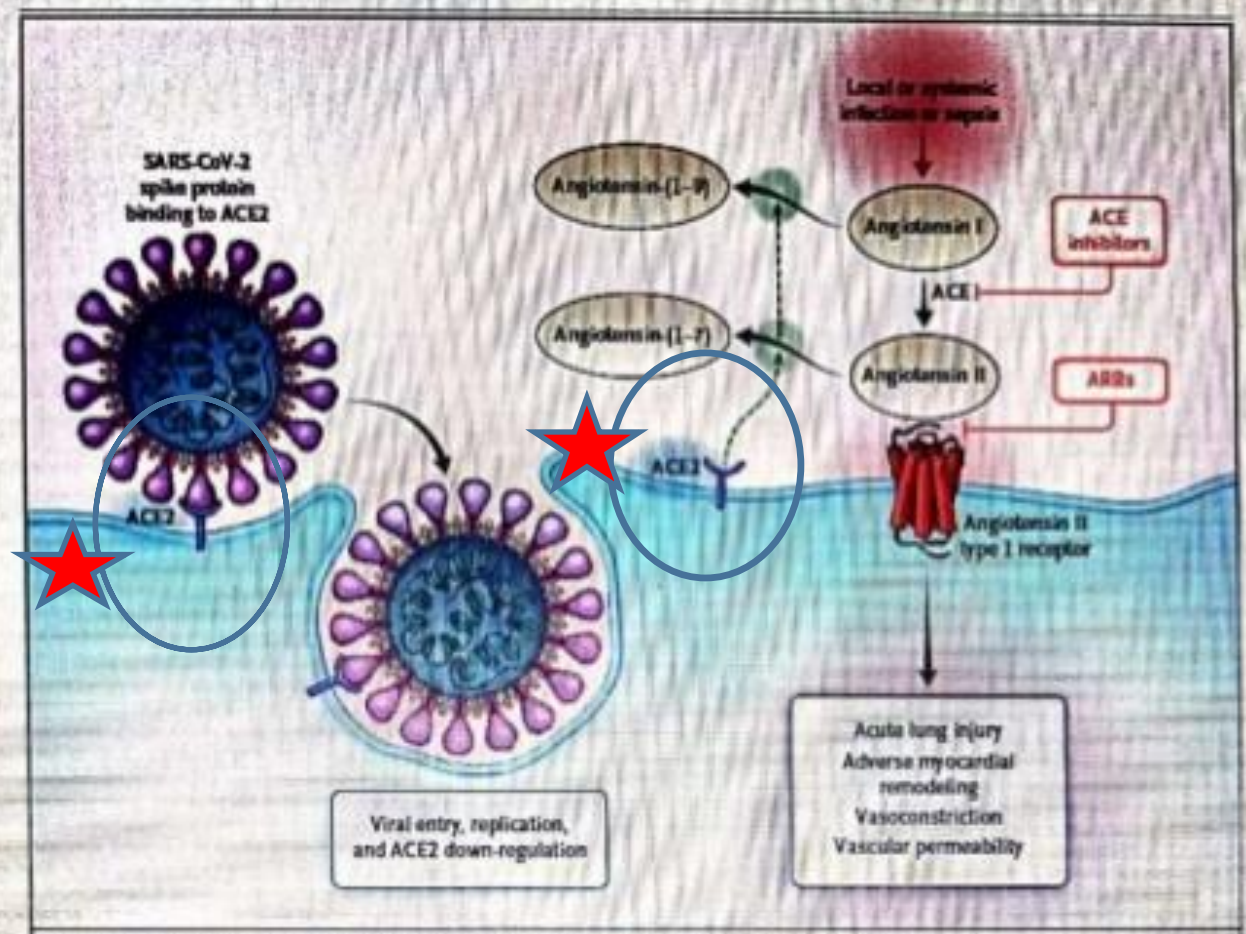



Figure 1. **Interaction between SARS-CoV-2 and the Renin–Angiotensin–Aldosterone System.**

Shown is the initial entry of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) into cells, primarily type II pneumocytes, after binding to its functional receptor, angiotensin-converting enzyme 2 (ACE2). After endocytosis of the viral complex, surface ACE2 is further down-regulated, resulting in unopposed angiotensin II accumulation. Local activation of the renin–angiotensin–aldosterone system may mediate lung injury responses to viral insults. ACE denotes angiotensin-converting enzyme, and ARB angiotensin-receptor blocker.

## Ferrario LM et al (Circulation 2005)
## Ishiyama Y et al( Hypertension 2014)

- Drugs blocking the renin angiotensin system increase the expression of ACE2 enzyme

# NEJM June 2020
# Mehra MR et al

- 169 hospitals
- 8910 patients, all covid admissione
- Europe,Asia,N America
- Mortality rate 5,8%

## Mehra et al ( NEJM)
## Factors associated with mortality:

65 years and over

Coronary artery disease

Congestive cardiac failure

Arrhythmias

COPD

Current smoking

NOT…ACE inhibitors or ARB use

## Health and age factors - risk of getting serious complications

- COPD ,Moderate to severe Asthma
- CHF ,CAD ,Cardiomyopathies
- T2DM
- CKD CLD
- Obese and BMI > 30
- Sickle cell disease
- Cancer
- Immunocompromised
- Pregnancy
- CVA

# HIGH RISK GROUP

- Adults 60 years and older
- Children younger than 2 years old
- Pregnant women and women up to 2 weeks after the end of pregnancy
- People who live in nursing homes and other long-term care facilities

# Henry BM et al (Int Urol Nephrol 2020)

- Meta analysis of 4 studies, n=1385
- 273 severe disease
- Hypertension commoner in those with more severe disease
- As was with CKD

# ACE Inhibitors in Covid: metanalysis

- Reduction of mortality and critical illness was reduced by 23%, mainly by ACE inhibitors
- Pirola CJ et al  J Infect 2020

# ACEI/Sartan usage: evidence on mortality

- Zhang et al Circ Res 2020
- All cause mortality drops 30-37% in in hospital setting

# New York

- Reynolds et al  NEJM 2020
- 4357 patients
- Same incidence of severe covid disease in ace inhibitors,ARBs usage

# China

- Zhou F et al  Hypertension 2020
- 1554 patients
- Hospitalised patients with ace inhibitors, ARB use ,had lower mortality at day 28, compared with other antihypertensives(HR=0.32)

# Italy

- Mancia G et al ( NEJM 2020 )
- n= 3652
- No association with RAS blocker usage

- Despite more cardiovascular disease in RAS blocker patients, no increased adverse outcomes
- Trial of losartan in covid started …NCT04312009
- High use of loop diuretics,spironolactones**..?

Mehra et al postulates for cv disease in covid viraemia:

- Vascular cell endothelial dysfunction
- Inflammation associated myocardial depression
- Stress cardiomyopathy
- Host responses ,with ensuing arrhythmias and demand related ischaemia

# COVID -Heart

**CVD - secondary to acute lung injury, which leads to increased cardiac workload, potentially problematic in patients with pre existing HF**

**CSS - result in plaque instability**

**infiltration of the myocardium by interstitial mononuclear inflammatory cells**

Aside from arterial and venous thrombotic complications presenting as acute coronary syndromes (ACS) and venous thromboembolism (VTE), myocarditis plays an important role in patients with acute heart failure (HF)

Wide range of arrhythmias

# COVID -Heart

- A large Chinese study analyze[illegible] 72 314 patient records which consisted of 44 672 (61.8%) confirmed cases, 16 186 (22.4%) suspected cases, and 889 (1.2%) asymptomatic cases.[4] Among confirmed cases in this study, 12.8% had hypertension, 5.3% diabetes and 4.2% CVD
- infection-induced myocarditis and ischaemia.

# ECHO findings

- Hani M et al,Can J Cardiology 2020
- N=79
- Right ventricular dilation 41%
- RV dysfunction 27%, associated with inceased D Dimer,CRP
- 89% normal or above normal LV function

Table 1

Risk factors for QT prolongation and torsades de pointes

| General risk factors | Illness-related risk factors |
| --- | --- |
| [illegible][3] | Hypokalemia[5] |
| Use of multiple QT-prolonging medicati[illegible][16] | Hypomagnesemia[5] |
| [illegible][3] | Sepsis[16] |
| | Myocardial injury, i[illegible]emia, or heart failure[16] |
| | Renal impairment[16] |
| | Bradycardia (heart rate <60 bpm)[5] |
| | Recent conversion from atrial fibrillation[3] |

# Arrhythmias

- Incidence

- Case series report the occurrence of unspecified arrhythmias in 17% of hospitalized patients with COVID-19 (n=23 of 138), with higher rate in ICU patients (44%, n=16) compared to non-ICU patients (7%, n=7)

- Acute Coronary Syndromes
- Incidence

- There is no current available data on the incidence of ACS in COVID. However, we presume that due to the presence of ACE2 receptors on the endothelium, and the known increased risk of ACS in influenza that there is a possible increased incidence of ACS among COVID-19 patients.

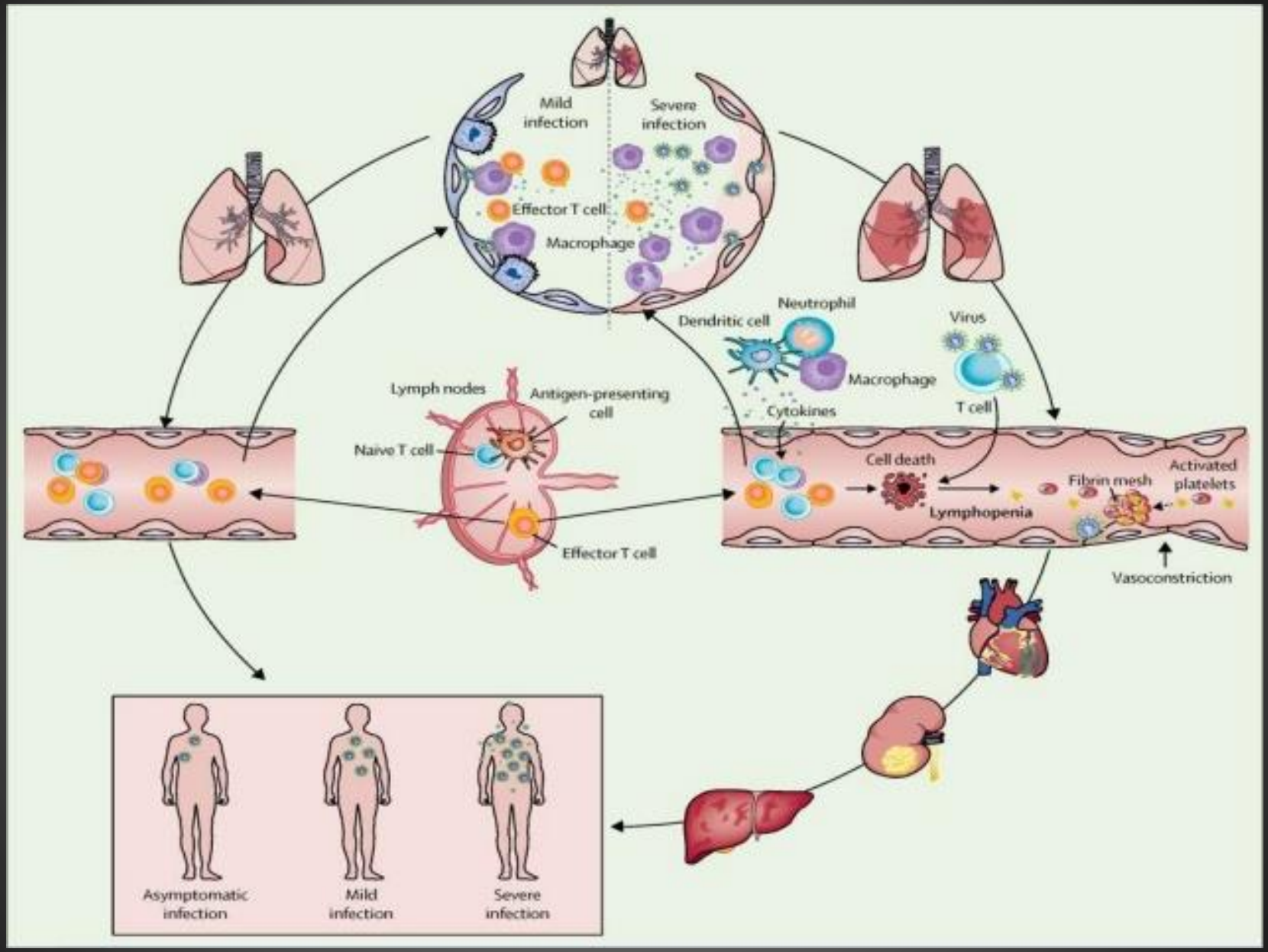
- The incidence of ACS is about 6 times as high within seven days of an influenza diagnosis than during the control interval - incidence ratio 6.05 (95% CI, 3.86 to 9.50) (Kwong et al, NEJM, 2018).

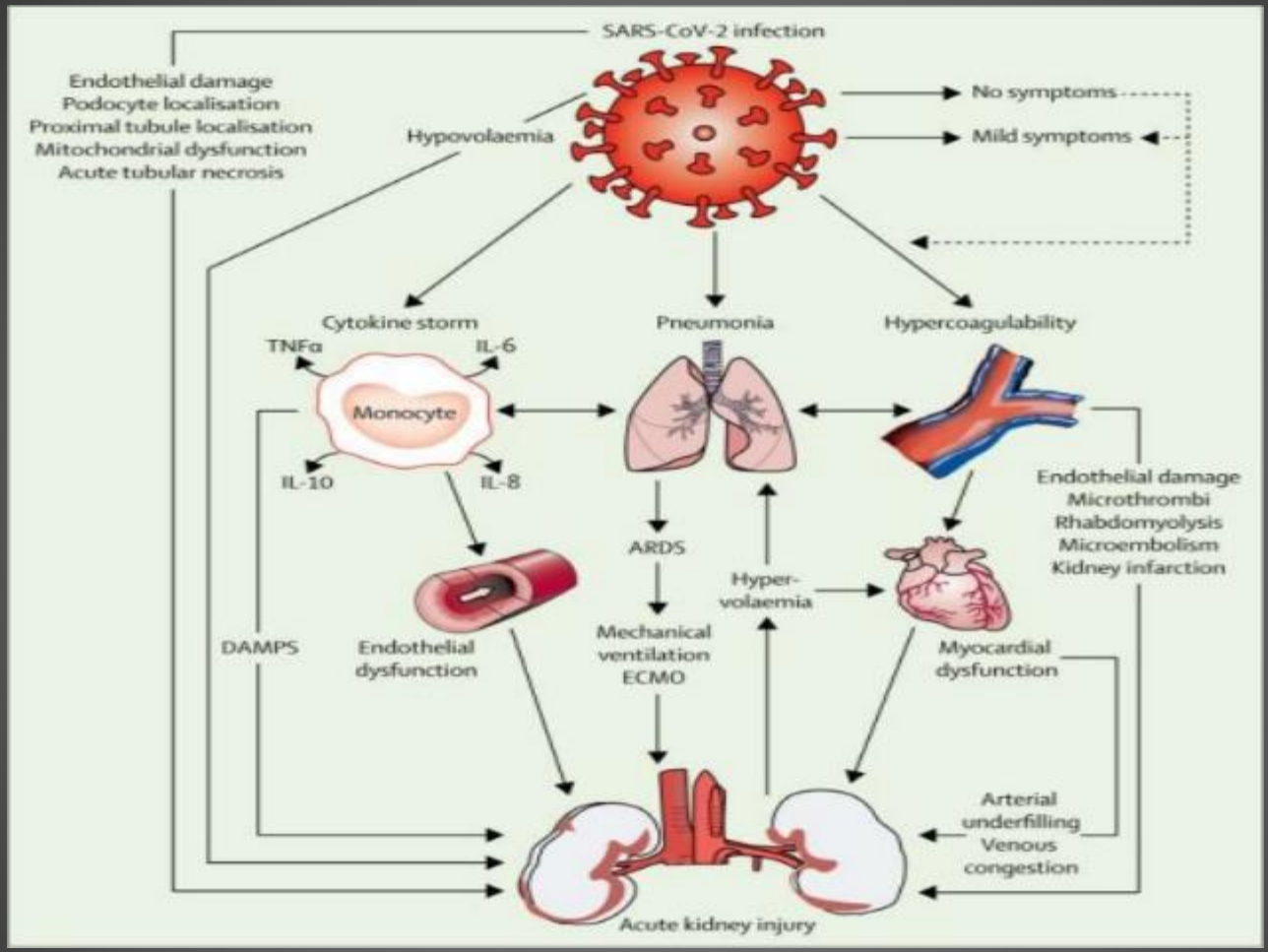
# Referred to ICU

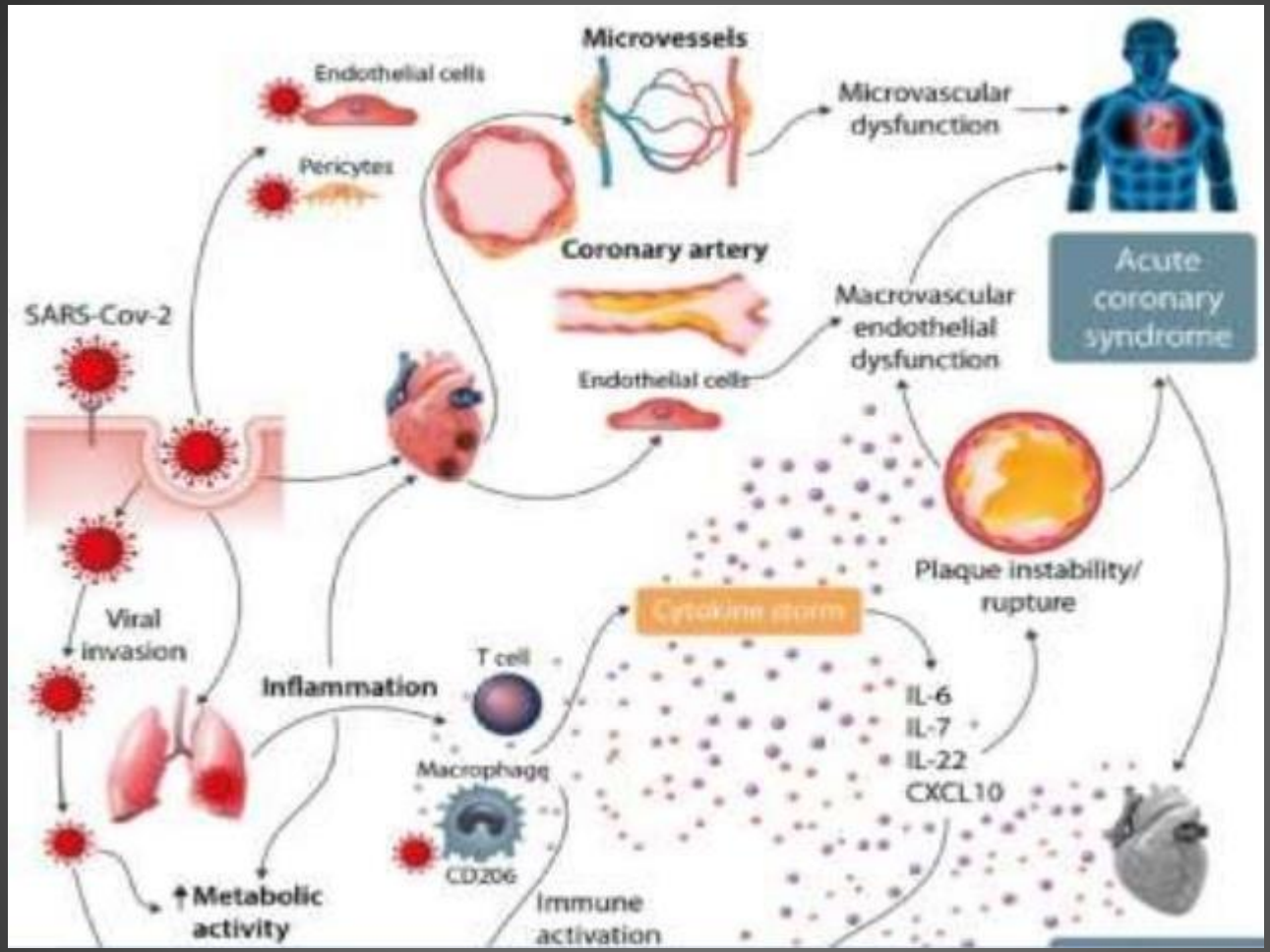
- Grassel et al, JAMA 2020
- Hypertension commonest referral comorbidity
- Next, CV disease; then dyslipidaemia
- Those demising in ICU, hypertension commonest comorbidity

# Presentation, on arrival

- Clerkin et al Circulation 2020
- Fried JA et al  Circulation 2020
- Covid can present on admission with de novo coronary artery disease or severe myocarditis


Mild infection
Severe infection
Effector T cell
Macrophage
Neutrophil
Dendritic cell
Virus
Macrophage
T cell
Cytokines
Lymph nodes
Antigen-presenting cell
Naive T cell
Effector T cell
Cell death
Activated platelets
Fibrin mesh
Lymphopenia
Vasoconstriction
Asymptomatic infection
Mild infection
Severe infection


SARS-CoV-2 infection
Endothelial damage
Podocyte localisation
Proximal tubule localisation
Mitochondrial dysfunction
Acute tubular necrosis
Hypovolaemia
No symptoms
Mild symptoms
Cytokine storm
Pneumonia
Hypercoagulability
TNFα
IL-6
Monocyte
IL-10
IL-8
ARDS
Endothelial damage
Microthrombi
Rhabdomyolysis
Microembolism
Kidney infarction
Hyper-
volaemia
DAMPS
Endothelial
dysfunction
Mechanical
ventilation
ECMO
Myocardial
dysfunction
Arterial
underfilling
Venous
congestion
Acute kidney injury


Microvessels
Endothelial cells
Pericytes
Microvascular dysfunction
Coronary artery
Endothelial cells
Macrovascular endothelial dysfunction
Acute coronary syndrome
SARS-Cov-2
Viral invasion
Inflammation
T cell
Macrophage
CD206
Cytokine storm
IL-6
IL-7
IL-22
CXCL10
Plaque instability/ rupture
↑Metabolic activity
Immune activation

# Cytokine storm Syndrome -CSS

- CSS is an accentuated *immune* response to triggers such as viral infections
- It results from an excess -proinflammatory and inadequate anti-inflammatory stimuli
- Proinflammatory stimuli - interleukin (IL)–1β, IL-2, IL-6, IL-7, IL-12, IL-18, tumor necrosis factor (TNF)–α, interferon (IFN)–γ, and granulocyte colony-stimulating factor (GCSF)
- Anti-inflammatory stimuli include regulatory T cells, cytokines such as IL-10, transforming

# CSS

- Increased production of IFNγ by hematopoietic stem cells in response to viral infections is thought to trigger CSS
- CSS - unremitting fever and MODS including ARDS and acute cardiac and renal injury
- Laboratory abnormalities include cytopenias, increased ferritin, D-dimer, and increased serum levels of proinflammatory cytokines
- Significant increased mortality in patients with elevated ferritin (>1200 ng/mL) and elevated IL-

# Shock

- Acute onset of new and sustained hypotension (MAP < 65 or SBP < 90) with signs of hypoperfusion requiring IVF or vasopressors to maintain adequate blood pressure
- Patients rarely present in shock on admission
- Natural history seems to favor the development of shock after multiple days of critical illness.
- Etiology:
- The range of reasons for shock is wide and more variable than for most patients and may includes:
  - Myocardial dysfunction
  - Secondary bacterial infection
  - Cytokine storm

- Prognosis

- Increased serum creatine, BUN, AKI, proteinuria, or hematuria are each independent risk factors for in-hospital death (Cheng et al, medRxiv, 2020 preprint)

- In two other studies, non-survivors had higher BUN and creatinine and higher rates of AKI (Wang et al, JAMA, 2020; Yang et al, Lancet Respir Med, 2020).
- Another study found that higher BUN and creatinine are associated with progression to ARDS, and higher BUN (though not creatinine) is associated with death (HR 1.06-1.20)
- Based on previous data from SARS, AKI was associated with poor prognosis as 91.7% of patients with AKI died vs 8.8% without AKI, p < 0.0001) (Chu et al, Kidney Int, 2005).

- Management:

- Discontinue all medications that can contribute to AKI (e.g. NSAIDs, ACE inhibitors, ARBs, and diuretics in volume depleted patients) and avoid using iodinated contrast with CT imaging as much as possible

to determine if there is a pre-renal component to AKI, especially in patients with clinical or laboratory signs suggestive of intravascular volume depletion (e.g. hypotension, tachycardia, dry mucous membranes, FENa<1% and/or FEurea<35%).

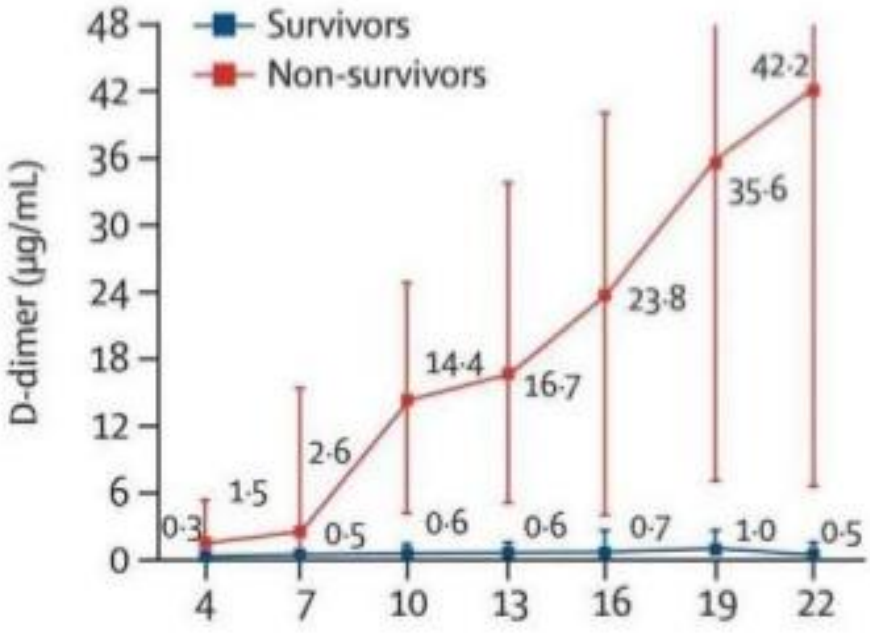
- Be cautious with fluid administration in patients with severe hypoxemia

- ***Consult nephrology for patients with any of the following:***

- ***Creatinine clearance <30 ml/min/1.73m2***
- ***Oliguria: urine output <500cc/day or <0.5cc/Kg/hour***
- ***Volume overload not improving with diuretics***
- ***Hyperkalemia (>5.5) not responsive to dietary K restriction and diuretics***

# disseminated intravascular coagulation

**hematologic abnormalities seen in COVID-19**




Progressive rise in D-dimer often portends death. This raises a question of whether treatment of DIC could be disease-modifying.

Zhou F et al. Lancet 3/9/20

# Mount Sinai COVID-19 Anticoagulation Algorithm

**Definition of high risk for progression to ICU**

- There is insufficient evidence to precisely define "high-risk" or provide specific cut-off values for individual factors
- Clinicians should consider a combination of exam findings (e.g, labored breathing, RR >24, decreased $O_2$ sat<90%), increased $O_2$ requirement (eg, ≥4L NC), and lab biomarkers (eg, elevated CRP, elevated creatinine, rising d-dimer >1.0).

**Rationale for early anticoagulation**

- Pathophysiology of COVID-19 associated respiratory disease is consistent with pulmonary vascular thromboemboli with increased dead space ventilation
- Autopsy studies have demonstrated venous thromboembolism in deceased coronavirus patients[1]
- Early anticoagulation is necessary to prevent propagation of microthrombi at disease presentation
- Anticoagulation may be associated with decreased mortality[2]

**Rationale for choice of anticoagulant**

- Heparins bind tightly to COVID-19 spike proteins[3,4]
- Heparins also downregulate IL-6 and directly dampen immune activation[5]
- DOACs do not appear to have these anti-inflammatory properties

**References**


1. Xiang-Hua et al. Am J Respir Crit Care Med, 182 (3), 436-7. PMID: 20675682
2. Tang et al. J Thromb Haemost 2020 Mar 27. PMID: 32220112
3. Belouzard et al. Proc Natl Acad Sci, 2009 106 (14), 5871-6. PMID: 19321428
4. de Haan et al. J Virol. 2005 Nov; 79(22): 14451–14456. PMID: 16254381
5. Mummery et al. J Immunol, 2000. 165 (10), 5671-9. PMID: 1106792

# QUESTION & ANSWER SESSION

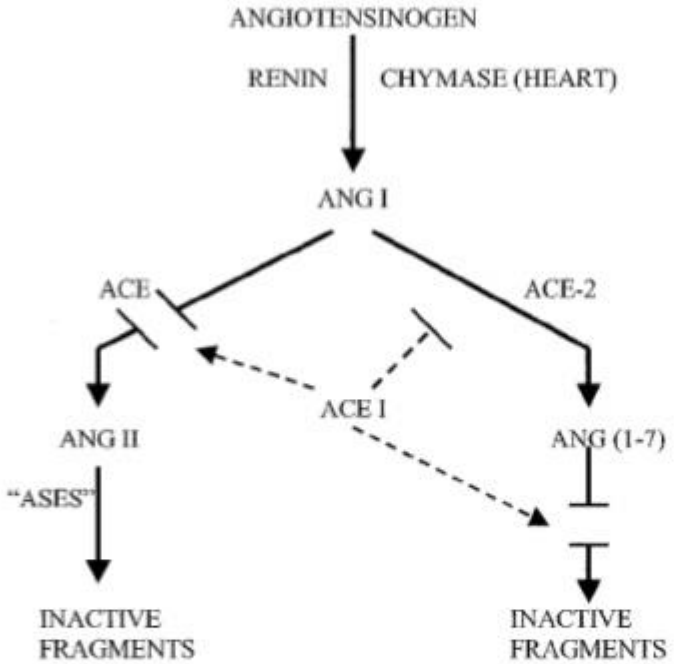
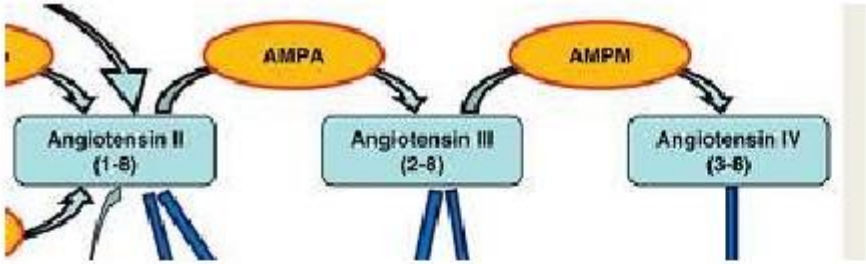
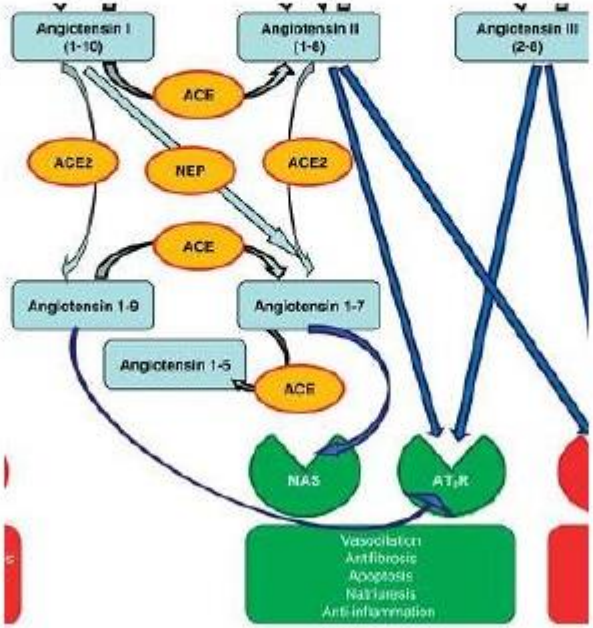



FIG. 2. Schematic representation of the pathways of formation and metabolism of ANG (1–7) and the role of ACE and the newly discovered enzyme ACE-2. The inhibitory actions of ACEI are depicted in *dashed lines* with *arrows* and *railroad tracks*. ASES, Angiotensinases.




•AT2R

- •Inhibits MAPKs, activates NO/cGMP and phospho-lipase A2 pathways
- •**Stimulation** with non-peptide agonist, **compound 21,** improved myocardial function in rats with myocardial infarction **independently of BP effects**, along with anti-inflammatory action and NF-k B inhibition




•Mas

- •Promotes Akt phosphorylation,NO release.
- •**Stimulation with a synthetic peptide** induced vasorelaxation, **reduced BP** in spontaneously hypertensive rats (SHR) and showed **antiarrhythmic effect**s.

Funke-Kaiser H et al. **J Renin Angiotensin Aldosterone Syst 2010**;11:7 – 17
Rompe F et al. **Hypertension 2010**;55:924 – 931

Savergnini SQ et **al.Hyp ertension 2010**;56:112 – 120

- Pedominantely in endothiuelm of coronary and renal vasculature
- ACE 2 probably counterbalances the enzymatic actions of ACE
- Unlike ACE, this enzyme does not convert Ang I to Ang II and its activity is not affected by ACE inhibitors