Renin–Angiotensin–Aldosterone System Inhibitors in Patients with Covid-19

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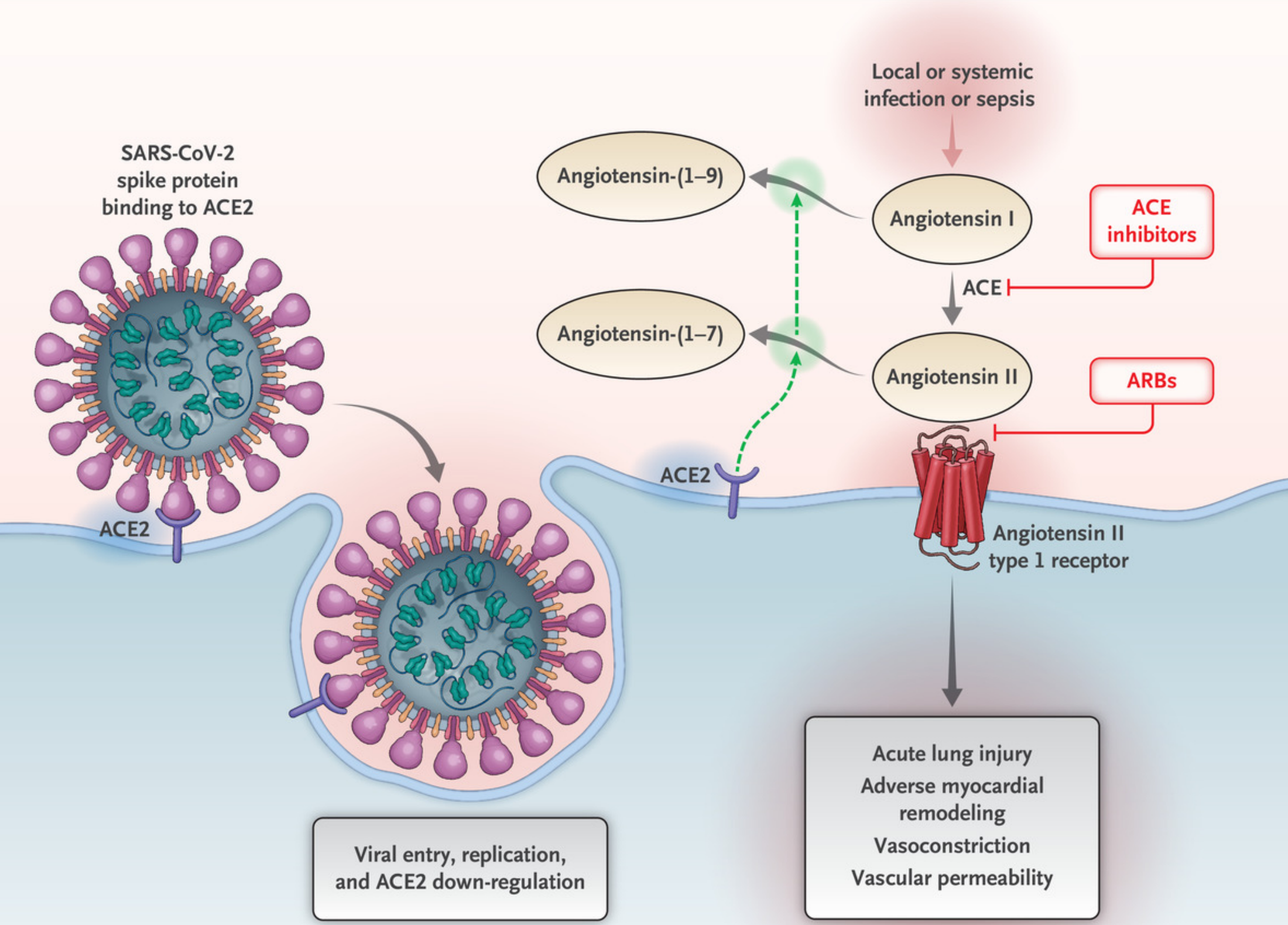
Angiotensin-Converting Enzyme 2 (ACE2)

- ACE2 is expressed broadly (oral and nasal mucosa, nasopharynx, lung, stomach, small intestine, colon, skin, lymph nodes, thymus, bone marrow, spleen, liver, kidney, and brain)
- Major: degrades angiotensin II to angiotensin-(1–7)
- Minor: degrades angiotensin I to angiotensin-(1–9)
- ↓ vasoconstriction, ↓ sodium retention, ↓ fibrosis
- ↓ RAAS activation

- Receptor of both SARS-CoV-1 (SARS) and SARS-CoV-2 (Covid-19)


SARS-CoV-2
spike protein
binding to ACE2
ACE2
Viral entry, replication,
and ACE2 down-regulation
Local or systemic
infection or sepsis
Angiotensin-(1–9)
Angiotensin I
ACE inhibitors
ACE
Angiotensin-(1–7)
Angiotensin II
ARBs
ACE2
Angiotensin II
type 1 receptor
Acute lung injury
Adverse myocardial
remodeling
Vasoconstriction
Vascular permeability

To know **we don't know** actually

- ACE inhibitors in clinical use do not directly affect ACE2 activity.

Biochem J 2004;383:45-51

- Some animal models show that ARBs may increase messenger RNA expression or protein levels of ACE2 in tissue and others showing no effect.

Circulation 2005;111:2605-2610; lin Sci (Lond) 2012;123:649-658

To know **we don't know** actually

- Effects on ACE2 should not be assumed to be uniform across RAAS inhibitors
- Plasma ACE2 level ≠ activity of the full-length membrane-bound form
- Even if RAAS inhibitors (ACEI, ARB, & others) modify ACE2 levels or activity (or both) in target tissue beds, clinical data are lacking to indicate whether this would in turn facilitate greater engagement and entry of SARS-CoV-2 spike protein.

Pathophysiology

- SARS & Covi-19 gain initial entry through ACE2
- SARS & Covi-19 subsequently down-regulate ACE2 expression

- ACE2 → cleave angiotensin II
- Covid-19 → ACE2⬇ → angiotensin II⬆ → organ injury⬆

- ACE2 → myocardial recovery + injury response
- Covid-19 → ACE2⬇ → myocardial recovery⬇

- Provision of recombinant ACE2 protein (投予合成的ACE2蛋白) may be beneficial in restoring balance to the RAAS network and potentially preventing organ injury !? (ClinicalTrials.gov number, NCT04287686)

Maintenance or Discontinuation of RAAS Inhibitors with Covid-19

- RAAS inhibitors have established benefits in protecting the kidney and myocardium, and their withdrawal may risk clinical decompensation in high-risk patients.

- DC RAASi in chronic symptomatic HF → P't ↘
- DC RAASi in asymptomatic DCM HF → P't ↘
- DC RAASi in post-MI → risk of myocardial injury ↗
- DC RAASi in HTN → risky, challenging in practice
- DC RAASi in CKD → uncertain effects

Conclusion

- RAASi is proven therapies for various disease
- RAASi effect on ACE2 (& affect the propensity for or severity of Covid-19) is theoretical concerns based on incomplete experimental evidence, and unable readily translate to humans.
- RAASi should be continued in patients in otherwise stable condition who are at risk for, are being evaluated for, or have Covid-19.

原本guideline建議用的ACEi/ARB繼續用，等待進一步clinical trials