Pharmaceutical care in treatment of COVID-19

Foroud shahbazi PharmD

Introduction

- The first cases of coronavirus disease 2019 (COVID-19) were reported from Wuhan, China in early December 2019, now known to be caused by a novel beta-coronavirus, named as Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

Review of Emerging Pharmacotherapy for the Treatment of Coronavirus Disease 2019

JAMA | Review

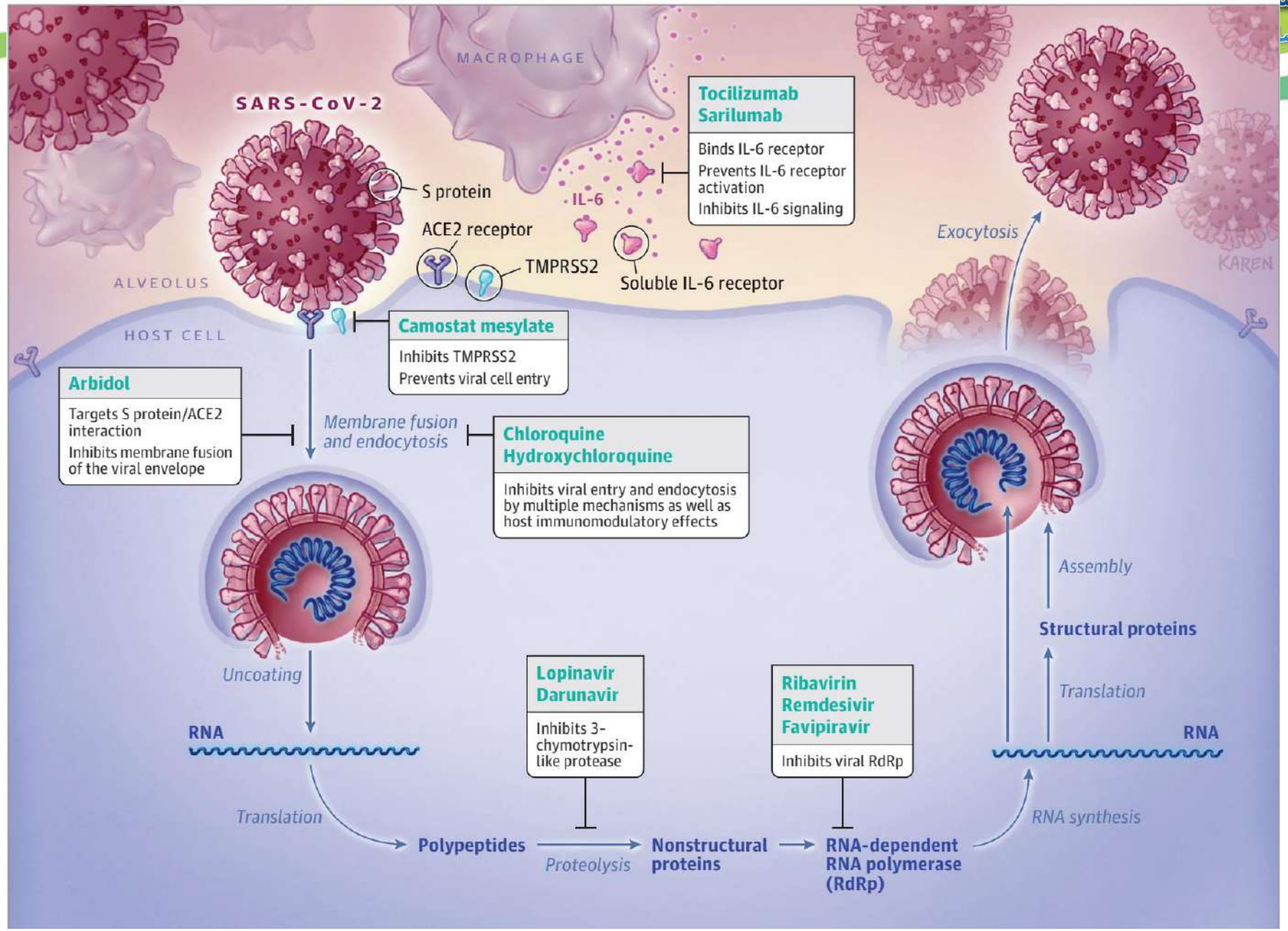
Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19)
A Review

Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19

Potential treatment for COVID-19

- Chloroquine
- Hydroxychloroquine
- Hydroxychloroquine and azithromycin?
- Lopinavir/ritonavir
- Favipiravir
- Ribavirin
- Interferons
- IVIGs

JAMA. doi:10.1001/jama.2020.6019


MACROPHAGE
SARS-CoV-2
S protein
ACE2 receptor
TMPRSS2
IL-6
Soluble IL-6 receptor
Tocilizumab
Sarilumab
Binds IL-6 receptor
Prevents IL-6 receptor activation
Inhibits IL-6 signaling
Exocytosis
ALVEOLUS
HOST CELL
KAREN
Camostat mesylate
Inhibits TMPRSS2
Prevents viral cell entry
Arbidol
Targets S protein/ACE2 interaction
Inhibits membrane fusion of the viral envelope
Membrane fusion and endocytosis
Chloroquine
Hydroxychloroquine
Inhibits viral entry and endocytosis by multiple mechanisms as well as host immunomodulatory effects
Assembly
Structural proteins
Translation
RNA
Uncoating
Lopinavir
Darunavir
Inhibits 3-chymotrypsin-like protease
Ribavirin
Remdesivir
Favipiravir
Inhibits viral RdRp
Translation
Polypeptides
Proteolysis
Nonstructural proteins
RNA-dependent RNA polymerase (RdRp)
RNA synthesis

Hydroxychloroquine

- History ?
  - Malaria
  - Arthritis Rheumatoid
  - Systemic lupus erythematosus

Hydroxychloroquine: Mechanism of action

- Blockade of viral entry by:
  - Inhibiting glycosylation of host receptors proteolytic processing,
  - Inhibit endosomal acidification.
- Additional immunomodulatory effects:
  - Inhibition of cytokine production,
  - Autophagy,
  - Lysosomal activity in host cells

Evidence

- No high-quality evidence exists for the efficacy of chloroquine/ hydroxychloroquine treatment of SARS or MERS
- A series of more than 100 COVID-19 cases resulting in improved radiologic findings, enhanced viral clearance, and reduced disease progression.

Biosci Trends. 2020; 14(1):72-73. doi:10.5582/bst.2020.01047

Hydroxychloroquine

- A recent open-label nonrandomized French study of 36 patients (20 in the hydroxychloroquine group and 16 in the control group) reported improved virologic clearance with hydroxychloroquine, 200 mg, by mouth every 8 hours compared with control patients receiving standard supportive care.
- Virologic clearance at day 6, measured by nasopharyngeal swabs, was 70% (14/20) vs 12.5% (2/16) for the hydroxychloroquine and control groups, respectively (P = .001).

Hydroxychloroquine

- Addition of azithromycin to hydroxychloroquine in 6 patients resulted in numerically superior viral clearance (6/6, 100%) compared with hydroxychloroquine monotherapy (8/14, 57%)

Int J Antimicrob Agents. Published online March 20, 2020. doi:10.1016/j.ijantimicag.2020.105949

- In a pilot study in China 30 patients were randomized to hydroxychloroquine 400 mg/day (it is unclear if this was divided) for five days, or usual care.
  - There was no difference between groups in viral clearance at day seven, length of stay, or time to defervescence.

- In 62 hospitalized patients with mild disease, 31 patients were randomized to hydroxychloroquine 200 mg twice daily.
  - Time to recovery (defervescence and cough remission) was shortened by about one day in the treatment group.
  - On day six, pneumonia was improved per CT in more patients in the treatment group.
  - Four patients progressed to severe disease, all in the control group

No evidence of clinical efficacy of hydroxychloroquine in patients hospitalised for COVID-19 infection and requiring oxygen: results of a study using routinely collected data to emulate a target trial

Matthieu Mahévas 1, Viet-Thi Tran 2*, Mathilde Roumier 3*, Amélie Chabrol 4, Romain Paule 3, Constance Guillaud 1, Sébastien Gallien 5, Raphael Lepeule 5, Tali-Anne Szwebel 6, Xavier Lescure 7, Frédéric Schlemmer 8, Marie Matignon9, Medhi Khellaf 1, Etienne Crickx 1, Benjamin Terrier 6, Caroline Morbieu 6, Paul Legendre 6, Julien Dang 2, Yoland Schoindre 3, Jean-Michel Pawlotski 10, Marc Michel 1, Elodie Perrodeau 2, Nicolas Carlier 11, Nicolas Roche 11, Victoire de Lastours 12, Luc Mouthon 6, Etienne Audureau 1, Philippe Ravaud 2, Bertrand Godeau 1, Nathalie Costedoat-Chalumeau 2.6

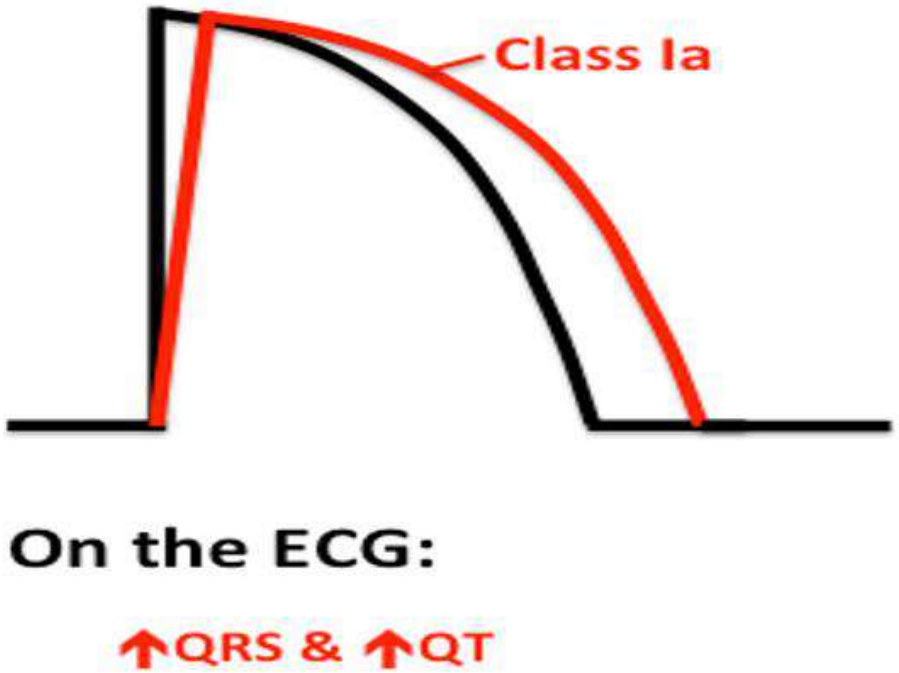
- 181 patients with SARS-CoV-2 pneumonia; 84 received HCQ within 48 hours of admission (HCQ group) and 97 did not (no-HCQ group).

Table 2: Primary and secondary outcomes. Weighted proportions, RRs and 95% CIs were obtained by inverse probability treatment weighting. *two missing data were removed from analysis. Abbreviations: CI, confidence interval; ICU, intensive care unit.

	HCQ (n=84)		No HCQ (n=97)		RR (95% IC)
	Raw	Weighted proportion	Raw	Weighted proportion	
Death or transfer to ICU	16/84 (19.0)	20.5	21/97 (21.6)	22.1	0.93 (0.48 to 1.81)
Day 7 mortality	3/84 (3.6)	2.8	4/97 (4.1)	4.6	0.61 (0.13 to 2.90)
Occurrence of acute respiratory distress syndrome*	24/84 (28.6)	27.7	23/95 (24.2)	24.1	1.15 (0.66 to 2.01)

Potential adverse effects

- What are the potential adverse effects of chloroquine or hydroxychloroquine and azithromycin?
  - Prolongation of the QTc interval



Caution when HCQ combined with

- Azithromycin
- FQs
- Amiodarone
- Methadone
- Fingolimod
- Citalopram,
- Haloperidol
- Domperidone
- Ondansetron

Risk	Drug Categories				
	Antiarrhythmic Drugs	**Common Antibacterial and Antifungal Drugs**	**Prokinetic and Antiemetic Drugs**	**Antipsychotics**	**Antidepressants**
Known risk	Amiodarone Disopyramide Dofetilide Dronedarone Flecainide Ibutilide Procainamide Quinidine Sotalol	Moxifloxacin Levofloxacin Ciprofloxacin Clarithromycin Erythromycin Azithromycin Fluconazole	Domperidone Chlorpromazine Ondansetron Droperidol	Haloperidol Thioridazine Pimozide	Escitalopram Citalopram
Possible risk		Telavancin Telithromycin Gemifloxacin Norfloxacin Ofloxacin	Dolasetron Granisetron Promethazine Tropisetron	Lithium Clozapine Risperidone Promethazine Perphenazine Aripiprazole	Clomipramine Desipramine Imipramine Mirtazapine Nortriptyline Trimipramine Venlafaxine
Conditional risk	Ivabradine	Amphotericin B Itraconazole Ketoconazole Metronidazole Posaconazole Voriconazole	Metoclopramide	Quetiapine Olanzapine Ziprasidone	Amitriptyline Doxepin Fluoxetine Fluvoxamine Paroxetine Setraline Trazodone
Alternatives		Penicillin Cephalosporins Doxycycline	Aprepitant		Bupropion (except in supratherapeutic dose)

J Am Heart Assoc. 2017 Dec 7;6(12).

Safety of hydroxychloroquine, alone and in combination with azithromycin, in light of rapid wide-spread use for COVID-19: a multinational, network cohort and self-controlled case series study

Jennifer C.E Lane, James Weaver, Kristin Kostka, Talita Duarte-Salles, Maria Tereza F. Abrahao, Heba Alghoul, Osaid Alser, Thamir M Alshammari, Patricia Biedermann, Edward Burn, Paula Casajust, Mitch Conover, Aedin C. Culhane, Alexander Davydov, Scott L. DuVall, Dmitry Dymshyts, Sergio Fernández Bertolín, Kristina Fišter, Jill Hardin, Laura Hester, George Hripcsak, Seamus Kent, Sajan Khosla, Spyros Kolovos, Christophe G. Lambert, Johan ver der Lei, Ajit A. Londhe, Kristine E. Lynch, Rupa Makadia, Andrea V. Margulis, Michael E. Matheny, Paras Mehta, Daniel R. Morales, Henry Morgan-Stewart, Mees Mosseveld, Danielle Newby, Fredrik Nyberg, Anna Ostropolets, Rae Woong Park, Albert Prats-Uribe, Gowtham A. Rao, Christian Reich, Jenna Reps, Peter Rijnbeek, Selva Muthu Kumaran Sathappan, Martijn Schuemie, Sarah Seager, Anthony Sena, Azza Shoaibi, Matthew Spotnitz, Marc A. Suchard, Joel Swerdel, Carmen Olga Torre, David Vizcaya, Haini Wen, Marcel de Wilde, Seng Chan You, Lin Zhang, Oleg Zhuk, Patrick Ryan, Daniel Prieto-Alhambra

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Results

- Data comprised 14 sources of claims data or electronic medical records from Germany, Japan, Netherlands, Spain, UK, and USA.
- Propensity score stratification and calibration using negative control outcomes were used to address confounding.
- Cox models were fitted to estimate calibrated hazard ratios (CalHRs) according to drug use.
- Estimates were pooled where I_2 <40%.

Results

- Results: Overall, 956,374 and 310,350 users of hydroxychloroquine and sulfasalazine, and 323,122 and 351,956 users of hydroxychloroquine-azithromycin and hydroxychloroquine-amoxicillin were included.
- No excess risk of SAEs was identified when 30-day hydroxychloroquine and sulfasalazine use were compared. SCCS confirmed these findings.
- When azithromycin was added to hydroxychloroquine, we observed an increased risk of 30-day **cardiovascular mortality** (CalHR2.19 [1.22-3.94]), **chest pain/angina** (CalHR 1.15 [95% CI 1.05-1.26]), and ***heart failure*** (CalHR 1.22 [95% CI 1.02-1.45])

Monitoring

- Electrocardiographic/QT interval monitoring:
  - Withhold the drugs in patients with baseline QT prolongation [e.g., QTc ≥500 msec or >550 ms if a baseline widening of QRS is present (>120 ms secondary to pacing or bundle branch block)] or with known congenital long QT syndrome.
  - Reduce dose or discontinue QTc-prolonging drug(s) if the QTc increases ≥ 60 ms from pretreatment value

- Correction of hypokalemia to levels of >4 mEq/L and hypomagnesemia to levels of >2 mg/dL.
- Avoid other QTc prolonging agents whenever feasible
- Avoid rapid intravenous administration of QTc-prolonging drugs
- Adjust doses of renally eliminated QTc-prolonging drugs in patients with acute kidney injury or chronic kidney disease

Drug–drug interactions

- In addition to being substrates for CYP2D6, chloroquine and hydroxychloroquine inhibit its activity, most likely by competitive inhibition.
- This has the potential to influence the fate of other drugs reliant on CYP2D6 for metabolism.
- For instance, hydroxychloroquine increases systemic exposure to orally administered metoprolol levels by about 65% and peak concentrations by 72%.

Drug–drug interactions

- Potentiate other CYP2D6 substrates (including carvedilol and many others),
- Weaken the effectiveness of prodrugs reliant on CYP2D6 for activation such as codeine and tramadol.
- May precipitate opioid withdrawal in patients who are taking these drugs regularly
- Both chloroquine and hydroxychloroquine increase serum digoxin concentrations, so like quinidine, these drugs probably block p-glycoprotein.

(Pharmacotherapy 2020;0(0):1–2) doi: 10.1002/phar.2387

Hypoglycemia

- Case reports have described severe hypoglycemia with both chloroquine and hydroxychloroquine in patients with malaria as well as those with lupus and other chronic diseases
  - Among 250 patients with poorly controlled type 2 diabetes who were unwilling to start insulin, hydroxychloroquine (400 mg/d) was associated with marked reductions in fasting plasma glucose, hemoglobin A1c and body weight, whereas hypoglycemia developed in 2% of participants over the 48-month study period.

Severe hypoglycemia

- For patients with severe or recurrent hypoglycemia, octreotide (50–100 μg administered intravenously or subcutaneously every 8 h) is a well tolerated somatostatin analogue that inhibits pancreatic insulin release and may be helpful in mitigating the rebound hyperinsulinemia than can ensue after large doses of intravenous dextrose

Neuropsychiatric effects

- Chloroquine and hydroxychloroquine are known to cause a wide spectrum of neuropsychiatric manifestations, including agitation, insomnia, confusion, mania, hallucinations, paranoia, depression, catatonia, psychosis and suicidal ideation.
- These can occur at all ages, during acute or chronic use, and in patients with and without a history of mental illness.
- Resolution is expected upon stopping the drug, although symptoms may not resolve quickly

Hematologic toxicities

- Many clinicians associate antimalarial agents with oxidative hemolysis, particularly in patients with severe variants of glucose-6-phosphate dehydrogenase (G6PD) deficiency.
- Primaquine is well known to cause this, but chloroquine and hydroxychloroquine are much less likely to do so.
- In a chart review of 275 rheumatology patients with established G6PD deficiency, no episodes of hydroxychloroquine-related hemolysis were identified over more than 700 months of treatment.
- Hematologic abnormalities including lymphopenia, eosinophilia and atypical lymphocytosis can be features of immunologically mediated idiosyncratic drug reactions.

Immunologically mediated adverse reactions

- Chloroquine and hydroxychloroquine have been implicated in severe cutaneous adverse reactions, including Stevens–Johnson syndrome, toxic epidermal necrolysis, DRESS (drug reaction with eosinophilia and systemic symptoms)

Overdose

- Mechanisms
  - Inhibition of sodium channels
  - Inhibition of potassium (hERG) channels
  - Profound hypokalemia from intracellular shifting, also contributing to dysrhythmias.
  - Hydroxychloroquine also results in inhibition of ATP-sensitive K+ channels on pancreatic beta-islet cells causing hypoglycemia

Overdose

- Sharing several manifestations in common with TCA
- Rapid onset of CNS toxicity (seizures and coma),
- Cardiovascular collapse
- Hypokalemia resulting from intracellular shifting.

- Negative inotropy
- Inhibition of diastolic depolarization
- Slowed cardiac conduction
- Prolonged refractory period
- Raised electrical threshold

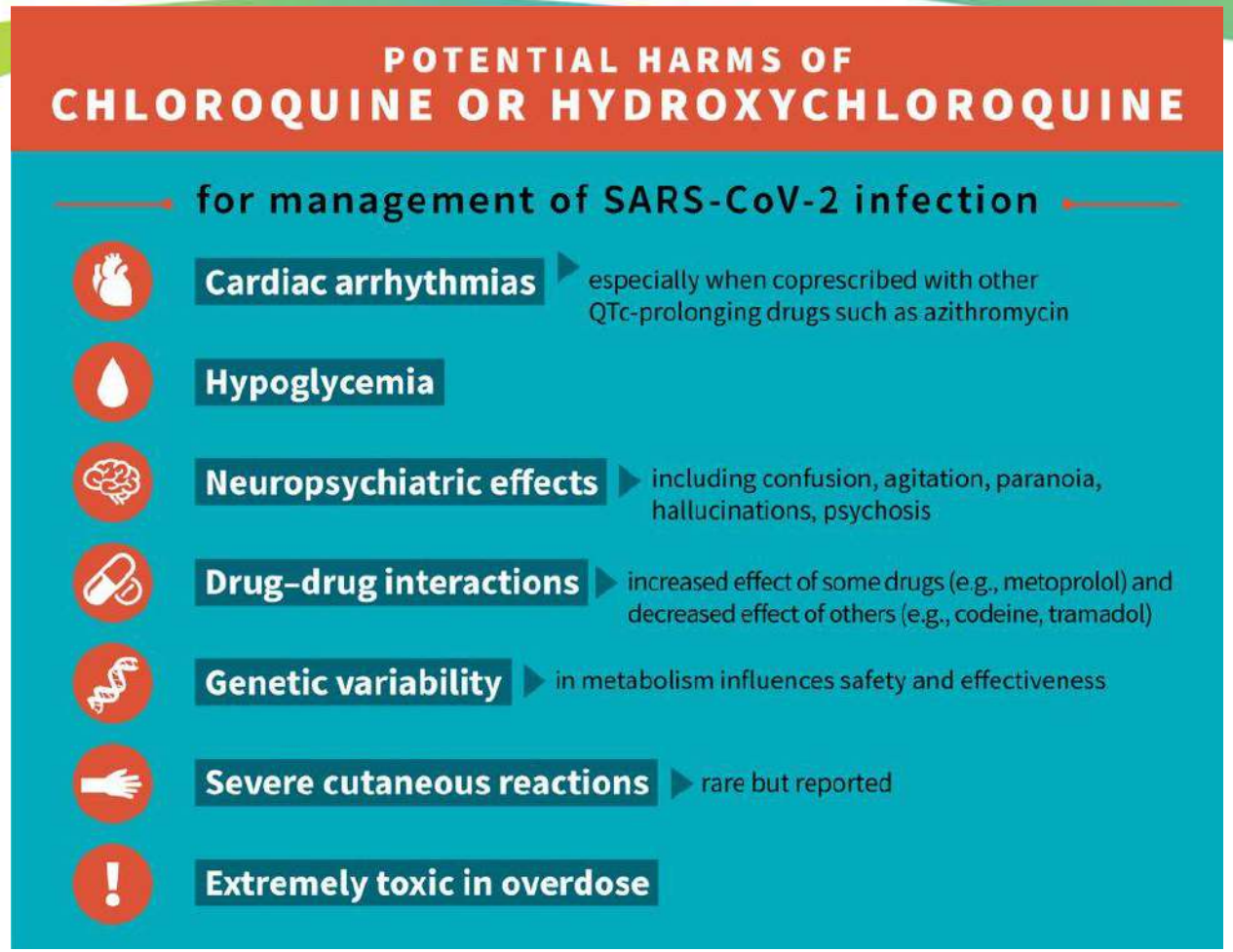
Overdose

- Treatment of overdose is largely supportive
- Activated charcoal,
- IV BZDs,
- Vasopressors as needed,
- NaHCO3 or hypertonic saline for substantial QRS widening and related arrhythmias,
- Judicious management of hypokalemia.

Diazepam

1. Central antagonism;
2. Anticonvulsant effect;
3. Antidysrhythmic effect;
4. pharmacokinetic interaction between diazepam and chloroquine
5. Decreased chloroquine-induced vasodilation

Dose: 2 mg/kg IV over 30 minutes followed by 1-2 mg/kg/day for 2-4 days.

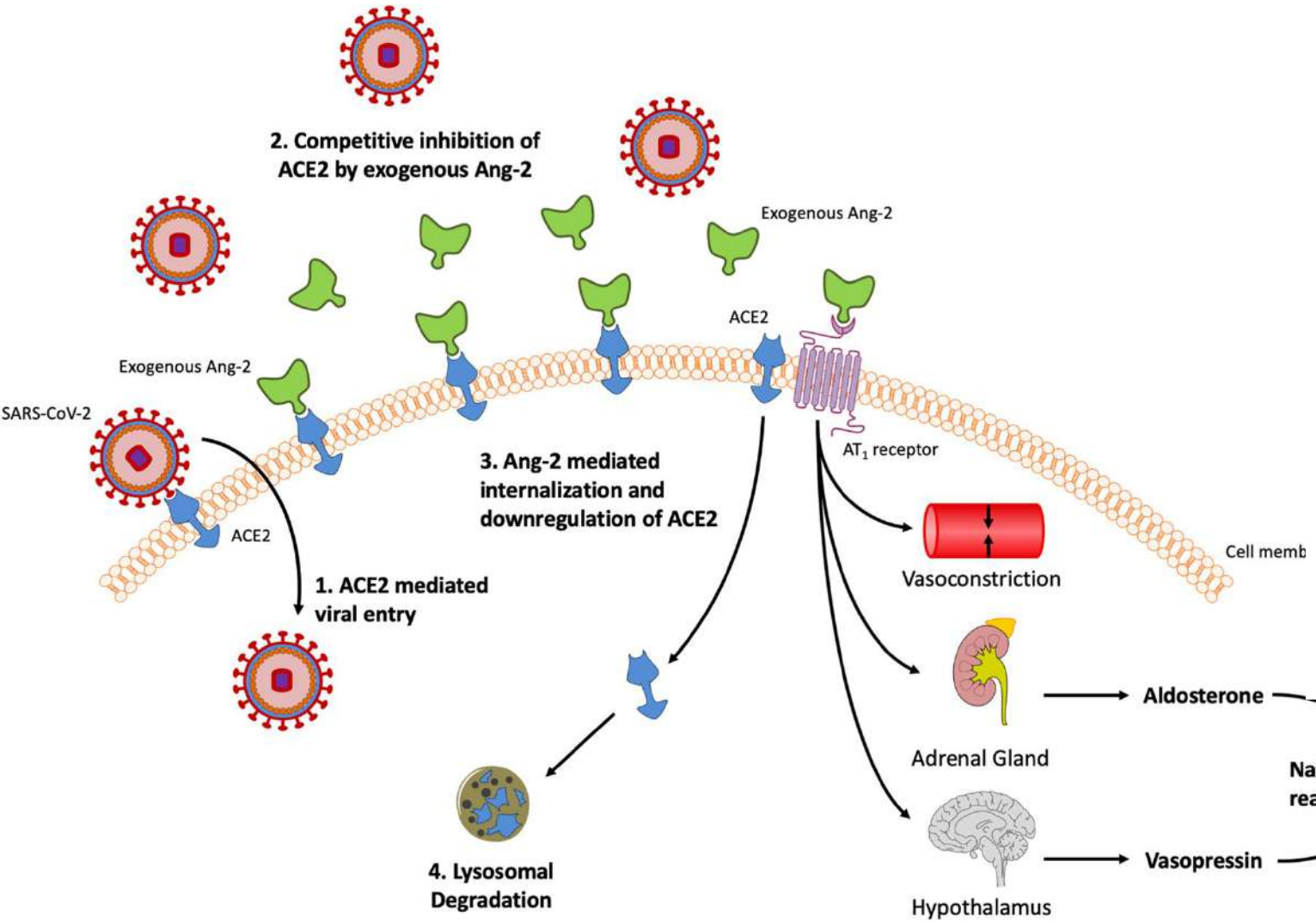


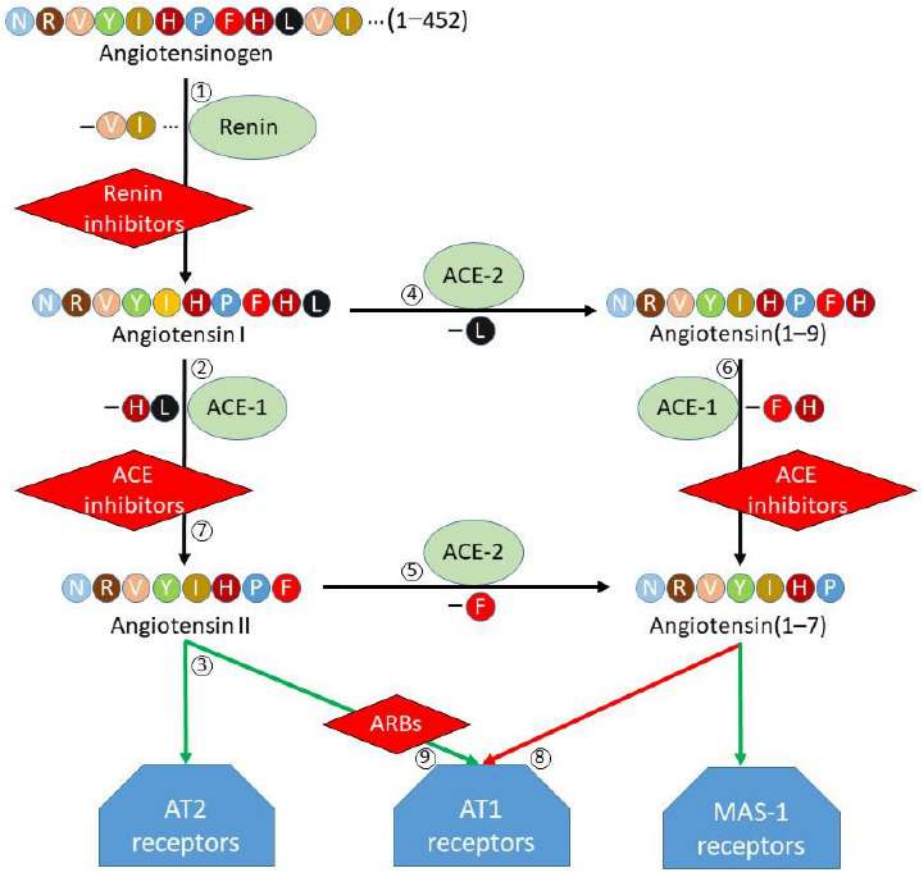
CMAJ April 08, 2020 cmaj.200528; DOI: https://doi.org/10.1503/cmaj.200528

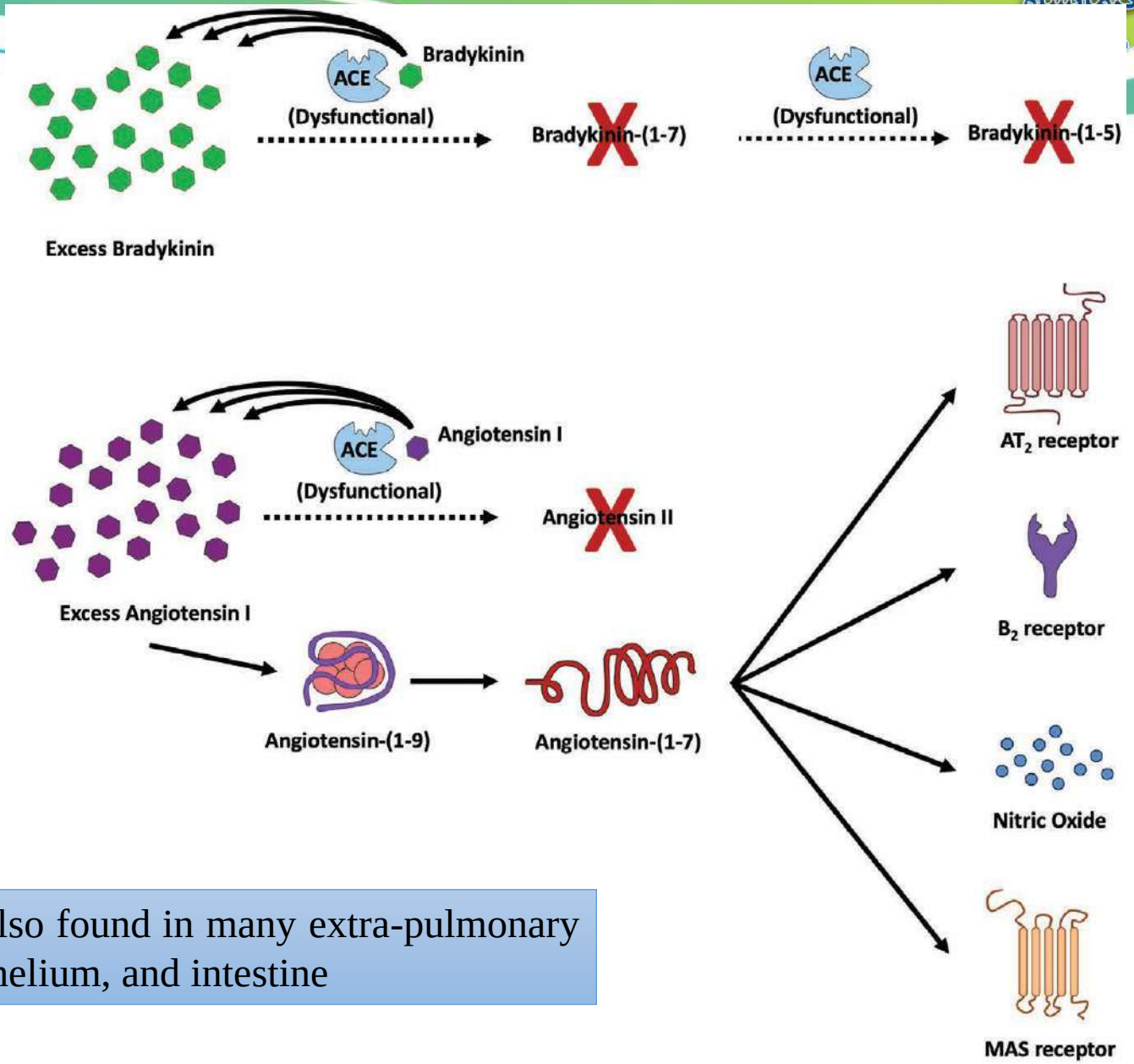
FAQs ABOUT COVID-19 AND PHARMACOTHERAPY

- Do ACE inhibitors or ARBs make COVID-19 worse?
  - The SARS-CoV-2 virus uses ACE2 to enter cells.
  - ACE inhibitors and ARBs may upregulate ACE2.
  - **In theory**, these drugs could thereby facilitate virus entry into cells.
  - There is currently no clinical evidence that patients taking an ACEI or ARB are more susceptible to COVID-19 or infection, or that these medications worsen outcomes.
  - But we do know that these drugs benefit patients with diabetic nephropathy and cardiovascular disease, populations at risk of severe COVID-19 disease

Angiotensin receptor blockers and COVID-19







Expression of the ACE2 receptor is also found in many extra-pulmonary tissues including heart, kidney, endothelium, and intestine

Society/Guideline	Key Recommendations
ACC Clinical Guidance (88)	• Establish protocols for diagnosis, triage, isolation of COVID-19 patients with CVD or CV complications • Develop acute myocardial infarction-specific protocols (i.e. PCI and CABG) for COVID-19 outbreak
ESC Council on Hypertension Statement on COVID-19 (89)	• Patients with hypertension should receive treatment with ACEi and ARB according to 2018 ESC/ESH guidelines despite COVID-19 infection status (95) • In, the case of shock, health care workers should continue or discontinue ACEi and ARB therapy on case-by-case basis
European Society of Hypertension (38)	• As above
Hypertension Canada (90)	• Patients with hypertension should continue their home blood pressure medical regimen
Canadian Cardiovascular Society (91)	• Continuation of ACEi, ARB, and ARNI therapy is strongly recommended in COVID-19 patients
Internal Society of Hypertension (92)	• Endorse the ESC Hypertension Statement (as above)

Can NSAIDs be used in COVID- 19-infected patients?

- Anecdotal reports regarding worse COVID-19 outcomes in patients taking NSAIDs have spread in the media and on social media, including via a tweet from a French health official.
- A French report suggested that NSAIDs could worsen infections, mainly Strep, perhaps by masking symptoms.
- There is currently no reliable clinical data supporting worse outcomes in patients taking NSAIDs or aspirin.

Can NSAIDs be used in COVID- 19-infected patients?

- Preclinical data is mixed on the potential effects of NSAIDs on COVID-19 (increased expression of ACE2, which the virus uses to enter cells, vs potential antiviral activity of NSAIDs).
- Patients taking low-dose aspirin should not stop taking it because of COVID-19 concerns.
- Neither the FDA nor Health Canada is advising changes to NSAID use due to COVID-19

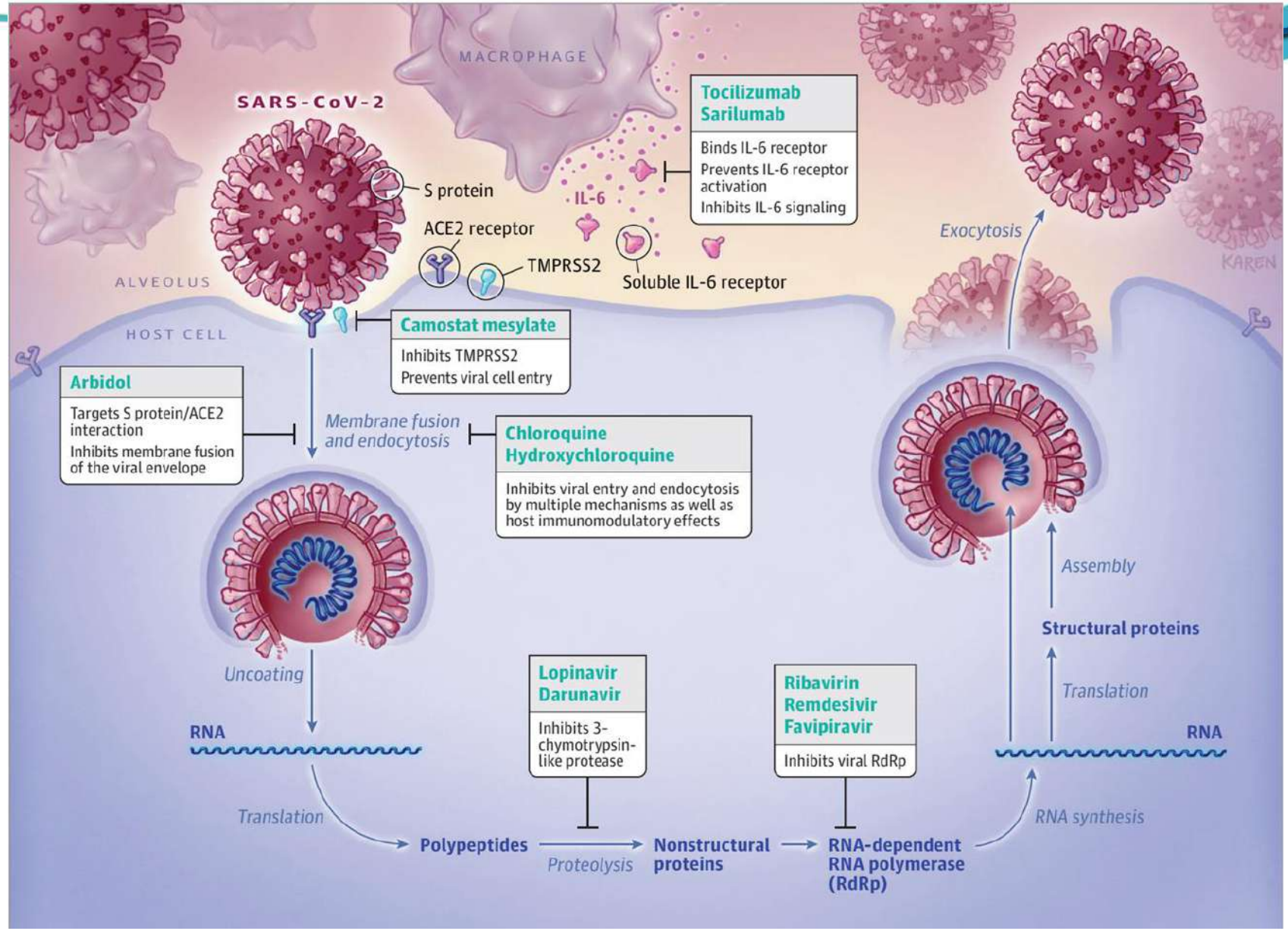
Are any supplements effective for prevention or treatment of COVID-19?

- There is no scientific evidence that any alternative remedies can prevent or treat COVID-19, and some products may not be safe.
- There is false information circulating that vitamin D is recommended by health officials.
- A study using honey as an adjunct to standard care for treatment of COVID-19 is planned, and intravenous vitamin C is being studied for treatment of severe COVID-19 disease (e.g., pneumonia, sepsis).
- Several studies are looking at multivitamin/mineral combos as adjuncts for treatment or prevention.

High-Dose Vitamin C for COVID-19

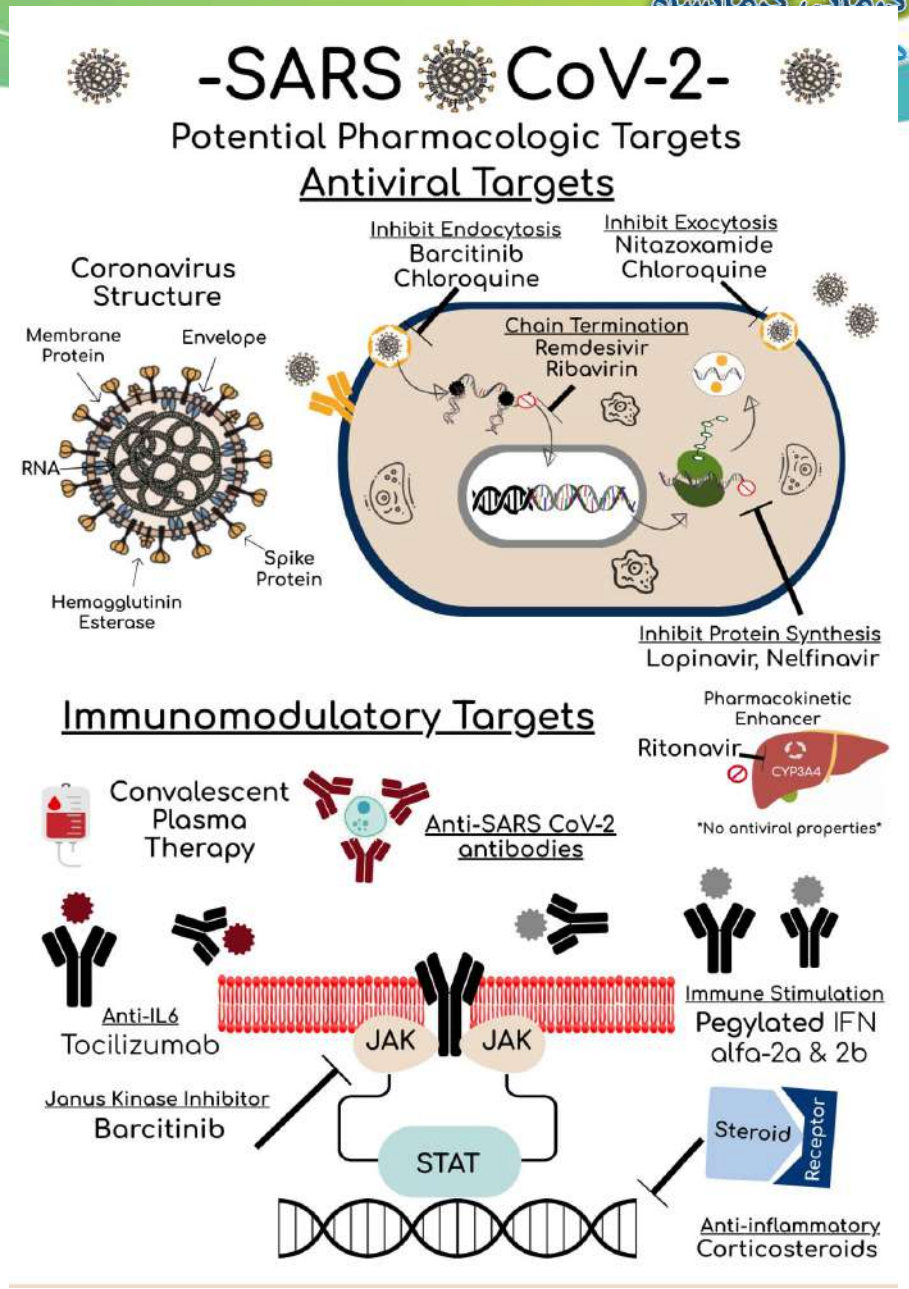
- New data out of China suggests that critically ill coronavirus disease 2019 (COVID-19) patients might benefit from high-dose IV **vitamin C** treatment.
- **Tell patients that these results are based on only observational data.**
  - There's no strong evidence that high dose IV vitamin C treatment is beneficial for COVID-19.
- **Also explain to your patients that the dose of vitamin C used in this study cannot be safely obtained from vitamin C dietary supplements.**
- Most patients in the study received vitamin C 10,000 mg – 20,000 mg daily; some received doses up to 50,000 mg. These doses can only be administered by a qualified healthcare provider through an IV. Orally, similar doses of vitamin C could cause serious gastrointestinal side effects

Lopinavir/ ritonavir



Chloroquine / Hydroxychloroquine	**Beta Blockers** • metoprolol, carvedilol, propranolol, labetalol **Antiarrhythmics** • QT-prolonging agents • Digoxin	CYP 2D6 inhibition: Dose reduction for beta blockers may be required. P-glycoprotein inhibition: Monitor digoxin level for possible dose reduction.	Use cautiously with antiarrhythmics
Fingolimod	**Bradycardia-Causing Agents:** • Beta blockers, Calcium channel blockers, Ivabradine **Antiarrhythmics** QT-Prolonging Medications: • Class 1A Antiarrhythmics • Class III Antiarrhythmics)	Sphingosine-1-phosphate receptor inhibition (on atrial myocytes): do not co-administer with class IA and III antiarrhythmics.	Use cautiously with other QT-prolonging drugs
Methylprednisolone	**Anticoagulants** • Warfarin	Unknown mechanism: Dose adjust based on INR.	Monitor INR

Therapy	Specific Interaction	MOA of Drug Interaction and Specific Dose Adjustments	Other Notes
Ribavirin	**Anticoagulants** Warfarin	Unknown mechanism of action: No dosage adjustment recommended.	Monitor INR
Lopinavir/Ritonavir	**Anticoagulants** • Apixaban • Rivaroxaban	CYP3A4 inhibition: Apixaban should be administered at 50% of dose (do not administer if requirement 2.5 mg per day). Rivaroxaban should not be co-administered.	Dabigatran and warfarin can be administered with caution
	Antiplatelet • Clopidogrel • Ticagrelor	CYP3A4 inhibition: Diminished effect of clopidogrel. Do not co-administer. Increased effect of ticagrelor. Do not co-administer.	Consider prasugrel if no contraindications. If other agents used, consider a testing-guided approach (e.g. $P2Y_{12}$ platelet function assay).
	Statin • Atorvastatin • Rosuvastatin • Lovastatin • Simvastatin	OATTP1B1 and BCRP inhibition: Rosuvastatin should be adjusted to maximum dose 10 mg/day. CYP3A4 inhibition: Atorvastatin should be adjusted to maximum dose 20 mg/day Lovastatin and simvastatin should not be co-administered.	Start at lowest possible dose of rosuvastatin and atorvastatin and titrate up. Pravastatin and pitavastatin can also be considered.
	Antiarrhythmics • QT-prolonging medication • Digoxin	P-glycoprotein inhibition: Monitor digoxin level for possible dose reduction.	Use cautiously with antiarrhythmics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Potential Pharmacologic Targets
Antiviral Targets
Coronavirus Structure
Membrane Protein
Envelope
RNA
Spike Protein
Hemagglutinin Esterase
Inhibit Endocytosis
Barcitinib
Chloroquine
Inhibit Exocytosis
Nitazoxamide
Chloroquine
Chain Termination
Remdesivir
Ribavirin
Inhibit Protein Synthesis
Lopinavir, Nelfinavir
Immunomodulatory Targets
Pharmacokinetic Enhancer
Ritonavir
CYP3A4
No antiviral properties
Convalescent Plasma Therapy
Anti-SARS CoV-2 antibodies
Anti-IL6
Tocilizumab
JAK
JAK
Immune Stimulation
Pegylated IFN alfa-2a & 2b
Janus Kinase Inhibitor
Barcitinib
STAT
Steroid Receptor
Anti-inflammatory
Corticosteroids

VTE prophylaxis:

- All patients (including non-critically ill) who require hospital admission for COVID-19 infection should receive prophylactic dose low molecular weight heparin (LMWH), unless they have contra-indications (active bleeding and platelet count < 25 x 10^9/L), to (a) inhibit thrombin generation which may (!) have benefit in reducing mortality, and (b) protect from venous thromboembolism.

- ***Use LMWH rather than oral anticoagulants***:
- Consider switching patients who take a direct oral anticoagulant (DOAC) or vitamin K antagonist (e.g. warfarin) to low molecular weight heparin (LMWH).

Major bleeding:

- For patients with major bleeding give empirical fresh frozen plasma (FFP) and red cells, followed by blood products determined by repeat coagulation testing:
  - If INR > 1.5 or aPTT ratio > 1.5, give FFP
  - If fibrinogen < 1.5 g/L, give cryoprecipitate or fibrinogen concentrate
  - If platelets < 50 x 10^9/L, give platelets.
  - If patient does NOT have DIC, also give tranexamic acid.
  - Do not use recombinant factor VIIa.


Thank
You!