The Impact of COVID-19 and Its Treatments On Cardiovascular Health

UTAH SOCIETY OF HEALTH-SYSTEM PHARMACISTS

Austin Lange, PharmD
PGY-1 Pharmacy Resident
St. Mark's Hospital
austin.lange@mountainstarhealth.com
Tuesday, March 22nd, 2022 at 3:30pm

1

Disclosure

- Relevant Financial Conflicts of Interest:
  - Presenter: Austin Lange, PharmD:
    - None
  - Mentor: Lisa Arrigo, RPh, BCPS:
    - None

2

Off-Label Uses of Medications

- Dexamethasone – COVID-19
- Baricitinib – COVID-19
- Tocilizumab – COVID-19
- Sotrovimab – COVID-19
- Molnupiravir – COVID-19
- Ritonavir-Nirmatrelvir – COVID-19
- Casirivimab and Imdevimab – COVID-19
- Bamlanivimab and Etesevimab – COVID-19
- Azithromycin – COVID-19
- Hydroxychloroquine – COVID-19
- Chloroquine – COVID-19
- Ivermectin – COVID-19
- Nitazoxanide – COVID-19
- Colchicine – COVID-19
- Anakinra – COVID-19
- Canakinumab – COVID-19
- Siltuximab – COVID-19

3

Learning Objectives

Pharmacists:

- Describe how the pathophysiology of COVID-19 can impact the cardiovascular system
- Differentiate cardiovascular manifestations of COVID-19
- Analyze the cardiovascular impact of medications used for COVID-19

4

Learning Objectives

Pharmacy Technicians:

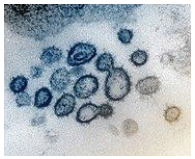
- Distinguish between typical COVID-19 symptoms and those that are potentially cardiovascular related
- List potential cardiac-related diagnoses that could be secondary to a COVID-19 infection
- Identify medications used to treat COVID-19 that may impact the cardiovascular system

Outline

- SARS-CoV-2 pathophysiology and how it can impact cardiovascular health
- Cardiovascular complications of COVID-19
  - Myocarditis
  - Heart failure
  - Arrhythmias
  - Acute Coronary syndrome
- Cardiovascular impact of medications used to treat COVID-19

Introduction and Pathophysiology

SARS-CoV-2



- Virus: Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)
- Disease: Coronavirus Disease 2019 (COVID-19)
- COVID-19 typically manifests as a respiratory illness
  - Cough, fever, myalgia, shortness of breath, congestion

- Cardiovascular abnormalities are also common
  - Myocarditis, heart failure (HF), arrhythmia, myocardial infarction (MI), stroke, deep venous thrombosis (DVT), pulmonary embolism (PE), and more

Lai CC, et al. (*Int J Antimicrob Agents*. 2020); Fox SE, et al. (*J Cardiovasc Pharmacol Ther*. 2021); https://commons.wikimedia.org/wiki/File:Novel_Coronavirus_SARS-CoV-2_(49534370233).jpg

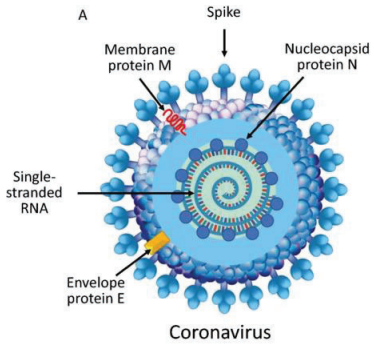
COVID-19 Incidence and Mortality

- By the end of 2020, one-third of the U.S. infected
- As of February 2022:
  - ❖ Over 400 million cases and 5.8 million deaths worldwide
- Cardiovascular disease (CVD) is prevalent among patients with COVID-19:
  - ❖ 7 - 17% of patients may experience myocardial injury during the infection

Pei S, et al. (*Nature*. 2020); https://coronavirus.jhu.edu/map.html; Clerkin KJ, et al. (*Circulation*. 2020); https://commons.wikimedia.org/wiki/File:Covid-19_San_Salvatore_09.jpg

9

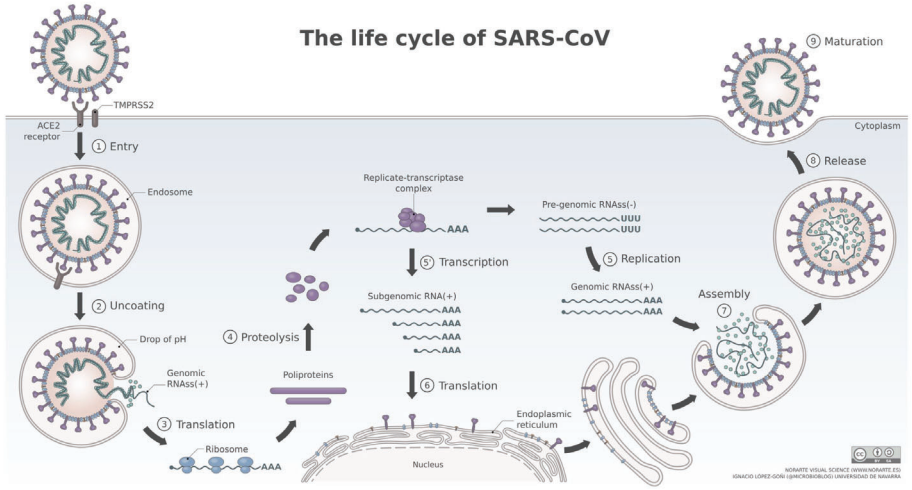
SARS-CoV-2 Virology



- Single-stranded RNA virus
- Binds to angiotensin-converting enzyme 2 (ACE-2) receptor through a spike glycoprotein
- ACE-2 receptor is expressed on
  - ❖ Pulmonary epithelial cells
  - ❖ Renal ductal cells
  - ❖ Cardiomyocytes
  - ❖ Vascular endothelial cells
  - ❖ Others

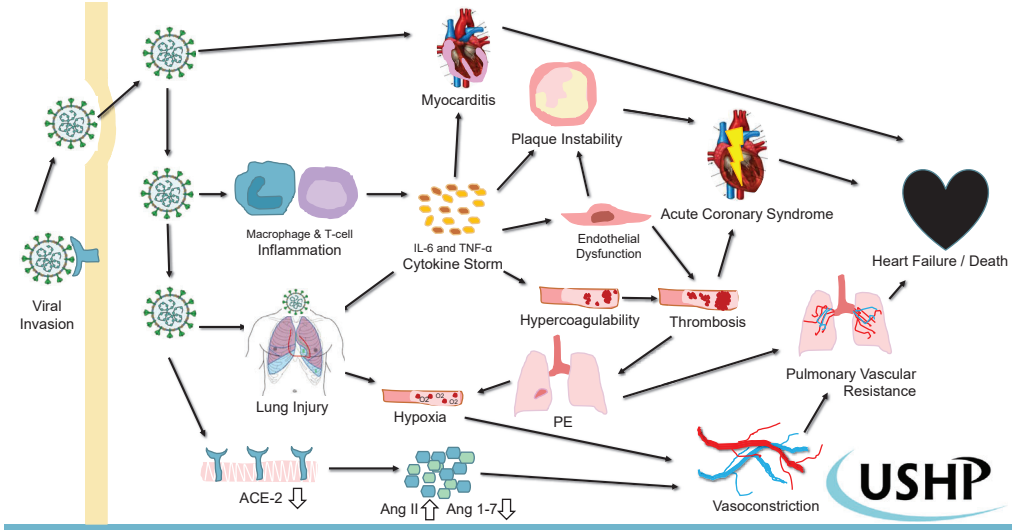
Fox SE, et al. (*J Cardiovasc Pharmacol Ther*. 2021); Peng X, et al. (*Cardiovasc Drugs Ther*. 2021); https://commons.wikimedia.org/wiki/File:Struktura_SARS-CoV_2.jpg

10



https://commons.wikimedia.org/wiki/File:SARS-CoV-2_cycle.png

11



Adeghate EA, et al. (*Heart Fail Rev*. 2021); Laino ME, et al. (*Clin Rev Allergy Immunol*. 2022); https://commons.wikimedia.org/wiki/File:NEW_SARS-COV-2.jpg; https://commons.wikimedia.org/wiki/File:Birikak.png; https://commons.wikimedia.org/wiki/File:Anatomical_plate_of_the_heart_(no_labels).png

12

Cardiac Symptoms and Abnormalities

- Symptoms: Palpitations, chest pain, hypertension / hypotension
- Can lead to new (or exacerbate) heart failure:
  - Lower extremity edema, dyspnea, and fatigue
- Cardiac laboratory and imaging abnormalities:
  - Elevated troponin and/or b-type natriuretic peptide (BNP)
  - Electrocardiogram (EKG) abnormalities
  - Cardiac image findings

Chen G, et al. (*PloS One.*); Adeghate EA, et al. (*Heart Fail Rev.* 2021)

13

Question for Pharmacists

Learning Objective: Describe how the pathophysiology of COVID-19 can impact the cardiovascular system

PollEv.com/USHP
Download the Poll Everywhere app and join USHP
Text USHP to 22333

Select all that apply: What cardiovascular manifestations can occur as a result of a COVID-19 infection?

A. Myocarditis
B. Heart Failure
C. Arrhythmia
D. Myocardial Infarction

14

Question for Pharmacy Technicians

Learning Objective: Distinguish between typical COVID-19 symptoms and those that are potentially cardiovascular related

PollEv.com/USHP
Download the Poll Everywhere app and join USHP
Text USHP to 22333

Which of the following symptoms of a COVID-19 infection is *most likely* related to cardiovascular abnormalities?

A. Shortness of breath
B. Cough
C. Fever
D. Bilateral lower extremity edema

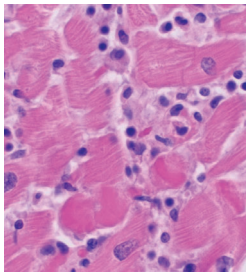
15

COVID-19 and Myocarditis

Myocarditis

- Inflammation of the heart muscle (myocardium)
  - May reduce the heart's ability to pump
  - May cause arrhythmias
- Presentation:
  - Asymptomatic, chest pain, dyspnea, fatigue, arrhythmia
- Left ventricular remodeling and dilated cardiomyopathy → heart failure

Myocarditis Diagnostics



- Endomyocardial biopsy (EMB)
  - Diagnostic gold standard
- EKG
  - Typically abnormal, but neither specific nor sensitive
- Echocardiography (Echo)
  - Useful to exclude - does not identify specifics of myocarditis
- Cardiac MRI (CMR)
  - Myocardial edema, hyperemia/capillary leak, and fibrosis/necrosis
- Laboratory value elevation does not confirm the diagnosis
  - Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and cardiac enzymes (CK-MB, troponin 1, troponin T)

Myocarditis in COVID-19

- Patients with COVID-19 are **16 times** more likely to develop myocarditis
  - 95% CI 14.1 – 17.2)

General Population: **9** per 100,000	COVID-19: **150** per 100,000

- In a prospective cohort study of 100 COVID-19 patients, 60% had on-going myocardial inflammation on cardiac MRI at a mean of 71 days post-infection

Management of myocarditis in COVID-19

- Supportive care
- Treat underlying infection
- Ensure guideline-directed medical therapy (GDMT) for HF treatment
  - ACE-I or ARBs, diuretics, aldosterone antagonists, and beta-blockers
- If cardiogenic shock:
  - Inotropes, vasopressors, mechanical circulatory support devices, ECMO

Vaccinations and Myocarditis

- In a study of over 2.5 million vaccinated people within the Israeli health care system who had received at least one dose of the Pfizer mRNA vaccine:

Incidence of myocarditis:

COVID-19: **150** per 100,000	General Population: **9** per 100,000	Pfizer Vaccination: **2.13** per 100,000 (95% CI 1.56 - 2.70)

- In a study of over 38 million people who were 1-28 days after 2nd vaccination or who were positive for COVID-19,

Incidence Risk Ratio (IRR) of myocarditis:

Pfizer **IRR: 1.30** 95% CI 0.98 - 1.72	Moderna **IRR: 9.84** 95% CI 2.69 - 36.03	Infection **IRR: 9.76** 95% CI 7.51 - 12.69

Mevorach D, et al. (*N Engl J Med* 2021); Patone, M, *et al.* (*Nat Med.* 2021).

21

COVID-19 and Heart Failure

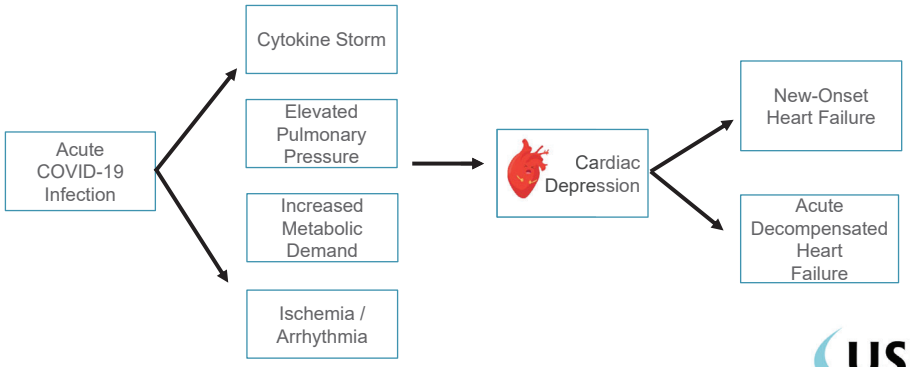
Heart Failure Background

- Functional or structural heart disorder of impaired ventricular filling or ejection
- Classified based on symptoms and left ventricular ejection fraction (LVEF)
  - **HFrEF**
    - Reduced ejection fraction (EF <40%)
  - **HFpEF**
    - Preserved ejection fraction (EF >50%)
- Symptoms:
  - Dyspnea
  - Weight gain
  - Edema
  - Fatigue
  - Chest pain
  - Nausea

Malik A, Brito D, Vaqar S, Chhabra L (*StatPearls*.. 2021)

23

Mechanism of COVID-19 in heart failure



Bader F, et al. (*Heart Fail Rev.* 2021)

24

Pre-existing Heart Failure

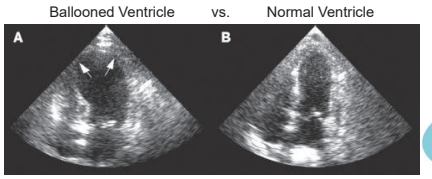
- Pre-existing heart failure is an independent predictor of in-hospital death for patients with COVID-19 based on a study of nearly 9000 subjects
  - ❖ (15.3%, vs. 5.6% among those without heart failure (OR 2.48; 95% CI 1.62 - 3.79)
  - Reduced immunity
  - Frailty
  - Decreased hemodynamic reserve to cope with severe infection

Maher MR, et al. (*N Engl J Med 2020*) (Bader F, et al. (*Heart Fail Rev.* 2021)

25

New-Onset Heart Failure

- Etiologies leading to new-onset heart failure in COVID-19:
  - **Myocarditis** - previously discussed
  - **Takotsubo ("stress") cardiomyopathy** - reversible cardiac dysfunction characterized by ballooning of the left ventricle in the setting of extreme physical or emotional stress



  - **Atrial Fibrillation**
  - **Myocardial Infarction**

Haussner W, et al (*Am J Emerg Med.* 2022).

26

Management of heart failure in COVID-19

- GDMT can be continued
  - No evidence to suggest a detrimental effect of ACE-I or ARBs
- Judicious use of fluids to avoid volume overload
- Hemodynamic instability:
  - Inotropes, vasopressors, temporary mechanical circulatory support, ECMO
- Manage underlying pulmonary disease

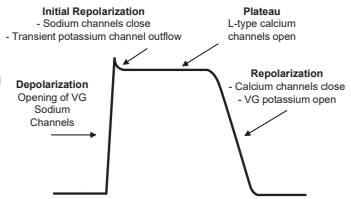
Maher MR, et al. (*N Engl J Med 2020*); *Li J, et al.* (JAMA Cardiology. *2020*)

27

COVID-19 and Arrhythmias

Arrhythmia in COVID-19

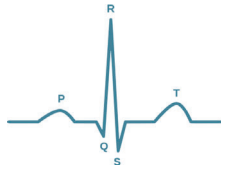
- Inflammatory cytokines → sympathetic overactivation
- IL-6 and TNF-a: cardiac potassium and calcium channels
- Hypoxia: L-type calcium channels and anaerobic metabolism
- Myocarditis: remodeling, ischemia, gap junction, ion-channel
- Post-inflammatory myocardial fibrosis and scarring
- Kidney and GI dysfunction can lead to electrolyte abnormalities
- Medications (discussed later)



Pandat, S, Zhu Z, Fuentes-Rojas S, Schurmann P. (*Methodist Debakey Cardiovasc J.* 2021)

Monitoring of arrhythmia in COVID-19

- Obtain EKG to assess baseline QTc and/or before any QTc prolonging drugs
- Telemetry monitoring considered with documented cardiac arrhythmias, suspected myocardial ischemia, or other indications
- 99th percentile QTc values:
  - ❖ Males: 470 milliseconds
  - ❖ Females: 480 milliseconds



Gandhi RT, Lynch JB, Del Rio C. (*N Engl J Med.* 2020); Giudicessi JR, Noseworthy PA, Friedman PA, Ackerman MJ. (*Mayo Clin Proc.* 2020); https://commons.wikimedia.org/wiki/File:QRS_normal.svg.

Arrhythmia incidence in COVID-19

Type	Reported Incidence
Sinus Tachycardia	40 - 55%
Sinus Bradycardia	5 - 25%
Atrial Fibrillation/Atrial Flutter	2 - 12%
Supraventricular Tachycardia (SVT)	0.6 - 6%
Pre-ventricular contractions (PVCs)	0 - 28%
Non-sustained ventricular tachycardia (NSVT)	0 - 15%
Sustained Ventricular Tachycardia/Fibrillation or TdP	0 - 1.4%
AV Block	0 - 1.4%
Postural orthostatic tachycardia syndrome (POTS)	4 - 22%
Inappropriate sinus tachycardia (IST)	3 - 4 %

Pandat, S, Zhu Z, Fuentes-Rojas S, Schurmann P. (*Methodist Debakey Cardiovasc J.* 2021)

Atrial fibrillation (AF)

- In a 2021 meta-analysis of 21,653 patients hospitalized with COVID-19:
  - ❖ Prevalence of AF: 11%
    - 2.3 - 3.4% in general population
  - ❖ AF 6-fold higher prevalence in severe vs. non-severe disease (19% vs. 3%)
  - ❖ Increased risk of all-cause mortality for:
    - AF (OR: 2.98, 95% CI 1.91 - 4.66)
    - New-onset AF (OR 2.32, 95% CI 1.60 - 3.37)

Li Z, Shao W, Zhang J, et al. (*Front Cardiovasc Med.* 2021); https://commons.wikimedia.org/wiki/File:Heart_conduct_atrialfib.gif#/media/File:Heart_conduct_atrialfib.gif; https://commons.wikimedia.org/wiki/File:Heart_conduct_sinus.gif#/media/File:Heart_conduct_sinus.gif

Bradycardia

- 2020 multi-center retrospective analysis of over 1000 COVID-19 patients:

	PROFOUND (<50 BPM)	ABSOLUTE (<60 BPM)
Incidence	13%	24.9%
Mortality Rate	25.5%	18%

- Mortality rate of whole population was 18.7%
- Patients with <60 BPM were 6.59 times more likely to die than those >60 BPM
  - (95% CI 2.83 - 15.36)

Kumar S, et al. (*Clin Cardiol. 2021*)

Management of arrhythmia in COVID-19

- Medical management during the COVID-19 pandemic is nearly standard
- Rate Control: Beta-blockers could be a concern
  - Alternative: non-dihydropyridine calcium channel blockers
- Bradyarrhythmia: permissive hyperthermia an option
  - No specific guidance outside of standard treatment used in non-COVID-19 patients
- If patients receiving QTc prolonging medication, consider discontinuing therapy

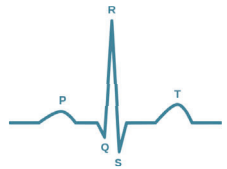
Pandat, S, Zhu Z, Fuentes-Rojas S, Schurmann P. (*Methodist Debakey Cardiovasc J.* 2021); Douedi S, et al. (*J Arrhythm.* 2021)

34

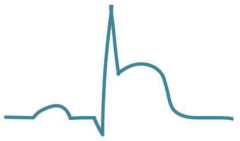
COVID-19 and Acute Coronary Syndrome

Acute Coronary Syndrome

- Suspicion of ST-elevated Myocardial Infarction (STEMI) or Non-ST-elevated Myocardial Infarction (NSTEMI)
- Myocardial Infarction:
  - Cardiac troponins above 99th percentile AND one of:
    - Symptoms
    - EKG changes
    - Pathological Q waves
    - Imaging of new loss of viable myocardium or wall motion abnormality (Echo)



Normal morphology

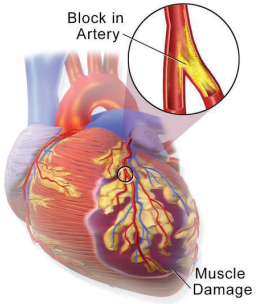

ST-segment elevation

Thygesen K, et al. (*J Am Coll Cardiol*)

36

Type-1 vs. Type-2 Myocardial Infarction

- **Type-1:**
  Acute atherothrombotic coronary artery disease typically caused by plaque rupture or erosion
- **Type-2:**
  Mismatch in oxygen supply and demand due to hemodynamic or respiratory abnormalities
  COVID-19 usually causes TYPE-2



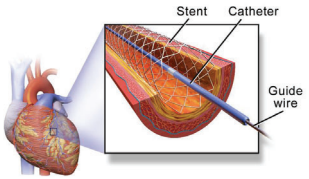
Myocardial Infarction in COVID-19

- Danish study of 5119 patients with COVID-19:
  - 17 patients experienced their 1st-ever MI
    IRR of 5.9 (95% CI 1.9 - 18.2, p=0.002)

- Mount Sanai Health System study of 4695 patients with COVID-19:
  - ❖ evaluated for acute and chronic myocardial injury
    - Chronic: 6.8%
    - Acute: 24.9%
    - All-cause mortality at 6-months: 23.6%
      - 13% of patients w/o MI versus:
        - 43% with chronic myocardial injury (HR 4.17, 95% CI 3.44 - 5.06; p<0.001)
        - 47.3% with acute myocardial injury (HR 4.72, 95% CI 4.15 - 5.36; p<0.001)

Management of MI in COVID-19

- For every 10 minute delay in percutaneous coronary intervention (PCI) there is an additional 3.31 deaths per 100 patients
  - PCI preferred over fibrinolysis
- Consideration of risk vs. benefit in life-threatening COVID-19 infection
- Typical pharmacologic treatment:
  1. Therapeutic anti-coagulation
  2. Aspirin
  3. P2Y12 inhibitor
  4. Beta blockers
  5. Statins
  6. ACE-I / ARB



Question for Pharmacists

Learning Objective: Differentiate cardiovascular manifestations of COVID-19

What method is considered the gold-standard for evaluating myocarditis?

A. Endomyocardial Biopsy (EMB)
B. Electrocardiogram (EKG)
C. Echocardiography (Echo)
D. Cardiac MRI (CMR)

PollEv.com/USHP
Download the Poll Everywhere app and join USHP
Text USHP to 22333

Question for Pharmacy Technicians

Learning Objective: List potential cardiac-related diagnoses that could be secondary to a COVID-19 infection

PollEv.com/USHP
Download the Poll Everywhere app and join USHP
Text USHP to 22333

Which of the following can be directly attributed to a COVID-19 infection:

A. Lung Cancer
B. Glaucoma
C. Urinary Tract Infection
D. Myocarditis

USHP

41

Cardiovascular implications of COVID-19 medications

Dexamethasone (Decadron®)

FDA	Not approved for COVID-19, but mainstay of treatment
MOA	Glucocorticoid that suppresses neutrophil migration and lymphocyte proliferation (anti-inflammatory)
Use	Patient's requiring supplemental oxygen or mechanical ventilation
Dosing	6mg IV or PO for 10 days or until discharge for patients who require respiratory support
Potential CV Impact	• Hypertension • Dyslipidemia • Fluid retention • Sodium ↑/potassium ↓

USHP

Ahmed MH, Hassan A. (*SN Compr Clin Med*. 2020); RECOVERY Collaborative Group, et al. (*N Engl J Med*. 2021); https://commons.wikimedia.org/wiki/File:Dexamethasone_Structural_Formula_V1.svg

43

Remdesivir (Veklury®)

FDA	Fully FDA approved in COVID-19
MOA	Nucleotide analog → prevents viral RNA synthesis by resembling natural ATP substrate
Use	COVID-19 symptom onset within prior 10 days
Dosing	200mg IV infusion on day 1 followed by 100mg IV infusion daily for 4 days or until discharge
Potential CV Impact	• QTc prolongation • Bradycardia • T-wave abnormalities • Hypotension

USHP

Beigel JH, et al. (*N Engl J Med*. 2020); https://commons.wikimedia.org/wiki/File:Remdesivir.svg

44

Baricitinib (Olumiant®)

FDA	Approved via Emergency Use Authorization (EUA)
MOA	Janus Kinase (JAK) inhibitor that modulates inflammatory responses, exhibiting inhibition of IL-6-induced phosphorylation
Use	• High-flow (HFNC) oxygen or non-invasive ventilation • ≥1 elevated inflammatory marker
Dosing	• 4 mg PO daily for 14 days or until discharge • Dose adjustment if eGFR < 60 mL/min/1.73 m^2
Potential CV Impact	• DVT/PE • No evidence of arrhythmia

Kalil AC, et al. (*N Engl J Med.* 2021); Marconi VC, et al. (*Lancet Respir Med.* 2021); https://commons.wikimedia.org/wiki/File:Baricitinib_structure.svg

45

Tocilizumab (Actemra®)

FDA	Approved via EUA
MOA	Recombinant monoclonal antibody that binds to IL-6 receptors, inhibiting inflammatory action
Use	• HFNC, or invasive / non-invasive ventilation • CRP ≥ 7.5 mg/dL
Dosing	One-time 8mg/kg IV infusion (up to 100kg --- max dose 800mg)
Potential CV Impact	• Hypertension • DVT • Infections • Thrombocytopenia • ***Shortens QTc***

https://www.fda.gov/media/150321/download

46

Sotrovimab (Xevudy®)

FDA	Approved via EUA
MOA	Immunoglobulin G-1 monoclonal antibody that binds to the spike protein receptor binding domain, inhibiting an undefined step after virus attachment and prior to fusion of membranes
Use	High risk COVID-19 positive patients NOT admitted and NOT requiring oxygen support
Dosing	One-time 500mg IV infusion
Potential CV Impact	No concerning adverse effects at this time

Gupta A, Gonzalez-Rojas Y, Juarez E, et al. (*N Engl J Med.* 2021);

47

Molnupiravir (Lagevrio®)

FDA	Approved via EUA
MOA	Increases frequency of viral RNA mutations by acting as a substrate for RNA polymerase
Use	Mild-to-moderate severity COVID-19 positive non-hospitalized adults within 5 days of symptom onset
Dosing	800mg (four 200mg capsules) PO every 12 hours for 5 days
Potential CV Impact	• Nothing of concern • No concerning drug-drug interactions reported

Jayk Bernal A, et al. (*N Engl J Med.* 2022); https://www.fda.gov/media/155054/download.; https://commons.wikimedia.org/wiki/File:Molnupiravir.svg

48

Ritonavir-Nirmatrelvir (Paxlovid®)

FDA	Approved via EUA
MOA	Nucleotide analog → prevents viral RNA synthesis by resembling natural ATP substrate
Use	Mild-to-moderate severity COVID-19 positive non-hospitalized adults within 5 days of symptom onset
Dosing	• Nirmatrelvir 300mg PO (two 150mg tablets) with ritonavir 100mg PO • All three pills taken together twice daily for 5 days
Potential CV Impact	• ***Drug interactions*** • Edema • Hyper/Hypotension

https://www.fda.gov/media/155050/download; https://commons.wikimedia.org/wiki/File:Ritonavir_structure.svg

49

Ritonavir-Nirmatrelvir (Paxlovid®)

Ritonavir: Cytochrome P450 (CYP) and P-glycoprotein (P-gp) inhibitor

- *Many common cardiovascular medications could be impacted including:*

Consider alternate therapy if patient is taking:

- Amiodarone
- Clopidogrel
- Dofetilide
- Ivabradine
- Rivaroxaban
- Ticagrelor
- Many others

Consider withholding these therapies if patient taking:

- Atorvastatin
- Rosuvastatin
- Lovastatin
- Simvastatin
- Tacrolimus
- Opiate pain medication
- Many others

https://www.covid19treatmentguidelines.nih.gov/therapies/statement-on-paxlovid-drug-drug-interactions/

50

1) Casirivimab and Imdevimab (REGEN-COV®)

2) Bamlanivimab and Etesevimab

- No longer authorized for use in the United States due to unlikelihood of activity against the predominant omicron variant
- Targets spike protein, which undergoes mutation from variant-to-variant

https://www.covid19treatmentguidelines.nih.gov/therapies/anti-sars-cov-2-antibody-products/anti-sars-cov-2-monoclonal-antibodies/

51

Azithromycin (Zithromax®)

FDA	• NOT approved for treatment of COVID-19 • NIH recommends **against** use
MOA	Macrolide antibiotic with immunomodulatory activity, which works to decrease inflammatory cytokines and inhibit neutrophil activation
Potential CV Impact	• QTc prolongation

Oldenburg CE, et al. (*JAMA*. 2021); https://commons.wikimedia.org/wiki/File:Azithromycin_structure.svg

52

Hydroxychloroquine (Plaquenil®)

FDA	• NOT approved for treatment of COVID-19 • NIH recommends **against** use
MOA	Antimalarial that increases endosomal pH, inhibiting fusion of SARS-Cov2 to cell membranes
Potential CV Impact	• QTc prolongation • Drug interactions (minor CYP2D6 substrate)

RECOVERY Collaborative Group, et al. (*N Engl J Med*. 2020); Self WH, et al. (*JAMA. 2021)*

53

Chloroquine (Aralen®)

FDA	• NOT approved for treatment of COVID-19 • NIH recommends **against** use
MOA	Antimalarial that increases endosomal pH, inhibiting fusion of SARS-Cov2 to cell membranes. Also, chloroquine inhibits glycosylation of the ACE-2 receptor, possibly interfering with receptor binding
Potential CV Impact	• QTc prolongation • Drug interactions (minor CYP2D6, 2C8, 3A4 substrate)

Karalis V, Ismailos G, Karatza E. (*Saf Sci*. 2020); https://www.covid19treatmentguidelines.nih.gov/therapies/antiviral-therapy/chloroquine-or-hydroxychloroquine-and-or-azithromycin;

54

Ivermectin (Stromectol®)

FDA	• NOT approved for treatment of COVID-19 • NIH reports insufficient evidence to recommend either for or against its use
MOA	Antiparasitic drug typically used for onchocerciasis or strongyloidiasis. In COVID-19, thought to inhibit transport proteins and interfere with attachment
Potential CV Impact	• Tachycardia • Edema • Orthostatic hypotension • Drug interactions (minor CYP3A4 and P-gp substrate)

Ahmed S, et al. (*Int J Infect Dis. 2021);* Yu WL, Toh HS, Liao CT, Chang WT. *Cardiovasc Drugs Ther*. 2021)

55

Nitazoxanide (Alinia®)

FDA	• NOT approved for treatment of COVID-19 • NIH recommends **against** use
MOA	Antiparasitic drug typically used for cryptosporiduium or giardia infections. In COVID-19, not fully elucidated, but nitazoxanide inhibits host enzymes which can impair protein processing
Potential CV Impact	• No concerns reported

Rocco PRM, et al. (*Eur Respir J*. 2021); https://www.covid19treatmentguidelines.nih.gov/therapies/antiviral-therapy/nitazoxanide

56

Colchicine (Colcrys®)

FDA	• NOT approved for treatment of COVID-19 • NIH recommends **against** use
MOA	Anti-inflammatory typically used for gout and pericarditis. In COVID-19, shows potential in decreasing cytokines
Potential CV Impact	• Drug interactions (major CYP3A4 and Pgp substrate)

Tardif JC, et al. (*Lancet Respir Med*. 2021); https://www.covid19treatmentguidelines.nih.gov/therapies/immunomodulators/colchicine

Anakinra (Kineret®)

FDA	• NOT approved for treatment of COVID-19 • NIH reports insufficient evidence to recommend either for or against its use
MOA	Recombinant Interleukin-1 (IL-1) receptor antagonist that suppresses inflammatory effects
Potential CV Impact	• Infection • PE

CORIMUNO-19 Collaborative group. (*Lancet Respir Med*. 2021); Kyriazopoulou E, et al. (*Nat Med*. 2021); https://www.covid19treatmentguidelines.nih.gov/therapies/immunomodulators/interleukin-1-inhibitors/

Canakinumab (Ilaris®)

FDA	• NOT approved for treatment of COVID-19 • NIH recommends **against** use
MOA	Human monoclonal antibody that targets the beta subunit of IL-1, which suppresses inflammatory effects
Potential CV Impact	• No concerns reported

Caricchio R, et al. (*JAMA*. 2021); https://www.covid19treatmentguidelines.nih.gov/therapies/immunomodulators/interleukin-1-inhibitors/

Siltuximab (Sylvant®)

FDA	• NOT approved for treatment of COVID-19 • NIH recommends **against** use
MOA	Chimeric monoclonal antibody that binds to interleukin-6 to inactivate signaling
Potential CV Impact	• Edema • Hypotension

https://www.medrxiv.org/content/10.1101/2020.04.01.20048561v4; https://www.covid19treatmentguidelines.nih.gov/therapies/immunomodulators/interleukin-6-inhibitors/nt

Question for Pharmacists

Learning Objective: Analyze the cardiovascular impact of medications used for COVID-19

PollEv.com/USHP
Download the Poll Everywhere app and join USHP
Text USHP to 22333

Which of the following medications should we be especially concerned with regarding drug-drug interactions that may elicit cardiovascular adverse effects?

A. Molnupiravir (Lagevrio®)
B. Baricitinib (Olumiant®)
C. Ritonavir-Nirmatrelvir (Paxlovid®)
D. Sotrovimab (Xevudy®)

Question for Pharmacy Technicians

Learning objective: Identify medications used to treat COVID-19 that may impact the cardiovascular system

PollEv.com/USHP
Download the Poll Everywhere app and join USHP
Text USHP to 22333

Which medication is given as an intravenous (IV) infusion rather than by mouth (PO)?

A. Molnupiravir (Lagevrio®)
B. Remdesivir (Veklury®)
C. Baricitinib (Olumiant®)
D. Ritonavir-Nirmatrelvir (Paxlovid®)

References

1. Lai CC, Shih TP, Ko WC, Tang HJ, Hsueh PR. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): The epidemic and the challenges. *Int J Antimicrob Agents*. 2020;55(3):105924. doi:10.1016/j.ijantimicag.2020.105924
2. Fox SE, Heide RSV. COVID-19: The Heart of the Matter-Pathological Changes and a Proposed Mechanism. *J Cardiovasc Pharmacol Ther*. 2021;26(3):217-224. doi:10.1177/1074248421995356
3. Pei S., Yamana T.K., Kandula S. *et al.* Burden and characteristics of COVID-19 in the United States during 2020. *Nature* **598,** 338–341 (2021). https://doi.org/10.1038/s41586-021-03914-4
4. Johns Hopkins Coronavirus Resource Center. https://coronavirus.jhu.edu/map.html. Accessed February 7, 2022
5. Clerkin KJ, Fried JA, Raikhelkar J, et al. Coronavirus disease 2019 (COVID-19) and cardiovascular disease. Circulation 2020;141:1648-55.
6. Peng X, Wang Y, Xi X, et al. Promising Therapy for Heart Failure in Patients with Severe COVID-19: Calming the Cytokine Storm. *Cardiovasc Drugs Ther*. 2021;35(2):231-247. doi:10.1007/s10557-020-07120-8
7. Adeghate EA, Eid N, Singh J. Mechanisms of COVID-19-induced heart failure: a short review. Heart Fail Rev. 2021 Mar;26(2):363-369. doi: 10.1007/s10741-020-10037-x. Epub 2020 Nov 16.
8. Laino ME, Ammirabile A, Motta F, et al. Advanced Imaging Supports the Mechanistic Role of Autoimmunity and Plaque Rupture in COVID-19 Heart Involvement [published online ahead of print, 2022 Jan 28]. *Clin Rev Allergy Immunol*. 2022;1-15. doi:10.1007/s12016-022-08925-1
9. Chen G, Li X, Gong Z, et al. Hypertension as a sequela in patients of SARS-CoV-2 infection. *PLoS One*. 2021;16(4):e0250815. Published 2021 Apr 28. doi:10.1371/journal.pone.0250815
10. Castiello T, Georgiopoulos G, Finocchiaro G, et al. COVID-19 and myocarditis: a systematic review and overview of current challenges. *Heart Fail Rev*. 2022;27(1):251-261. doi:10.1007/s10741-021-10087-9
11. Niazi S, Niazi F, Doroodgar F, Safi M. The Cardiac Effects of COVID-19: Review of articles. *Curr Probl Cardiol*. 2022;47(2):100981. doi:10.1016/j.cpcardiol.2021.100981
12. Ammirati E, Frigerio M, Adler ED, et al. Management of Acute Myocarditis and Chronic Inflammatory Cardiomyopathy: An Expert Consensus Document. *Circ Heart Fail*. 2020;13(11):e007405. doi:10.1161/CIRCHEARTFAILURE.120.007405

References

13. Agdamag ACC, Edmiston JB, Charpentier V, et al. Update on COVID-19 Myocarditis. *Medicina (Kaunas)*. 2020;56(12):678. Published 2020 Dec 9. doi:10.3390/medicina56120678
14. Boehmer TK, Kompaniyets L, Lavery AM, et al. Association Between COVID-19 and Myocarditis Using Hospital-Based Administrative Data — United States, March 2020–January 2021. MMWR Morb Mortal Wkly Rep 2021;70:1228–1232. DOI: http://dx.doi.org/10.15585/mmwr.mm7035e5external icon.
15. Puntmann VO, Carerj ML, Wieters I, et al. Outcomes of Cardiovascular Magnetic Resonance Imaging in Patients Recently Recovered From Coronavirus Disease 2019 (COVID-19). *JAMA Cardiol*. 2020;5(11):1265–1273. doi:10.1001/jamacardio.2020.3557
16. Hazebroek MR, Everaerts K, Heymans S. Diagnostic approach of myocarditis: strike the golden mean. *Neth Heart J*. 2014;22(2):80-84. doi:10.1007/s12471-013-0499-3
17. Agdamag ACC, Edmiston JB, Charpentier V, Chowdhury M, Fraser M, Maharaj VR, Francis GS, Alexy T. Update on COVID-19 Myocarditis. Medicina (Kaunas). 2020 Dec 9;56(12):678. doi: 10.3390/medicina56120678. PMID: 33317101; PMCID: PMC7764165.
18. Kamarullah W, Nurcahyani, Mary Josephine C, Bill Multazam R, Ghaezany Nawing A, Dharma S. Corticosteroid Therapy in Management of Myocarditis Associated with COVID-19; a Systematic Review of Current Evidence. *Arch Acad Emerg Med*. 2021;9(1):e32. Published 2021 Apr 16. doi:10.22037/aaem.v9i1.1153
19. Mevorach D, Anis E, Cedar N, et al. Myocarditis after BNT162b2 mRNA vaccine against Covid-19 in Israel. N Engl J Med 2021;385:2140-2149.
20. Patone, M., Mei, X.W., Handunnetthi, L. *et al.* Risks of myocarditis, pericarditis, and cardiac arrhythmias associated with COVID-19 vaccination or SARS-CoV-2 infection. *Nat Med* (2021). https://doi.org/10.1038/s41591-021-01630-0
21. Malik A, Brito D, Vaqar S, Chhabra L. Congestive Heart Failure. In: *StatPearls*. Treasure Island (FL): StatPearls Publishing; November 2, 2021.
22. Bader F, Manla Y, Atallah B, Starling RC. Heart failure and COVID-19. Heart Fail Rev. 2021 Jan;26(1):1-10. doi: 10.1007/s10741-020-10008-2. PMID: 32720082; PMCID: PMC7383122.
23. Mehra MR, Desai SS, Kuy S, Henry TD, Patel AN. Cardiovascular Disease, Drug Therapy, and Mortality in Covid-19 [retracted in: N Engl J Med. 2020 Jun 4;:]. *N Engl J Med*. 2020;382(25):e102. doi:10.1056/NEJMoa2007621

References

24. Haussner W, DeRosa AP, Haussner D, et al. COVID-19 associated myocarditis: A systematic review. *Am J Emerg Med*. 2022;51:150-155. doi:10.1016/j.ajem.2021.10.001
25. Li J, Wang X, Chen J, Zhang H, Deng A (2020) Association of renin-angiotensin system inhibitors with severity or risk of death in patients with hypertension hospitalized for coronavirus disease 2019 (COVID-19) infection in Wuhan, China. JAMA Cardiol 5(7):1–6. https://doi.org/10.1001/jamacardio.2020.1624
26. Pandat S, Zhu Z, Fuentes-Rojas S, Schurmann P. Arrhythmias in COVID-19. *Methodist Debakey Cardiovasc J*. 2021;17(5):73-82. Published 2021 Dec 15. doi:10.14797/mdcvj.1039
27. Gandhi RT, Lynch JB, Del Rio C. Mild or Moderate Covid-19. N Engl J Med. 2020 Oct 29;383(18):1757-1766. doi: 10.1056/NEJMcp2009249. Epub 2020 Apr 24. PMID: 32329974.
28. Giudicessi JR, Noseworthy PA, Friedman PA, Ackerman MJ. Urgent Guidance for Navigating and Circumventing the QTc-Prolonging and Torsadogenic Potential of Possible Pharmacotherapies for Coronavirus Disease 19 (COVID-19). *Mayo Clin Proc*. 2020;95(6):1213-1221. doi:10.1016/j.mayocp.2020.03.024
29. Li Z, Shao W, Zhang J, et al. Prevalence of Atrial Fibrillation and Associated Mortality Among Hospitalized Patients With COVID-19: A Systematic Review and Meta-Analysis. *Front Cardiovasc Med*. 2021;8:720129. Published 2021 Oct 13. doi:10.3389/fcvm.2021.720129
30. Kumar S, Arcuri C, Chaudhuri S, et al. A novel study on SARS-COV-2 virus associated bradycardia as a predictor of mortality-retrospective multicenter analysis. *Clin Cardiol*. 2021;44(6):857-862. doi:10.1002/clc.23622
31. Douedi S, Mararenko A, Alshami A, et al. COVID-19 induced bradyarrhythmia and relative bradycardia: An overview. *J Arrhythm*. 2021;37(4):888-892. Published 2021 Jun 14. doi:10.1002/joa3.12578
32. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth Universal Definition of Myocardial Infarction (2018). *J Am Coll Cardiol*. 2018;72(18):2231-2264. doi:10.1016/j.jacc.2018.08.1038
33. Modin D, Claggett B, Sindet-Pedersen C, et al. Acute COVID-19 and the Incidence of Ischemic Stroke and Acute Myocardial Infarction. *Circulation*. 2020;142(21):2080-2082. doi:10.1161/CIRCULATIONAHA.120.050809
34. Kini A, Cao D, Nardin M, et al. Types of myocardial injury and mid-term outcomes in patients with COVID-19. *Eur Heart J Qual Care Clin Outcomes*. 2021;7(5):438-446. doi:10.1093/ehjqcco/qcab053

References

35. Scholz KH, Maier SKG, Maier LS, et al. Impact of treatment delay on mortality in ST-segment elevation myocardial infarction (STEMI) patients presenting with and without haemodynamic instability: results from the German prospective, multicentre FITT-STEMI trial. *Eur Heart J*. 2018;39(13):1065-1074. doi:10.1093/eurheartj/ehy004
36. Saad M, Kennedy KF, Imran H, et al. Association Between COVID-19 Diagnosis and In-Hospital Mortality in Patients Hospitalized With ST-Segment Elevation Myocardial Infarction. *JAMA*. 2021;326(19):1940-1952. doi:10.1001/jama.2021.18890
37. Ahmed MH, Hassan A. Dexamethasone for the Treatment of Coronavirus Disease (COVID-19): a Review [published online ahead of print, 2020 Oct 31]. *SN Compr Clin Med*. 2020;1-10. doi:10.1007/s42399-020-00610-8
38. RECOVERY Collaborative Group, Horby P, Lim WS, et al. Dexamethasone in Hospitalized Patients with Covid-19. *N Engl J Med*. 2021;384(8):693-704. doi:10.1056/NEJMoa2021436
39. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the Treatment of Covid-19 - Final Report. *N Engl J Med*. 2020;383(19):1813-1826. doi:10.1056/NEJMoa2007764
40. Kalil AC, Patterson TF, Mehta AK, et al. Baricitinib plus remdesivir for hospitalized adults with COVID-19. *N Engl J Med*. 2021;384(9):795-807.
41. Marconi VC, Ramanan AV, de Bono S, et al. Efficacy and safety of baricitinib for the treatment of hospitalised adults with COVID-19 (COV-BARRIER): a randomised, double-blind, parallel-group, placebo-controlled Phase 3 trial. *Lancet Respir Med*. 2021;9(12):1407-1418.
42. FDA EUA. https://www.fda.gov/media/150321/download. Accessed February 5, 2022
43. Gupta A, Gonzalez-Rojas Y, Juarez E, et al. Early Treatment for Covid-19 with SARS-CoV-2 Neutralizing Antibody Sotrovimab. *N Engl J Med*. 2021;385(21):1941-1950. doi:10.1056/NEJMoa2107934
44. Jayk Bernal A, Gomes da Silva MM, Musungaie DB, et al. Molnupiravir for Oral Treatment of Covid-19 in Nonhospitalized Patients. *N Engl J Med*. 2022;386(6):509-520. doi:10.1056/NEJMoa2116044
45. FDA EUA. https://www.fda.gov/media/155054/download. Accessed February 5, 2022
46. FDA EUA. https://www.fda.gov/media/155050/download. Accessed February 5, 2022
47. COVID-19 Treatment Guidelines

References

48. Oldenburg CE, Pinsky BA, Brogdon J, et al. Effect of Oral Azithromycin vs Placebo on COVID-19 Symptoms in Outpatients With SARS-CoV-2 Infection: A Randomized Clinical Trial. *JAMA*. 2021;326(6):490-498. doi:10.1001/jama.2021.11517
49. RECOVERY Collaborative Group, Horby P, Mafham M, et al. Effect of Hydroxychloroquine in Hospitalized Patients with Covid-19. *N Engl J Med*. 2020;383(21):2030-2040. doi:10.1056/NEJMoa2022926
50. Self WH, Semler MW, Leither LM, et al. Effect of Hydroxychloroquine on Clinical Status at 14 Days in Hospitalized Patients With COVID-19: A Randomized Clinical Trial. *JAMA*. 2020;324(21):2165–2176. doi:10.1001/jama.2020.22240
51. Karalis V, Ismailos G, Karatza E. Chloroquine dosage regimens in patients with COVID-19: Safety risks and optimization using simulations. *Saf Sci*. 2020;129:104842. doi:10.1016/j.ssci.2020.104842
52. Ahmed S, Karim MM, Ross AG, et al. A five-day course of ivermectin for the treatment of COVID-19 may reduce the duration of illness. *Int J Infect Dis*. 2021;103:214-216. doi:10.1016/j.ijid.2020.11.191
53. Yu WL, Toh HS, Liao CT, Chang WT. A Double-Edged Sword-Cardiovascular Concerns of Potential Anti-COVID-19 Drugs. *Cardiovasc Drugs Ther*. 2021;35(2):205-214. doi:10.1007/s10557-020-07024-7
54. Rocco PRM, Silva PL, Cruz FF, et al. Early use of nitazoxanide in mild COVID-19 disease: randomised, placebo-controlled trial. *Eur Respir J*. 2021;58(1):2003725. Published 2021 Jul 8. doi:10.1183/13993003.03725-2020
55. Tardif JC, Bouabdallaoui N, L'Allier PL, et al. Colchicine for community-treated patients with COVID-19 (COLCORONA): a phase 3, randomised, double-blinded, adaptive, placebo-controlled, multicentre trial. *Lancet Respir Med*. 2021;9(8):924-932. doi:10.1016/S2213-2600(21)00222-8
56. CORIMUNO-19 Collaborative group. Effect of anakinra versus usual care in adults in hospital with COVID-19 and mild-to-moderate pneumonia (CORIMUNO-ANA-1): a randomised controlled trial. *Lancet Respir Med*. 2021;9(3):295-304. doi:10.1016/S2213-2600(20)30556-7