COVID-19 Outcome in Heart Transplant and Heart Failure

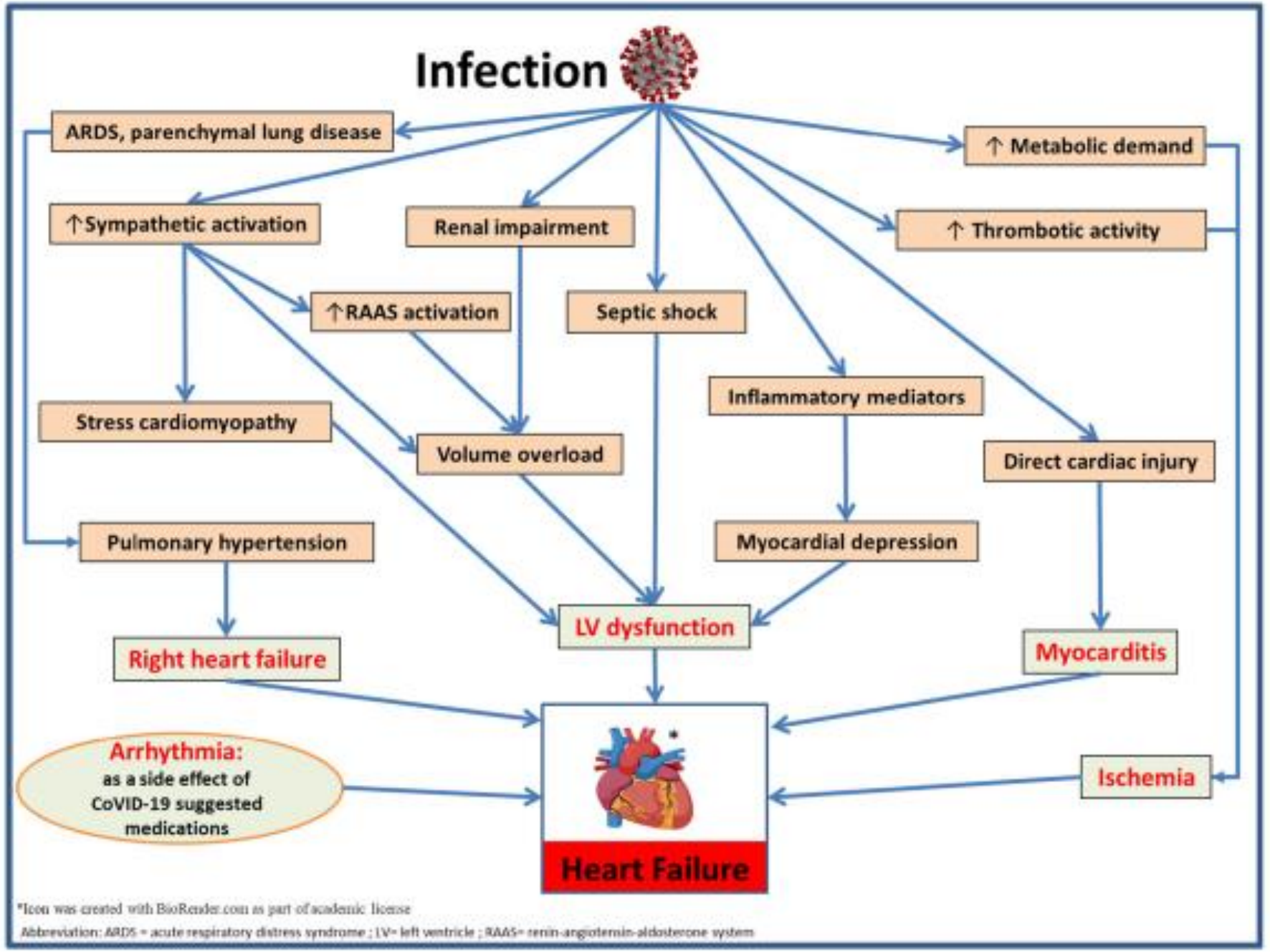
Lee R. Goldberg, MD, MPH, FACC
Section Chief, Advanced Heart Failure and Cardiac Transplant
Vice Chair of Medicine for Informatics
Professor of Medicine, University of Pennsylvania
Philadelphia, PA

Disclosures

- Zoll/Respircardia – Consultant, Research funding
- Abbott – Consultant
- Viscardia – Consultant

Background

- COVID Infection can led to cardiovascular complications
  - Heart failure exacerbation for those with pre-existing cardiovascular disease
  - Acute myocardial infarction
  - Acute pulmonary embolism
  - Acute heart failure
    - Acute MI
    - Acute myocarditis



Heart Failure Reviews (2021) 26:1–10

Exacerbation of Existing Heart Failure

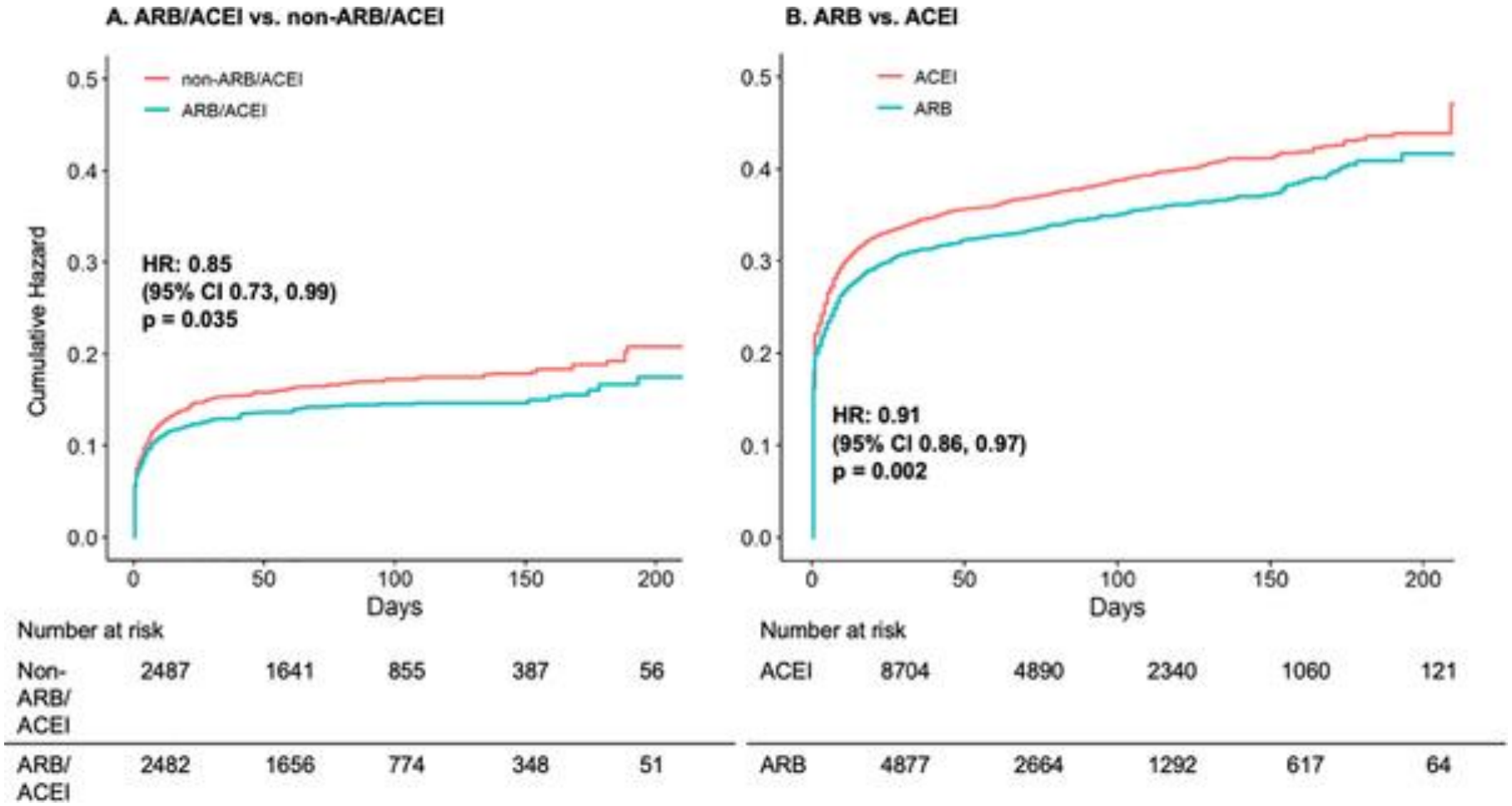
- HF patients are at especially increased risk due:
  - Reduced immunity
  - General frailty
  - Reduced hemodynamic ability to cope with more severe infections
- HF patients tend to have more comorbidities that are all associated with worse COVID outcomes
  - Diabetes
  - Obesity
  - Renal Disease
  - ? “increased pulmonary fluid”

Angiotensin Renin Drugs

- SARS-CoV-2 spike glycoproteins bind to angiotensin-converting enzyme 2 (ACE2) receptors on the cell's outer surface
- This raised the concern that patients on ACE or ARB may be at higher risk in the setting of COVID due to up-regulation of ACE2 receptors
- Heart failure guidelines mandate the use of ACE/ARB/ARNI as first line agents

Observational Study of ACE/ARB

- All cause hospitalization or mortality



PLOS ONE 16(4): e0248080

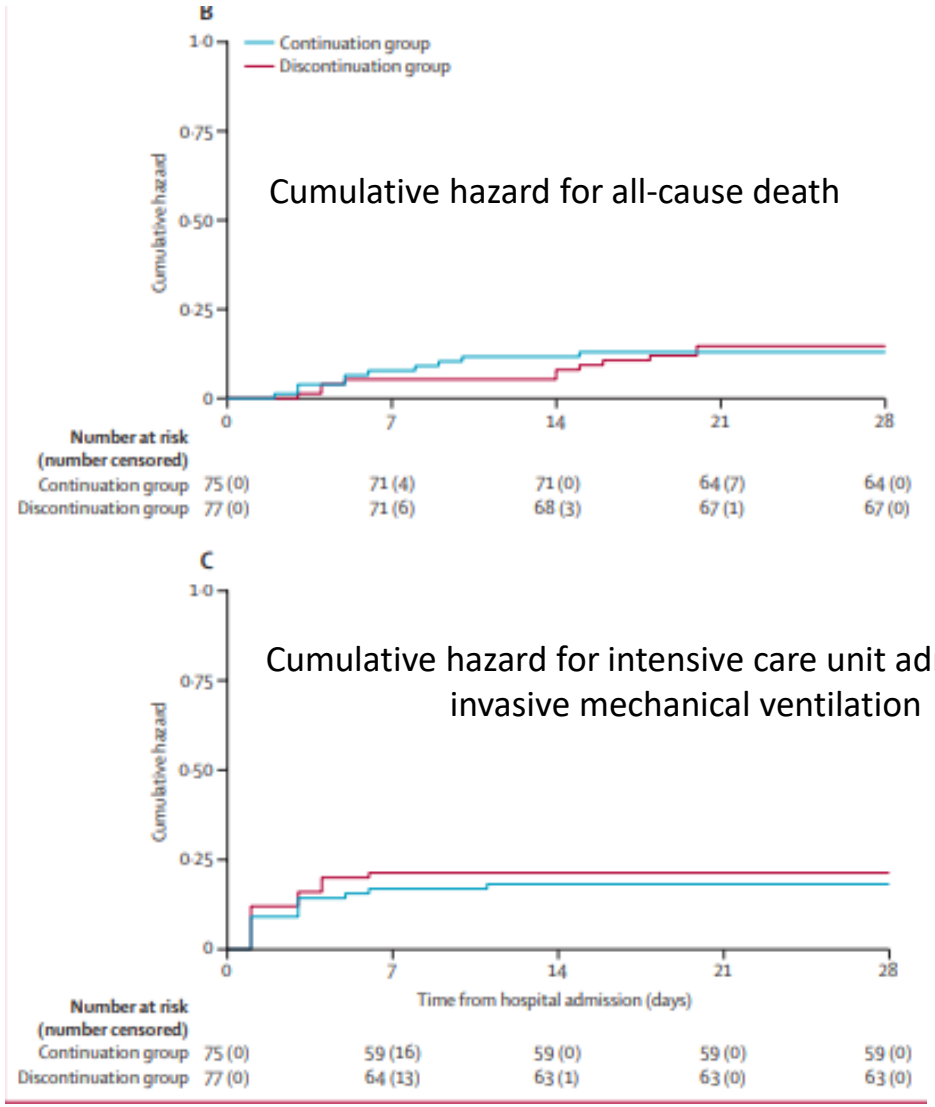
Outcomes of Withdrawal of ACE/ARB

	Continuation of ACEI or ARB therapy (n=75)	Discontinuation of ACEI or ARB therapy (n=77)	Treatment effect* (95% CI)	p value
Primary endpoint				
Global rank score	73 (40 to 110)	81 (38 to 117)	8 (−13 to 29)	0·61
Secondary endpoints				
All-cause death	11 (15%)	10 (13%)	1·00 (0·42 to 2·36)	0·99
Length of hospitalisation, days	6 (3 to 11)	5 (3 to 10)	−1 (−4 to 2)	0·56
Length of intensive care unit stay or invasive mechanical ventilation, days	13 (6 to 17)	15 (6 to 27)	2 (−12 to 178)	0·59
Area under of the curve of the SOFA score adjusted for death	12 (3 to 23)	7 (2 to 20)	−4 (−13 to 5)	0·38
Exploratory endpoints				
Intensive care unit admission or invasive mechanical ventilation	16 (21%)	14 (18%)	0·84 (0·43 to 1·66)	0·61
Hypotension requiring haemodynamic support	9 (12%)	8 (10%)	0·86 (0·34 to 2·17)	0·74

Data are median (IQR) or n (%) unless otherwise specified. ACEI=angiotensin-converting enzyme inhibitor. ARB=angiotensin receptor blocker. SOFA=Sequential Organ Failure Assessment. *For continuous outcomes, the treatment effect is the β-coefficient from unadjusted regression analyses except for the primary endpoint analysis, which was adjusted for age, sex, race or ethnicity, pre-existing heart failure, pre-existing chronic lung disease, and ACEI versus ARB therapy at baseline; for binary outcomes, the treatment effect is the hazard ratio. For binary outcomes other than death, death was addressed as a competing risk. Median length of intensive care unit stay or invasive mechanical ventilation was only calculated among those individuals who were transferred to the intensive care unit or required mechanical ventilation.

Table 2: **Primary, secondary, and exploratory endpoints**

Lancet Respir Med 2021; 9: 275–84



Cumulative hazard for all-cause death

Cumulative hazard for intensive care unit admission or invasive mechanical ventilation

Heart failure as a manifestation of COVID-19 infection in previously healthy individuals

- Myocarditis
- Myocardial infarction
- Right ventricular failure
  - Pulmonary hypertension in the setting of lung involvement
  - Pulmonary emboli

Myocarditis – Definition/Diagnosis

- Condition defined by the presence of cardiac symptoms
  - Chest pain
  - Dyspnea
  - Palpitations
  - Syncope
  - Elevated Cardiac Troponin
- Abnormal
  - Electrocardiographic (ECG)
  - Echocardiographic
  - Cardiac Magnetic Resonance
  - Histopathology on biopsy or autopsy
- Absence of flow-limiting coronary artery disease

J Am Coll Cardiol 2022;79:1717–1756.

COVID Myocarditis

- Cardiovascular manifestations of COVID occur in 20 to 30% of hospitalized patients
- Cardiovascular complications are associated with worse outcomes
- Many case reports have been published
- Likely under-reported
- Variable guidance for the management of myocarditis

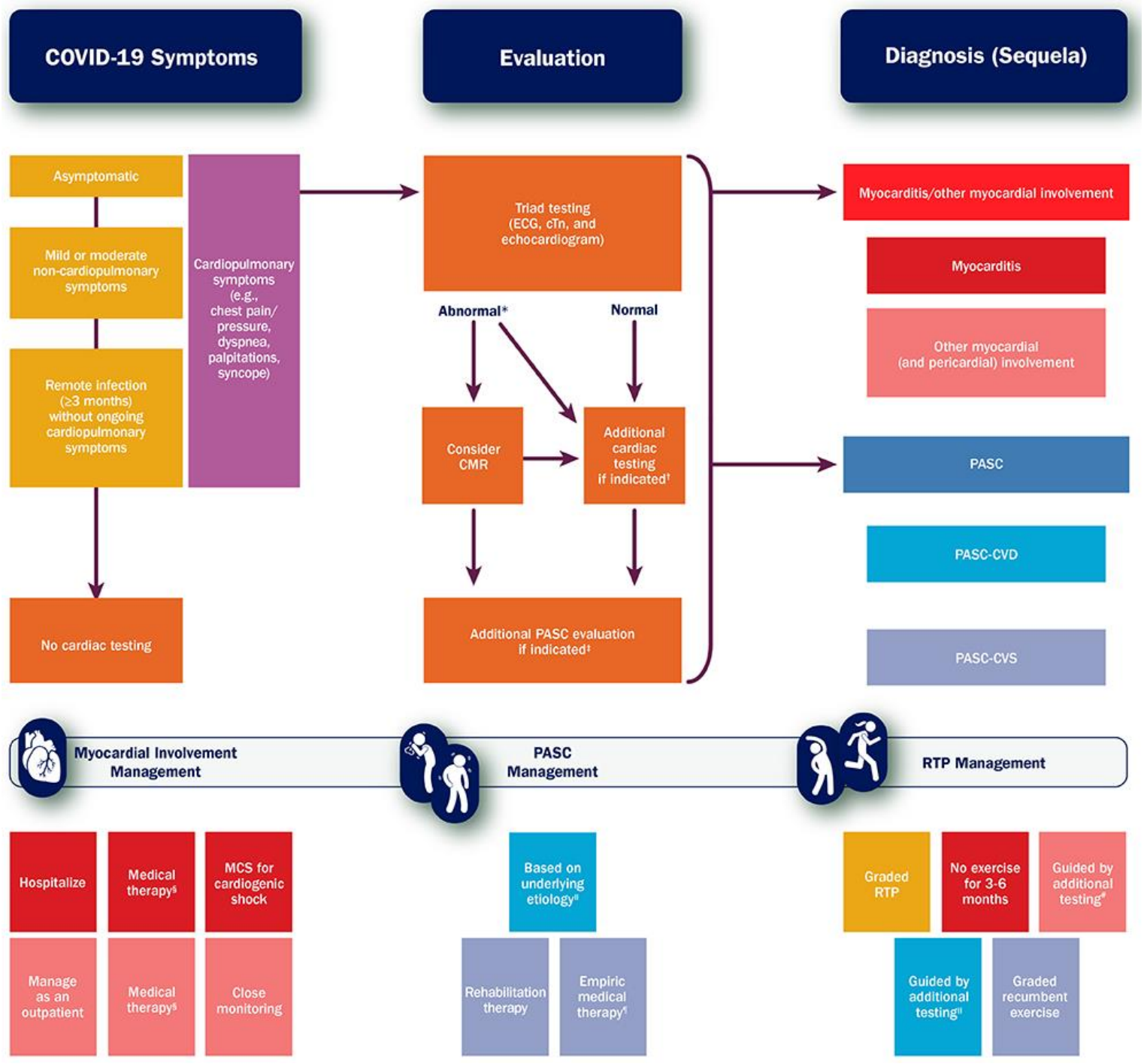
Cizgici AY, Agus HZ, Yildiz M. COVID-19 myopericarditis: it should be kept in mind in today's conditions. Am J Emerg Med. 2020.

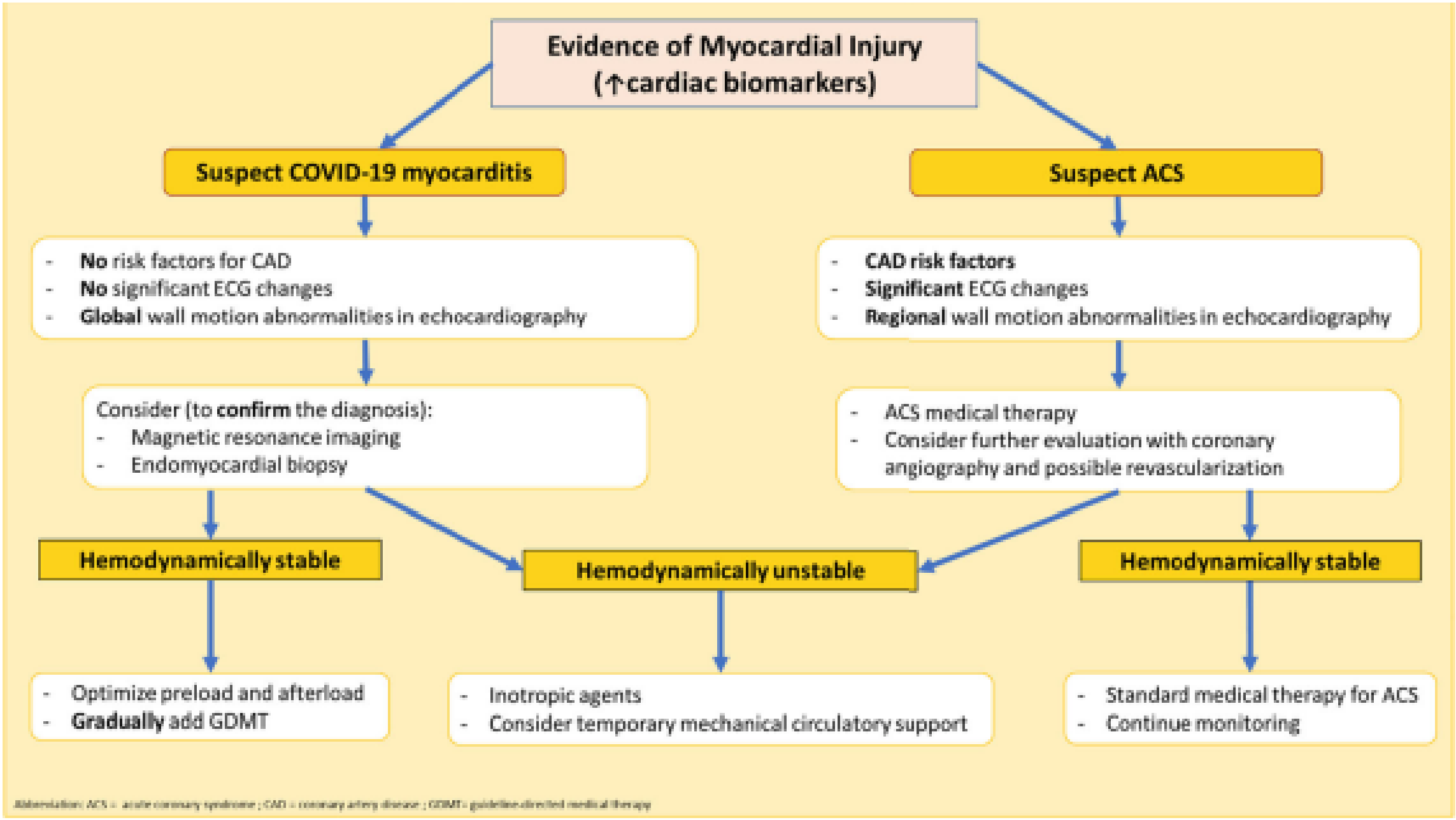
Shi S, QinM, Shen B, Cai Y, Liu T, Yang F, et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. JAMA Cardiol. 2020; 5:802–10.

Sawalha K, Abozenah M, Kadado AJ, Battisha A, Al-Akchar M, Salerno C, Hernandez-Montfort J, Islam AM. Systematic Review of COVID-19 Related Myocarditis: Insights on Management and Outcome. Cardiovasc Revasc Med. 2021 Feb;23:107-113. doi: 10.1016/j.carrev.2020.08.028. Epub 2020 Aug 18. PMID: 32847728; PMCID: PMC7434380.

EXPERT CONSENSUS DECISION PATHWAY

2022 ACC Expert Consensus Decision Pathway on Cardiovascular Sequelae of COVID-19 in Adults: Myocarditis and Other Myocardial Involvement, Post-Acute Sequelae of SARS-CoV-2 Infection, and Return to Play





Heart Fail Rev (2021) 26:1–10

Epidemiology of COVID Myocarditis

- A recent population-based study of young adults (aged <20 years) from 48 U.S. health care organizations estimated the incidence of myocarditis with COVID-19 at about 450 per million
- Challenging and incomplete assessments suggest that the incidence is likely higher
- Fulminant myocarditis is rare

Singer ME, Taub IB, Kaelber DC. Risk of myocarditis from COVID-19 infection in people under age 20: a population-based analysis. medRxiv. Published online July 27, 2021.

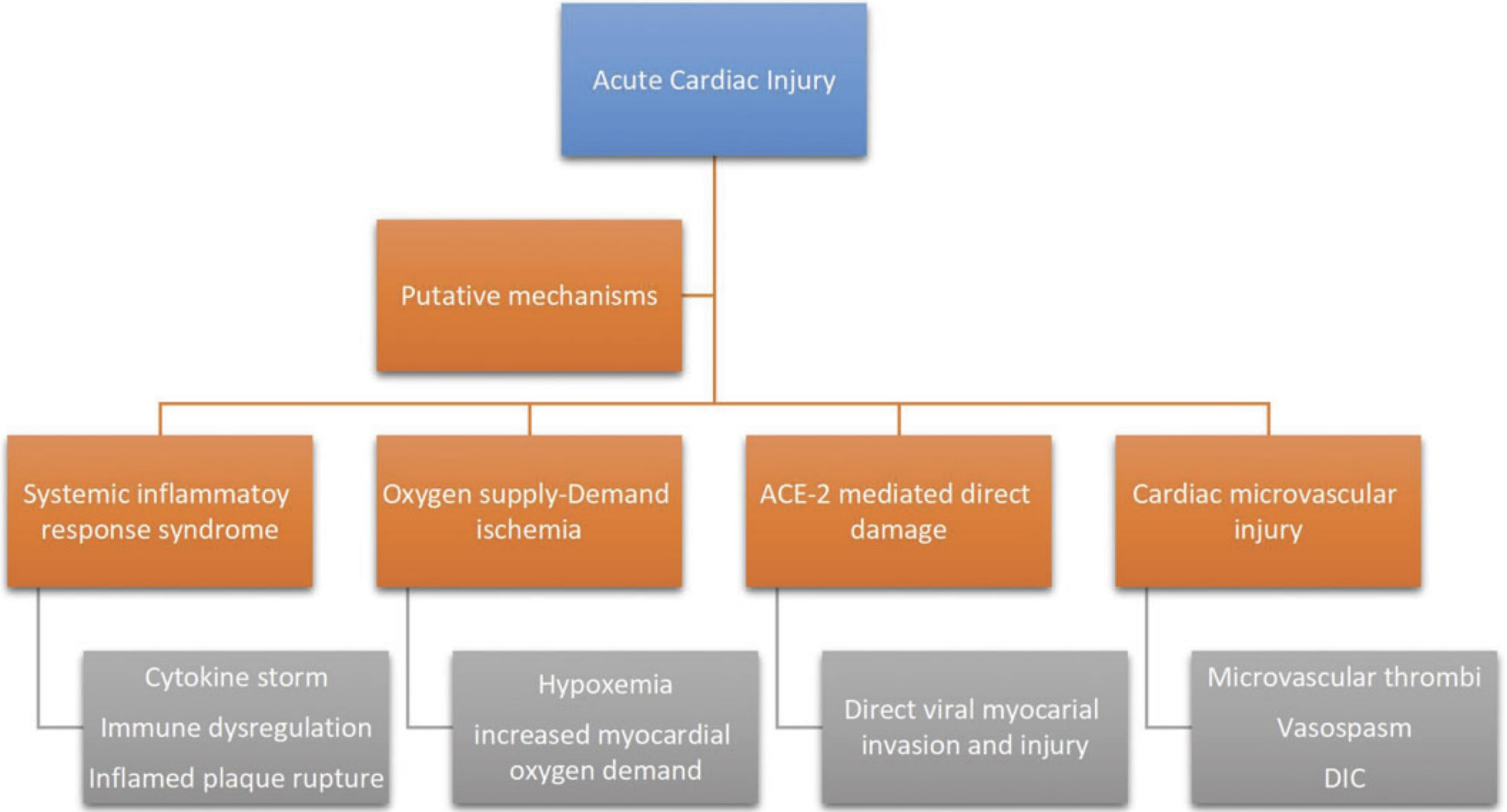
Heart Fail Rev. 2022;27:251–261.

Differential Diagnosis

- Myocarditis
- Acute coronary syndrome (myocardial infarction type 1)
- Demand ischemia (myocardial infarction type 2)
- Multisystem inflammatory syndrome in children (MIS-C)
- Multisystem inflammatory syndrome in adults (MIS-A)
- Takotsubo/stress cardiomyopathy
- Cytokine storm
- Acute cor pulmonale resulting from macropulmonary or micropulmonary emboli
- Myocardial injury from chronic conditions like pre-existing heart failure
- Acute viral infection unmasking subclinical heart disease

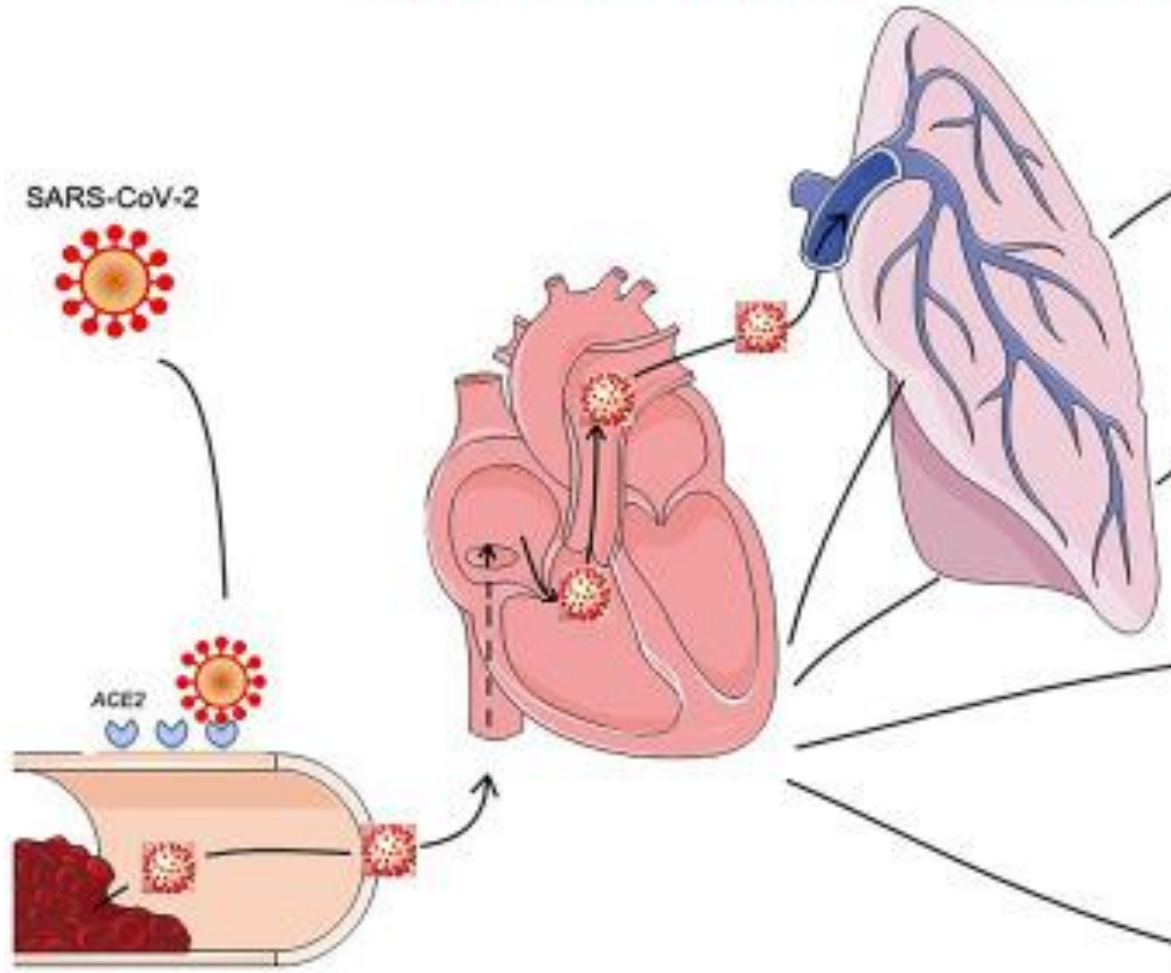
J Am Coll Cardiol 2022;79:1717–1756.

Mechanisms of Acute Cardiac Injury



Postgrad Med J 2021;**97**:655–666

Myocarditis in COVID-19: current evidence from 38 cases



Demographics

>50years--> 14 out of 38
<50years--> 24 out of 38
♂--> 24 out of 36 ♀---> 12 out of 36

Diagnosis

Raised troponin-> 36 out of 37
Abnormal ECG--> 32 out of 36
Abnormal echo--> 27 out of 34
≥1 abnormality in CMR--> 25 out of 25

Treatment

Steroids--> 13, Antibiotics--> 14
Heart Failure treatment--> 14
Hydroxychloroquine-->10,
Tocilizumab--> 4
Anticoagulants--> 8, Vasopressors--> 13

Prognosis

Recovered--> 28 out of 33
Died--> 5 out of 33

Castiello T, Georgiopoulos G, Finocchiaro G, Claudia M, Gianatti A, Delialis D, Aimo A, Prasad S. COVID-19 and myocarditis: a systematic review and overview of current challenges. Heart Fail Rev. 2022 Jan;27(1):251-261. doi: 10.1007/s10741-021-10087-9. Epub 2021 Mar 24. PMID: 33761041; PMCID: PMC7988375.

Pathophysiology of Myocarditis

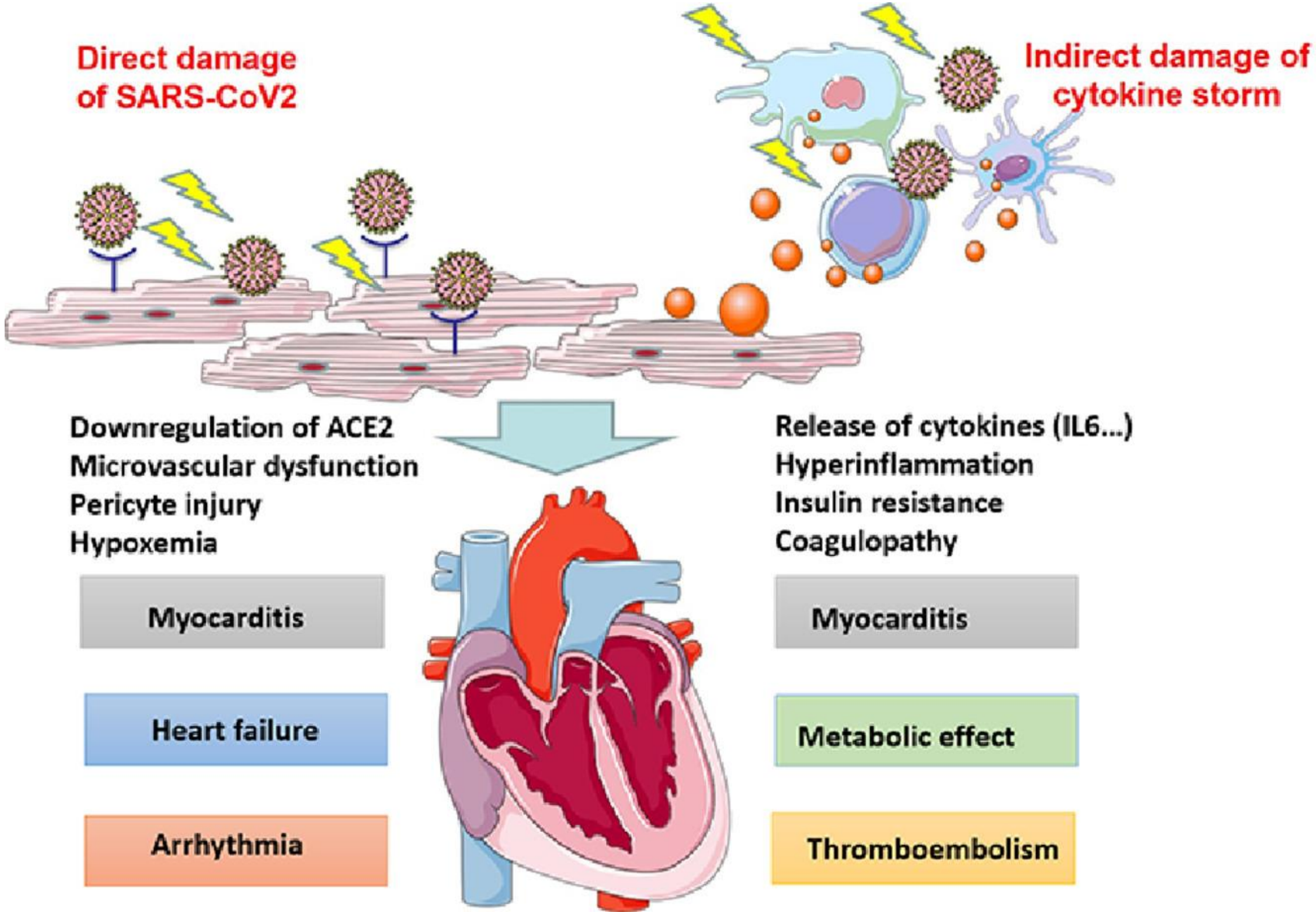
- COVID-19 RNA has been found in the interstitial myocardium
- COVID-19 gene specific sequences were found in some myocardial biopsies
- One case series detected COVID-19 genome in 5 of 104 biopsies with “suspected myocarditis”
- COVID-19 may not be very “cardiotropic”

Shi S, Qin M, Shen B, Cai Y, Liu T, Yang F, Gong W, Liu X, Liang J, Zhao Q, Huang H, Yang B, Huang C. *Association of Cardiac Injury With Mortality in Hospitalized Patients With COVID-19 in Wuhan.* JAMA cardiology: China; 2020.

Escher F, Pietsch H, Aleshcheva G, Bock T, Baumeier C, Elsaesser A, Wenzel P, Hamm C, Westenfeld R, Schultheiss M, Gross U, Morawietz L, Schultheiss H-P. Detection of viral SARS-CoV-2 genomes and histopathological changes in endomyocardial biopsies. ESC Heart Failure. 2020;7:2440–2447.

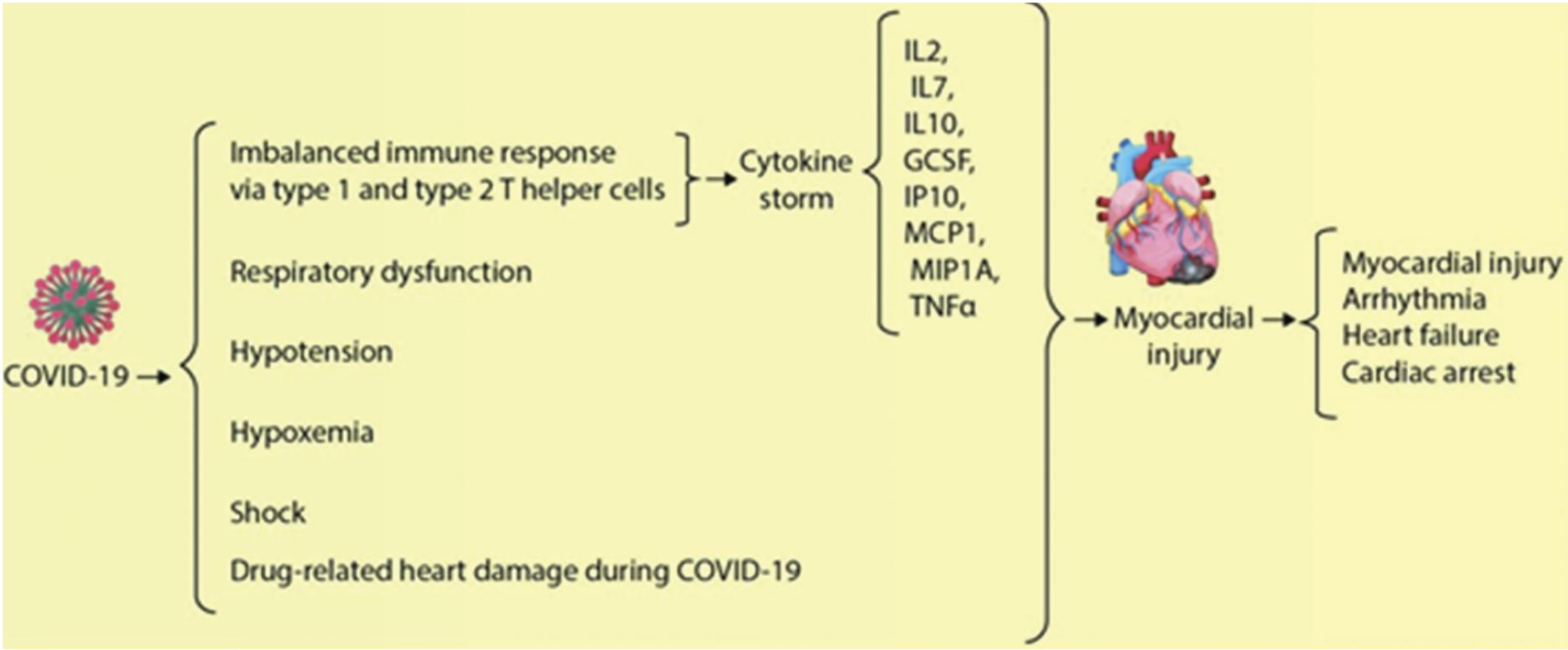
Pathophysiology

- First reported case of biopsy proven myocarditis had lymphocytic myocarditis (Dallas Criteria) but was virus negative
  - Suggests an immune mediated mechanism
  - Virus triggers cascade of hyper-inflammatory response
  - Role of “cytokine storm” in driving myocardial inflammation
- May explain rare cases of vaccine myocarditis
- Additional cases found to have small vessel “arterial obliteration” due to vasculitis and/or thrombosis leading to ischemic injury and inflammation



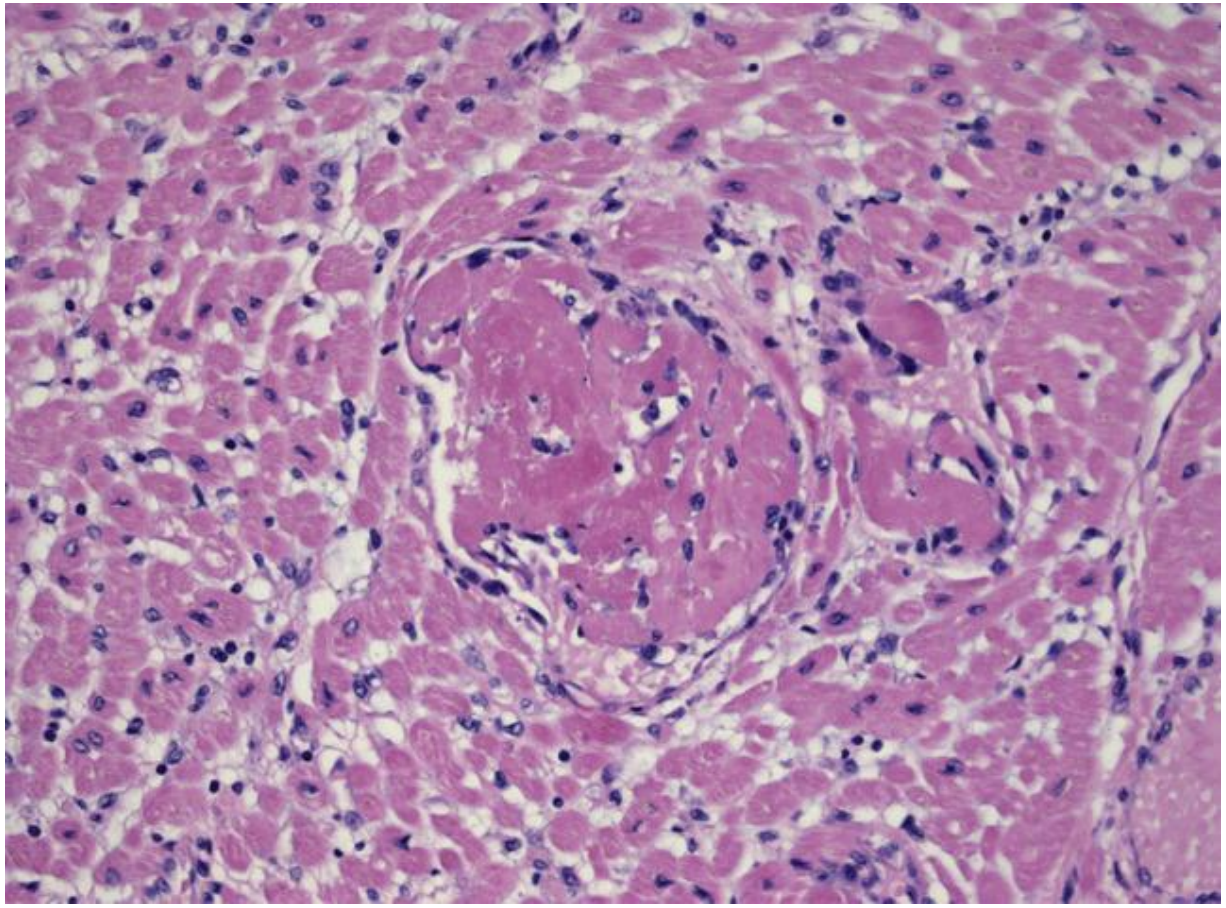
Am J Med Sci. 2021 Jan;361(1):14-22.

Cytokine Storm



EXPERT REVIEW OF ANTI-INFECTIVE THERAPY 2021, VOL. 19, NO. 3, 345–357

Ischemic Injury not Myocarditis



Numerous microthrombi of the left ventricle without evidence of an inflammatory infiltrate; the detection on tissue by molecular technique for SARS-CoV-2 was negative. Myocyte necrosis due to ischemia but not myocarditis

Heart Fail Rev. 2022 Jan;27(1):251-261

Prognosis in Myocarditis

- Elevated troponin levels are associated with worse outcome
- Despite this, in one review, 28 out of 38 cases were discharged from the hospital with recovered cardiac function
- Rarely, patients have gone on to require durable ventricular assist device or cardiac transplant
- Symptoms typically resolve in 3 months or less but some cases can last up to 12 months

Severity of COVID Does Not Predict Cardiac Involvement

- Myocarditis can be present even after resolution of the upper respiratory tract infection
- Occurrence of myocardial injury is **independent of pre-existing cardiovascular risks**

J Am Coll Cardiol 2022;79:1717–1756.

Treatment of Myocarditis

- Most treatment is supportive
  - Includes mechanical circulatory support – VAD or ECMO
  - Heart failure therapies – ACE/ARB/ARNI, beta blockers
- As there may be several pathophysiologic mechanisms several different treatments have been proposed
  - Inflammation – steroids, colchicine, toclizumab, anakinra, canakinumab
  - Thrombosis – anticoagulants, antiplatelet
  - Viral infection – antivirals – remdesivir

Pathway Recommendations

- For patients with suspected pericardial involvement, treatment with NSAIDs, colchicine, and/or prednisone is reasonable
- Intravenous corticosteroids may be considered in those with suspected or confirmed COVID-19 myocarditis with hemodynamic compromise or MIS-A
- Empiric use of corticosteroids may also be considered in those with biopsy evidence of severe myocardial infiltrates or fulminant myocarditis, balanced against infection risk

J Am Coll Cardiol 2022;79:1717–1756.

Pathway Recommendations

- As appropriate, guideline-directed medical therapy for heart failure should be initiated and continued after discharge.
- Myocarditis following COVID-19 mRNA vaccination is rare.
  - Highest observed rates have been in young male individuals (aged 12-17 years) after the second vaccine dose.
- COVID-19 vaccination is associated with a very favorable benefit-to risk ratio for all age and sex groups evaluated thus far
- In general, vaccine-associated myocarditis should be diagnosed, categorized, and treated in a manner analogous to myocarditis following SARS-CoV-2 infection.

J Am Coll Cardiol 2022;79:1717–1756.

Micro and Macro Vascular Occlusion

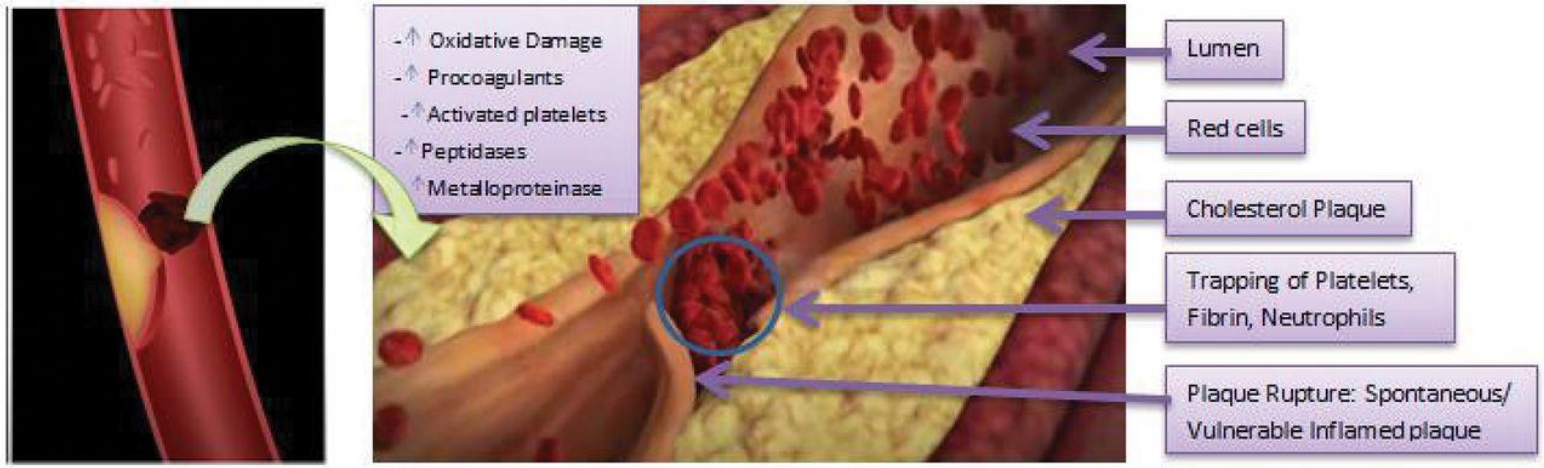
- COVID-19 predisposes to arterial and venous thrombosis that raises mortality and is attributed to the inflammatory state, endothelial dysfunction, platelet activation and blood stasis
- The most common pattern is pulmonary arterial thrombosis resulting in thrombotic occlusion of small- to mid-sized pulmonary arteries and subsequent infarction of lung parenchyma

Journal of Cardiovascular Pharmacology and Therapeutics 2021, Vol. 26(1) 12-24

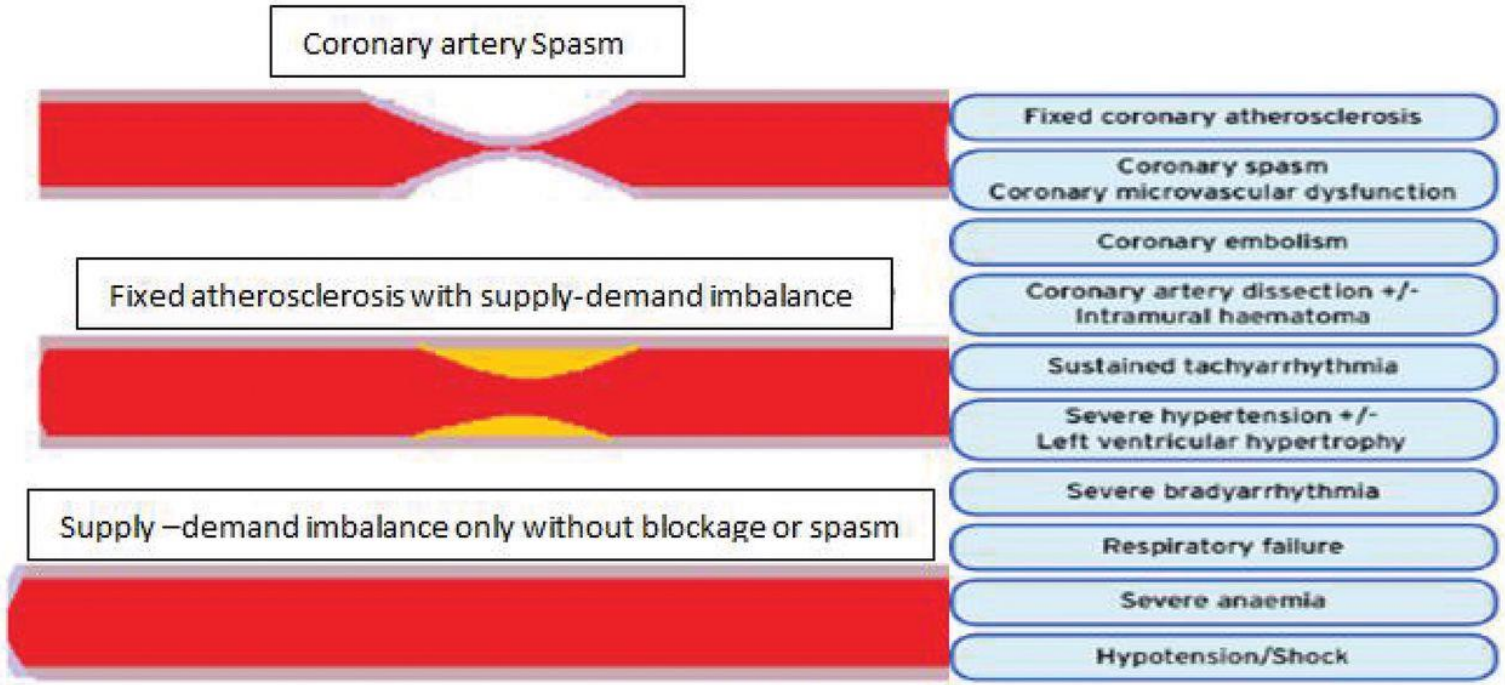
Micro and Macro Vascular Occlusion

- Biomarkers related to coagulation, platelet activation and inflammation have been suggested as useful diagnostic and prognostic tools for COVID-19-associated coagulopathy;
  - D-dimer remains a key biomarker employed in clinical practice
- Current guidelines or consensus statements can guide thromboprophylaxis and treatment of these thrombotic complications specifically adapted to COVID-19 patients

Journal of Cardiovascular Pharmacology and Therapeutics 2021, Vol. 26(1) 12-24



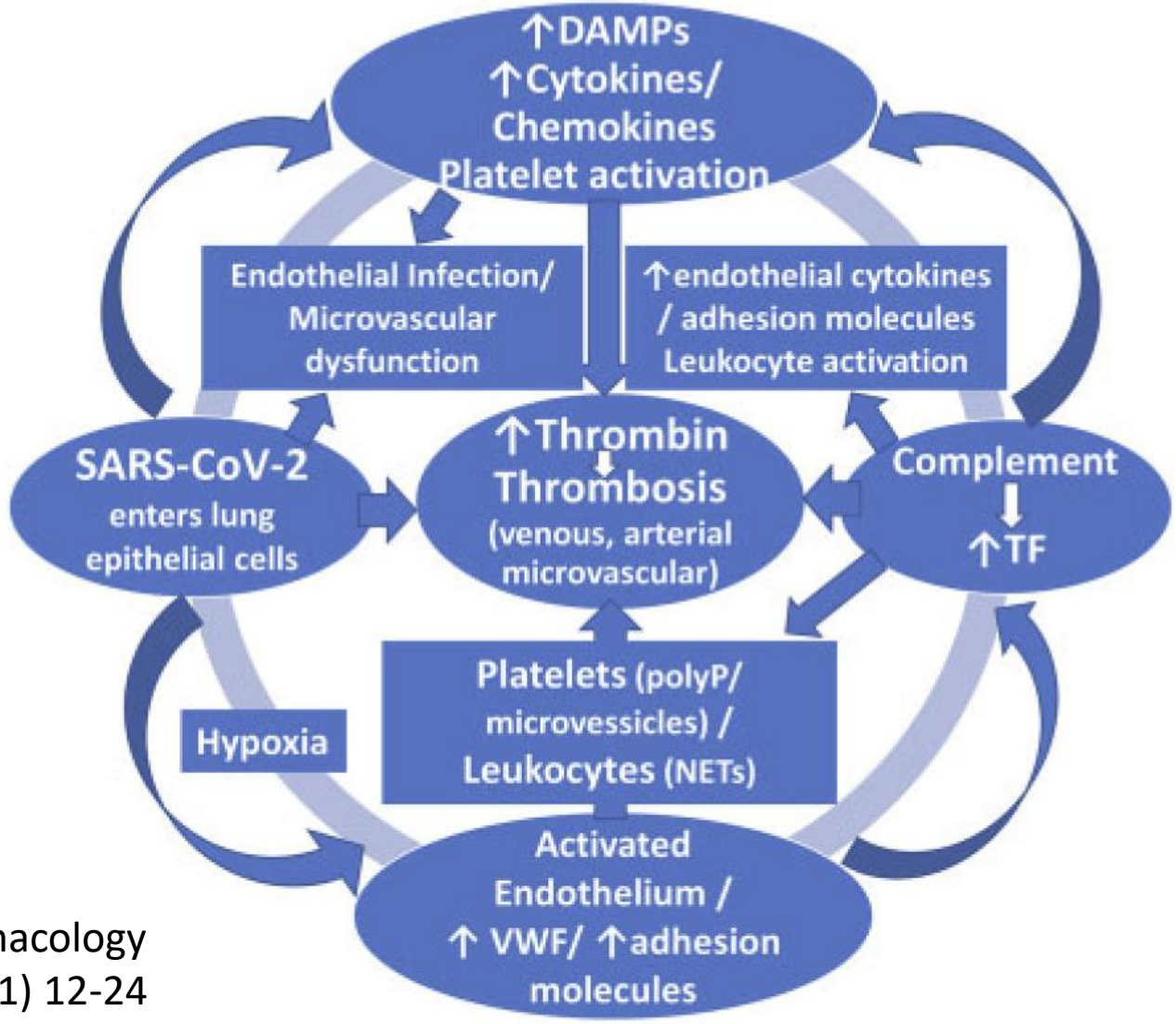
Type – 1 Myocardial Infarction



Type-2 Myocardial Infarction

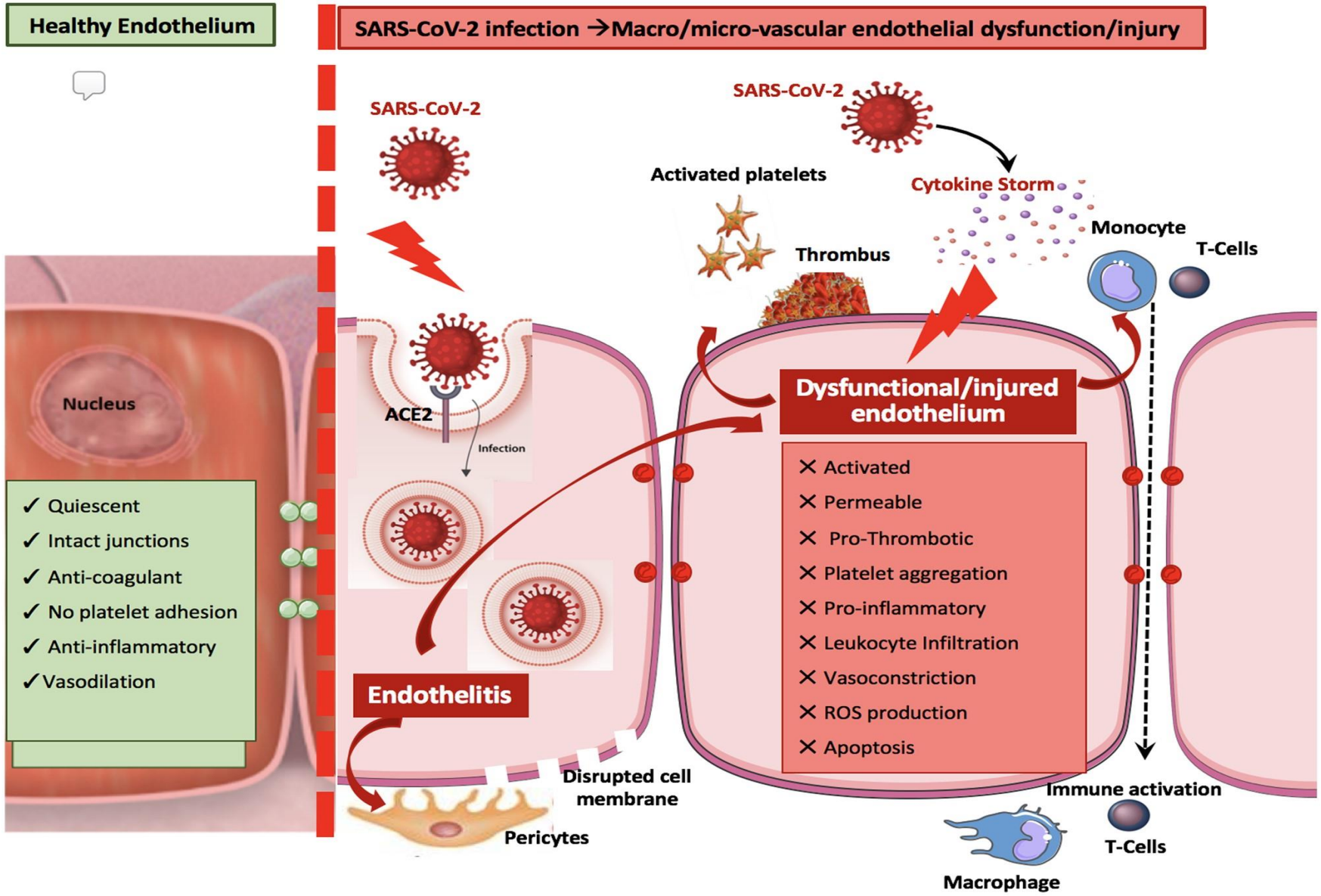
Postgrad Med J 2021;**97**:655–666

Proposed Mechanism COVID-19 Coagulopathy



Journal of Cardiovascular Pharmacology and Therapeutics 2021, Vol. 26(1) 12-24

Pathophysiology of Endothelial Dysfunction in COVID-19



Cardiovasc Res, Volume 116, Issue 14, 1 December 2020, Pages 2177–2184

Thrombotic Complications

- Deep vein thrombosis
- Pulmonary emboli
- Acute myocardial infarction
- Stroke
- Ischemic limbs

- Treatment – identify and treat the acute complication
  - Anticoagulation
  - Antiplatelet
  - Thrombolytic
  - Procedure – PCI, Intracerebral, etc.

Thromboprophylaxis

- Thromboprophylaxis in acutely or critically ill hospitalized patients with COVID-19 using LMWH or fondaparinux over UFH; or LMWH, fondaparinux or UFH over DOAC
- Recommending against use of antiplatelet agents (unless indicated)
- Recommending current standard dose anticoagulant thromboprophylaxis over intermediate (LMWH bid or increased weight-based dosing) or full treatment dosing
- Recommending inpatient thromboprophylaxis only over inpatient plus extended thromboprophylaxis after hospital discharge

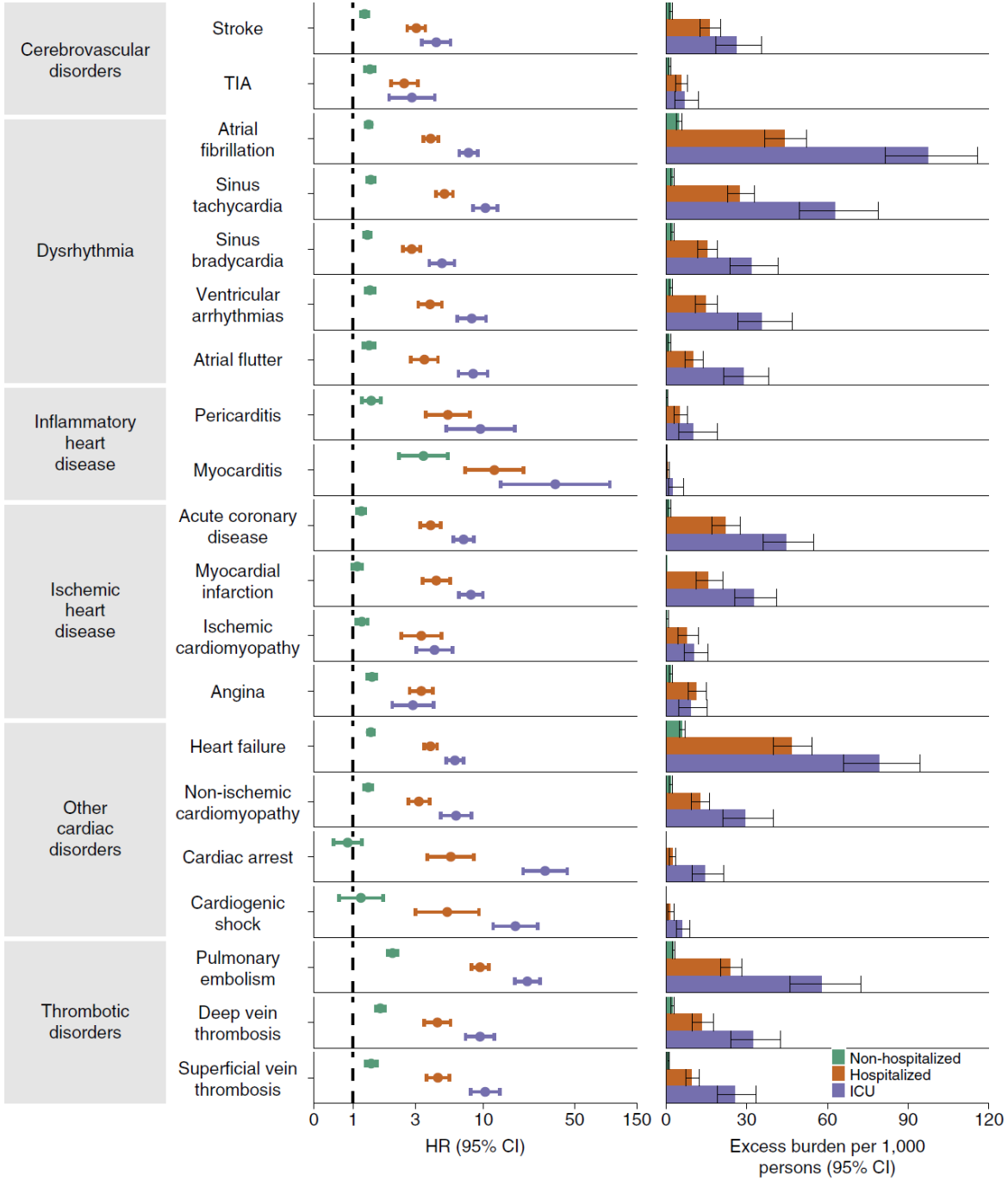
Journal of Cardiovascular Pharmacology and Therapeutics 2021, Vol. 26(1) 12-24

Long Term Cardiovascular Impacts

- Beyond 30 days after infection increased risk of incident cardiovascular disease including
  - Cerebrovascular disorders
  - Dysrhythmias
  - Ischemic and non-ischemic heart disease
  - Pericarditis
  - Myocarditis
  - Heart failure
  - Thromboembolic
- Risks evident even among individuals who were not hospitalized during the acute phase of the infection and increased in a graded fashion according to the care setting during the acute phase (non-hospitalized, hospitalized and admitted to intensive care).

Nature Medicine, VOL 28, March 2022, 583–590

Risks and 12-month burdens of incident post-acute COVID-19 composite cardiovascular outcomes compared with the contemporary control cohort by care setting of the acute infection.



Nature Medicine, VOL 28, March 2022, 583–590

COVID-19 and Heart Transplant

- Heart transplant patients potentially at higher risk of severe disease and mortality due to COVID-19 given complex comorbidities and concomitant immunosuppression therapy
- Early experience
  - Single center US - mortality rate of 25% among 28 heart transplant patients with COVID-19
  - Italy – 2 centers - 26 heart transplant patients with a 27% overall mortality
  - Those on corticosteroids seemed to do better

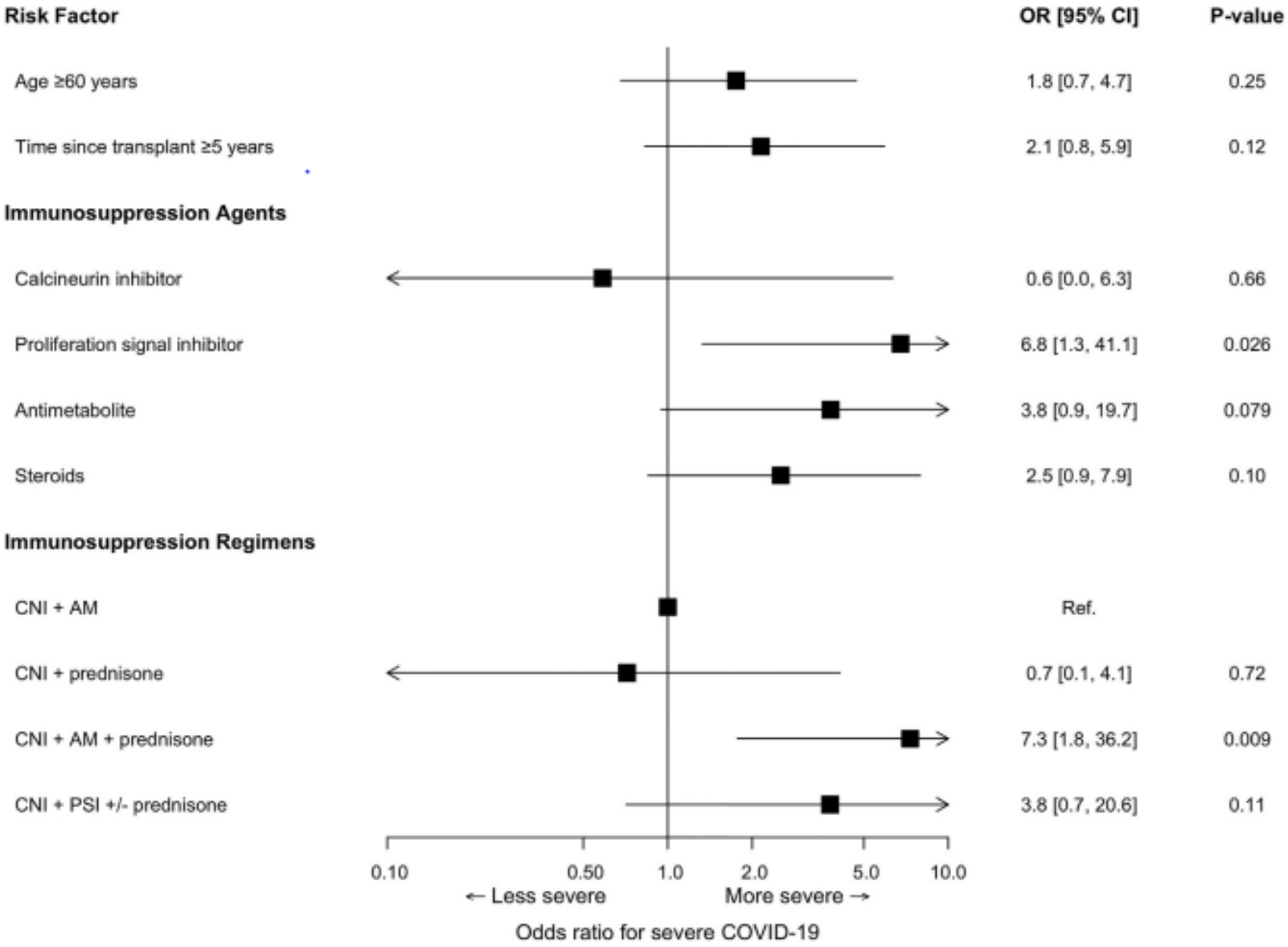
JAMA Cardiol 2020;5:1165.
J Heart Lung Transplant 2020;39:1081-8

Multi-center Trans-CoV-VAD registry

- March 2020 through October 2020 (Pre-Vaccination)
- 99 patients with heart transplant were diagnosed with COVID-19
- The median age was 60 years (IQR, 46-69), 25 (25%) were female and 44 (44%) were white.
- The median time post-transplant to infection was 5.6 (IQR, 2.0-13.7) years
- Mortality 15%

The Journal of Heart and Lung Transplantation, Vol 40, No 9, September 2021

Risk Factors in Heart Transplant for Severe Disease



The Journal of Heart and Lung Transplantation, Vol 40, No 9, September 2021

Vaccination and Heart Transplant

- 77 Post-transplant patients – 2 doses of mRNA vaccine
  - Low rate of adverse events
    - Mostly pain at injection site
    - After second dose – no clinal rejection
  - At a mean 21 days following thesecond dose, IgG anti-RBD antibodies were detectable in 14 (18%) HT recipients
  - Immune sera neutralized SARS-CoV-2 pseudo-virus in 8 (57%) of those with IgG anti-RBD antibodies
  - Mycophenolate mofetil and first year post-transplant – less response

J Heart Lung Transplant 2021;40:759–762

Post-transplant Strategy

- Vaccinate pre-transplant when possible – best strategy as post-transplant response rates are lower
- Post Transplant - Three doses in initial series plus 1 booster – increases response
- Tixagevimab and cilgavimab - both are monoclonal antibodies
  - Administered by two injections every six months
  - In addition to vaccination
- COVID illness
  - Monoclonal antibodies
  - Remdesivir
  - Dexamethasone

Conclusions

- COVID -19 is associated with a variety of cardiovascular complications
- The unifying mechanism appears to be inflammation that can persist for up to 12 months after infection
- Myocarditis can range from mild to fulminant but the vast majority fully recover
- Thrombotic complications can occur due to inflammation and endothelial dysfunction
- Inflammation and cardiovascular events can persist up to 12 months
- Heart Transplant patients are at high risk of COVID-19 morbidity and mortality