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Introduction

The first infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) was reported in December 2019. The ensuing and still ongoing pandemic continues to present significant public health challenges with important cardiovascular consequences. Despite the rapid development of effective vaccine programs, coronavirus disease (COVID-19) cases persist with newly evolving longer-term effects. Patients living with heart failure (HF) serve as a particularly vulnerable population wherein worse clinical outcomes ensue in the setting of acute COVID-19. Questions pertaining to mechanisms of disease activity, the unique vulnerability attributable to pre-existing cardiovascular disease, and the natural history of post-acute sequela are the subject of avid ongoing research. Changes in patterns of care for patients with chronic diseases have prompted dramatic shifts in care delivery, with increased reliance on remote monitoring systems and virtual visits. Heart failure care has been uniquely impacted in this regard.

The present document, compiled by a multidisciplinary group of investigators, serves to outline the natural history of COVID-19 and its effects on the heart, pertinent discoveries, implications for clinical care, and remaining gaps in knowledge at the nexus of HF and COVID-19 in adults. As an important disclaimer, new information on COVID-19 steadily emerges. The references and concepts in this paper reflect the state of knowledge at the time of review and writing but are subject to change, predicated on anticipated future discovery. This scientific statement is intended, therefore, to serve as a document whereby progress may be subsequently assessed.

Pathophysiology

Viral Infection and Cardiovascular Disease
Early during the pandemic, it became apparent that infection with SARS-CoV2 resulted in systemic manifestations beyond respiratory compromise, with significant yet heterogenous presentations observed involving the cardiovascular system.[1,2] These ranged from asymptomatic biomarker elevations to HF and cardiogenic shock requiring hemodynamic support.[3-6] Case reports of COVID-19 myocarditis garnered significant attention, yet confirmation of causation has proven elusive.

Myocardial injury and Myocarditis - Defining the Problem
Before delineating mechanisms by which viral infections may lead to cardiac pathologies, it is first critical to review commonly employed terms of myocardial injury or cardiac injury. Myocardial injury can be defined most universally by elevations in serum troponin concentrations,[7] but has also been reported in the context of findings on advanced imaging. Main findings include abnormalities on cardiac magnetic resonance imaging (cMR) in T1 and T2

mapping, and late gadolinium enhancement, among others.[8] The diagnosis of myocarditis, however, rests upon recognition of a clinical syndrome with abnormalities noted across multiple parameters.[9,10] Though pathological assessment of cardiac tissue by endomyocardial biopsy has been emphasized, the sensitivity of findings may vary. Further, it is increasingly recognized that cardiac injury from SARS-CoV-2 may not require myocyte death or an inflammatory cell infiltration.[11,12] Thus, the term myocarditis has been reported in many settings based on varying criteria, including elevation in troponin concentrations, clinical signs of congestion, decrements in ejection fraction, and/or abnormal cMR findings, amongst others, in the absence of other explanatory causes.

Viral Infection and Myocardial Injury

To elucidate the role of viral infection in causing myocardial injury and potentially myocarditis, proposed mechanisms range from direct cellular invasion to active induction of detrimental immune responses (inflammatory or autoimmune). Endemic viruses such as coxsackie A and B, echoviruses, parvovirus B19, and viruses from the Herpesviridae family (such as human herpesvirus 6 (HHV6), Epstein-Barr virus (EBV), and cytomegalovirus (CMV)) display primary cardiovascular tropism or lymphotropism and persistence in cardiac tissue, whereas human immunodeficiency virus (HIV), influenza A and B virus infections can also result in myocardial injury and myocarditis by enhanced immune system activation.[12–15] Epidemic H1N1 influenza strains such as the causative agent in the 1918 pandemic or the 2019 H1N1pdm09 virus have been correlated with myocarditis, with histological studies in the latter displaying degenerated myocytes, infiltration of lymphocytes, and interstitial edema, but less often viral infiltration in myocytes itself.[16] Seasonal coronaviruses have not previously been associated with cardiac abnormalities. In contrast, myocarditis and cardiomyopathy have now been reported with all three epidemic-prone beta-coronaviruses: Middle East Respiratory Syndrome (MERS) virus and Severe Acute Respiratory Syndrome associated coronaviruses (SARS-CoV and SARS-CoV-2).[17–20] Infiltration of macrophages has been reported,[21] but autopsy studies and some endomyocardial biopsy reports in cases of severe or fatal SARS-CoV-2 infections have not commonly demonstrated classic lymphocytic myocarditis based on Dallas or European Society of Cardiology (ESC) working group criteria.[9,10,22,23]

Compared to SARS-CoV, SARS-CoV-2 targets angiotensin-converting enzyme 2 (ACE-2) receptors with greater affinity and across a broader range of organ systems, allowing its spike protein to gain cell entry mediated by host serine proteases TMPRSS2, cathepsin B, and cathepsin L.[24–26] ACE-2 is expressed on a large variety of cardiac cells including cardiomyocytes, pericytes, fibroblasts, and endothelial cells, as well as infected leukocytes and macrophages discovered in the myocardium.[27] The latter suggests localization of virus to the heart at least during transient viremia.[28] The proposed mechanisms of cardiac injury in COVID-19 patients include direct infection with fusion of myocytes and apoptosis of cardiac and vascular endothelial cells, damage via pro-inflammatory dysregulated cytokine storm in response to the infection, and propensity towards the development of micro-embolic and thrombotic involvement in

vasculature.[12,20,29,30] Rare cases of acute myocardial infarction with high thrombus burden were reported in patients with COVID-19 and may have also contributed to ventricular dysfunction and, in some cases, cardiogenic shock.[31–33] Additionally, due to reports of SARS-CoV-2 preceding autoimmune and autoinflammatory conditions such as multisystem inflammatory syndrome in children (MIS-C) and adults (MIS-A), the role of infection leading to an immune response against self-epitopes has also been invoked.[34–37] Secondarily, respiratory dysfunction and hypoxemia, as well as dysregulation of the renin-angiotensin-aldosterone system (RAAS), likely also contribute to cardiac findings in patients with COVID-19.[12] Thromboembolic complications such as deep vein thrombosis and pulmonary emboli, in addition to rises in pulmonary pressures from COVID-19-induced parenchymal lung disease leading to right heart failure have also been described.[38,39]

While precise pathophysiologic pathways may be multifactorial and incompletely understood, myocardial injury is more commonly encountered amongst patients with pre-existing cardiovascular (CV) disease and is associated with worse clinical outcomes, including admission to the intensive care unit (ICU), ventricular dysfunction, arrhythmias, and death in patients with COVID-19. The degree of myocardial injury and myocardial stretch, as evidenced by cardiac troponin and natriuretic peptide elevations, have further shown to be strong predictors of adverse outcomes.[4,40–42]

COVID-19 in Patients with a History of HF

Early in the pandemic, advanced age and cardiometabolic comorbidities including diabetes, obesity, and hypertension were observed to be commonly associated with more severe forms of COVID-19.[43,44] Mechanistic understanding of SARS-CoV2 viral entry via the ACE-2 receptor led to concerns that patients with preexisting dysregulation of this neurohormonal axis, including patients with HF, may be particularly susceptible to severe COVID-19 and its related complications.[45–47] This concern for increased susceptibility was reinforced by historical presentations of cardiac findings in other viral respiratory infections, such as influenza. For example, in a retrospective analysis of over 8 million individuals with HF from the National Inpatient Sample, those diagnosed with influenza during hospitalization had higher rates of in-hospital mortality, acute respiratory failure, and acute renal failure even after propensity matching.[48] Together, these data identified patients with HF as possibly more vulnerable to serious adverse events associated with COVID-19.

The incremental risk of poor in-hospital outcomes in patients with COVID and HF history has been demonstrated in two large retrospective studies. One analysis of 6,439 patients admitted with COVID-19 across a large health system in New York City from February to June 2020 included 422 (6.6%) patients with HF. The study found that a history of HF was associated with prolonged length of stay, increased need for ICU level of care, and greater rates of mechanical

ventilation. Overall mortality among the cohort was 25.8%, though those with pre-existing HF had significantly higher mortality as compared to those without (40.0% vs. 24.9%; hazard ratio [HR] 1.88, 95% confidence interval [CI]:1.27 to 2.78).[49] Importantly, the effect of prior history of HF on worsening outcomes was observed across the spectrum of left ventricular ejection fraction and RAAS inhibitor use. Similar findings were reported using in a large, all-payer database inclusive of >1,000 health care entities and health systems which included 132,312 patients with HF hospitalized from April to June 2020.[50] Those with a history of HF and hospitalization with COVID-19 had significantly greater in-hospital resource utilization, including higher rates of ICU admission, mechanical ventilation and renal replacement therapy as compared to those hospitalized with COVID-19 without HF. Among patients hospitalized with COVID-19, 24.2% of those with a history of HF died compared to 14.2% without a history of HF. In addition to increased mortality, history of HF also predicted greater morbidity in those hospitalized with COVID-19, with 41.0% of survivors requiring post-acute care services as compared to 18.6% among those hospitalized with COVID-19 without a history of HF.[50] Overall, these data suggest that patients with a history of HF (regardless of ejection fraction) represent a vulnerable group with greater predilection for COVID-19-related morbidity and mortality (**Central Figure**).

Recognition of Acute Heart Failure in Patients with COVID-19

Challenges in recognition of HF may be encountered due to overlapping symptoms with respiratory compromise typically associated with COVID-19, including shortness of breath and pulmonary infiltrates on imaging. For example, both HF and pneumonia in the setting of COVID-19 can present with ground-glass opacities and thickened interlobular septae. Assessment of congestion, including signs and symptoms, as well as objective evidence either by elevated natriuretic peptides or pulmonary congestion on imaging, should occur routinely to help distinguish possible presenting features of HF; however natriuretic peptides may also be elevated in the setting of pulmonary embolism or acute respiratory distress syndrome.[51] In cases of suspected HF, pleural effusions, cardiomegaly, pulmonary vein enlargement maybe be more apparent and readily resolved with diuretic therapy.

Despite the aforementioned diagnostic limitations, assessment of congestion is relevant not only for those patients with a history of HF but also in identifying new or incident HF. The point prevalence of new HF diagnoses in the setting of COVID-19 has not been well reported; however, observational studies suggest SARS-CoV2-related incident HF is likely infrequent. In an adjunct study of the same 6439 patients hospitalized with COVID-19 in New York City, only 37 (0.6%) were discharged with a new diagnosis of HF.[49,52] Of these, 13 presented with shock (cardiogenic (n=4), septic (n=6), mixed (n=3)) and 5 patients presented with acute coronary syndrome. Notably, only eight patients had neither CV disease nor any CV risk factors, whereas

14 had a history of overt CV disease, and the other 15 had one or more risk factors that could have predisposed to the development of HF. The eight individuals with new HF in the absence of CV risk factors tended to be younger, with lower body mass indices and fewer comorbidities than other new HF diagnosis patients.

Evidence of Myocardial Injury in the Subacute Setting

Mechanisms of viral injury leading to myocardial edema or fibrosis have been described to explain the high rates of left ventricular diastolic and systolic dysfunction in patients without epicardial or microvascular occlusions.[53] In the subacute setting, cMR has revealed a high frequency of cardiac involvement in various forms, including changes in systolic function, raised myocardial native T1 representing potential capillary leak, fibrosis in addition to raised myocardial native T2 typically indicative of myocardial edema, myocardial late gadolinium enhancement indicating fibrosis, or pericardial enhancement.[19] For example, in a recent case series of 148 patients with positive troponin and severe COVID-19 in hospitals in London, 54% of hospitalized patients had MRI abnormalities at a mean of 68 days after discharge, with 32% inflammatory and 28% ischemic patterns.[8] A majority of patients (89%) had normal LV function (ejection fraction 67% +/- 11). The rate of cMR abnormalities in young, previously healthy athletes who survived COVID-19 infection appears much lower, between 0.6 and 3%.[54] Increased recognition of cardiac involvement as evidenced by advanced imaging techniques point to direct and indirect effects of SARS-CoV2 infection on the cardiovascular system that may reflect new HF or potential for the development of HF over time.[55]

Management of Heart Failure During the COVID-19 Pandemic

Medical Management

Despite aforementioned concerns regarding a potentially increased propensity for more severe disease by way of enhanced viral entry via upregulated ACE2 receptors in patients on RAAS pathway inhibitors,[47] accumulating retrospective and prospective data as well as a joint statement by the American College of Cardiology (ACC)/American Heart Association (AHA)/Heart Failure Society of America (HFSA) affirm that RAAS pathway inhibitors should generally not be discontinued in patients with HF who are at risk for or hospitalized with COVID-19.[56–59] In fact, discontinuation of these medications in patients not only with HF but also hypertension and coronary artery disease has not been shown to improve outcomes and likely deprives patients of evidence-based therapy.[57]

Statins have been studied as treatment in COVID-19. Multiple observational studies have shown improved outcomes among patients on chronic statin therapy who are hospitalized for COVID-19, potentially due to their pleiotropic and anti-inflammatory effects,[60–62] while randomized clinical trials are ongoing or will soon be reported. Patients with an alternative indication for statin therapy should remain on therapy, as there is no evidence that halting of statins is beneficial in patients with COVID-19. In light of the known pro-thrombotic state associated with COVID-19 infection, various anticoagulation strategies are under investigation. Although retrospective data suggested benefits for intermediate- or full-dose anticoagulation,[63] prospective studies have shown different findings based on disease severity.[64–66] At a minimum,

all hospitalized HF patients with COVID-19 infection should receive prophylactic doses of anticoagulation, and some may benefit from therapeutic anticoagulation.[67] Those with an alternative indication for therapeutic anticoagulation should continue this therapy provided there are no contraindications. Randomized control trial data have also informed the utility of corticosteroids in improving 28-day mortality amongst patients hospitalized with COVID-19.[68] In an open-label trial of dexamethasone (intravenous or oral), 28% of patients had some form of heart disease. Patients with HF should be offered steroids among those requiring oxygen or invasive mechanical ventilation. Similarly, antiviral agents, monoclonal antibodies, and/or other immunomodulating therapies (i.e., tocilizumab) should be offered to patients with HF in the appropriate clinical settings. Special attention may need to be paid to effective circulating volume in the setting of such therapies, particularly in patients with HF on chronic diuretic therapy.

Therapy	Key pharmacologic considerations among Patients with Heart Failure & COVID-19
RAAS inhibition (ACEi, ARB, ARNI)	*RAAS inhibition and guideline-directed medical therapy **should not** be disrupted in the acute setting of COVID-19 or thereafter*
Statin	*Currently, insufficient evidence to support routine statin use without other indications for statin therapy. However, patients on statin therapy should not have care disrupted*
Anticoagulation	*Evidence to guide recommendations as to optimal anticoagulation regimens for patients with HF has been recently completed with further data are forthcoming; recommendations may be different based on the severity of disease (moderate vs. critically ill) per ACTIV-4 findings*
Steroids & Immunomodulating therapies (Intravenous immunoglobulin) or monoclonal antibodies	*May require careful monitoring of volume status and additional decongestive therapy as indicated*
Antiviral agents	*No evidence to support differential approach to use among patients with HF*

Temporary Mechanical Circulatory Support

Data regarding the use of temporary MCS for patients with COVID-19 and cardiogenic shock are primarily limited to case reports and small case series.[69–71] Cardiogenic shock in patients with COVID-19 should thus be managed similarly to those without COVID-19, with appropriate pharmacological therapies selected based on clinical presentation. If MCS is indicated, veno-arterial extracorporeal membrane oxygenation (VA ECMO) is often preferred for hemodynamic support as well as oxygenation, as most patients have significant coexisting pneumonia. In

ARDS with profound hypoxemia, differential oxygenation gradients may exist between blood traveling through the native circulation (arising from cardiac ejection) and the ECMO pump. In such scenarios, conversion to veno-arterial-venous (VAV) ECMO cannulation strategy can be considered to deliver fully oxygenated blood through the pulmonary circulation while preventing compromise to cardiac recovery. Although data remains limited, the Extracorporeal Life Support Organization (ELSO) put forth specific guidelines regarding ECMO use in patients with COVID-19.[72] In one report of 22 patients with COVID-19 on ECMO, 21 patients had respiratory failure while 7 had cardiac failure requiring arterial support.[73] Ultimately, 12 patients (54.5%) survived hospitalization. ELSO suggests that pre-pandemic criteria for selection for ECMO candidates should be used; however, these may not be universally applicable if resources are constrained.[72]

Impact of Pandemic on Evaluation for Advanced Heart Failure Therapies

The pandemic has also impacted care for patients with HF without COVID-19 due to significant changes in healthcare delivery.[67] The early phases necessitated a reallocation of various hospital resources, increasing use of telemedicine, and placing limitations on elective procedures and testing. Thus, less urgent evaluations for left ventricular assist devices (LVAD) and heart transplantation (HT) faced significant delays.[74] For example, cardiopulmonary exercise testing was often deferred since this test is an aerosolizing procedure and therefore requires special precautions. Similarly, placement of implantable cardioverter-defibrillators (ICDs), stress testing, right heart catheterization, and other non-emergent diagnostic and therapeutic procedures were postponed early on and subsequently depending on COVID-19 case volume.[74] Care adaptations have since largely allowed for resumption of these services in many hospitals but still require negative pre-procedural COVID testing.

Left Ventricular Assist Devices

As the pandemic continues with varying densities of infection, decisions regarding new implantation of durable LVADs were and continue to be highly dependent on various factors, including local policies, rate of SARS-CoV-2 infection in the surrounding area, and the availability of relevant resources, including ICU capacity. In settings of high rates of SARS-CoV-2 infection placing strain on hospital resources, LVAD implantation should be limited to the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) status 1-3 patients in whom implantation has unequivocal benefit among appropriately selected patients.[75] Considerations should be given to the feasibility of outpatient LVAD follow-up care in the early post-operative period to minimize the risk of exposure to SARS-CoV-2. The social evaluation is particularly relevant and should include an assessment of home conditions that may place patients at increased risk for acquiring COVID-19 in the vulnerable post-operative phase.

Special considerations are required for patients on LVAD support who contract COVID-19.[76]This population is at risk for severe COVID-19 infection due to advanced age (in many circumstances), increased number of comorbid conditions, and potentially compromised

cellular immunity leading to a functionally immunosuppressed status.[77] Cases have been reported of COVID-19 complicated by cytokine release syndrome leading to ARDS and multiorgan failure.[78] Additionally, COVID-19 infection is associated with a pro-inflammatory and pro-thrombotic milieu which could pose additional problems in LVAD supported patients who are already at increased risk for stroke and thrombosis. In cases of COVID-19 pneumonia-associated RV dysfunction, adjustments may need to be made to LVAD speed considering inotropic support for the right ventricle. Prone positioning may present unique challenges in patients with LVADs due to fear of driveline displacement or worsening of right ventricular hemodynamics,[79] but is reported to have been conducted safely in highly monitored settings.[75]

Cardiac Transplantation

Heart transplant waitlist activity and volume were also impacted during the peak of the COVID-19 pandemic in the United States. Particularly during the early months, there was a significant increase in inactivated transplant candidates, with fewer new candidates added to the waitlist.[80] Donor recovery also decreased due to concerns regarding potential for COVID-19 positivity, initial lack of access to COVID-19 testing, and limitations in organ procurement organizations (OPO) operation in the setting of COVID-19 associated policies around limited hospital access and travel. The number of heart transplants performed concomitantly declined even in regions with a lower prevalence of COVID-19 due to the effects of organ sharing.[80] At many centers, only patients requiring hospital admission who qualified as UNOS tiers 1-3 remained active on the transplant list wherein the risk of mortality due to HF was deemed to outweigh the risk of COVID-19 exposure and need for resource conservation.[81]

The pandemic catalyzed many centers to switch to noninvasive surveillance strategies for ambulatory transplant recipients to detect rejection. Use of gene expression profiling and measurements of donor-derived cell-free DNA minimized exposure to healthcare personnel,[82,83] mainly as endomyocardial biopsies were performed more selectively. Downstream clinical implications of this modified workflow on rejection rates and graft function and associated survival outcomes in heart transplant recipients are of importance and undergoing further study.

The impact of COVID-19 infection among heart transplant recipients have been published in select reports. Amongst these, two New York Hospitals reported outcomes of 28 and 22 patients, respectively, and a group from Italy reported on 47 heart transplant recipients diagnosed with COVID-19. All three groups reported a case fatality of 25 to 30%, highlighting the need for extra caution as to the avoidance of exposure to COVID-19 in heart transplant recipients, as well as the need to triage to higher levels of care if COVID-19 is contracted for such immunocompromised patients.[84–86] A recent study of 99 patients with heart transplants and COVID-19 found a death rate of 15% and 64% required hospital admission[87]. Concerning immunosuppression, reducing the dosage of calcineurin inhibitors and reducing or temporarily discontinuing antimetabolites in the setting of COVID-19 infection may be considered on an individual basis. Yet, data as to optimal approaches are lacking.[88] Additionally, drug interactions with COVID-19 therapeutics should be reviewed. Current vaccines against SARS-CoV-2 appear less effective in immunosuppressed patients,[89,90] stressing the importance of continued

infection control measures for heart transplant recipients, especially as social measures imposed to combat SARS-CoV-2 transmissions are relaxed. It is incumbent upon transplant programs to disseminate this information to coordinators and patients, and efforts to ensure vaccination among transplant patients and those on the waitlist should be prioritized. Optimal vaccination strategies, including whether additional doses are required to confer immunity for solid organ transplant recipients have been subject of active investigation,[91–93] and the U.S. Food and Drug Administration (FDA) recently authorized additional vaccine doses for immunocompromised individuals, including those with solid organ transpant.[94]

COVID-19 Testing and Assessment Prior to Advanced Therapies Evaluation and Surgery
Before heart transplant surgery, donor and recipient testing for COVID-19 is routinely performed. According to a guidance document from the International Society for Heart and Lung Transplantation (ISHLT), donor testing should be performed within 72 hours of organ donation using polymerase chain reaction (PCR)-based testing by nasopharyngeal/oropharyngeal swab, sputum/tracheal aspiration, or bronchoalveolar lavage.[75] There have been reports of donor-to-recipient SARS-CoV-2 transmission during lung transplantation despite negative donor upper respiratory tract testing,[95] though it is unclear if this applies to other forms of organ donation (including heart transplant donation) or if lower respiratory tract testing (e.g., bronchoalveolar lavage) would be a more optimal testing strategy. Potential algorithmic considerations regarding candidate and donor testing are presented in **Figure 1**.[75]

Hospitalized patients actively listed for heart transplant should be cohorted in a COVID-19 free hospital location when possible. Ideally, nurses and additional staff caring for patients with COVID-19 should not be concomitantly assigned to patients awaiting transplant.[81] PCR-based testing for COVID-19 should generally be performed for asymptomatic candidates within 5 days of surgery if a surgical date is known or if any new symptoms or exposures develop.

Heart transplantation and non-urgent surgical, electrophysiology, and catheter procedures for HF should likely be deferred if a candidate tests positive by PCR.[75,96] Patients should only be reactivated or scheduled for procedures when clinical symptoms have resolved, >28 days have passed since the onset of symptoms, and/or 2 successive PCR-based tests at least 24-48 hours apart resulted negative. Additionally, patients should not have sustained COVID-19-related end-organ damage. Enhanced imaging with high-resolution chest computed tomography may provide incremental risk assessment in select asymptomatic cases wherein COVID-19 PCR is positive. For asymptomatic patients, 14 days after diagnosis and 2 successive negative tests may serve as reasonable criteria for reactivation. For candidates at high risk for HF-related mortality without HT, decisions need to be individualized, and such timelines need to be considered in the clinical context of risk/benefit assessment.[75] There is limited evidence to guide similar recommendations for LVAD surgery; however, similar approaches could be considered. Of note, life-saving surgery (i.e., pump thrombosis requiring exchange) should not be denied based on a positive PCR test alone – such patients should be offered surgery if clinically indicated, provided they do not have contraindications, with appropriate precautions in place.

Challenges and Innovations in HF Care Delivery During the Pandemic

Emergency department visits and hospitalizations for non-COVID-19 life-threatening diagnoses significantly declined in the first half of 2020 compared to historical norms,[97,98] including reduced admissions for acute coronary syndrome and HF.[99,100] An excess in cardiac arrest and sudden death in the community during the peak of the pandemic was attributed to avoidance and fear of undue exposure.[101,102] These realized secondary effects of the pandemic necessitated expeditious innovations in care delivery platforms specific to patients with HF.[74]

Technology was leveraged to facilitate virtual clinical assessments and data collection **(Figure 2)**.[103] Regulatory reform by Centers for Medicare and Medicaid with expanded reimbursement of telemedicine encounters may have aided greater adoption of these modalities. All aspects of care, including care for patients with LVAD or transplant, were transformed to limit patient contact. As mentioned, gene expression profile and cell-free DNA testing partially substituted endomyocardial biopsies, particularly among centers that had not readily adopted noninvasive surveillance testing for transplant patients. Home anticoagulation monitoring and blood draws minimized in-person visits.[104] Though virtual visits have been associated with better adherence to clinic follow-up (likely related to the relative ease of access and reduced burden of transportation),[105] video examination alone (without supplemental remote monitoring and laboratory data) may be particularly challenging in the evaluation of high-risk patients who need careful and safe adjustment of guideline-directed medical therapies.[106,107] Although assessing jugular venous distension and lower extremity edema by video examination is possible, supplemental data to inform intravascular volume status are frequently necessary for optimal decision-making.[67,108] The impact of televisits in place of in-person visits on outcomes is unknown and requires investigation.

The global pandemic has accelerated remote monitoring technology innovation.[109] Despite equivocal results of previous efforts,[110] more recently, implantable remote pulmonary artery (PA) pressure monitoring in patients with HF and moderate symptoms has been shown to reduce HF-related hospitalizations,[111] 30-day readmissions,[112] and maintain euvolemia during guideline-directed medical therapy optimization,[113] including patients with preserved ejection fraction.[114] Enhanced use of implantable hemodynamic monitoring during the pandemic to provide intravascular volume data and better guide HF treatment decisions has been reported.[115,116] Certain implantable cardiac defibrillator systems include diagnostic and monitoring solutions to predict HF events.[117] Particular algorithms can, for example, integrate a multivariate index of heart sounds, respiration rate, thoracic impedance, and physical activity to attempt to predict the degree of congestion, with early evidence of association with fewer HF hospitalizations.[118] However, the utility of this technology in differentiating HF from COVID-19-related lung injury yielded mixed results.[119,120]

The post-pandemic world of remote monitoring and telemedicine for patients with HF is likely to include all forms of care including virtual, in-person, and remote assessments. Wearables will may see accelerated adoption,[121] as smartwatch heart rate and rhythm monitoring may

effectively trigger the need to seek medical attention.[122] Single-lead ECG and multivariate monitoring have also been employed with promising results, leveraging machine learning algorithms to detect subclinical myocardial dysfunction.[123] Economic support for the integration of such innovative platforms, along with appropriately designed workflows and processes to promote patient-activated therapy[124] are required to advance telemedicine beyond the pandemic.

Racial, Ethnic, and Socioeconomic Disparities

The COVID pandemic has illuminated the impact of the vast inequities within the health system in the United States. Those with less access to health care are more likely to get COVID, have greater morbidity and mortality from COVID, and are least likely to get vaccinated.[125,126,127] In a nearly 8000 patient analysis of the retrospective observational COVID-19 registry organized through the AHA, Black (26%) and Hispanic (33%) patients together comprised over half of hospitalized patients and were noted to be younger and more likely to be uninsured.[128] Despite being younger, Black patients had a higher prevalence of preexisting conditions such as diabetes, hypertension, obesity. Also, they were at increased risk of adverse outcomes such as mechanical ventilation and renal replacement therapy. Though there was no difference in major adverse cardiac events including death across race and ethnicity, 53% of all death was observed in Black and Hispanic patients representing a greater burden of morbidity and mortality in these otherwise underrepresented minority groups. These observations are unfortunately rooted in a long-standing history of health care disparities wherein lack of access to healthy food, low healthcare literacy, and inability to practice social distancing due to housing density, among other factors, are disproportionately encountered amongst Black and Hispanic patients.[129] Further compounding egregious observations of poor outcomes amongst these groups in the acute setting of COVID-19 is a greater hesitancy amongst these same populations to undergo vaccination due to fear and mistrust of healthcare systems at large.[126] Efforts to mitigate risk and improve rates of vaccination among underrepresented populations require special attention.

The Post-Acute Sequelae of COVID-19 Syndrome and Heart Failure

Persistent Symptoms & Evidence of Cardiac Injury
While acute cases continue to arise in many countries around the globe, post-acute infection symptoms indicative of non-linear recovery have been reported. After hospital discharge, patients (including those with no prior history of HF) may experience prevalent fatigue, muscle weakness, mild cognitive dysfunction (e.g., fogginess), and sleep difficulties for up to 6 months.[130] In fact, early studies have outlined not only the persistence of symptoms but also the appearance of new symptoms, as well as detection of clinical signs suggesting that patients across the entire spectrum of acute infection can continue on to have post-acute sequelae of SARS-CoV-2 infection (PASC), also referred to as "long COVID." Regardless of hospitalization, impaired physical functioning and reduced exercise capacity can persist for weeks to months afterward and can negatively impact psychological well-being.[131] Though there are no reports

to date to suggest a predisposition for PASC among patients with HF, understanding its underlying pathophysiology has implications for individual recovery, health systems preparedness, and identification of tailored therapeutic interventions. Cardiac rehabilitation programs may be of particular benefit,[132] tailored not only to patients with a history of HF but also to younger patients with *de novo* cardiac sequelae. A recent study of confirmed COVID-19 patients who had no cardiac complaints two weeks after diagnosis showed that recovered patients were more likely than healthy or risk-matched controls to have elevated cardiac injury biomarkers and abnormalities on cardiac magnetic resonance imaging.[19] Post-COVID myopericarditis has also been reported 6 to 8 weeks after diagnosis; currently limited to rare cases, myocarditis and pericarditis have also been reported after vaccination, particularly in younger adults.[133–135] Despite worrisome early cohort studies with wide-ranging patient-reported symptoms and anecdotal clinical practitioner experience with COVID-19 survivors, PASC as a syndrome remains ill-defined.[136] Better understanding of pathobiological underpinnings of prolonged symptoms and associated ramifications are the subject of avid investigation, and longitudinal studies are needed with appropriate controls to help identify virus-specific versus critical illness-related cardiopulmonary limitations noted among patients with persistent symptoms.

Vaccination Against COVID-19

Within the first few months of the COVID-19 pandemic and publication of the genetic sequence of SARS-CoV-2, an effort of unprecedented speed commenced to develop and test vaccine candidates. Vaccine manufacturers engineered strategies to introduce viral antigens or gene sequences to elicit immune responses to the virus spike protein, leading to reduced viral entry into host cells and thereby attenuated infection.[137] The first SARS-CoV-2 vaccines to receive Emergency Use Authorization (EUA) by the Food and Drug Administration in the United States were messenger ribonucleic acid (mRNA) and viral vector vaccines, and both were shown to significantly reduce symptomatic COVID-19. The viral vector platform involves replication of deficient adenovirus that is engineered to deliver the SARS-CoV-2 genetic material to immune cells in order to express and present antigenic proteins to lymphocytes. Both vaccines rely on the production of antibodies to confer protection. Though studies in solid organ transplant recipients have found that most participants did not mount a significant antibody response following an initial vaccine dose and variable responses after second dose,[89,138–140] vaccination remains safe[90] and is strongly encouraged by multiple transplant societies.[141–143] As mentioned previously, booster doses are now recommended for solid organ recipients.

Geographic variability in the infrastructure required to vaccinate as many individuals as possible within a short time frame and vaccine hesitancy have affected overall vaccine uptake around the globe. Patients with pre-existing cardiovascular disease, including HF, often were prioritized in earlier vaccination waves given the well-defined link between preexisting cardiovascular disease and more severe COVID-19 related adverse outcomes.[144] Experience with influenza vaccine has demonstrated that despite strong support from professional cardiology organizations and the Center for Disease Control and Prevention for annual vaccination, vaccine

uptake in patients with HF is disappointingly low, coupled with consistent rates of vaccine

Strategies shown to combat vaccine hesitancy and expand implementation

- Clinician to patient education
- Clinician audit and feedback
- Patient outreach
- Messaging that "a vaccine is reserved for you."
- Point-of-care reminders
- Active-choice and intention prompts

refusal.[145,146] Factors associated with COVID-19 vaccine hesitancy mirror what has been previously shown with other vaccines, including uncertainty about vaccine efficacy, underappreciation of the necessity of vaccination, and general mistrust of vaccines. Given the poor outcomes demonstrated in observational studies among patients with HF who acquire COVID-19, educational and community efforts are needed to increase vaccination rates in this particularly vulnerable population.

Implementation trials in adjacent vaccination domains have indicated that behavioral economic principles, including intention prompts and active-choice interventions, increased flu vaccination uptake across large populations.[147,148] Similar trials of COVID-19 vaccination-related messaging
are underway (NCT 04660703).

Impact of the pandemic on ongoing clinical research

The conduct and interpretation of cardiovascular clinical trials have been severely affected by the COVID-19 pandemic.[149] Recruitment in trials has been challenging as many recruiting sites were either completely prohibited from recruiting new patients or these activities had been severely curtailed.[150,151] Ongoing trials have had challenges with study assessments and ascertainment of endpoints. While many trials have successfully converted some in-person visits to virtual visits, this approach has not been practical when face-to-face procedures were required, such as for a 6-minute walk test, echocardiogram, or venipuncture for blood specimens. Outcomes trials have similarly been affected due to increasing difficulty in ascertaining outcomes and have been impacted by the decline in event rates for hospitalizations and urgent outpatient visits for cardiovascular events seen during the pandemic.[99] These factors influence trials regardless of whether individual patients contract COVID-19.

In clinical trials, several analytic approaches (as sensitivity analyses) have been proposed to address some of the issues related to the pandemic, ranging from censoring at the start of the pandemic to excluding events thought to be COVID-19 related.[152] For example, in the study of intravenous ferric carboxymaltose in HF patients with iron deficiency, the investigators performed a prespecified pre-COVID-19 sensitivity analysis, censoring patients in each country at the date when its first COVID-19 patient was reported.[153] Additionally, the broad-ranging impact of the pandemic and associated financial challenges led to premature termination of some HF trials, including the Effect of Sotagliflozin on Cardiovascular Events in Patients With Type 2 Diabetes Post Worsening Heart Failure (SOLOIST-WHF) trial.[154] Because of the influence of the pandemic on patients' quality of life, interpretation of patient-related outcomes will prove especially challenging. Academic groups, industry, and regulatory authorities have issued several recommendations to address issues related to the conduct and interpretation of clinical trials during the pandemic.[155–157] Overall, the challenges faced during the conduct and operation of these trials during the pandemic may inform alternative strategies for patient consent, participation, and engagement which may ultimately make trial design more resilient.

The Clinician Voice

The pandemic has resulted in significant emotional and psychological tolls for clinicians at all levels of training. Studies have shown higher rates of depression, anxiety, and insomnia among physicians during the pandemic.[158,159] Sources of stress include limited access to personal protective equipment, concerns about personal safety and that of loved ones related to COVID-19 exposure, and financial challenges associated with hiring freezes.[160] Due to variable in-person closures of schools and daycare programs, clinicians have been challenged to find alternate sources of childcare. Social distancing has compounded these stresses, leading to isolation. Moving forward, it is imperative for organizations and institutions to provide adequate support systems for access to mental health, emergency childcare, and mentorship. During peak infection rates, trainees may have been particularly affected, given their responding clinician role in academic medical centers. In addition, deferral of HF-specific testing, including cardiopulmonary testing, right heart catheterizations, and endomyocardial biopsies,[67,161] may have led to decreased procedural exposure and training in competencies. Heart failure trainees may have been particularly impacted by reduced HF admissions and restrictions placed on donor procurement and operating room personnel. Nursing programs were temporarily suspended (as students were unable to maintain adequate clinical practice hours), extending time needed for licensure and certification. The practical realities and constraints of educating during the pandemic have led to the rise of innovative educational strategies and virtual platforms for education and data gathering from diverse knowledge dissemination platforms.[162,163]

The Patient Voice

From a patient perspective, the journey through COVID-19 is frequently paved with uncertainty and anxiety compounded by a barrage of information appearing almost daily across national and international media and news platforms. Marked heterogeneity in disease presentation

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and course, variability in response to hospital-initiated therapies, and inability to predict and assure full recovery, even with mild disease, all contribute to stress when suspecting or receiving a COVID-19 diagnosis.

In patients with pre-existing HF, symptoms of acute HF decompensation and pulmonary manifestations of COVID may overlap, or mild chronic HF may become unstable. Additional challenges are imposed by potential medication changes, altered fluid balance, and other potential hazards, for example, deconditioning. For patients with mild HF who are recuperating from COVID-19 at home, understanding the cause of new or worsening cardiac-related symptoms, particularly chest pain or palpitations, can be stressful. Although chest pain is a relatively common symptom of COVID-19 and is frequently non-specific, it could also represent a more serious cardiovascular event, including myocarditis, coronary ischemia, or pulmonary embolism. Patients need to be empowered to seek care if chest pain is persistent, recurrent, occurs with exertion, or is associated with other known markers of COVID-19 instability.[131,164]

During the peaks of the pandemic, family/caregiver/supporter presence was minimized, requiring novel adaptations in care (**Table 1**). Early engagement with Palliative Care and Supportive Cardiology services has been shown to provide essential care in many disease contexts but may provide particular benefit in COVID-19. Engaging in early goals of care conversations, particularly given the challenges in in-person communication and uncertainty surrounding illness trajectory is essential. Other limitations imposed during hospitalization, including restriction of patients' mobilization outside of their room and bundling of care to purposely limit the number of personnel interactions, affect patients' mental and emotional health. Quarantining and social distancing forced hospital personnel to develop new ways of communicating and supporting patients from afar that may have advantages even post COVID-19.[165,166] Healthcare systems should consider the need for psychological and occupational health support for patients, particularly those with protracted illness courses.[167]

Knowledge Gaps and Future Directions

Tremendous progress in the battle against COVID-19 has been made in a short period, including the rapid development, validation, and distribution of vaccines. Nonetheless, several critical knowledge gaps and challenges remain[168] (**Figure 3**). Further investments are needed to establish a deeper understanding of the short-and long-term sequela of COVID-19 infection and the pandemic in general across all stakeholders.

Pathophysiology

Firstly, important questions remain regarding the pathobiology of disease, principally regarding the effects of COVID on the heart. Though it is evident that patients with cardiovascular disease and HF in particular are at greater risk for more significant morbidity and mortality due to COVID, it is uncertain why. Additional questions remain, especially regarding the degree and nature of myocardial injury, including COVID myocarditis. As with other causes of viral myocarditis, it is uncertain whether direct myocardial injury occurs from viral infection or whether cardiovascular sequelae are secondary to an unchecked immune response. In vitro and

in vivo model systems have been developed to help elucidate mechanisms of COVID myocarditis; ideally, this ongoing work will have implications beyond COVID-19.

Treatment of COVID-19

One of the most pressing concerns remains the lack of therapeutics to effectively and reliably treat COVID-19. Though several therapies are available, they are only variably effective, particularly for severe infections. Results of ongoing studies will determine the efficacy of both novel and existing therapeutic agents. Of particular interest to the cardiovascular community is the effectiveness of specific anticoagulants in the prevention and treatment of COVID-19 associated thromboembolic complications. Whether or not tailored approaches are needed for patients with HF, left ventricular assist devices, or transplantation remains to be understood. Notably, healthcare system investment in mitigating disparities of contraction and outcomes with COVID-19 among Black and Hispanic communities should be a public health priority.

Vaccination

Specific questions persist regarding patients with advanced HF and, in particular, those who have undergone cardiac transplantation. Despite initial optimism, it appears solid organ transplant patients have worse outcomes with COVID-19 than expected. Recent data also suggests these patients have a lower response to immunization. If this is the case, it is clear that mitigation strategies need to be developed, and the U.S. FDA now recommends booster shots for immunocompromised patients, including those with solid organ transplantation. Whether immunosuppression should be altered for these patients at the time of vaccine administration is uncertain. Furthermore, the timing and frequency of booster vaccination for non-transplanted HF patients remain unclear. Isolated cases of myocarditis and HF have been reported in the setting of vaccination.[169,170] Understanding underlying mechanisms, as well as patients more vulnerable to such reactions, will be of importance.

Post-Acute Covid Sequalae (PASC) Syndrome

One of the most vexing challenges posed by COVID-19 revolves around the various PASC syndromes associated with previous infection. These syndromes are increasingly recognized as a significant cause of morbidity among COVID survivors and present with a myriad of symptoms, including a high prevalence of dysautonomia. Further study is required to elucidate the mechanisms of disease and accordingly develop effective therapeutic strategies. In particular, evidence of cardiac injury may predispose to the development of HF over time. How these patients should be followed longitudinally remains to be defined.

Impact of Remote Monitoring and Telemedicine on Outcomes

The COVID pandemic will have a lasting impact, leading to fundamental changes in care delivery for patients living with HF. Structural changes were rapidly applied to allow telemedicine and remote monitoring accompanied by technological advances to support these changes. The impact of these on quality and outcomes remains uncertain, but data continue to accrue.

Psychosocial Impacts of the Pandemic

The COVID-19 pandemic may also result in a lasting psychological impact on recovered patients, families, and clinicians. In addition to longer-term physical sequela of COVID-19 infection, patients with protracted illness courses may experience significant debility and post-traumatic stress disorder (PTSD) after recovery. [171] Optimal methods for screening for mental health conditions including anxiety, depression, and PTSD amongst survivors and their families remain an important area of further study. Finally, the pandemic placed monumental burdens on the healthcare workforce, leading to reports of clinician burnout which may persist even after the pandemic abates.[172,173] Identifying novel strategies to screen for and mitigate mental health disturbances among healthcare professionals remain critical.

Priorities for Future Research at the Intersection of COVID-19 and HF

- Pathobiological understanding of mechanisms of cardiac injury
- Optimal anticoagulation strategies in patients with HF and severe COVID-19
- Vaccine response & durable immunity in patients with advanced HF and cardiac transplantation
- Large, registry-based data capture to understand incidence, clinical features, and sequela of PASC among patients with HF
- Innovative implementation approaches to promote current and ongoing vaccination efforts, and HF medication optimization
- Effective data capture on long-term effects of COVID-19 on patients with HF
- Care interventions focused on mental, emotional, and spiritual health of patients, families, and clinicians afflicted by the COVID-19 pandemic

Conclusions

The present scientific statement summarizes clinical and research discovery at the nexus of HF and COVID-19 to date at the time of review and writing. Patients with HF are uniquely susceptible to adverse outcomes in the setting of COVID-19 infection, highlighting the importance of vaccination in this population. Incident HF is rare in the setting of acute COVID-19, while sustained markers of myocardial injury in the post-acute setting lend questions as to whether HF may be a future consequence. Early phases of the pandemic prompted substantial shifts in care delivery, resulting in enhanced use of noninvasive and remote monitoring technologies and increases in telemedicine. Yet, the impact of these shifts will require exploration. Pathophysiologic underpinnings of COVID-19-related myocardial injury and post-acute sequelae are the focus of ongoing investigation. Concepts presented herein are subject to change as new information and discovery emerge pertaining to COVID-19 and the umbrella of heart failure populations, including MCS and heart transplantation.

Figure Legends:

Figure 1: Algorithmic considerations for heart transplant candidate and donor SARS-CoV 2 Testing

Figure 2: Virtual care adaptations during the COVID-19 pandemic

Figure 3: Knowledge and gaps and areas of ongoing study

Central Figure: The Nexus of Heart Failure and COVID-19

Table 1. Solutions that Support Families/Caregivers and Supporters from Afar When Hospitalization Quarantining Rules are in Place

Communication Methodology	Support benefits:
Web-based video-enabled teleconferencing with camera (i.e., smartphone apps such as FaceTime, Zoom, Skype)	Families/Caregivers/Supporters and Patients ● May enhance psychosocial and psychological well-being ● Ability to visualize each other may reduce anxiety and stress ● Allows for confirmation that patients' conditions match communication received from clinical personnel
	Families/Caregivers/Supporters and Hospital Professionals ● Enhanced level of psychosocial support to meet patient needs ● Can use for shared-decision making or family conferences & discussions that require consensus or consent for clinical trials ● Can be used to prepare families for next steps: improving health (discharge readiness) or deteriorating health (physical environment changes; surgery; palliative care). ● Decreases misinformation and unreliable data being shared ● May reinforce verbal communication and create normalization of current patient status
Voice-only teleconferencing	This format may be perceived as lower-quality communication that can affect communication satisfaction between parties and overall distress related to visitation restrictions Families/Caregivers/Supporters and Hospital Professionals ● May enhance access to healthcare professionals, especially if inquiring about remaining informed of the plan of care or current patients' condition
Personal signs, photos, quotes, etc. taped to hospital room doors or walls	Patients and Hospital Professionals ● Reminds patients that there is a purpose to the work they are living through during hospitalization – a life after discharge ● Allows clinicians to "do something" to support families and patients in a personal way ● Provides clinicians with a view of patients as people with lives outside of the hospital environment ● May decrease psychological burden of healthcare professionals who are struggling with difficult emotions and regret
Short (<2 minutes) taped recordings	Families/Caregivers/Supporters and Patients ● Reminder that families, although not present, are thinking of the patient – can be replayed as often as desired to decrease stress and promote joy.

Early engagement with hospital-based support services	• Early engagement of palliative care services to support patients and facilitate communication. • Early discussion with patients and families on engagement of chaplain or spiritual services.

Figure 1:

Figure 2:

Figure 3:

GAPS in KNOWLEDGE & AREAS FOR RESEARCH AT THE NEXUS of COVID-19 & HEART FAILURE

Post Acute Covid Sequelae
- Heart Failure as a manifestation
- Mechanisms
- Frequency

Telemedicine & Remote Monitoring
- Outcomes
- Equity & Access

Optimal Treatment
- Anticoagulation strategies
- Immunosuppression in OHT

Pathophysiology
- Mechanisms of myocardial injury
- Myocarditis

Clinical Trials
- Decentralized trials
- Remote content
- Data censoring
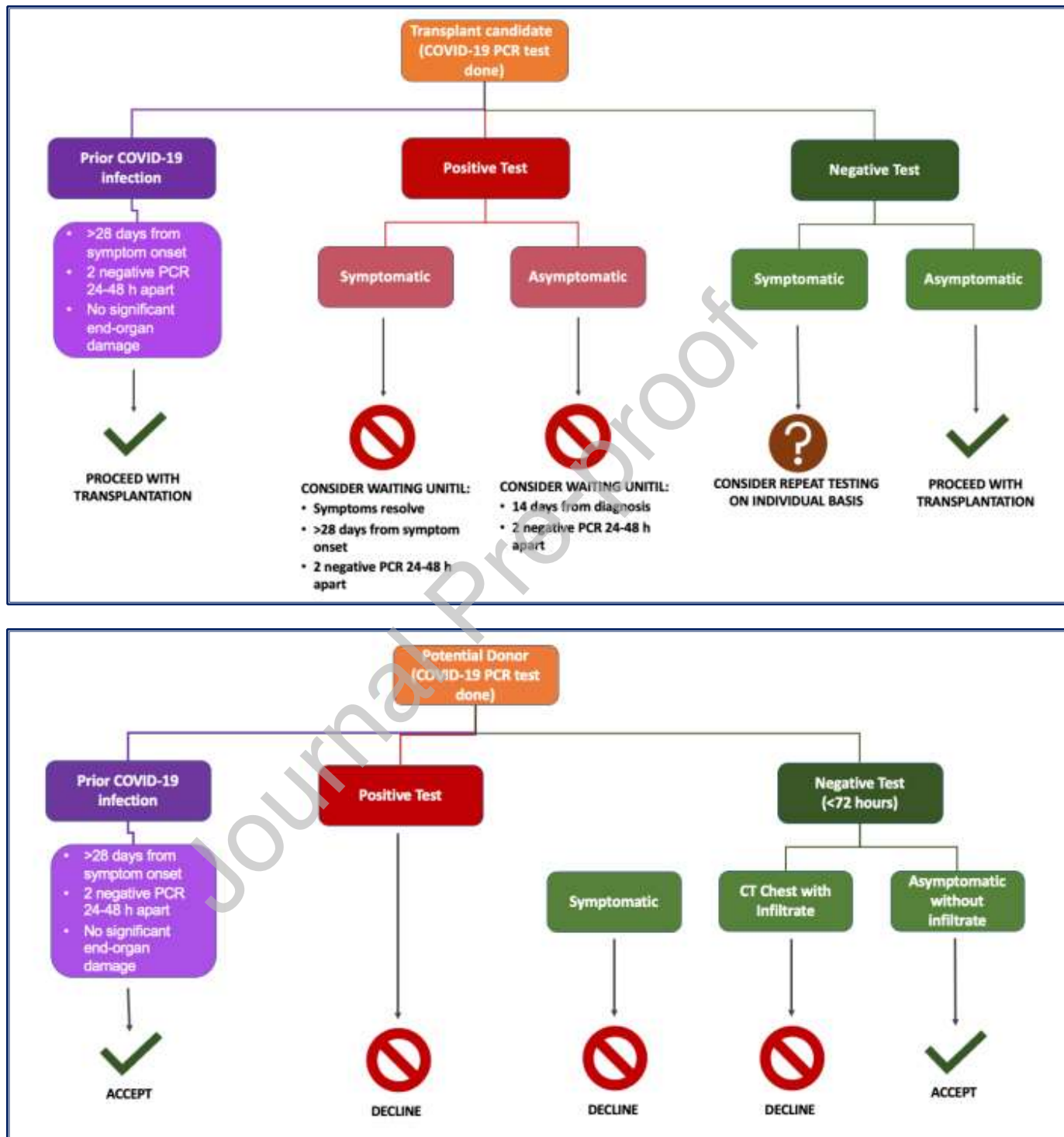
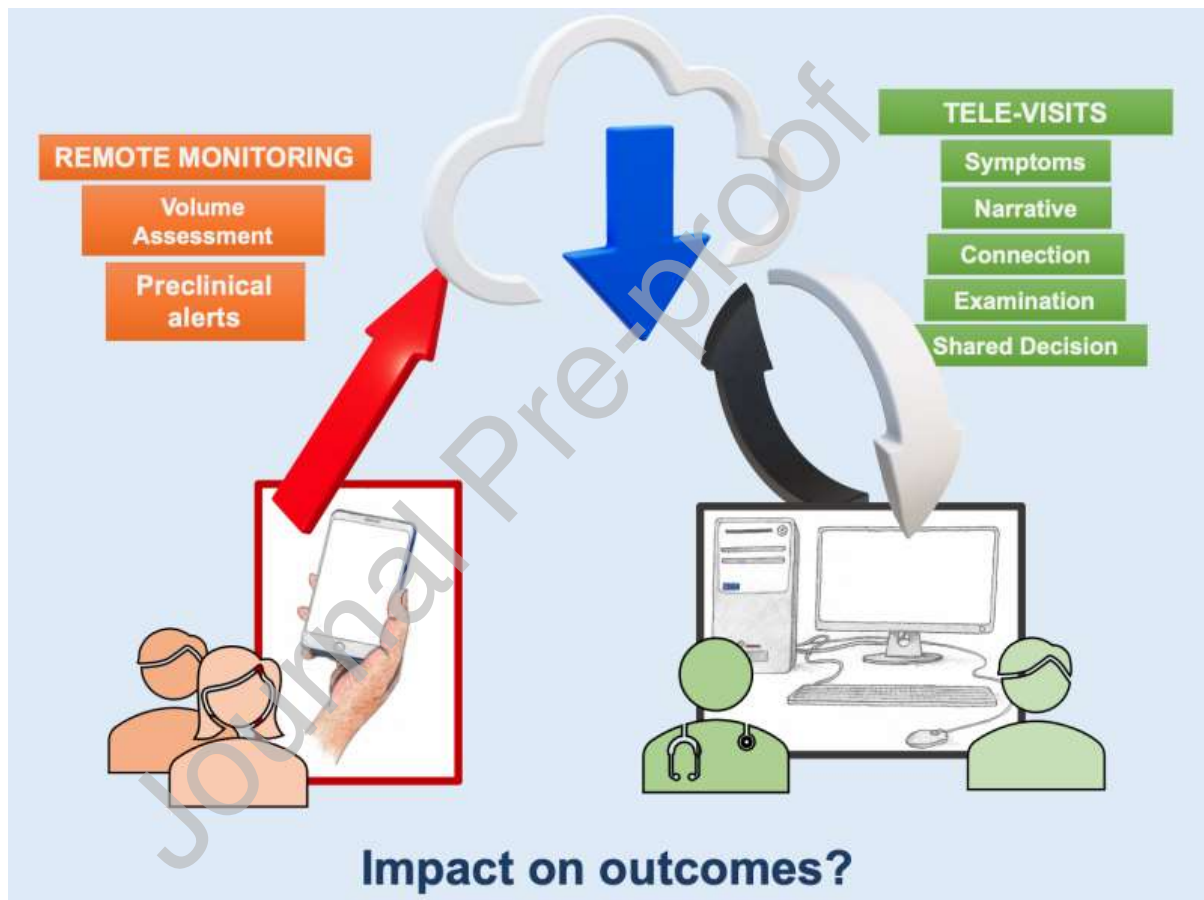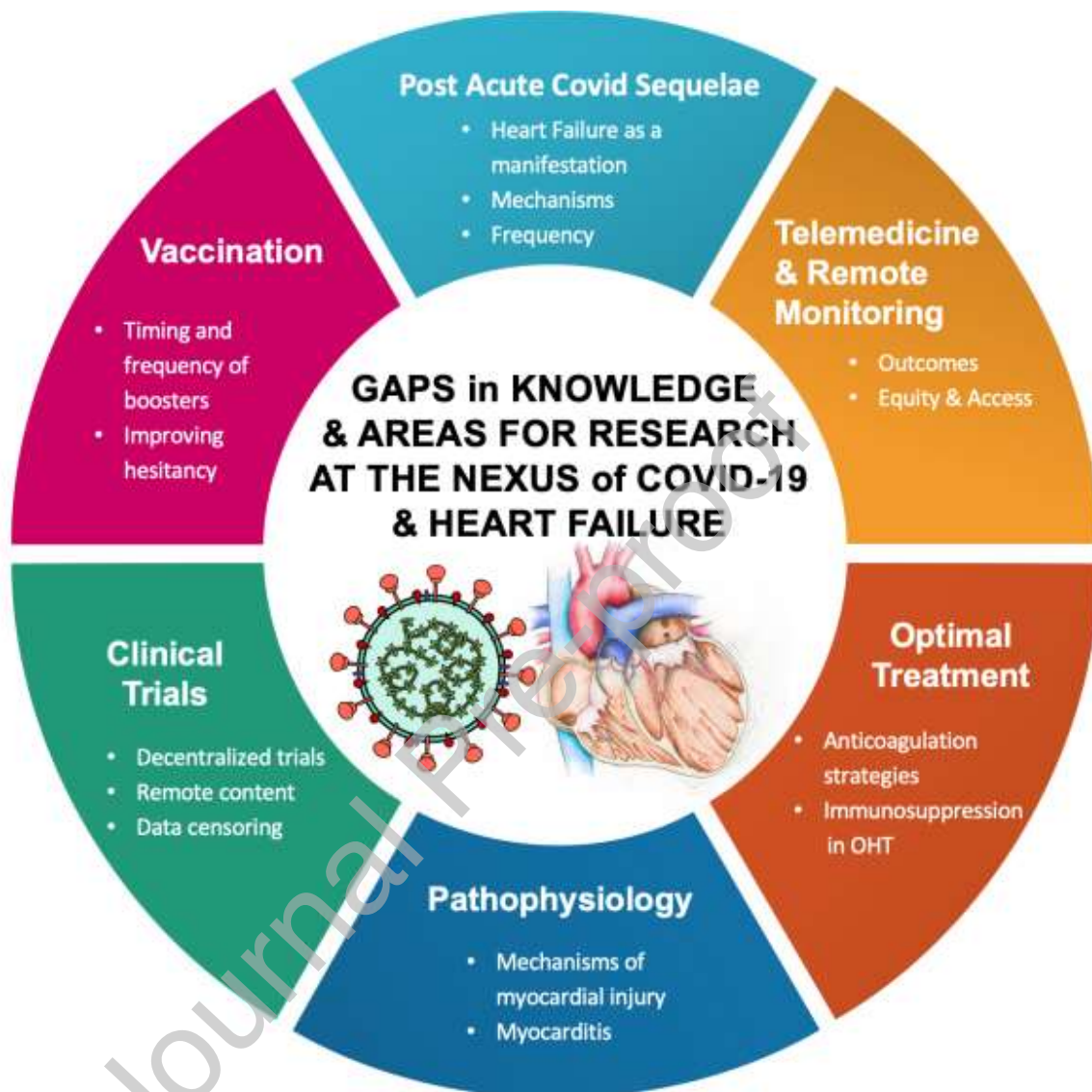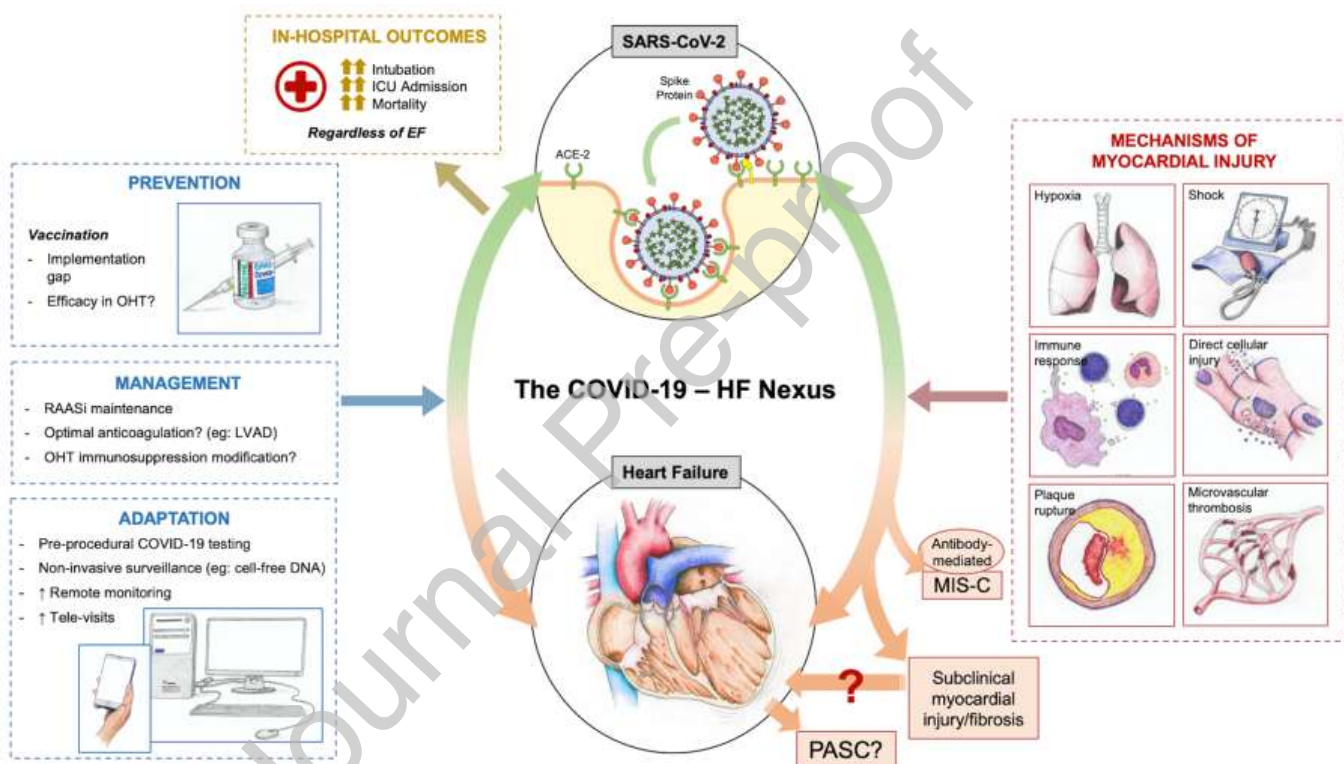**Vaccination**
- Timing and frequency of boosters
- Improving hesitancy

* The authors would like to thank Dr. Martha Gulati for the conceptual design of this graphic

Central Figure:

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