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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



A Report of the American College of Cardiology Solution Set Oversight Committee

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## PREFACE

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The American College of Cardiology (ACC) has a long history of developing documents (eg, decision pathways, health policy statements, appropriate use criteria) to provide members with guidance on both clinical and nonclinical topics relevant to cardiovascular care. In most circumstances, these documents have been created to complement clinical practice guidelines and to inform clinicians about areas where evidence may be new and evolving or where sufficient data may be more limited. Despite this, numerous care gaps continue to exist, highlighting the need for more streamlined and efficient processes to implement best practices in service to improved patient care.

Central to the ACC's strategic plan is the generation of "actionable knowledge"—a concept that places emphasis on making clinical information easier to consume, share, integrate, and update. To this end, the ACC has evolved from developing isolated documents to developing integrated "solution sets." Solution sets are groups of closely related activities, policy, mobile applications, decision support, and other tools necessary to transform care and/or improve heart health. Solution sets address key questions facing care teams and attempt to provide practical guidance to be applied at the point of care. They use both established and emerging methods to disseminate information for cardiovascular conditions and their related management. The success of the solution sets rests firmly on their ability to have a measurable impact on the delivery of care. Because solution sets reflect current evidence and ongoing gaps in care, the associated content will be refined over time to best match changing evidence and member needs.

Expert Consensus Decision Pathways (ECDPs) represent a key component of solution sets. The methodology for ECDPs is grounded in assembling a group of clinical experts to develop content that addresses key questions facing our members across a range of high-value clinical topics.<sup>1</sup> This content is used to inform the development of various tools that accelerate real-time use of clinical policy at the point of care. They are not intended to provide a single correct answer; rather, they encourage clinicians to ask questions and consider important factors as they define treatment plans for their patients. Whenever appropriate, ECDPs seek to provide unified articulation of clinical practice guidelines, appropriate use criteria, and other related ACC clinical policy. In some cases, covered topics will be addressed in subsequent clinical practice guidelines as the evidence base evolves. In other cases, these will serve as stand-alone policy.

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Chair, ACC Solution Set Oversight Committee*

## 1. INTRODUCTION

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The novel coronavirus disease 2019 (COVID-19) pandemic has had an unprecedented impact worldwide. In the United States alone, more than 78 million cases have been reported, with greater than 948,000 deaths attributed directly to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection as of the writing of this ECDP.<sup>2</sup> Among patients hospitalized for COVID-19, various abnormalities in cardiac testing (eg, electrocardiographic abnormalities, elevated cardiac biomarkers)<sup>3-5</sup> and a wide range of cardiovascular complications (eg, myocardial injury, thrombosis, arrhythmia) have been reported.<sup>4-7</sup>

For some patients infected with SARS-CoV-2, cardiac symptoms (eg, chest pain, shortness of breath, fatigue, and palpitations) persist, lasting months after the initial illness.<sup>8,9</sup> Laboratory and imaging evidence of myocardial injury and involvement has also been observed in both symptomatic and asymptomatic individuals,<sup>4,10,11</sup> as well as after receipt of the COVID-19 mRNA vaccine.<sup>12</sup> For clinicians treating these individuals, a growing number of questions exist related to evaluation and management of these conditions, as well as safe resumption of physical activity.

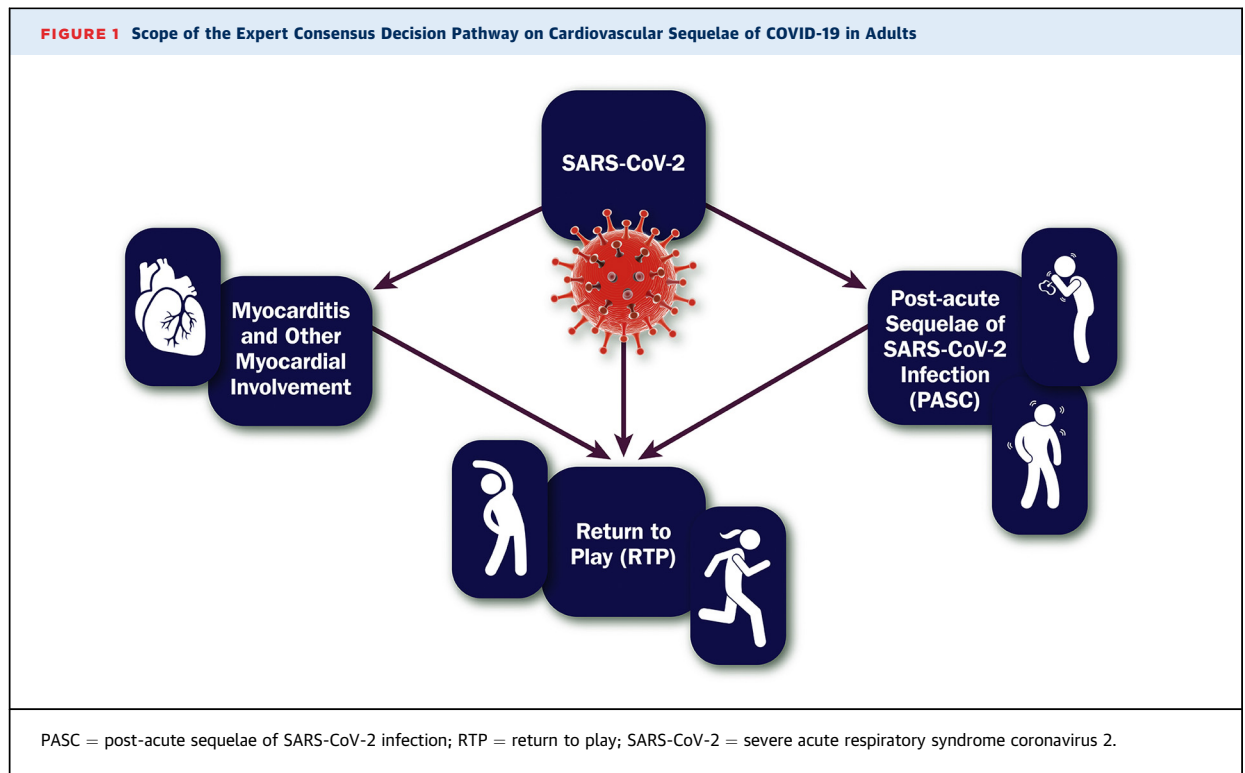
To help gather further insights, the ACC held a virtual Heart House Roundtable in May 2021, bringing together experts in the following areas: 1) myocarditis; 2) post-acute sequelae of SARS-CoV-2 infection (PASC); and 3) sports cardiology. This ECDP represents a key output from that meeting and is intended to serve as a resource for clinicians caring for these patients, largely in the outpatient setting. More specifically, this document attempts to address commonly asked questions regarding the care of adults (aged  $\geq 18$  years) with cardiac symptoms (eg, chest pain, dyspnea, palpitations, syncope) after SARS-CoV-2 infection. In the absence of robust clinical trial data, it is intended to provide practical guidance related to evaluation and management.

## 2. METHODS

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### 2.1. Background

On May 26, 2021, the ACC's Cardiovascular Conundrums in the COVID-19 Era Roundtable was convened to bring together expert clinicians along with a broad set of stakeholders, including representatives from patient advocacy groups, professional societies, and content experts, to discuss ongoing questions faced by cardiovascular clinicians caring for individuals with COVID-19. Participants in this ACC Heart House Roundtable identified the need for expert consensus guidance regarding the evaluation and management of patients with ongoing cardiac symptoms, along with resumption of physical activity after SARS-CoV-2 infection.



## 2.2. Process

Guidance issued in this document was informed by scientific evidence presented and expert opinions considered during the Heart House Roundtable, with additional review and deliberation by the writing committee. Although practical approaches and ongoing gaps in knowledge were discussed during the Roundtable meeting, this document is a separate and independent endeavor that specifically aims to address some of the most common questions that were raised. The work of the writing committee was supported exclusively by the ACC without commercial support. Writing committee members volunteered their time to this effort. Conference calls of the writing committee were confidential and attended only by committee members and society staff.

The ACC and the Solution Set Oversight Committee recognize the importance of avoiding real or perceived relationships with industry (RWI) or other entities that may affect clinical policy. The ACC maintains a database that tracks all relevant relationships for ACC members and persons who participate in ACC activities, including those involved in the development of ECDPs. ECDPs follow ACC RWI policy in determining what constitutes a relevant relationship, with additional vetting by the Solution Set Oversight Committee.

ECDP writing groups must be chaired or co-chaired by an individual with no relevant RWI. Although vice chairs and writing group members may have relevant RWI, they

must constitute less than 50% of the writing group. Relevant disclosures for the writing group and comprehensive disclosures for external peer reviewers can be found in [Appendixes 1 and 2](#). To ensure complete transparency, a comprehensive list of disclosure information for the writing group, including relationships not pertinent to this document, is available in a [Supplemental Appendix](#). Writing group members are discouraged from acquiring relevant RWI during the writing process.

## 3. RATIONALE

### 3.1. Scope of the Document

Recognizing that COVID-19 may have short- and long-term impacts on multiple organ systems, recommendations made in this ECDP are restricted to some of the more common cardiovascular sequelae in adults. Evaluation of cardiovascular symptoms after SARS-CoV-2 infection is imperative, and this document focuses on conditions that clinicians may struggle to diagnose and manage—myocarditis and PASC—while providing guidance on return to play (RTP) (see [Figure 1](#)). Recommendations made in this ECDP are intended to be applied to a broad, unselected population; individualized approaches may be needed for specific populations (eg, those who are pregnant, those with adult congenital heart disease, those with pre-existing heart failure).<sup>13</sup> Finally, although other cardiovascular sequelae exist with COVID-19 (eg, thrombosis), they are not covered in this ECDP.

### 3.1.1. Myocarditis and Other Myocardial Involvement

Myocarditis has been recognized as a rare but serious complication of SARS-CoV-2 infection as well as COVID-19 mRNA vaccination. Other myocardial abnormalities have also been noted on cardiac magnetic resonance imaging (CMR), even in the absence of cardiac symptoms. In this section, we review potential underlying mechanisms for these conditions and preferred approaches for their evaluation and management.

### 3.1.2. Post-acute Sequelae of SARS-CoV-2 Infection

PASC encompasses a constellation of symptoms that emerge or persist weeks to months after recovery from COVID-19.<sup>14,15</sup> Although evidence guiding the care of these patients continues to evolve, there is a need to develop common taxonomies and approaches to care that can be updated iteratively as new data become available. In this section, we segment PASC patients into 2 groups—those with discernable cardiovascular disease (PASC-cardiovascular disease [CVD]) and those with test results that are either normal or unable to fully explain reported symptoms (PASC-cardiovascular syndrome [CVS])—and present patient-centered approaches to their evaluation and management.

### 3.1.3. Return to Play

Early in the pandemic, reports of significant myocardial injury among patients hospitalized with COVID-19 raised concern about risks borne by athletes as part of RTP after SARS-CoV-2 infection. Since then, the prevalence of clinical myocarditis, myocardial involvement, and myocardial injury has been further defined among athletes. Several large observational studies have also helped outline the utility and drawbacks of different diagnostic strategies. In this section, we review the compilation of data, update RTP recommendations, and highlight areas of future investigation.

## 4. ASSUMPTIONS AND DEFINITIONS

To limit inconsistencies in interpretation and to develop guidance that is complementary to current terminology, specific definitions and assumptions were considered by the writing committee in the development of consensus recommendations:

### 1. Clinical spectrum of SARS-CoV-2 infection:<sup>16</sup>

- 1.1. *Asymptomatic (or presymptomatic)*: Individual who tests positive for SARS-CoV-2 infection but has no symptoms consistent with COVID-19;
- 1.2. *Mild illness*: Individual who has symptoms or signs of COVID-19 (eg, fever, cough, sore throat, and malaise), without dyspnea or abnormal chest imaging;

- 1.3. *Moderate illness*: Individual who has lower respiratory disease (eg, pneumonia) with oxygen saturation  $\geq 94\%$  on room air at sea level;

- 1.4. *Severe illness*: Individual who has lower respiratory disease with oxygen saturation  $< 94\%$  on room air at sea level, ratio of arterial partial pressure of oxygen to fraction of inspired oxygen ( $\text{PaO}_2/\text{FiO}_2$ )  $< 300$  mm Hg, a respiratory rate  $> 30$  breaths per minute, or infiltrates involving  $> 50\%$  of the lung fields on chest imaging;

- 1.5. *Critical illness*: Individual who has lower respiratory disease with respiratory failure, septic shock, and/or multiple organ dysfunction.

2. *Myocarditis*: Condition defined by the presence of cardiac symptoms (eg, chest pain, dyspnea, palpitations, syncope), an elevated cardiac troponin (cTn), and abnormal electrocardiographic, echocardiographic, CMR, and/or histopathologic findings on biopsy or postmortem evaluation in the absence of flow-limiting coronary artery disease.

3. *Myocardial involvement*: Condition defined by abnormal myocardium manifest by electrocardiographic, echocardiographic, CMR and/or histopathologic findings, with or without symptoms and with or without an elevated cTn.

4. *Myocardial injury*: Condition defined by a cTn level above the 99<sup>th</sup> percentile upper reference limit.<sup>17</sup>

5. *PASC*: Condition defined by a constellation of symptoms that emerge or persist after recovery from COVID-19, usually lasting for 4-12 weeks and beyond.

6. *Athlete*: Individual who places a high premium on exercise training, competition, and sports achievement, extending across the age spectrum from youth (aged  $< 18$  years) to masters-level (aged  $> 35$  years) participation.

## 5. PATHWAY SUMMARY GRAPHIC

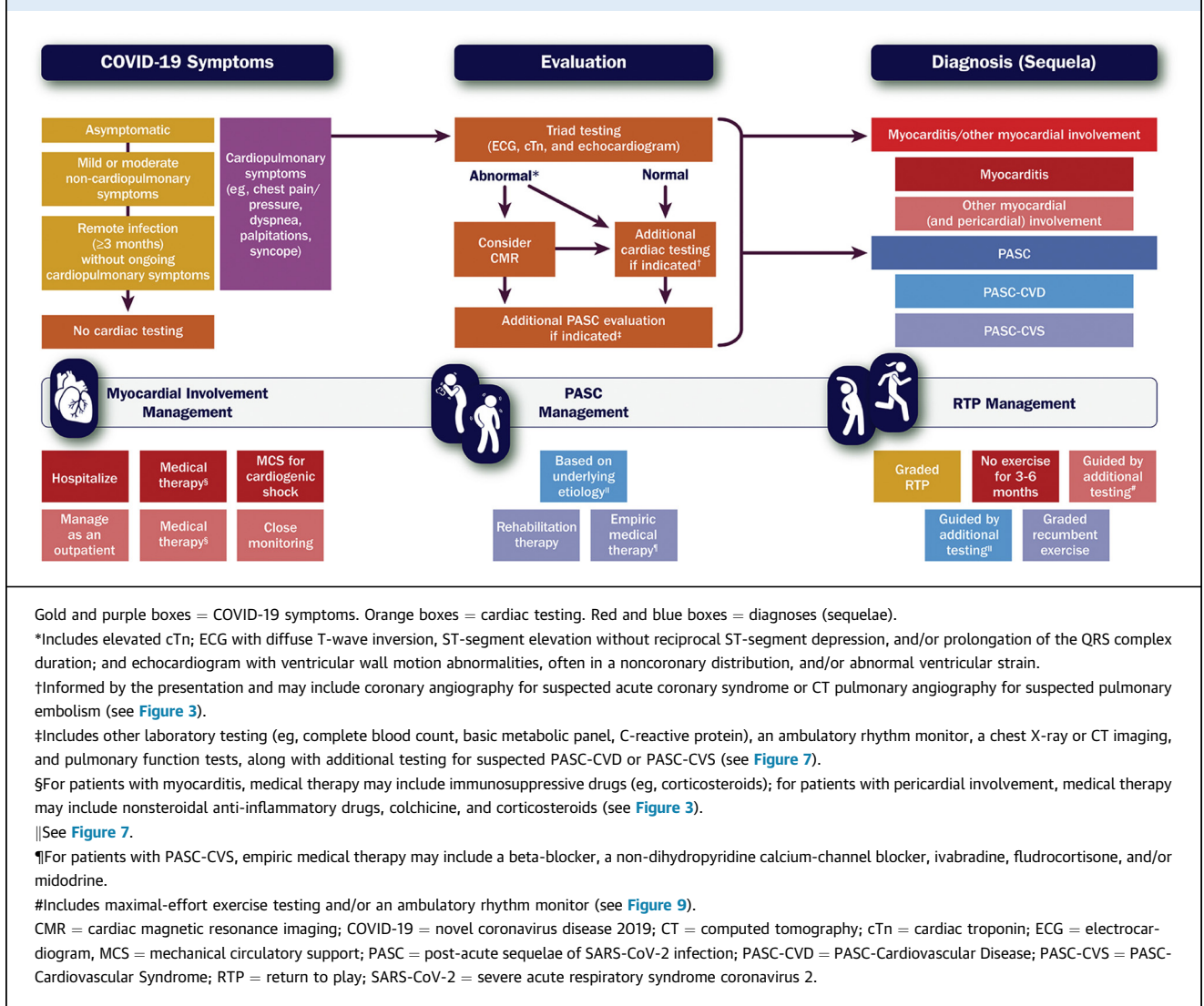
**Figure 2** provides a framework for the evaluation of cardiovascular symptoms after SARS-CoV-2 infection and management of myocarditis/other myocardial involvement, PASC, and RTP.

## 6. DESCRIPTION OF PATHWAY

### 6.1. Section 1: Myocarditis and Other Myocardial Involvement

#### 6.1.1. Overview

Infection with SARS-CoV-2 and complications of COVID-19 mRNA vaccination have drawn increased attention to myocarditis (and pericarditis) during the COVID-19

**FIGURE 2** Framework for Evaluating and Managing Cardiovascular Sequelae of COVID-19 in Adults

pandemic. Early case reports of fulminant myocarditis, combined with frequently observed increases in cTn among patients hospitalized with COVID-19, led to initial concern that myocardial involvement was common.<sup>3</sup> Although cases of severe myocarditis with both viral infection and vaccination remain relatively rare, they do exist, and have complicated immunization efforts.<sup>18</sup> At the same time, various abnormalities on CMR (and positron emission tomography [PET]) have been reported in those with COVID-19, even in the absence of cardiac symptoms.<sup>11,19</sup> Collectively, these findings challenge our understanding of viral-mediated myocardial (and pericardial) involvement<sup>20-25</sup> and raise questions about the pandemic's long-term cardiovascular consequences.

The definition and approach to diagnosis of myocarditis following SARS-CoV-2 infection continues to evolve,

reflecting advances in diagnostic testing (particularly CMR) and improved understanding of its immunopathogenesis. Older definitions based on pathology (eg, Dallas and immunohistologic criteria)<sup>26</sup> historically relied upon abnormal histopathologic findings on endomyocardial biopsy, with myocyte necrosis and inflammatory myocardial infiltrates that were nonischemic in origin.<sup>27</sup> Subsequent definitions have incorporated use of an elevated cTn and abnormalities on CMR and fluorodeoxyglucose (FDG)-PET to characterize and diagnose myocarditis in the absence of endomyocardial biopsy (eg, Lake Louise criteria).<sup>28-30</sup> Importantly, however, numerous ambiguities exist with this approach, driven, in part, by discrepant findings and diverse practices in CMR and the lack of a standardized clinical definition for myocarditis.<sup>31</sup> The absence of uniform methods for

noninvasively evaluating these patients further limits comparison of diagnostic methods and has posed a barrier to the development of normative ranges and prognostic cutoffs that can be used to inform subsequent management steps.<sup>31</sup> Furthermore, existing definitions of myocarditis were developed in models of viral-mediated inflammation with focal areas of necrosis (infarct-like myocarditis); in contrast, the underlying myocardial processes with COVID-19 appear to be more heterogeneous and diffuse.

Myocardial injury with COVID-19 has been extensively reported, with rates widely varying depending upon the population studied.<sup>4</sup> The underlying causes are numerous and include but are not limited to myocarditis,<sup>22</sup> acute coronary syndrome (myocardial infarction type 1),<sup>17</sup> demand ischemia (myocardial infarction type 2),<sup>25,32-35</sup> multisystem inflammatory syndrome in children (MIS-C) and multisystem inflammatory syndrome in adults (MIS-A),<sup>20,21,24</sup> takotsubo/stress cardiomyopathy,<sup>36,37</sup> cytokine storm,<sup>34</sup> acute cor pulmonale resulting from macropulmonary or micropulmonary emboli,<sup>23,25</sup> myocardial injury from chronic conditions like pre-existing heart failure,<sup>38-41</sup> and acute viral infection unmasking subclinical heart disease.<sup>38</sup> Because 1 or more of these etiologies may coexist, it can sometimes be challenging to identify a specific underlying cause.

Cognizant of the wide spectrum of potential myocardial involvement that may be seen with COVID-19, we have chosen to focus on myocarditis and other forms of cardiac involvement. For those with myocardial injury unrelated to these conditions (most often observed in those hospitalized for COVID-19), a targeted evaluation and management plan should be undertaken based on the suspected underlying cause.<sup>4,42</sup>

### 6.1.2. Definitions and Clinical Presentation

A variety of terms and associated definitions are offered in the following text, highlighting the spectrum of myocardial abnormalities that may be seen with COVID-19.

**Myocarditis:** This condition is defined by the presence of 1) cardiac symptoms (eg, chest pain, dyspnea, palpitations, syncope); 2) an elevated cTn; and 3) abnormal electrocardiographic (eg, diffuse T-wave inversion, ST-segment elevation without reciprocal ST-segment depression, prolongation of the QRS complex duration), echocardiographic (eg, left ventricular [LV] wall motion abnormalities, often noted in a noncoronary distribution), CMR (eg, nonischemic late gadolinium enhancement [LGE] pattern with prolonged native T<sub>1</sub> and T<sub>2</sub> relaxation times), and/or histopathologic findings on biopsy or postmortem evaluation (eg, inflammatory myocardial infiltrates associated with myocyte degeneration and necrosis) in the absence of flow-limiting epicardial coronary artery disease. It is further categorized into levels of

certainty (possible, probable, and definite) based on the number of features present.

- **Possible myocarditis:** This includes individuals with: 1) cardiac symptoms; 2) an elevated cTn; and 3) abnormal electrocardiographic and/or echocardiographic findings but a) absence of acute myocarditis by endomyocardial biopsy or CMR or b) circumstances where neither biopsy nor CMR were performed. Ideally, flow-limiting coronary artery disease would have been excluded in men older than 50 years and women older than 55 years.
- **Probable myocarditis:** This condition is defined by all features of possible myocarditis, but follow-up CMR and/or biopsy within 6 months of SARS-CoV-2 infection demonstrates abnormalities consistent with previous myocarditis.
- **Definite myocarditis:** This condition is defined by all features of possible myocarditis, but CMR and/or biopsy performed at the time of SARS-CoV-2 infection demonstrates findings consistent with active myocarditis.

**Myocardial involvement:** This broader term is intended to include myocardial abnormalities noted to occur in the setting of SARS-CoV-2 infection that do not meet the criteria for possible, probable, or definite myocarditis. Importantly, affected individuals may or may not have cardiac symptoms and may have wide variation in presentation, ranging from asymptomatic individuals (eg, athletes who have undergone screening with CMR)<sup>43</sup> to those evaluated at autopsy.<sup>44,45</sup>

**Myocardial injury:** This condition is defined by a cTn level (preferably using a high-sensitivity assay) above the 99th percentile upper reference limit.<sup>17</sup> This may be related to widely varying mechanisms, ranging from demand ischemia to cytokine storm. Regardless of the etiology, myocardial injury with COVID-19 carries a worse prognosis.

### Symptoms

Fever, dyspnea, cough, and chest pain are among the most common symptoms with COVID-19 myocarditis.<sup>46</sup> Additional symptoms include other types of chest discomfort, postexertional fatigue, palpitations, and syncope.<sup>47</sup> Although symptoms may resolve within 3 months of initial diagnosis, persistence of symptoms for greater than 12 months has been reported.<sup>48</sup>

### Severity

Symptomatology and hemodynamics should be used to help define myocarditis severity. Although historically categorized as asymptomatic, mild, moderate, and fulminant,<sup>49</sup> assessment may alternatively be made with a 4-grade symptom scale for chest pain,<sup>50</sup> dyspnea,<sup>51</sup> and functional status.<sup>52</sup> Importantly, symptom intensity does



not correlate particularly well with left ventricular ejection fraction (LVEF), nor with levels of cTn, natriuretic peptides, and C-reactive protein. Classic findings on CMR include increased native T<sub>1</sub> (fibrosis or inflammation) and T<sub>2</sub> (inflammation or edema) signals along with non-ischemic LGE.

Although fulminant myocarditis with cardiogenic shock can occur with COVID-19,<sup>53-55</sup> distributive shock resulting from sepsis and/or a hyperinflammatory state can occur as well. In a systematic review of 41 cases of myocarditis associated with COVID-19, cardiogenic shock and distributive shock were noted in 27% and 12% of individuals, respectively.<sup>46</sup> Of note, these rates exceed that seen with viral myocarditis unrelated to COVID-19.<sup>56</sup>

### 6.1.3. Epidemiology

#### Incidence and Prevalence

Historically, viral infection has been regarded as the most common cause of myocarditis. Its reported prevalence is variable and has been estimated at 10 to 106 cases per 100,000 people worldwide, with an annual incidence of 1.8 million.<sup>57</sup> With COVID-19, the true incidence of myocarditis has proven challenging to assess because of ambiguous definitions, evaluation of nonrepresentative populations, and lack of systematic data collection. Although 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,<sup>22</sup> prospective and retrospective studies of hospitalized patients, autopsy data, and CMR suggest that the overall incidence is higher. Fortunately, fulminant myocarditis appears to be quite rare.<sup>53-55</sup>

Echocardiographic data from prospective, cross-sectional studies of patients hospitalized for COVID-19 suggest that myocardial dysfunction may be present in up to 40%.<sup>58,59</sup> This can range from abnormal ventricular strain to overt left and right ventricular systolic dysfunction.<sup>60</sup> Although the latter may be global, wall motion abnormalities with myocarditis are classically segmental in a noncoronary distribution. Pericardial effusion and thickening may also be seen (especially in cases of myopericarditis); however, data on their frequency and degree of overlap with myocarditis are limited.<sup>61</sup> In selected studies, these echocardiographic findings correlate with cTn levels<sup>10</sup> and risk of mortality.<sup>59,62</sup> The underlying mechanisms for this (eg, myocarditis, demand ischemia, stress cardiomyopathy, right ventricular pressure overload), however, are not always clearly defined.

CMR is the most sensitive imaging modality for identifying myocardial (and pericardial) involvement. It has been used in several studies to evaluate symptomatic and asymptomatic individuals with COVID-19, in both hospital and ambulatory settings. In a study of 100 patients (33%

hospitalized) imaged a median of 71 days after testing positive for COVID-19, nonischemic LGE was found in 20% and prolonged native T<sub>1</sub> and T<sub>2</sub> relaxation times in 73% and 60%, respectively.<sup>11</sup> Similar findings have been observed in other CMR studies, with variable degrees of LGE and mapping abnormalities in those convalescing from COVID-19.<sup>19,63-67</sup> When performed in athletes as part of a RTP screening protocol, various abnormalities have been noted, with 0.6%-3% of subjects meeting modified Lake Louise criteria for clinical myocarditis.<sup>43,68,69</sup> Variability in observed findings with CMR likely reflect differences in the populations studied, timing relative to infection onset, and the specific imaging protocols and interpretations used. It is likely, however, that MIS-C represents an important subset, with limited case series demonstrating widely varying rates of imaging abnormalities suggestive of myocarditis (0%-51%).<sup>20,21,70-72</sup>

Autopsy findings among those with COVID-19 have also varied. In a study of 277 cardiac autopsies from 22 studies, classic myocarditis was identified in 7.2%, non-myocarditis inflammatory infiltrate in 12.6%, single-cell ischemia in 13.7%, and acute myocardial infarction in 4.7%.<sup>25</sup> At least one cardiovascular histopathologic abnormality (eg, macrovascular or microvascular thrombus, inflammation, or intraluminal megakaryocytes) was noted in 47.8%. Collectively, these data suggest that although fulminant myocarditis as a cause of death is rare (using historical histopathologic criteria), nonspecific cardiac inflammation and/or injury is not.

#### Risk Factors

Identification of risk factors for myocarditis with COVID-19 is still an area of active investigation. In general, viral myocarditis unrelated to SARS-CoV-2 is more common in men. Although a similar pattern has been observed in those with COVID-19, one cannot exclude the possibility of selection bias. In a large review of 38 patients with myocarditis associated with SARS-CoV-2 infection, however, 26 (68%) were men.<sup>54</sup> Male predominance has also been observed in studies of myocarditis in athletes,<sup>43,68,73,74</sup> MIS-C,<sup>20,21,70-72</sup> and myocarditis following vaccination for COVID-19.<sup>12</sup> By comparison, a greater number of risk factors exist for myocardial injury with COVID-19, such as advanced age, male sex, underlying cardiovascular disease, obesity, diabetes mellitus, hypertension, immunosuppression, and severe systemic disease.<sup>33-35</sup>

### 6.1.4. Mechanisms

Viral-induced myocarditis has historically been defined by three phases: acute viral exposure with an innate immune response (<1 week); activation of an acquired immune response with cytokine and chemokine release (1-4 weeks); and disease progression with clearance of the

virus and development of fibrosis, remodeling, and cardiomyopathy (>4 weeks).<sup>75,76</sup> Although cases of myocarditis following SARS-CoV-2 infection are rare, they largely follow this pattern, with a delay in onset after viral infection of days to weeks. For some individuals with myocarditis, elevation of cTn and abnormalities on CMR may be observed early after infection; much more often, however, there is delayed onset of cardiac symptoms, elevation of cardiac biomarkers, and abnormalities on cardiac imaging. Because of variation in how these patients are evaluated and varying sensitivity thresholds of the different imaging methods used, the exact incidence of myocarditis with COVID-19 remains unclear.

Investigators have proposed several mechanisms by which SARS-CoV-2 may contribute to myocarditis and other forms of myocardial involvement, including direct virus invasion, host inflammatory or immune responses, and microvascular angiopathy. Emerging data indicate that a maladaptive host immune response occurs, with excessive activation of innate immune pathways, a surge of proinflammatory cytokines, deregulated thromboinflammation, thrombotic microangiopathy, endothelial dysfunction, and even molecular mimicry.<sup>77-80</sup> Other hypothesized contributing mechanisms include demand ischemia, stress cardiomyopathy, and hypoxia-induced myocardial injury.<sup>81</sup> Although baseline comorbidities, including metabolic syndrome, hypertension, and cardiovascular disease, may potentiate these effects along with subsequent adverse outcomes, they are not required for cardiovascular involvement, as seen in MIS-C.

Even though SARS-CoV-2 mRNA has been detected in the myocardium of 25%-50% of COVID-19 patients undergoing autopsy, the virus is largely found in pericytes and within the subendothelium, not within cardiac myocytes. Autopsy findings have also largely demonstrated the absence of diffuse lymphocytic myocarditis or confluent myocyte necrosis—findings typically observed with other forms of viral myocarditis.<sup>25,82-85</sup> Although lymphocytic infiltration has been noted on endomyocardial biopsy of some patients with myocardial involvement by CMR,<sup>11</sup> it is more often characterized by increased CD68+ macrophage or monocytic infiltration, endothelialitis, microvascular dysfunction, and individual cell necrosis.<sup>44,45,79,83,85-102</sup> Importantly, CMR has also provided additional insights with the identification of nonischemic myocardial and pericardial LGE, along with prolonged native T<sub>1</sub> and T<sub>2</sub> relaxation times among some in this population.<sup>11,63-67</sup>

### 6.1.5. Evaluation

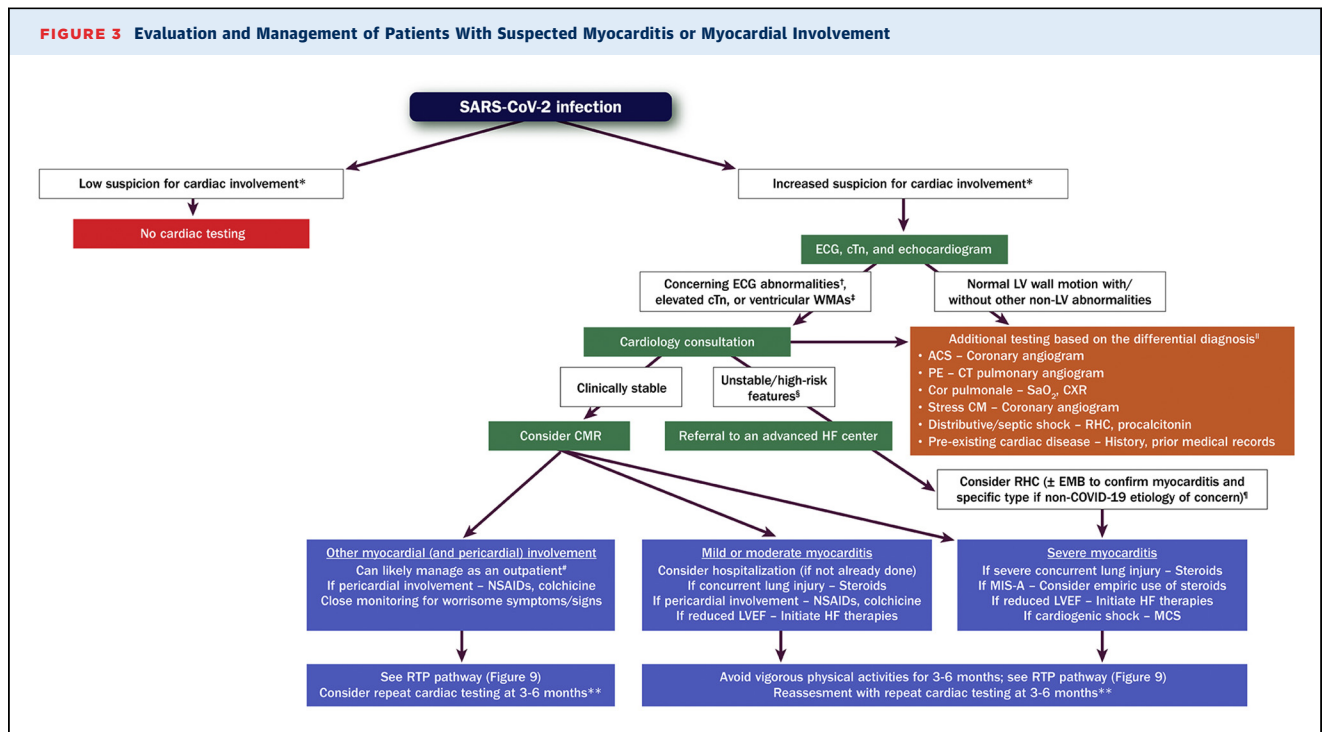
Cognizant of 1) the spectrum of myocardial involvement that may be seen with COVID-19; 2) the timing of

evaluation relative to SARS-CoV-2 infection; and 3) the range of diagnostic tests available, the writing committee proposes a multiparametric approach to help guide decision-making (see **Figure 3**). This is limited, however, by a paucity of evidence about how best to diagnose and manage myocarditis and other forms of myocardial involvement with COVID-19.<sup>31</sup>

Among patients with SARS-CoV-2 infection, pre-existing cardiovascular disease and other cardiovascular and noncardiovascular risk factors (eg, advanced age, male sex, immunosuppression) represent important determinants of clinical presentation.<sup>53,65,81,103,104</sup> When suspicion for cardiac involvement is low, no further cardiac testing is generally recommended. In contrast, when suspicion for cardiac involvement is moderate or high, initial testing should generally consist of an electrocardiogram (ECG), measurement of cTn (preferably using a high-sensitivity assay), and an echocardiogram (trans-thoracic or point-of-care ultrasound). Because patients hospitalized with an elevated cTn face higher risk of adverse outcomes,<sup>34</sup> closer monitoring for potential deterioration is usually warranted.

In those with a rising cTn, ECG abnormalities concerning for myocarditis (eg, diffuse T-wave inversion, ST-segment elevation without reciprocal ST-segment depression, prolongation of the QRS complex duration), and/or echocardiographic abnormalities concerning for myocarditis (eg, ventricular wall motion abnormalities often in a noncoronary distribution, abnormal ventricular strain),<sup>105</sup> cardiology consultation is recommended. Importantly, the presence of normal LV wall motion and/or other non-LV echocardiographic abnormalities should invite testing for other conditions, informed by the presentation (eg, coronary angiography for suspected acute coronary syndrome, computerized tomography (CT) pulmonary angiography for suspected pulmonary embolism).

In those with suspected myocardial involvement, CMR is recommended if the patient is hemodynamically stable. In symptomatic patients, CMR is the most sensitive method to exclude ischemia and preexisting cardiomyopathies<sup>106</sup> while confirming cardiac changes due to SARS-CoV-2 infection, including myocardial inflammation, nonischemic epicardial scar, and pericardial effusion/enhancement, all of which are demonstrable after 4 weeks.<sup>106,107</sup> For patients who are unstable or exhibit high-risk features (eg, hypotension, ventricular arrhythmias), evaluation at an advanced heart failure center is recommended. Endomyocardial biopsy should be considered in those with clinical deterioration, particularly if heart block or ventricular arrhythmias are present and obstructive coronary artery disease has been excluded.<sup>83,108-110</sup>

**FIGURE 3** Evaluation and Management of Patients With Suspected Myocarditis or Myocardial Involvement

Green boxes = cardiac testing for evaluation of myocarditis/myocardial involvement. Orange box = other cardiac/noncardiac testing. Purple boxes = management.

\*Informed by symptoms suggestive of cardiac involvement, including chest pain/pressure, dyspnea, palpitations, and syncope.

†Includes diffuse T-wave inversion, ST-segment elevation without reciprocal ST-segment depression, and prolongation of the QRS complex duration.

‡Often in a noncoronary distribution; may also include abnormal ventricular strain.

§Includes hypotension, cardiogenic shock, sustained ventricular arrhythmias, and/or advanced atrioventricular block.

¶This is an incomplete list of potential etiologies.

‡Testing for viral genomes should be performed on frozen heart tissue to exclude other causes of myocarditis, if possible.

#Assumes chest pain is the only symptom, LV systolic function is preserved, and there are no ventricular arrhythmias.

\*\*Includes an ECG, echocardiogram, ambulatory rhythm monitor, and CMR.

ACS = acute coronary syndrome; CM = cardiomyopathy; CMR = cardiac magnetic resonance imaging; COVID-19 = novel coronavirus disease 2019; CT = computed tomography; cTn = cardiac troponin; CXR = chest X-ray; ECG = electrocardiogram; EMB = endomyocardial biopsy; HF = heart failure; LV = left ventricular; LVEF = left ventricular ejection fraction; MCS = mechanical circulatory support; MIS-A = multisystem inflammatory syndrome in adults; NSAIDs = nonsteroidal anti-inflammatory drugs; PE = pulmonary embolism; RHC = right heart catheterization; SaO<sub>2</sub> = arterial oxygen saturation; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; WMAs = wall motion abnormalities.

### 6.1.6. Management

Management of patients with myocardial involvement in the setting of COVID-19 is primarily dictated by the clinical presentation and course. Because myocarditis is associated with a heightened risk of cardiac complications early in the disease course,<sup>34,111</sup> a proactive management plan should be in place.

#### Asymptomatic (Subclinical) Myocardial Involvement

Asymptomatic myocardial involvement has been reported following SARS-CoV-2 infection (eg, following CMR screening of athletes as part of a RTP protocol). Because most asymptomatic individuals do not undergo cardiac testing, however, this group is likely to be quite small. Recognizing that the long-term consequences of this condition are not known, it is still reasonable to manage these individuals expectantly, with instruction

to share any worrisome symptoms or signs (eg, chest pain, shortness of breath, syncope, edema) should they occur. For those interested in resuming physical activity, further recommendations are provided in the RTP section.

#### Symptomatic Myocardial Involvement and Myocarditis

The treatment approach for symptomatic myocardial involvement in the setting of COVID-19 greatly depends upon the patient's clinical presentation, as well as the severity of abnormalities noted on testing. Acknowledging the potential for overlap between some forms of myocardial involvement and possible myocarditis, patients who have chest pain as their only symptom, preserved LV systolic function, and no ventricular arrhythmias can likely be managed in the ambulatory setting with close monitoring for worrisome symptoms or

signs (eg, shortness of breath, syncope, edema). Consideration should be given to follow-up testing (eg, ECG, echocardiogram, ambulatory rhythm monitor, CMR) 3-6 months after presentation, particularly in those with ongoing cardiac symptoms and/or findings suggestive of significant/worsening myocardial involvement.

In those with definite myocarditis that is either mild or moderate in severity, hospitalization is recommended (if not already done), ideally at an advanced heart failure center. Those with a fulminant course (eg, those with cardiogenic shock, sustained ventricular arrhythmias, and/or advanced atrioventricular block) should be managed similar to other forms of cardiogenic shock at centers with expertise in advanced heart failure, mechanical circulatory support (including use of V-A extracorporeal membrane oxygenation), and other advanced therapies.<sup>112,113</sup>

Further decision-making about treatment depends upon whether concurrent pneumonia is present. In general, patients with myocarditis and COVID-19 pneumonia with ongoing need for supplemental oxygen should be treated with corticosteroids.<sup>114</sup> For those with associated pericardial involvement, nonsteroidal anti-inflammatory drugs may be used to help alleviate chest pain and inflammation.<sup>115</sup> Low-dose colchicine or prednisone may be added for persistent chest pain, with a plan to taper the dose based on symptoms and clinical findings.

Treatment of myocarditis in stable patients should be based on standard pathways unrelated to COVID-19. A low-dose beta-blocker along with a renin-angiotensin-aldosterone system inhibitor may be used empirically in patients with mildly reduced LV systolic function and stable hemodynamics. A beta-blocker may also be helpful in patients with supraventricular arrhythmia, if hemodynamically stable. In fact, treatment with intravenous metoprolol tartrate was observed to improve respiratory status in a small, randomized trial of patients with COVID-19 and acute respiratory distress syndrome requiring mechanical ventilation.<sup>116</sup> Beta-blockade can, however, precipitate cardiogenic shock in patients with greater compromise of cardiac function.

Use of intravenous corticosteroids may be considered in those with suspected or confirmed COVID-19 myocarditis with hemodynamic compromise or MIS-A, a hyper-inflammatory state with acute heart failure and/or cardiogenic shock in the absence of sepsis, as this approach was associated with a favorable prognosis in a small series.<sup>77,117</sup> MIS-A is often associated with delayed-onset myocarditis, and affected individuals may have high levels of inflammatory biomarkers and ferritin.<sup>80</sup> Although similar presentations have been observed in children (MIS-C),<sup>118</sup> a review of treatment approaches for this condition is beyond the scope of this ECDP.

Empiric use of immunosuppressive therapy (eg, corticosteroids) may also be considered in those with biopsy evidence of severe myocardial inflammatory infiltrates or fulminant myocarditis, balanced against infection risk.<sup>113</sup> It is important to note, however, that these biopsy findings are very rare in COVID-19, and the magnitude of benefit from such immune-modifying therapy is not fully known.<sup>45</sup>

Once a patient with cardiogenic shock or hemodynamic instability from suspected myocarditis has stabilized, CMR should be performed (before hospital discharge) to confirm the diagnosis and assess the extent of ventricular dysfunction and inflammation. Guideline-directed medical therapy for heart failure should be initiated before discharge and titrated as appropriate in the outpatient setting. Strenuous physical activity should be avoided for 3-6 months, as outlined in the RTP section. Importantly, follow-up surveillance testing (eg, ECG, echocardiogram, ambulatory rhythm monitor, CMR) can be helpful in all patients with myocarditis to: 1) gauge recovery of cardiac function and inflammation; 2) guide heart failure management; and 3) assess prognosis.

### 6.1.7. Postvaccination Myocarditis

#### Clinical Presentation

Myocarditis following COVID-19 mRNA vaccination is an entity separate from but related to myocarditis following SARS-CoV-2 infection.<sup>119</sup> In case reports and case series of vaccine-associated myocarditis, chest pain has been noted in the vast majority,<sup>12</sup> occurring most commonly 2-3 days after the second mRNA vaccine dose.<sup>12</sup> Much less often, it has been observed after the first dose.<sup>12</sup> ST-segment elevation has been the most common ECG abnormality, and most cases have reported an elevated cTn level, peaking approximately 3 days after vaccination. Other laboratory findings include elevated natriuretic peptide and C-reactive protein levels. Although a small percentage have had an LVEF <50% by echocardiography, CMR findings suggestive of myocarditis have been present in most who were tested,<sup>120</sup> with evidence of LGE and myocardial edema. In these cases, testing failed to identify evidence of SARS-CoV-2, other viral infection, or autoimmune disorders.<sup>12</sup> Fortunately, most patients have had a nonfulminant course, with symptom resolution along with improved laboratory tests and imaging findings, with or without treatment.<sup>12,120,121</sup>

#### Epidemiology and Risk Factors

Available data from the U.S. Vaccine Adverse Event Reporting System suggest that myocarditis following COVID-19 mRNA vaccination is rare.<sup>12,122</sup> As of June 11, 2021, the reported rate of myocarditis following administration of the second dose of the COVID-19 mRNA vaccine was 40.6 cases per million in male individuals aged

12-29 years and 2.4 cases per million in male individuals aged  $\geq 30$  years.<sup>123</sup> Corresponding rates in female individuals for these age groups were 4.2 and 1.0 cases per million after the second vaccine dose, respectively. Male individuals aged 12-17 years and 18-24 years had the highest reported rates of postvaccination myocarditis, with 62.8 and 50.5 cases per million following the second vaccine dose, respectively. Among 323 individuals <30 years of age with adjudicated postvaccination myocarditis, 90% were male, with a median age of 19 years. Importantly, even though 96% of these individuals were hospitalized, most had a mild clinical course, with no reported deaths.

Similar findings have been observed in other retrospective analyses using coded clinical data to screen for cases of postvaccination myocarditis. In a study that evaluated 5.1 million Israelis treated with 2 doses of a COVID-19 mRNA vaccine between December 2020 and May 2021, 136 cases of definite or probable postvaccination myocarditis were identified.<sup>124</sup> Although most affected individuals (95%) had a mild clinical course, one individual died. Myocarditis risk in the overall population was higher after the second dose (risk difference of 18 per million) and was highest among male individuals between the ages of 16 and 19 years (risk difference of 137 per million). Consistent findings were observed in a separate study of 2.5 million Israelis who were part of a large health care organization, where the incidence of postvaccination myocarditis after at least one dose of a COVID-19 mRNA vaccine was 21 cases per million for the all-comer population and 107 cases per million for male individuals aged 16-29 years.<sup>125</sup> Finally, a higher rate of vaccine-associated myocarditis was observed in a study of 153,438 individuals in the Kaiser Permanente health system between December 2020 and October 2021.<sup>126</sup> After receiving a second mRNA vaccine dose, rates of myocarditis among male individuals aged 12-17 years and 18-24 years were 377 and 537 cases per million, respectively. This was driven, in part, by identification of affected individuals through combined use of coded clinical data with specific search terms within the electronic medical record.

Accrued observational data also suggest that rates of postvaccination myocarditis may differ between the 2 mRNA vaccines (BNT162b2 [Pfizer-BioNTech] and mRNA-1273 [Moderna]), particularly after the second dose. In a population-based cohort study using individual-level data for nearly 5 million individuals in the Danish Vaccination Register, rates of postvaccination myocarditis were noted to be higher with the mRNA-1273 (Moderna) vaccine.<sup>127</sup> Similar observations were noted in an analysis of patient-level data for more than 38 million vaccinated adults in the English National Immunisation database, where rates of postvaccination myocarditis were higher

with the mRNA-1273 (Moderna) vaccine.<sup>128</sup> Of note, a small but significantly increased risk of postvaccination myocarditis was also observed after the first dose of the adenoviral vector (non-mRNA) vaccine, ChAdOx1 (University of Oxford); however, this effect was not observed with the second dose.<sup>128</sup>

### Mechanism

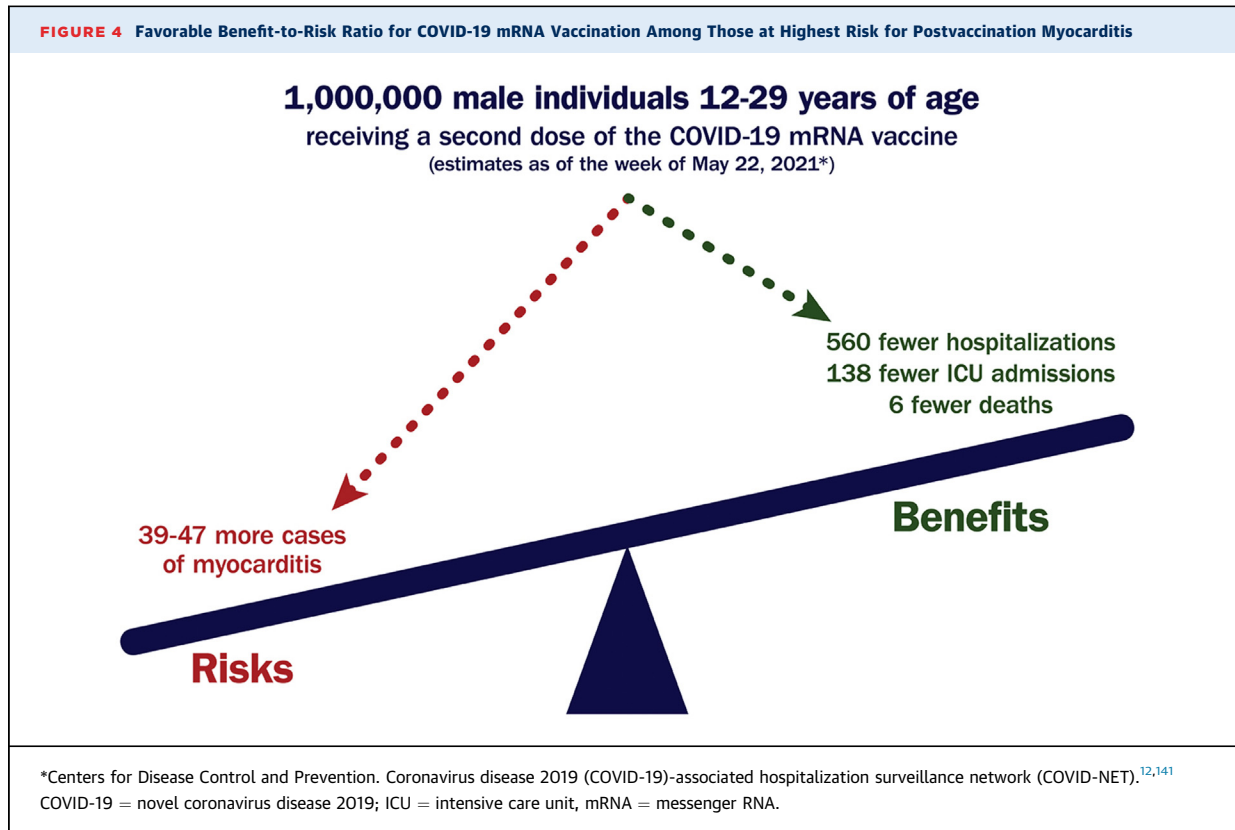
Although the exact mechanism of vaccine-associated myocarditis is not currently known, it has been hypothesized that molecular mimicry (between the spike protein of SARS-CoV-2 and self-antigens), autoantibody formation, triggered immune dysregulation with activation of natural killer cells, and a dysregulated cytokine and immune response to mRNA may all play a role.<sup>12,129,130</sup> The observed male predominance may also be related to sex hormone differences in immune response.<sup>131</sup>

Endomyocardial biopsy has been reported in only a small number of cases of postvaccination myocarditis. In 2 cases, specimens showed inflammatory infiltrates largely consisting of T cells and macrophages, admixed with eosinophils, B cells, and plasma cells.<sup>18</sup> In other cases, biopsy has failed to demonstrate myocardial infiltrates<sup>132</sup> and evidence of myocarditis.<sup>133</sup> Cases reported to date do not suggest a delayed hypersensitivity reaction, such as a serum sickness-like reaction or eosinophilic infiltrate.<sup>134</sup> Furthermore, no cases have had associated thrombotic events, thrombocytopenia, or disseminated intravascular coagulation.<sup>12</sup>

### Benefit-to-Risk Ratio

Currently approved COVID-19 mRNA vaccines are highly effective and have been shown to be safe in large-scale trials.<sup>135,136</sup> Most reported systemic reactions have been mild and transient, albeit more common among younger individuals and after the second vaccine dose. Adverse cardiovascular effects in these trials have been largely isolated, with an incidence of <0.05%, and there have been no reported cases of myocarditis. Rates of hypertension, bradycardia, atrial fibrillation, acute coronary syndrome, cerebrovascular events, and heart failure have been similar between vaccine and placebo arms.

Importantly, a very favorable benefit-to-risk ratio exists with the COVID-19 vaccine for all age and sex groups evaluated thus far.<sup>12,121,123,128,137,138</sup> This is particularly true when inventorying the severe risks of SARS-CoV-2 infection, including a mortality rate of 1-10 per million individuals aged 12-29 years. As of May 22, 2021, it was estimated that for every 1 million male individuals aged 12-29 years administered a second dose of the COVID-19 mRNA vaccine, approximately 39-47 cases of myocarditis would be expected, but 560 hospitalizations, 138 intensive care unit admissions, and 6 deaths would be prevented (see **Figure 4**).<sup>123</sup> In addition, beyond helping to mitigate the risk



of hospitalization and death related to SARS-CoV-2 infection, vaccination can help reduce the risk of related complications, such as myocarditis, MIS-A,<sup>139</sup> and PASC.<sup>12,140</sup>

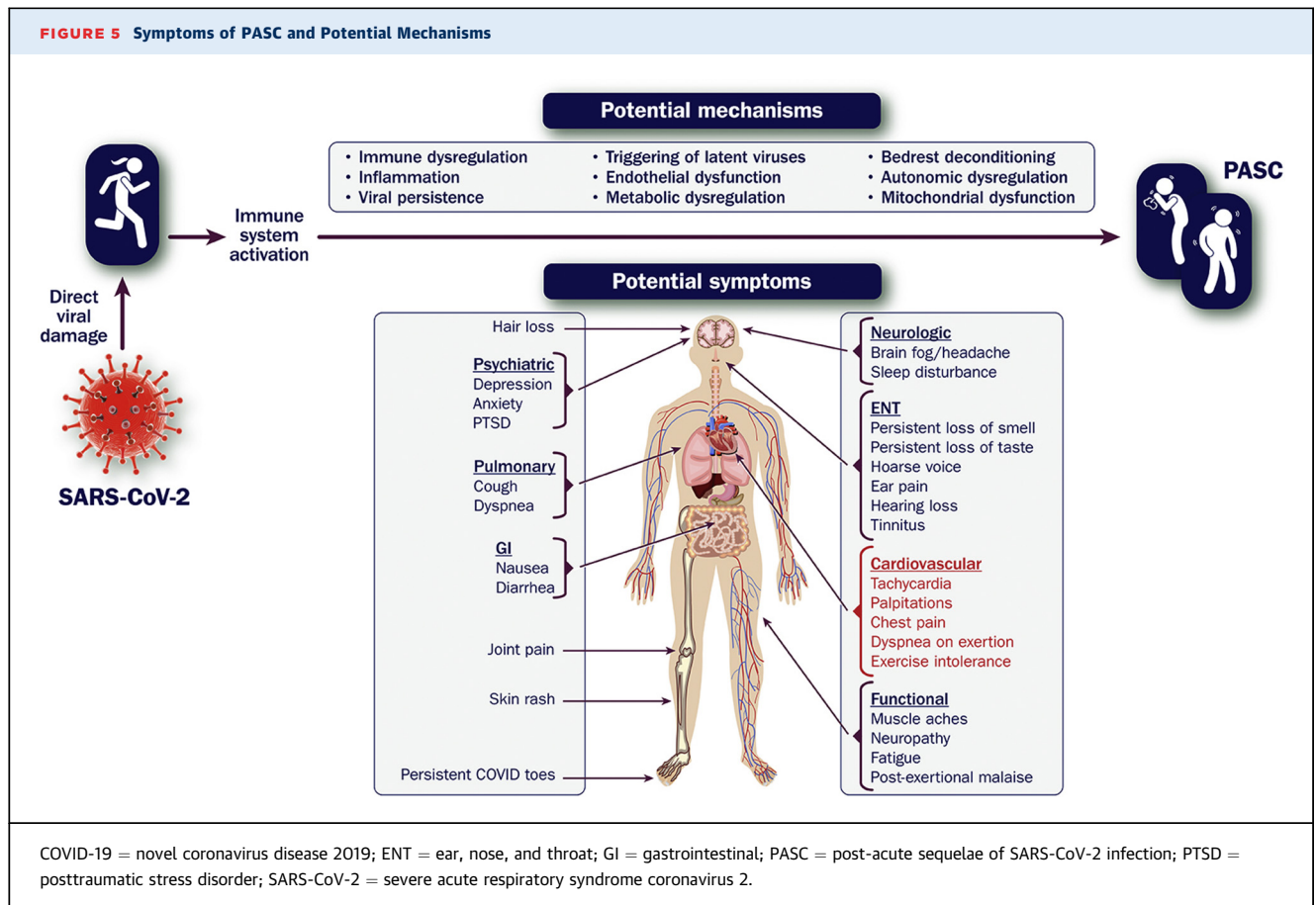
### Evaluation and Management

In general, vaccine-associated myocarditis should be diagnosed, categorized, and treated in a manner analogous to myocarditis following SARS-CoV-2 infection (see [Figure 3](#)). Individuals presenting with chest pain early after receiving the COVID-19 mRNA vaccine should be evaluated for possible myocarditis. Initial testing should include an ECG, measurement of cTn, and an echocardiogram. If myocarditis is suspected, cardiology consultation and further testing with CMR should be performed. Evaluation for current (and potentially prior) SARS-CoV-2 infection is also recommended. Coronary angiography and endomyocardial biopsy are rarely indicated unless a significant level of concern exists for flow-limiting coronary artery disease or specific forms of myocarditis (eg, giant cell).

Patients with 1) chest pain; 2) an elevated cTn; 3) abnormal electrocardiographic, echocardiographic, and/or CMR findings; 4) concerning arrhythmias; and/or 5) hemodynamic instability should be hospitalized for close monitoring. For those with rapidly improving symptoms, a normal or improving cTn level, and a normal LVEF, anti-

inflammatory medications may not be needed. Use of nonsteroidal anti-inflammatory drugs, colchicine, and corticosteroids should be considered, however, in those with ongoing symptoms. Analogous to fulminant myocarditis related to SARS-CoV-2 infection, intravenous corticosteroids, along with other forms of circulatory support, may be considered in those with LV systolic dysfunction, worsening heart failure, ventricular arrhythmias, and/or hemodynamic instability. Once clinically stable, guideline-directed medical therapy for heart failure should be initiated, with continuation at discharge. In addition, strenuous physical activity should be avoided for 3-6 months, as outlined in the RTP section.

Limited data currently exist regarding the safety of COVID-19 vaccination for individuals with a history of myocarditis or pericarditis unrelated to COVID-19 mRNA vaccines. Centers for Disease Control and Prevention (CDC) guidelines currently recommend that such individuals be vaccinated against COVID-19 after their myocarditis/pericarditis episode has completely resolved.<sup>142</sup> In contrast, the guidelines recommend that no further doses of any COVID-19 vaccine be given to those who developed myocarditis/pericarditis following COVID-19 mRNA vaccination. The guidelines acknowledge that this decision should be informed, however, by an individual's risk for severe COVID-19 illness.



### 6.1.8. Future Directions

The incidence, risk factors, mechanisms, preferred diagnostic and therapeutic approaches, and prognosis for viral-mediated and mRNA vaccine-associated myocarditis remain incompletely understood. Because of this, additional systematic, cross-sectional data are needed to describe the frequency, type, and severity of myocarditis and myocardial involvement observed. Randomized trials are also needed to better understand the preferred means to test and treat patients with myocarditis related both to SARS-CoV-2 infection and mRNA vaccination. Although randomized trials in myocarditis have been challenging historically, the current pandemic has created unique opportunities for further investigation.

## 6.2. Section 2: Post-acute Sequelae of SARS-CoV-2 Infection

### 6.2.1. Overview

PASC is a term used to describe a constellation of new, returning, or persistent health problems experienced by individuals 4 or more weeks after SARS-CoV-2 infection.<sup>15</sup> Patients with this condition commonly experience wide-ranging symptoms, including fatigue, cognitive

dysfunction, sleep disturbance, and exercise intolerance. Reported symptoms encompass nearly every organ system, with varying impacts on quality of life (see [Figure 5](#)).

Chest pain, dyspnea, and palpitations represent some of the key symptoms that draw attention to the cardiovascular system. Affected individuals may also experience elevated blood pressure, tachycardia out of proportion to that expected for effort, and/or drops in oxygen saturation. Given that the pathophysiology of PASC is poorly understood and the underlying drivers may be heterogeneous, a unifying explanation is often lacking. Added to this is a paucity of data to help guide diagnosis, treatment, and prognosis.

Cognizant of this, we nonetheless propose a systematic approach to assist in the evaluation and management of PASC, recognizing that the evidence base will evolve over time. Importantly, patient-centered care models are needed to optimally address this condition, with coordination by multidisciplinary teams that include primary care clinicians, specialists (eg, pulmonologists, cardiologists, neurologists, rheumatologists, psychiatrists, infectious disease experts), social workers, psychologists, and physical therapists.

### 6.2.2. Definition

PASC is a heterogeneous disorder without a universally accepted definition for its widely varying presentations. Patients with PASC have symptoms that present after SARS-CoV-2 infection, usually persisting for 4-12 weeks and beyond.<sup>143,144</sup> Although some groups have differentiated an earlier “postacute period” (4-12 weeks after acute infection) from a later “chronic period” (>12 weeks after acute infection), it is not clear whether this distinction is important as it relates to the underlying mechanisms, evaluation, or management and whether symptoms that extend even beyond 12 months should be considered separately.<sup>111,145,146</sup> The United Kingdom’s National Institute for Health Care and Excellence has defined PASC as a condition in which symptoms and signs developing during or after an infection consistent with COVID-19 continue for more than 12 weeks and are not explained by an alternative diagnosis.<sup>147</sup> This definition mirrors that of the World Health Organization, which defines PASC as a condition that occurs in individuals with a history of probable or confirmed SARS-CoV-2 infection (usually 3 months from the onset of COVID-19), with symptoms that last for at least 2 months that are not explained by an alternative diagnosis.<sup>14</sup> The CDC uses an earlier timepoint and defines PASC as a wide range of new, returning, or ongoing health problems that are present 4 or more weeks after first being infected with SARS-CoV-2.<sup>15</sup> Irrespective of the definition used, it is important to realize that individuals without symptoms in the days or weeks after infection can still develop PASC.<sup>15</sup>

Details related to a patient’s acute illness can help place persistent symptoms into context and identify alternative diagnoses. For example, those with extensive lung injury, requirement for mechanical ventilation, and/or serious cardiovascular complications may experience protracted sequelae related to the initial insult. Some patients may experience postintensive care syndrome, which includes physical, cognitive, and mental health problems that can either be directly or indirectly related to critical illness from SARS-CoV-2 infection.<sup>148</sup> Similarly, persistence and/or marked worsening of symptoms (eg, fever, lightheadedness, chest pain, shortness of breath, gastrointestinal symptoms) throughout the early post-acute period may suggest a hyperinflammatory state, such as MIS-A.<sup>149,150</sup>

PASC may occur in individuals with widely varying initial presentations, ranging from asymptomatic infection to critical illness.<sup>111</sup> Debilitating PASC symptoms have been reported in individuals with mild SARS-CoV-2 infection without underlying cardiopulmonary disease, resulting in declines in health status and quality of life that have affected their ability to return to work, participate in daily activities, or exercise.<sup>111,151-153</sup> Cardiac

evaluation in these patients may also fail to identify a specific etiology for their reported symptoms.<sup>154-158</sup> Collectively, this can be a source of tremendous frustration for patients and clinicians alike and may lead to significant variation in care.

### 6.2.3. Framework

To help provide clarity as to the potential etiology of cardiovascular symptoms with PASC, the writing committee proposes a taxonomy that differentiates known cardiovascular disease entities that can present during the early post-acute or chronic periods of COVID-19 (PASC-CVD) from cardiovascular symptoms that extend beyond the acute infection and are not fully explained by initial testing (PASC-CVS). Differentiating PASC-CVD from PASC-CVS can help direct appropriate referrals and establish pathways for efficient evaluation and management. Moreover, focused attention on these conditions can accelerate research and educational efforts aimed at improving outcomes.

Distinguishing between PASC-CVD and PASC-CVS may depend, in part, on the testing approach taken and the findings that follow. Of note, identified abnormalities may or may not relate to reported symptoms. Several echocardiographic studies have shown limited structural and functional abnormalities in those who have recovered from their acute illness<sup>159-161</sup> and in those with persistent cardiopulmonary symptoms suggestive of PASC. In a study of 145 patients recovering from COVID-19 (41% of whom had persistent symptoms) 60 and 100 days after infection, diastolic dysfunction was detected in 60% and 55%, respectively; LV systolic dysfunction, however, was detected in only 4 patients.<sup>160</sup> In a separate study of 47 patients convalescing from COVID-19 (an average of 67 days after diagnosis), CMR and FDG-PET were performed.<sup>19</sup> Nineteen patients (40%) had ongoing cardiac symptoms, and 8 (17%) were noted to have myocardial inflammation by FDG-PET that correlated with CMR abnormalities and laboratory markers of inflammation. Although cardiac symptoms were approximately twice as common in individuals with abnormalities on FDG-PET, this was not statistically significant. Recognizing that different imaging studies may identify less overt forms of underlying myocardial involvement,<sup>11,63,157</sup> it is not always clear whether identified abnormalities relate to prior SARS-CoV-2 infection, a different disease process, or an incidental finding unrelated to the current presentation.

#### PASC-CVD

PASC-CVD refers to a broad group of cardiovascular conditions that manifest  $\geq 4$  weeks after SARS-CoV-2 infection. Timing, however, may vary depending upon initial illness severity. PASC-CVD includes, but is not limited to,



myocarditis and other forms of myocardial involvement, pericarditis, new or worsening myocardial ischemia due to obstructive coronary artery disease, microvascular dysfunction, nonischemic cardiomyopathy with involvement of the left and/or right ventricles, thromboembolism, cardiovascular sequelae of pulmonary disease (eg, pulmonary hypertension, right ventricular failure), and arrhythmia (eg, atrial fibrillation, premature ventricular contractions, nonsustained ventricular tachycardia).

Discerning whether PASC-CVD began with acute infection, during illness resolution, or as a new condition postrecovery can be challenging. This is, in part, related to variability in the timing of clinical presentation and the type of diagnostic testing performed. Self-isolation may further limit early detection; moreover, some patients may choose to defer care, with the expectation that any lingering symptoms will improve over time. Where possible, evaluation and management strategies for the most common PASC-CVD entities (eg, cardiomyopathy, ischemic heart disease, arrhythmia) should follow existing guideline recommendations.

#### **PASC-CVS**

PASC-CVS is a heterogeneous disorder that includes widely ranging cardiovascular symptoms, without objective evidence of cardiovascular disease using standard diagnostic tests. Exercise intolerance and tachycardia are two of the most common reported symptoms; others include chest pain and dyspnea, with or without exercise intolerance. Additional accompanying symptoms include fatigue; cognitive complaints, including memory impairment, attention deficit, and poor executive function (frequently described as brain fog);<sup>162</sup> sleep disturbance or nonrestorative sleep; and postexertional malaise.

There are no established timelines for when a diagnosis of PASC-CVS should be considered. Importantly, its diagnosis should balance the potential benefits of early detection, diagnosis, and intervention against the pitfalls of unnecessary testing and medicalization of people who would otherwise recover without intervention. PASC-CVS should be considered when cardiovascular symptoms persist beyond a timeframe typical for the severity of acute infection and projected recovery based on a person's age and underlying health status. For example, it may be reasonable to consider PASC when symptoms persist beyond 4 weeks after mild acute infection, as opposed to waiting more than 12 weeks as suggested in the National Institute for Health and Care Excellence and World Health Organization definitions.

#### **Associated Conditions**

Patients with PASC-CVS may meet criteria for other established syndromes. Debate currently exists, however, as to whether these other conditions fully characterize the experience of patients with PASC-CVS phenotypes.

#### **Postural Orthostatic Tachycardia Syndrome**

Orthostatic intolerance with excessive tachycardia upon standing may reflect postural orthostatic tachycardia syndrome (POTS).<sup>163</sup> Patients with POTS generally have a heart rate >30 beats per minute above the supine heart rate after 5-10 minutes of quiet standing (and frequently >120 beats per minute) in the absence of orthostatic hypotension. Other postural symptoms are common, including palpitations, lightheadedness, weakness, fatigue, blurry vision, and exercise intolerance.<sup>164</sup> In a study of 152 patients with POTS predating COVID-19, 42% of cases were preceded by a viral infection.<sup>165</sup> Although much remains to be learned about the relationship between POTS and PASC,<sup>166</sup> it is important to recognize that other forms of tachycardia (eg, sinus, inappropriate sinus) may be commonly found.<sup>167</sup>

#### **Myalgic Encephalomyelitis/Chronic Fatigue Syndrome**

The clustering of exercise intolerance with symptoms of fatigue, postexertional malaise, and brain fog has prompted comparison of PASC to myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS).<sup>168</sup> ME/CFS is defined by a triad of symptoms: 1) substantial impairment in the ability to function at home or at work, lasting for more than 6 months, accompanied by profound fatigue of new or definite onset (but not lifelong) that is not appreciably alleviated by rest; 2) postexertional malaise; and 3) unrefreshing sleep.<sup>169</sup> Patients must also have either orthostatic intolerance or cognitive impairment.<sup>169</sup> Although ME/CFS has been reported after infection (eg, Epstein-Barr virus, cytomegalovirus, human herpesvirus 6 and 8, *Borrelia burgdorferi*), a direct link between infection and prolonged symptoms is usually lacking. Even though some have suggested that ME/CFS and PASC share a common pathophysiology (including immune and metabolic system dysregulation), ME/CFS still remains poorly understood, with relatively few practitioners experienced in diagnosing and treating it.

#### **6.2.4. Epidemiology**

Data suggest that as many as 10%-30% of individuals may experience prolonged symptoms following SARS-CoV-2 infection, a subset of which may relate to the cardiovascular system.<sup>9</sup> In a community sample of >500,000 U.K. residents participating in the REACT-2 (Real-Time Assessment of Community Transmission-2) study, one-third of those self-reporting a history of COVID-19 noted at least one symptom (such as shortness of breath, chest pain, or tiredness) and nearly 15% experienced 3 or more symptoms lasting 12 weeks or longer.<sup>153</sup> Similarly, in a study of Swedish health care workers, 10% reported persistent symptoms more than 8 months following mild infection, with dyspnea and palpitations among the top 10 symptoms reported.<sup>151</sup> Finally, in a study of patients

hospitalized for COVID-19 in Hong Kong, 10% reported tachycardia at 6 months, with no significant change at 12 months.<sup>146</sup>

Further insight comes from an online survey conducted by a self-organized group of citizen scientists attempting to better understand the long-term sequelae of COVID-19.<sup>152</sup> More than 3,700 self-described COVID-19 long haulers from 56 countries participated in the survey, most of whom were White women between the ages of 30 and 60 years. Only 8% were hospitalized for COVID-19, but >90% reported symptoms persisting beyond 35 weeks and one-half were unable to return to work at 6 months. Although fatigue, breathing difficulties, and cognitive impairment were the most common symptoms, 85% self-reported cardiovascular symptoms (eg, chest pain/burning, palpitations, tachycardia). Among those with tachycardia (n = 2,308), 73% were able to measure their heart rate and 52% noted a >30 beats per minute increase in heart rate with standing. Similar observations come from a separate survey of more than 5,000 individuals with prior COVID-19, where an average of 21 symptoms were reported >3 weeks after infection, with palpitations or persistent chest pain/pressure noted by more than one-third.<sup>170</sup>

Importantly, these studies have major design limitations, including response bias and lack of a control group. Moreover, few studies have assessed important nuances in symptom presentation that may suggest specific cardiovascular diagnoses or syndromes. For example, in a large observational study of 3,597 U.S. collegiate athletes, cardiovascular diagnoses (consistent with PASC-CVD) were found in a minority of those with persistent exertional chest pain or shortness of breath and in none with exercise intolerance.<sup>171</sup> Similarly, in a study of 126 consecutive patients with PASC evaluated in a cardiology clinic for cardiovascular symptoms, only 23% were found to have a corresponding cardiovascular diagnosis.<sup>158</sup> Because most had symptoms that could not be attributed to cardiovascular disease, there is a pressing need to more fully research this condition. It is anticipated that the ongoing multicenter, prospective CDC study that is comparing long-term outcomes of symptomatic adults who test positive for SARS-CoV-2 to those who test negative will help shed light on persistent symptom prevalence, duration, and trajectory.<sup>172</sup>

### 6.2.5. Mechanisms

Multiple mechanistic underpinnings for PASC-CVS have been proposed, including inflammation,<sup>173</sup> immune activation,<sup>173,174</sup> viral persistence,<sup>175</sup> triggering of latent viruses,<sup>176</sup> endothelial dysfunction,<sup>177,178</sup> impaired exercise metabolism,<sup>179</sup> and profound cardiac deconditioning following viral infection.<sup>180,181</sup> Importantly, some or all of these may be at play within a given patient. Rather than focusing on a specific mechanism (which may be a

challenge to identify and address), we present some of the most common cardiovascular symptoms and mechanisms that may underlie them.

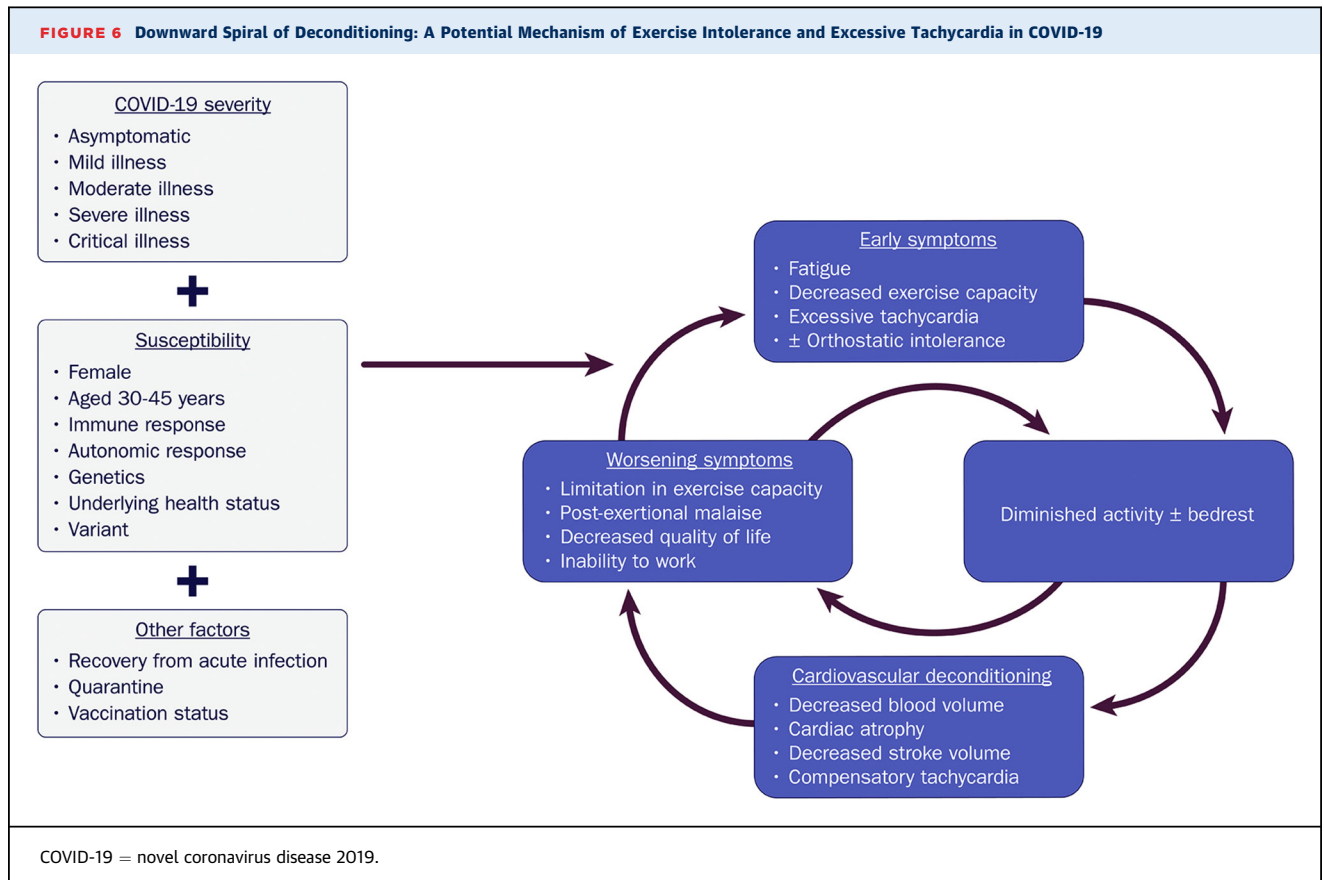
### Tachycardia and exercise intolerance

Under normal conditions, heart rate is determined by 3 factors: 1) intrinsic heart rate, 2) parasympathetic (vagal) neural tone, and 3) sympathetic (adrenergic) neural tone. Multiple central regulatory pathway inputs influence neural control of heart rate, both at rest and during exercise. This includes arterial and cardiac baroreceptors, feed-forward influences (central command), and feedback from group III mechanoreceptors and group IV metaboreceptors within skeletal muscle. Collectively, these inputs precisely regulate oxygen delivery, response of cardiac output to exercise, and changes in metabolic demand. Because heart rate and cardiac output are so tightly regulated, sinus tachycardia is usually an appropriate compensatory response and rarely reflects dysautonomia.<sup>166,182-184</sup>

Fatigue and exercise intolerance may have several underlying causes, including alterations in immune activity and metabolism. Identification of these changes in clinical settings, however, can be challenging. Deconditioning represents a final common pathway that can either incite or exacerbate these symptoms, triggered by as little as 20 hours of bedrest and a sudden decline in physical activity from baseline.<sup>181,185-187</sup> Reduced plasma volume and secondary cardiac atrophy may ensue,<sup>183</sup> with a shift in the LV pressure-volume curve (because of hypovolemia). This results in a reduced stroke volume at any degree of orthostatic stress and ultimately, compensatory tachycardia.<sup>182,183,188</sup>

Although some degree of deconditioning with moderate and severe illness may be unavoidable, it is unclear why limited durations of bedrest and modest physical inactivity in those who are asymptomatic or with mild COVID-19 illness result in similar degrees of deconditioning.<sup>181</sup> In a study of 247 patients with COVID-19 who isolated at home, fatigue and dyspnea were reported by 30% and 15%, respectively, at 6 months.<sup>189</sup> Underlying drivers for this include an enhanced hyperadrenergic state, volume dysregulation, mast cell activation, peripheral autonomic neuropathy, and/or autonomic dysfunction.<sup>166</sup> Regardless of the inciting cause, once symptoms develop, there is the potential for rapid decompensation in a downward spiral, where short periods of bedrest produce orthostatic/exercise intolerance and tachycardia, leading to further inactivity, worsening of cardiovascular deconditioning, and even more debilitating symptoms (see [Figure 6](#)).<sup>164</sup> In fact, this is considered to be one of the key mechanisms underlying POTS.<sup>184</sup>

Importantly, although exercise therapy is essential to recovery, standard exercise involving upright activity (eg, walking, jogging) may worsen symptoms of PASC-CVS,

**FIGURE 6** Downward Spiral of Deconditioning: A Potential Mechanism of Exercise Intolerance and Excessive Tachycardia in COVID-19

further prolonging recovery. This is because upright activity perpetuates the physiology of bedrest deconditioning,<sup>181</sup> including decreased blood volume, decreased venous return, and cardiac atrophy, with accompanying vagal withdrawal and sympathetic activation. Acknowledging that other mechanisms for fatigue, exercise intolerance, and excessive tachycardia likely exist, the construct of bedrest deconditioning provides a unifying explanation for these symptoms, as well as a paradigm to focus recovery.

### Chest pain

Multiple factors may contribute to chest pain (or other types of chest discomfort) with PASC-CVS in the absence of known forms of PASC-CVD. Vascular endothelial injury may result directly from SARS-CoV-2 infection or indirectly from an exaggerated immune response. Endothelial dysfunction resulting from acute infection or ongoing inflammation may also increase the potential for coronary vasospasm.<sup>177,190,191</sup> In a study of 11 PASC patients with angina and suspected ischemia, invasive coronary vasomotion testing revealed abnormal endothelial-dependent responses to acetylcholine in 82%; this was driven by a mix of endothelial-dependent and endothelial-independent (smooth muscle) effects.<sup>192</sup> Other potential contributors include myocardial and/or pericardial

disease that may have gone undetected with initial testing. Finally, chest pain is a common feature of POTS and ME/CFS; the underlying mechanisms for this, however, remain poorly understood.

### Dyspnea

Shortness of breath, cough, and pleuritic chest pain represent commonly reported symptoms with PASC. Some may also note inability to take a full breath or air hunger with exertion, prompting interruption of ambulation on flat ground and/or basic activities of daily living.

Although dyspnea is common in patients with myocardial ischemia, heart failure, and arrhythmia, it may also be seen in those with pulmonary complications following SARS-CoV-2 infection. These include: 1) pulmonary embolism, especially if dyspnea is accompanied by exercise-induced oxygen desaturation, tachycardia, and/or presyncope/syncope; 2) pneumonia; 3) impaired diffusion capacity for carbon monoxide; 4) pulmonary fibrosis; 5) neuromuscular weakness; 6) new or worsening asthma; and 7) bronchial hyperreactivity due to pulmonary vascular inflammation. Among patients hospitalized for COVID-19, lung function impairment is common 6 months after discharge.<sup>33,193,194</sup>

Unexplained dyspnea (in the absence of cardiopulmonary abnormalities) may also be seen with PASC and may

relate to deconditioning with poor cardiovascular fitness. In a study of 70 patients with COVID-19, 41 (59%) had persistent dyspnea at 3 months.<sup>195</sup> Although women were more likely to experience dyspnea, there was no association with age, baseline comorbidities, hospitalization for COVID-19, echocardiographic findings, or cardiac biomarkers. On cardiopulmonary exercise testing (CPET), however, those with dyspnea had a lower peak  $\text{VO}_2$ , lower  $\text{VO}_2$  at anaerobic threshold, and greater ventilatory inefficiency. Similarly, in a case-control study that compared 10 patients with unexplained dyspnea and exercise intolerance 11 months after COVID-19 to 10 age- and sex-matched controls, those with PASC had an appreciably lower peak aerobic exercise capacity.<sup>188</sup> Patients with PASC also had lower stroke volumes, lower left-sided filling pressures, higher heart rates, lower systemic oxygen extraction, and greater ventilatory inefficiency. Finally, in a study of 41 patients with PASC and unexplained dyspnea, ventilatory abnormalities were found in 88% by CPET.<sup>196</sup> Further studies are still needed to better understand drivers of dyspnea in this population, including assessment of pulmonary flow-volume loops during exercise to look for dynamic hyperinflation, expiratory flow limitation, and exercise-induced hypoxemia.

#### 6.2.6. Evaluation

A multidisciplinary approach should be used in the evaluation of most patients with PASC. Primary care clinicians are usually the first point of contact for these patients, helping to oversee and coordinate care with other specialists, including pulmonologists, cardiologists, neurologists, rheumatologists, psychiatrists, and infectious disease experts. Within this framework, a basic cardiopulmonary evaluation can usually be performed up front to determine the need for specialty care.

Although symptom type and severity should inform diagnostic testing, a reasonable initial approach for those with cardiovascular symptoms includes: 1) basic laboratory testing (eg, complete blood count, basic metabolic panel, cTn, C-reactive protein); 2) an ECG; 3) an echocardiogram; 4) an ambulatory rhythm monitor; 5) chest imaging (X-ray and/or CT); and/or 6) pulmonary function tests. Cardiology consultation is recommended for those with: 1) abnormal cardiac test results; 2) known cardiovascular disease with new or worsening symptoms or signs (eg, worsening dyspnea in a patient with known heart failure); 3) documented cardiac complications during SARS-CoV-2 infection; and/or 4) persistent cardiopulmonary symptoms that are not otherwise explained.

As part of a PASC evaluation, cardiologists should perform a thorough history and physical examination, reviewing all relevant tests to help determine the probability of PASC-CVD. Importantly, previously unrecognized

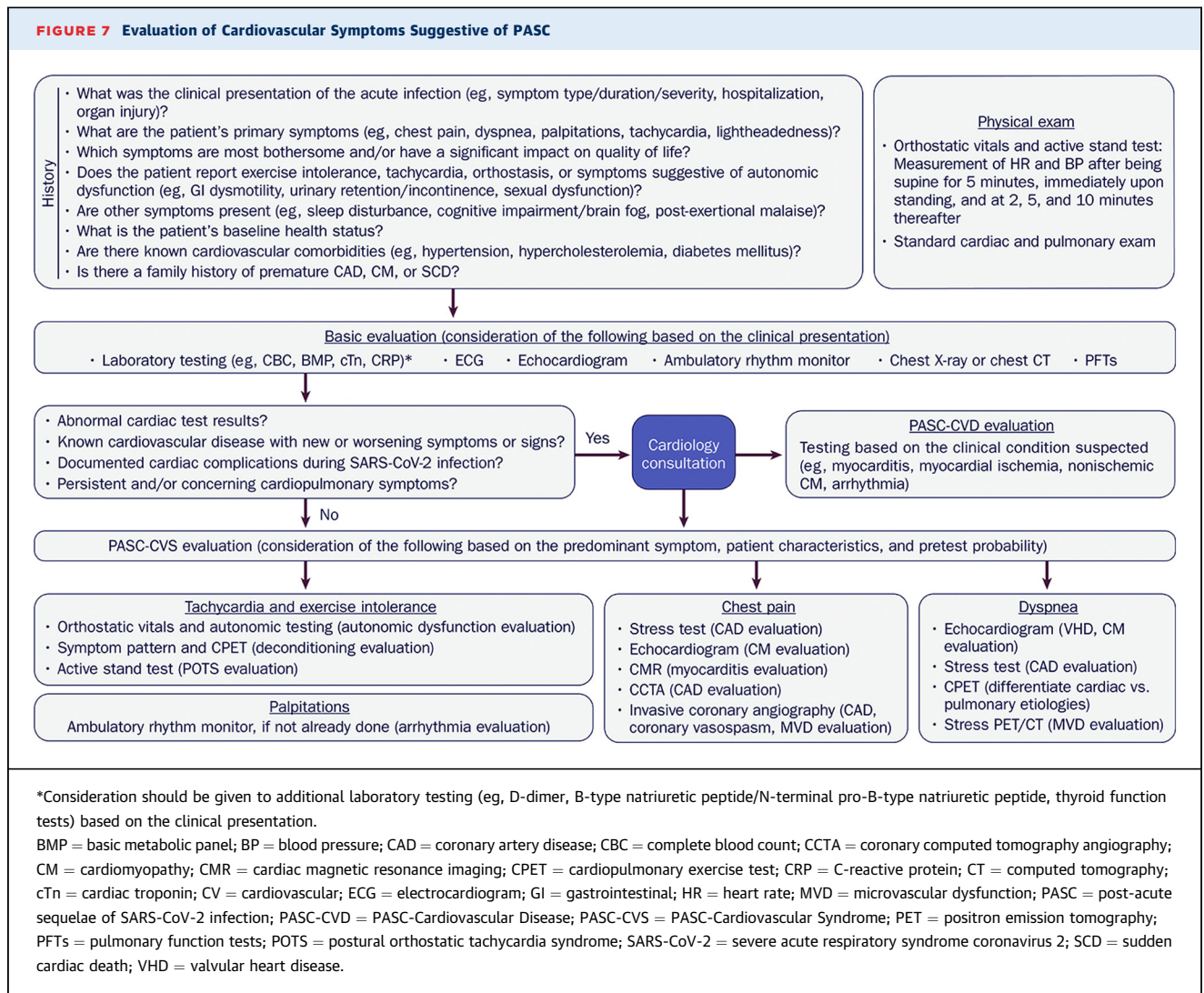
cardiac disease may only become clinically evident in the setting of acute illness. If myocarditis, pericarditis, or other myocardial involvement is suspected, further evaluation should be performed as recommended in the myocarditis section. Additional testing may also be required based on the clinical presentation (eg, CT pulmonary angiography for suspected pulmonary embolism). Ultimately, for those with persistent symptoms but without PASC-CVD, additional evaluation for PASC-CVS should be performed, dictated by: 1) the most prominent symptom(s); 2) the patient's baseline characteristics; and 3) the pretest probability of cardiovascular disease (see [Figure 7](#)).

#### Tachycardia and exercise intolerance

While other potential causes of tachycardia (eg, arrhythmia, heart failure, pulmonary embolism) are considered, initial outpatient testing should include a 10-minute active stand test to assess for dynamic changes in blood pressure and heart rate. This involves measurement of blood pressure and heart rate 5 minutes after being supine, immediately upon standing, and at 2, 5, and 10 minutes thereafter. Orthostatic hypotension is defined by a drop in systolic blood pressure of at least 20 mm Hg or diastolic blood pressure of at least 10 mm Hg within 3 minutes of standing. In the absence of orthostatic hypotension, POTS is defined by an increase in heart rate of >30 beats per minute in those aged  $\geq 19$  years or >40 beats per minute in those aged <19 years and/or a heart rate of >120 beats per minute during the 10-minute active stand test. Of note, tachycardia should last for more than 30 seconds and be accompanied by symptoms. It is also important that the patient stand quietly for the full 10 minutes, as an increase in heart rate may take time. Tachycardia unrelated to position is likely due to inappropriate sinus tachycardia, especially if the heart rate does not slow at night. If feasible, a 6-minute walk test can help to assess functional capacity, while monitoring heart rate and oxygen saturation.

Ambulatory rhythm monitoring should also be considered to exclude arrhythmia and define the pattern of heart rate elevation. Whereas the latter can likely be done with a 24- to 48-hour Holter monitor, longer-duration monitoring (eg, extended Holter monitor, event monitor) should be considered in those with episodic palpitations, depending upon their reported frequency. Mobile health devices capable of heart rate and ECG monitoring can also help in evaluation and surveillance monitoring during recovery.

Even though affected individuals may have a resting heart rate that is higher than that expected for one's age and training state, and higher than that reported before COVID-19, such increases may be physiologically appropriate and should not automatically invite assumption of autonomic dysregulation. Increases in heart rate may be

**FIGURE 7** Evaluation of Cardiovascular Symptoms Suggestive of PASC

observed at unexpected times throughout the day or night, including during sleep and sedentary periods. Some may also note excessive tachycardia in response to minimal exercise, with greater heart rate recovery times following activity. Ultimately, although potential underlying mechanisms for persistent tachycardia (eg, increased adrenergic tone, deconditioning) should be considered, they may prove challenging to discern in most clinical settings.

### Chest pain

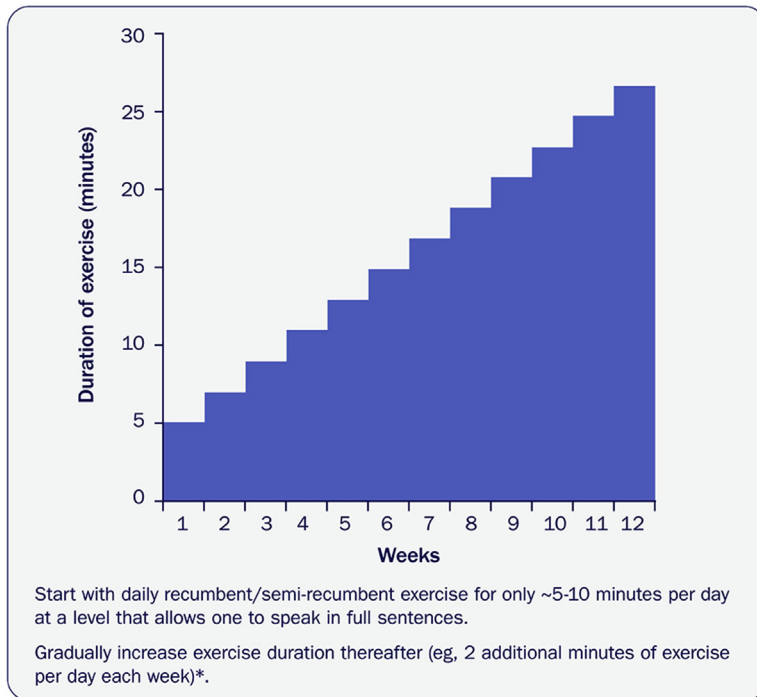
If not previously performed, an ischemia evaluation should be conducted based on guideline recommendations.<sup>197</sup> For low-risk patients, either coronary artery calcium testing or exercise testing without imaging is a reasonable first-line approach. For higher-risk patients, either CT coronary angiography or stress imaging (stress echocardiography, PET/single-photon emission computed tomography myocardial perfusion imaging, or CMR) should be performed, especially if there is an inability to

exercise and/or the ECG is uninterpretable. If microvascular dysfunction is suspected, PET myocardial perfusion imaging can be particularly useful; when unavailable, stress imaging using echocardiography, single-photon emission computed tomography myocardial perfusion imaging, or CMR should be considered. Invasive coronary angiography should be reserved for those with abnormal noninvasive test results or those in whom there is a very strong suspicion for obstructive coronary artery disease or vasospasm.<sup>158,192</sup> Invasive coronary vasomotor testing can help with evaluation of the latter; however, referral to a specialized center may be needed.

### Dyspnea

Given the proclivity of SARS-CoV-2 infection to involve the lungs, initial diagnostic testing should focus on exclusion of pulmonary processes. Most commonly, this involves a chest X-ray and/or a noncontrast CT scan of the lungs, along with pulmonary function testing. If

**FIGURE 8** Sample Recumbent Exercise Therapy Prescription



### Recumbent/Semi-recumbent Exercise



Cycling



Rowing

\*For a more precise prescription for exercise therapy with heart rate targets and patient exercise logs, see appendix to Bryarly et al.<sup>164</sup>

unrevealing, consideration should be given to CPET with flow-volume loops (if available) to characterize cardiac and pulmonary reserve. A CT pulmonary angiogram or ventilation-perfusion (V/Q) scan should also be considered if pulmonary embolism is suspected. Finally, an ischemia evaluation should be pursued if obstructive coronary artery disease or microvascular dysfunction is suspected.

#### 6.2.7. Management

Most treatment recommendations related to PASC-CVD should be based on current guidelines; those related to PASC-CVS largely depend on the underlying symptom(s).

#### Tachycardia and exercise intolerance

For those with tachycardia, exercise/orthostatic intolerance, and/or deconditioning, interventions normally used for POTS should be considered. The benefits of exercise training following bedrest deconditioning<sup>187,198</sup> and that resulting from POTS<sup>184,185,199</sup> are well-described. Exercise training increases cardiac mass and blood volume, improves ventricular compliance, and shifts the Frank-Starling curve upward, increasing stroke volume, improving maximal oxygen uptake, and ultimately increasing functional capacity.

To achieve these effects, however, specific types of exercise training are recommended. Importantly, such patients are usually unable to tolerate upright exercise (eg, power walking, jogging); moreover, upright exercise can worsen fatigue, resulting in postexertional malaise. This has led the U.K.'s NICE guidelines to caution against graded exercise therapy for patients recovering from COVID-19, specifically those diagnosed with ME/CFS.<sup>200</sup> However, not all exercise is problematic.<sup>201</sup> Instead of upright exercise, recumbent or semi-recumbent exercise (eg, rowing, swimming, or cycling) is recommended initially (see **Figure 8**), with transition to upright exercise over time as orthostatic intolerance resolves.<sup>185,198,202</sup>

In addition, exercise duration should be short initially, increasing gradually as functional capacity increases. Exercise intensity should also be at a submaximal level, sustained for the duration of exercise, with natural increases as tolerance improves. For example, patients should generally start with daily recumbent exercise for only ~5-10 minutes at a level that allows them to speak in full sentences; thereafter, gradual increases in exercise (eg, 2 additional minutes of exercise per day each week) are recommended (see **Figure 8**). These principles help to avoid worsening fatigue or setbacks and usually can be applied to all patients with deconditioning, regardless of

age and whether POTS is present.<sup>203</sup> This type of program has also been shown to support long-term cardiovascular health.<sup>204</sup> Ultimately, a formalized exercise program should be initiated. For some patients, this may be best done in a supervised setting with a physical therapist; alternatively, specific instructions may be provided on how to implement such a program at home or in a gym.<sup>164,199</sup>

Given the reduction in plasma volume that follows deconditioning,<sup>183-185</sup> nonpharmacological interventions should be considered that address this pathophysiology. This includes salt and fluid loading (provided blood pressure is controlled), elevation of the head of one's bed with 4-6-inch (10-15-cm) blocks during sleep, and use of support stockings (waist-high to ensure sufficient support of central blood volume).<sup>164</sup> Salt loading may be achieved through liberalized sodium intake (5-10 g or 1-2 teaspoons of table salt per day); salt tablets, however, should be avoided to minimize nausea and vomiting. Patients should also be encouraged to drink 3 liters of water or an electrolyte-balanced fluid per day. Attention should be paid to avoid factors that contribute to dehydration, such as consumption of alcohol and/or caffeine, ingestion of large heavy meals, and excessive heat exposure.<sup>164</sup>

Although no pharmacological therapies are currently approved for PASC-CVS, various treatments may be used empirically. For example, if palpitations predominate, a low-dose beta-blocker (eg, bisoprolol, metoprolol, nebivolol, propranolol) or a nondihydropyridine calcium-channel blocker (eg, diltiazem, verapamil) may be added and gradually titrated to slow the heart rate. This may help to modestly improve exercise tolerance and alleviate symptoms, and patients can be weaned from these therapies as their fitness and activity improve. Even though they have not been shown to consistently improve quality of life beyond exercise training in those with POTS,<sup>205</sup> nonselective beta-blockers that inhibit beta-2 adrenergic receptor-mediated vasodilation (eg, propranolol) may help to control debilitating symptoms in those with orthostatic intolerance with a hyperadrenergic state.<sup>206,207</sup> Propranolol may also prove useful in those with coexisting anxiety or migraine.

Ivabradine has also been used in those with severe fatigue exacerbated by beta-blockers and calcium-channel blockers. Support for this approach comes from a trial of 22 patients with POTS, where improvement in heart rate and quality of life was observed following treatment with ivabradine for one month.<sup>208</sup> Fludrocortisone (up to 0.2 mg taken at night) may also be used in conjunction with salt loading to increase blood volume and help with orthostatic intolerance; careful monitoring to guard against hypokalemia, however, is critical. Finally, midodrine (2.5-10 mg) may help with orthostatic intolerance,

with the first dose taken in the morning before getting out of bed and the last dose taken no later than 4 pm.

### Chest pain

For patients with chest pain without evidence of ischemia, a variety of empiric treatments may be considered. If the pain is pleuritic in nature or there is an underlying inflammatory component (eg, costochondritis), a 1- to 2-week trial of nonsteroidal anti-inflammatory drugs is reasonable, with addition of low-dose colchicine as needed. If the symptoms worsen with nonsteroidal anti-inflammatory drugs, esophagitis and esophageal spasm should be considered. For those with suspected endothelial dysfunction, a calcium-channel blocker, a long-acting nitrate, and/or ranolazine may be tried. Aspirin and a high-intensity statin represent key components in those with underlying atherosclerotic cardiovascular disease. Finally, some nutritional supplements (eg, beetroot extract, L-arginine) can increase nitric oxide and may be considered in those with persistent chest pain refractory to other therapies or in those with suspected microvascular dysfunction. Beetroot extract can be taken 1 hour before exercise to achieve maximal vasodilation, and L-arginine may be used at a dose of 4 mg twice a day.<sup>209-211</sup>

### Dyspnea

For patients with dyspnea unrelated to cardiovascular disease, consideration should be given to pulmonary consultation to guide further evaluation and management. Importantly, low preload states can result in dyspnea, underscoring the importance of volume loading and recumbent exercise, as described in the tachycardia and exercise intolerance section.<sup>212</sup> Physical therapy that incorporates aerobic training and diaphragmatic breathing exercises can be a helpful adjunct to address underlying ventilatory abnormalities and muscle dysfunction,<sup>196,213</sup> as noted with other pulmonary diseases.

### 6.2.8. Future Directions

Both PASC-CVD and PASC-CVS may be encountered after SARS-CoV-2 infection, with varying effects on quality of life. Because much remains to be learned about these conditions,<sup>214</sup> substantial opportunities exist to better understand their epidemiology, underlying mechanisms, and best approaches for evaluation and management.<sup>214</sup> In addition, little is also currently known about the incidence of PASC in children, those with vaccine breakthrough infection, and those affected by newer SARS-CoV-2 variants (eg, Delta, Omicron). All of this underscores the need to conduct studies that leverage rigorous data collection and precise enrollment to define best practices for distinct phenotypes.<sup>172,215,216</sup> Given that the total cost of PASC to patients and their families, the health care system, payers, and society at large is likely to

**TABLE 1 Case Series Evaluating the Prevalence of Myocarditis, Other Myocardial Involvement, and Pericardial Involvement in Athletes Following SARS-CoV-2 Infection\***

Case Series	Competition Level	Sample Size	CMR Strategy	Age, Mean or Median Years	Sex, % Female	Symptomatic, n (%)	Myocarditis or Pericarditis, n (%)	Additional Observations
Rajpal et al <sup>223</sup> (Online September 11, 2020)	Collegiate	26	All athletes	20	42%	12 (46%)	Myocarditis: 4 (15%) Pericarditis: 0 (0%)	LGE: 12 (46%) Pericardial effusion: 2 (8%)
Brito et al <sup>74</sup> (Online November 4, 2020)	Collegiate	54	Symptomatic athletes and those with an abnormal ECG and/or echocardiogram (N = 48, 89%)	19	15%	38 (70%)	Myocarditis: 0 (0%) Pericarditis: 19 (40%)	Any CMR abnormality: 27 (56%)
Vago et al <sup>226</sup> (Online December 16, 2020)	Professional	12	All athletes	23	83%	10 (83%)	Myocarditis: 0 (0%) Pericarditis: 0 (0%)	NA
Clark et al <sup>224</sup> (Online December 17, 2020)	Collegiate	59 with COVID-19 60 athlete controls 27 healthy controls	All subjects	20 25 30	63%	46 (78%)	Myocarditis: 2 (3%) Pericarditis: 1 (2%)	RV insertion point LGE: 13 (22%) with COVID-19, 10 (24%) of 41 athlete controls evaluated with gadolinium, 0 (0%) healthy controls
Starekova et al <sup>73</sup> (Online January 14, 2021)	Collegiate	145	All athletes	20	26%	111 (77%)	Myocarditis: 2 (1%) Pericarditis: 0 (0%)	RV insertion point LGE: 38 (26%) Mid-myocardial LGE: 2 (1%)
Malek et al <sup>227</sup> (Online January 20, 2021)	Professional	26	All athletes	24	81%	20 (77%)	Myocarditis: 0 (0%) Pericarditis: 1 (4%)	Any CMR abnormality: 5 (19%), includes 1 mid-myocardial LGE (4%)
Hendrickson et al <sup>228</sup> (Online May 11, 2021)	Collegiate	137	Selective (based on abnormal triad testing, N = 5, 4%)	20	32%	112 (82%)	Myocarditis: 0 (0%) Pericarditis: 0 (0%)	Abnormal ECG: 0 (0%) Abnormal cTn: 4 (3%) Abnormal echocardiogram: 4 (3%) Any CMR abnormality (of those tested): 0 (0%)
Hwang et al <sup>229</sup> (Online June 24, 2021)	Collegiate	55	Selective (based on abnormal triad testing, N = 8, 15%)	NA	NA	38 (69%)	Myocarditis: 0 (0%) Pericarditis: 1 (2%)	Abnormal ECG: 3 (5%) Abnormal cTn: 1 (2%) Abnormal echocardiogram: 6 (11%) Any CMR abnormality (of 8 tested): 2 (25%)

\*Studies included standard triad testing (ECG, cTn, and echocardiogram) or standard triad testing along with mandated CMR.

CMR = cardiac magnetic resonance imaging; cTn = cardiac troponin; ECG = electrocardiogram; LGE = late gadolinium enhancement; NA = not available; RV = right ventricle.

be substantial, there is a critical need to identify ways to better meet the needs of those with this condition.

### 6.3. Section 3: Return to Play

#### 6.3.1. Overview

Observation of myocardial injury among patients hospitalized with COVID-19,<sup>33,217,218</sup> coupled with uncertainty around cardiovascular sequelae after mild illness,<sup>11</sup> fueled early apprehension regarding the safety of competitive sports for athletes recovering from SARS-CoV-2 infection. Several consensus screening recommendations have followed,<sup>219,220</sup> including 2 by the ACC's Sports and Exercise Cardiology Council,<sup>221,222</sup> endorsing a conservative RTP screening approach consisting of so-called triad testing<sup>43</sup> with a 12-lead ECG, cTn (preferably using a high-sensitivity assay), and an echocardiogram. Subsequent protocols incorporating universal CMR in U.S. collegiate

athletes identified myocardial and pericardial involvement in some recovering from COVID-19.<sup>73,74,223,224</sup> Data from large registries have demonstrated, however, an overall low prevalence of clinical myocarditis,<sup>43,68,69</sup> without a rise in reported acute adverse cardiac events.<sup>43,69</sup> Cognizant of additional data that has accrued over the past year, we provide updated guidance related to resumption of athletics and intense exercise training after SARS-CoV-2 infection. Included below is a summary of literature related to athletes with COVID-19 and a practical, evidence-based framework to guide RTP evaluation.

#### 6.3.2. Epidemiology

Multiple studies have affirmed that myocarditis is a common cause of sudden cardiac death in athletes.<sup>225</sup> Unfortunately, early RTP recommendations related to COVID-19 were limited by: 1) an uncertain prevalence of



**TABLE 2** Registries Evaluating the Prevalence of Myocarditis, Other Myocardial Involvement, and Pericardial Involvement in Athletes Following SARS-CoV-2 Infection

Registry	Competition Level	Sample Size	CMR Strategy	Age, Mean Years	Sex, % Female	Symptomatic, n (%)	Myocarditis or Pericarditis, n (%)	Additional Observations
Martinez et al <sup>69</sup> (Online March 4, 2021)	Professional	789	Selective, based on abnormal triad testing, (N = 30, 4%)	25	2%	460 (58%)	Myocarditis: 3 (0.4%) Pericarditis: 2 (0.3%)	Abnormal ECG: 9 (1%) Abnormal cTn: 6 (0.8%) Abnormal echocardiogram: 19 (2%) Any CMR abnormality: 5/30 (17%)
Moulson et al <sup>43</sup> (Online April 17, 2021)	Collegiate (Total N = 3,018)	2,820	Selective, based on symptoms or abnormal triad testing, (N = 119, 4.2%)	20	32%	2,022 (67%)	Myocarditis: 12 (0.4%) Pericarditis: 3 (0.1%)	Abnormal ECG: 12 (0.4%) Abnormal cTn: 9 (0.3%) Abnormal echocardiogram: 15 (0.5%) Any CMR abnormality: 15/119 (13%)
		198	Nonselective, all athletes	NA	NA	62 (31%)*	Myocardial involvement:† 6 (3%)	Definite or probable myocardial involvement:† 3 (2%)
Daniels et al <sup>68</sup> (Online May 27, 2021)	Collegiate	1,597	All athletes	NA	40%	NA	Myocarditis:‡ 37 (2%) Pericarditis: 0 (0%)	Clinical myocarditis: 9 (0.6%)

\*N = 62 with moderate COVID-19 symptoms or abnormal baseline cardiac testing.

†Myocardial involvement defined as: 1) definite: T<sub>1</sub> abnormality + LGE and T<sub>2</sub> abnormality, or T<sub>2</sub> abnormality + additional supportive criteria (LVEF ≤45%, pericardial effusion or enhancement, or cTn level above the 99th percentile upper reference limit); 2) probable: T<sub>1</sub> abnormality + LGE and 1 or more supportive criterion; or 3) possible: isolated T<sub>1</sub> abnormality or LGE.

‡Myocarditis defined as clinical or subclinical (CMR-defined myocardial inflammation in the absence of symptoms suggestive of clinical myocarditis and elevated cTn).

CMR = cardiac magnetic resonance imaging; cTn = cardiac troponin; ECG = electrocardiogram; LGE = late gadolinium enhancement; LVEF = left ventricular ejection fraction; NA = not available.

myocarditis with SARS-CoV-2 infection; 2) unknown rates of adverse outcomes with exercise resumption; and 3) reports of significant myocardial injury and poor outcomes among some hospitalized patients.<sup>10,11</sup>

### 6.3.3. Case Series

Initial reports detailing the prevalence of myocardial involvement in athletes with COVID-19 were largely single-center studies using CMR as an additional screening tool. In the first published case series of largely asymptomatic U.S. collegiate athletes who underwent triad testing along with screening CMR,<sup>223</sup> 4 of 26 (15%) athletes met modified CMR Lake Louise criteria<sup>29</sup> for myocarditis, 8 (31%) had evidence of LGE without edema, and none had pericarditis.<sup>223</sup> This was followed soon thereafter by a study of 54 asymptomatic or minimally symptomatic student-athletes, of whom 19 (40%) demonstrated evidence of pericarditis with pericardial enhancement and/or pericardial effusion; no athlete, however, fulfilled CMR criteria for myocarditis.<sup>74</sup> It is noteworthy that no other COVID-19 athlete study has reported similar degrees of pericardial involvement.

Additional small, single-center case series have followed<sup>73,224,226-229</sup> (see [Table 1](#)), all limited by: 1) lack of appropriate controls as well as independent and blinded review of imaging studies; 2) heterogeneity in CMR abnormalities; and 3) lack of a standardized approach to timing of CMR acquisition (ranging from 10-40+ days after testing positive for COVID-19). Data

from these studies, along with well-publicized cases in the media,<sup>230-232</sup> have nonetheless led some organizations to mandate the use of CMR to screen all competitive athletes following SARS-CoV-2 infection.

### 6.3.4. Registries

Throughout 2020, multiple large registries were created to track U.S. professional and collegiate athletes who had recovered from COVID-19. Both the U.S. professional cohort (N = 789)<sup>69</sup> and multicenter collegiate Outcomes Registry for Cardiac Conditions in Athletes (N = 3,018)<sup>43</sup> documented a significantly lower prevalence of myocarditis (0.6%-0.7%) among previously infected athletes, most of whom underwent cardiac triad testing regardless of symptomatology (see [Table 2](#)). Within these registries, CMR was generally obtained if any component of triad testing was abnormal or if symptoms were suggestive of myocarditis (excluding 198 athletes in the Outcomes Registry for Cardiac Conditions in Athletes with mandated CMR).<sup>43,69</sup> No adverse cardiac outcomes were reported as a direct consequence of COVID-19.<sup>43,69</sup>

Most recently, the Big Ten Conference published data on 1,597 athletes who underwent universal screening with CMR in addition to triad testing, irrespective of symptom status<sup>68</sup> (see [Table 2](#)). Abnormalities on CMR consistent with myocarditis<sup>29</sup> were reported in 2.3% of athletes. Similar to data from single-center studies, however, there was marked heterogeneity in the prevalence (0%-7.6%) and type of CMR abnormalities among the 13 programs

that participated. Results were also remarkably comparable to those of the Outcomes Registry for Cardiac Conditions in Athletes and the professional athlete registries, as only 9 athletes (0.6%) had findings consistent with clinical myocarditis.

### 6.3.5. Limitations of Screening With CMR

Although CMR is a powerful diagnostic tool capable of identifying tissue necrosis, inflammation, and edema, significant limitations exist when used as a screening tool for those infected with SARS-CoV-2. First, the modified Lake Louise criteria are predicated on a clinical suspicion of myocarditis and have not been validated as a screening tool for low-to-intermediate risk patients.<sup>29</sup> Moreover, diagnostic algorithms for myocarditis from the European Society of Cardiology and American Heart Association rely on both a clinical presentation suggestive of myocarditis and abnormal diagnostic testing.<sup>108,233</sup> Thus, the clinical relevance of abnormal tissue characterization on CMR in individuals without a clinical suspicion for myocarditis is unknown. Second, a paucity of athlete-specific normative data complicates use of CMR as a generalized screening tool in this population. For example, numerous studies have demonstrated nonspecific LGE in masters-level athletes.<sup>234</sup> A recent study also noted comparable rates of focal LGE at RV insertion points among athletes with SARS-CoV-2 (22%) and noninfected athlete controls (24%).<sup>224</sup> Third, parametric mapping requires a high level of expertise. Accordingly, marked heterogeneity in reported CMR results from different centers may relate to regional variations in CMR performance and interpreter bias, given the lack of blinded review by an independent core laboratory. Fourth, the absence of an appropriate control group limits the interpretation of clinical significance and application of these CMR findings in a testing algorithm. Finally, cost, limited availability, and equitable resource allocation all represent real-world challenges when considering use of CMR for RTP screening.

Importantly, to date, there have been no confirmed cases of cardiac demise in the registries of athletes with COVID-19.<sup>43,68,69</sup> In addition, most athletes at all levels of competition resume participation without undergoing CMR.

### 6.3.6. Evaluation and Management

The first consensus statement endorsed by the ACC Sports and Exercise Cardiology Section recommended that triad testing be part of RTP screening for all competitive athletes with symptoms.<sup>221</sup> Subsequent recommendations by this group were tempered, recommending cardiac testing only in those with moderate, severe, and/or worsening symptoms related to COVID-19.<sup>222</sup> Changes in consensus recommendations (see [Supplemental Appendix Tables 1 and 2](#)) reflected an effort to balance the uncertainty of

cardiac sequelae with mild illness,<sup>11,74,223</sup> the absence of robust prevalence data related to myocarditis or myocardial involvement,<sup>222</sup> and the time-sensitive need for guidance within the sports medicine community. Despite these changes, most collegiate and professional athletes continued with triad testing before RTP, even for those who were asymptomatic.<sup>43,68,69</sup> Recent data from multi-institutional registries, however, have now established a low prevalence of clinical myocarditis among competitive athletes with COVID-19.<sup>43,68,69</sup> In addition, symptoms suggestive of myocarditis can help to predict cardiac involvement.<sup>43</sup>

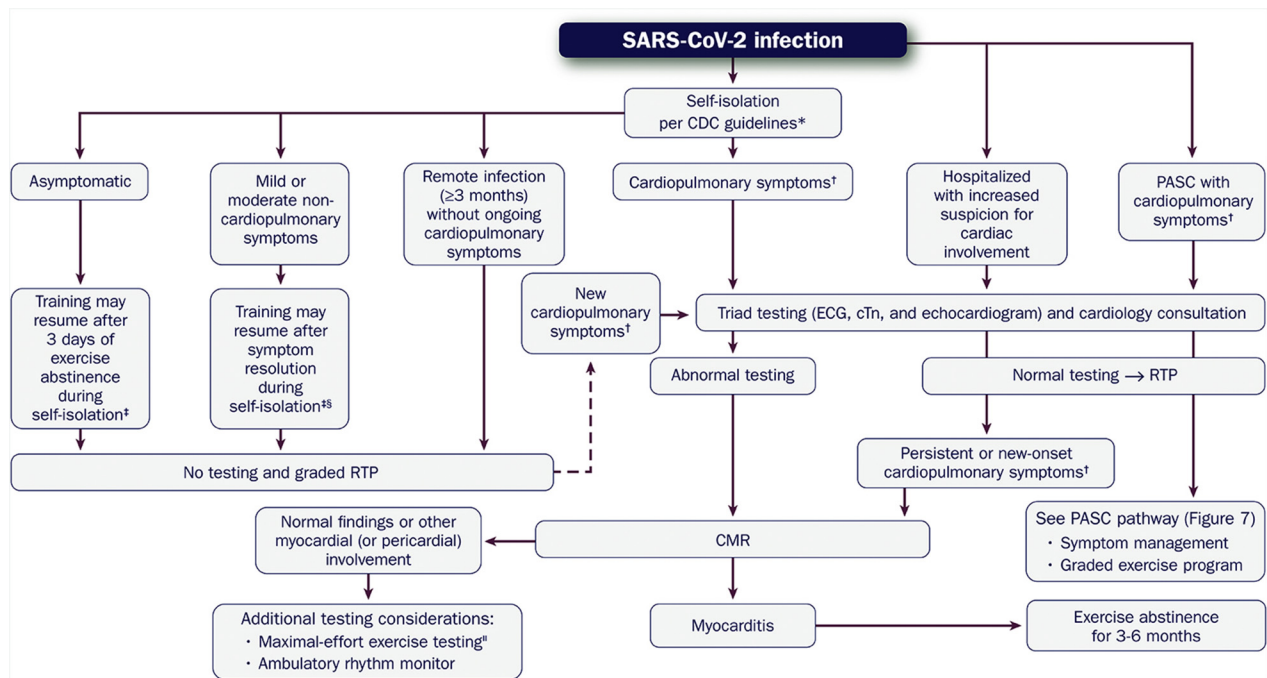
Historically, an athlete has been defined as an individual who places a high premium on exercise training, competition, and sports achievement.<sup>235</sup> Individuals who self-identify as athletes extend across the age spectrum, from youth sports (aged <18 years) to masters-level (aged >35 years) exercise enthusiasts.<sup>235</sup> Previous recommendations were given to individual athletic populations recovering from COVID-19, with encouragement to observe younger athletes (aged <21 years) for several weeks to monitor for the development of MIS-C.<sup>236,237</sup> Masters-level athletes may also have traditional risk factors for cardiovascular disease,<sup>238,239</sup> increasing the possibility of more severe manifestations with COVID-19.

Current data suggest that competitive athletes recovering from COVID-19 with mild, noncardiopulmonary symptoms are unlikely to have myocarditis and clinically significant myocardial involvement.<sup>43,69</sup> Consistent observations have been noted in an unselected, nonathletic cohort of infected health care workers (N = 149, aged 18-63 years), where mild symptoms were not associated with discernable cardiovascular pathology.<sup>66</sup> Instead, cardiopulmonary symptoms that are persistent are likely to be of greater relevance than age or competition level when assessing the probability of clinically-important myocardial disease.<sup>43</sup>

### 6.3.7. Return to Exercise and Athletic Training

For athletes recovering from COVID-19 with ongoing cardiopulmonary symptoms concerning for myocarditis or myocardial involvement (chest pain or tightness, dyspnea, palpitations, lightheadedness, or syncope) and/or those requiring hospitalization with increased suspicion for cardiac involvement, further evaluation should be performed before resuming exercise (see [Figure 9](#)). For all others who are asymptomatic or with symptoms less suggestive of a cardiopulmonary etiology (eg, fever [temperature  $\geq 100.4$  °F], chills, lethargy, myalgias), additional cardiac testing is not recommended.

Current CDC guidelines stipulate at least 5 days of self-isolation from symptom onset or upon testing positive for COVID-19.<sup>240</sup> Past consensus RTP guidance recommended that individuals abstain from exercise throughout a 10-

**FIGURE 9** Evaluation of the Athletic Patient Convalesced From COVID-19 and Guidance on RTP and/or Intense Training

\*CDC Guidelines: COVID-19 Quarantine and Isolation.<sup>240</sup>

†Cardiopulmonary symptoms include chest pain/tightness, dyspnea, palpitations, and lightheadedness/syncope; this also includes symptoms occurring  $\leq 1$  week following COVID-19 mRNA vaccination.

‡Strategies to minimize transmission of SARS-CoV-2 to other athletes 3-10 days following a positive COVID-19 test include 1) training in isolation, 2) participating in socially-distanced outdoor training, 3) training with a face mask in a well-ventilated facility with appropriate social distancing, and 4) participating in group training after a single negative NAAT (eg, RT-PCR test) or 2 negative rapid antigen tests 24-48 hours apart.

§Excludes prolonged, isolated anosmia/ageusia, which should not delay return to training.

¶Maximal-effort exercise testing should be deferred until myocarditis has been excluded.

CDC = Centers for Disease Control and Prevention; CMR = cardiac magnetic resonance imaging; COVID-19 = novel coronavirus disease 2019; cTn = cardiac troponin; ECG = electrocardiogram; NAAT = nucleic acid amplification test; PASC = post-acute sequelae of SARS-CoV-2 infection; RTP = return to play; RT-PCR = reverse transcription polymerase chain reaction, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

day self-isolation period, in part, because of the potential for clinical deterioration.<sup>221,222</sup> Studies demonstrating a lack of clinically significant myocardial involvement among athletes with mild COVID-19<sup>43,69</sup> suggest that such activity restriction is no longer necessary (see [Figure 9](#)). For asymptomatic athletes with COVID-19, 3 days of abstinence from training is recommended to ensure that symptoms do not develop.

For individuals with mild non-cardiopulmonary symptoms, exercise training should generally be withheld until symptom resolution. One exception is isolated anosmia or ageusia, which may have a more prolonged course. For athletes with cardiopulmonary symptoms, intense exercise training should be limited until symptoms resolve, self-isolation is complete, and further cardiac testing can be obtained. In addition, a graded RTP regimen should be emphasized in all individuals with prior COVID-19 to ensure close monitoring for new

cardiopulmonary symptoms. For those participating in organized competitive sports, graded exercise programs should be individualized and implemented, with support by athletic trainers and primary care sports medicine clinicians. For most individuals participating in high-level recreational athletics, a graded return-to-exercise program equates to more qualitative gradual increases in effort. This remains a point of key emphasis, as many high-level recreational exercise enthusiasts do not have immediate access to cardiac testing and sports cardiology referrals, regardless of symptom severity.

For athletes with cardiopulmonary symptoms, initial evaluation should ideally be with an ECG, cTn (high-sensitivity assay preferred), and an echocardiogram (see [Figure 9](#)). The presence of abnormal findings with triad testing or persistence of cardiopulmonary symptoms (specifically chest pain or tightness, palpitations, or syncope) after initial testing suggest that additional

evaluation with CMR should be performed. Maximal-effort exercise testing may be a useful adjunct in cases of persistent cardiopulmonary symptoms, only after myocarditis has been excluded with CMR. Based on the low prevalence of myocarditis observed in competitive athletes with COVID-19, it is also reasonable to apply these recommendations to high-school athletes (aged  $\geq 14$ -15 years) along with masters-level recreational exercise enthusiasts.

Use of CMR to screen athletes who are asymptomatic or with non-cardiopulmonary symptoms is likely to be low yield. Such testing may, however, be considered in those with abnormal triad testing along with increased concern of cardiac involvement or in those with either persistent or new cardiopulmonary symptoms. Importantly, further research is needed to better understand the significance of other forms of myocardial involvement detected by CMR,<sup>68,223</sup> particularly in the absence of symptoms.

### 6.3.8. Remote History of COVID-19

It is likely that clinicians will increasingly see asymptomatic athletes who are returning for sports physicals after having had COVID-19 without prior RTP evaluation. Regardless of the amount of time that has passed since infection, athletes who have remained asymptomatic or who have had non-cardiopulmonary symptoms and are exercising without limitation require no further cardiac testing. In contrast, for athletes with prior COVID-19 and a history of cardiopulmonary symptoms, the duration of time since symptom resolution and the athlete's current clinical status should dictate the approach. If  $< 1$  month has elapsed since resolution of cardiopulmonary symptoms, triad testing should be performed. If  $> 3$  months have elapsed since resolution of cardiopulmonary symptoms and no exercise limitations are present, no further cardiac testing is likely required. The rationale for this stems from prior guidance recommending avoidance of exercise for at least 3 months in cases of confirmed myocarditis.<sup>241</sup> Finally, if 1-3 months have elapsed since cardiopulmonary symptom resolution and athletes have returned on their own to training without exercise limitation, it is reasonable to allow continued exercise training without further cardiac evaluation. This decision should be individualized and based on clinical judgement, informed by the type and severity of prior symptoms. Factors warranting further cardiac evaluation include prior worrisome cardiopulmonary symptoms (eg, syncope, sustained exertional palpitations, and/or exertional chest tightness or dyspnea).

Regardless of vaccination status, a growing number of professional and collegiate athletes have been diagnosed with COVID-19, likely because of more transmissible variants (eg, Delta, Omicron). For those with recurrent

COVID-19, repeat cardiac testing is not warranted in the absence of cardiopulmonary symptoms. RTP guidance should follow the same pathway as those with initial infection (see [Figure 9](#)).

### 6.3.9. Nonspecific and Isolated Screening Abnormalities

In general, routine surveillance monitoring and/or additional testing of athletes who have successfully returned to play after COVID-19 is not recommended. Incidental findings of unclear significance may be encountered with such testing, particularly in those with lower pretest probability of concerning cardiac abnormalities. For example, detection of isolated LGE without concomitant edema has been reported with CMR.<sup>68,223,224</sup> Recognition of isolated LGE as a manifestation of resolving myocarditis should be more fully considered in those with: 1) a high clinical suspicion of myocarditis; 2) supportive abnormal findings on other testing (ECG, cTn); and 3) a pattern of LGE suggestive of myocarditis.<sup>242,243</sup> Additional abnormalities warranting evaluation include: 1) mildly reduced LV systolic function that may be representative of either exercise-induced cardiac remodeling or a pathologic phenotype;<sup>244</sup> 2) isolated cTn elevation; and/or 3) ECG abnormalities. With these findings, if it is determined that acute myocarditis is less likely, consideration can be given to maximal-effort exercise testing (with stress echocardiography if there is reduced LV systolic function to assess for appropriate augmentation with exercise)<sup>245</sup> and ambulatory rhythm monitoring.

### 6.3.10. Myocarditis and Exercise Training Restrictions

In a 2015 guidance document related to sports eligibility, individuals with clinical myocarditis were recommended to have 3-6 months of complete exercise abstinence.<sup>241</sup> Thereafter, decision-making regarding RTP would be based on: 1) absence of cardiopulmonary symptoms; 2) resolution of laboratory evidence of myocardial injury; 3) normalization of LV systolic function; and 4) absence of spontaneous/inducible cardiac arrhythmias on ECG monitoring and exercise stress testing. Whether this 3-month minimum of exercise abstinence independently reduces the risk of acute cardiac events is uncertain. In the Big Ten COVID-19 cardiac registry, 27 athletes (27 of 37, 73%) with clinical or subclinical myocarditis completed repeat CMR within 4-14 weeks after initially testing positive for COVID-19.<sup>68</sup> In 11 of these athletes (41%), LGE and T<sub>2</sub> mapping abnormalities had completely resolved after a median of 8 weeks. Whether this relatively rapid resolution reflects disproportionately subclinical findings, however, is unknown. Indeed, just 1 of 6 athletes with clinical myocarditis had resolution of inflammatory CMR findings after 10 weeks.<sup>68</sup> Collectively, these data suggest that it is reasonable to reassess for resolution of myocardial inflammation in those with

**TABLE 3 Summary of Diagnostic Criteria and Key Recommendations Related to Cardiovascular Sequelae of COVID-19 in Adults**

Myocarditis and other myocardial involvement	<ul style="list-style-type: none"> <li>■ Myocarditis is defined by: 1) cardiac symptoms (eg, chest pain, dyspnea, palpitations, syncope); 2) an elevated cTn; and 3) abnormal electrocardiographic, echocardiographic, CMR, and/or histopathologic findings on biopsy or postmortem evaluation in the absence of flow-limiting coronary artery disease.</li> <li>■ When there is increased suspicion for cardiac involvement with COVID-19, initial testing should consist of an ECG, measurement of cTn (preferably using a high-sensitivity assay), and an echocardiogram.</li> <li>■ Cardiology consultation is recommended for those with a rising cTn and/or ECG or echocardiographic abnormalities concerning for myocarditis.</li> <li>■ CMR is recommended in hemodynamically stable patients with suspected myocarditis.</li> <li>■ Hospitalization is recommended for patients with definite myocarditis that is either mild or moderate in severity, ideally at an advanced heart failure center. Patients with fulminant myocarditis should be managed at centers with an expertise in advanced heart failure, mechanical circulatory support, and other advanced therapies.</li> <li>■ Patients with myocarditis and COVID-19 pneumonia (with an ongoing need for supplemental oxygen) should be treated with corticosteroids.</li> <li>■ For patients with suspected pericardial involvement, treatment with NSAIDs, colchicine, and/or prednisone is reasonable.</li> <li>■ 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.</li> <li>■ As appropriate, guideline-directed medical therapy for heart failure should be initiated and continued after discharge.</li> <li>■ Myocarditis following COVID-19 mRNA vaccination is rare. The highest observed rates have been in young male individuals (aged 12-17 years) after the second vaccine dose.</li> <li>■ COVID-19 vaccination is associated with a very favorable benefit-to risk ratio for all age and sex groups evaluated thus far.</li> <li>■ In general, vaccine-associated myocarditis should be diagnosed, categorized, and treated in a manner analogous to myocarditis following SARS-CoV-2 infection.</li> </ul>
PASC	<ul style="list-style-type: none"> <li>■ PASC is defined as a constellation of new, returning, or persistent health problems experienced by individuals 4 or more weeks after SARS-CoV-2 infection.</li> <li>■ PASC-CVD refers to a broad group of cardiovascular conditions that include, but are not limited to, myocarditis and other forms of myocardial involvement, pericarditis, new or worsening myocardial ischemia, microvascular dysfunction, nonischemic cardiomyopathy, thromboembolism, cardiovascular sequelae of pulmonary disease, and arrhythmia.</li> <li>■ PASC-CVS is a heterogeneous disorder that includes widely-ranging cardiovascular symptoms, without objective evidence of cardiovascular disease using standard diagnostic testing. Common symptoms include tachycardia, exercise intolerance, postexertional malaise, palpitations, chest pain, and dyspnea.</li> <li>■ For patients with cardiovascular symptoms and suspected PASC, a reasonable initial testing approach includes: 1) basic laboratory testing (including cTn); 2) an ECG; 3) an echocardiogram; 4) an ambulatory rhythm monitor; 5) chest imaging (X-ray and/or CT); and/or 6) pulmonary function tests.</li> <li>■ Cardiology consultation is recommended for patients with PASC that have: 1) abnormal cardiac test results; 2) known cardiovascular disease with new or worsening symptoms or signs; 3) documented cardiac complications during SARS-CoV-2 infection; and/or 4) persistent cardiopulmonary symptoms that are not otherwise explained.</li> <li>■ Recumbent or semi-recumbent exercise (eg, rowing, swimming, or cycling) is recommended initially for PASC-CVS patients with tachycardia, exercise/orthostatic intolerance, and/or deconditioning, with transition to upright exercise as orthostatic intolerance improves. Exercise duration should also be short (5-10 minutes/day) initially, with gradual increases as functional capacity improves.</li> <li>■ Salt and fluid loading represent nonpharmacological interventions that may provide symptomatic relief for patients with tachycardia, palpitations, and/or orthostatic hypotension. Beta-blockers, nondihydropyridine calcium-channel blockers, ivabradine, fludrocortisone, and midodrine may be used empirically as well.</li> </ul>
RTP	<ul style="list-style-type: none"> <li>■ Athletes who are asymptomatic after recent SARS-CoV-2 infection may resume exercise training after 3 days of exercise abstinence during self-isolation.</li> <li>■ Athletes with mild or moderate non-cardiopulmonary symptoms after recent SARS-CoV-2 infection may resume exercise training after their symptoms have resolved.</li> <li>■ Athletes with remote infection (<math>\geq 3</math> months) without ongoing cardiopulmonary symptoms may resume exercise training without the need for additional testing.</li> <li>■ Athletes recovering from COVID-19 with ongoing cardiopulmonary symptoms (chest pain/tightness, palpitations, or syncope) and/or those requiring hospitalization with increased suspicion for cardiac involvement should undergo triad testing (ECG, cTn, and echocardiogram). Triad testing should also be performed in those developing new cardiopulmonary symptoms after resumption of exercise training.</li> <li>■ CMR is recommended if triad testing is abnormal or cardiopulmonary symptoms persist.</li> <li>■ Athletes with myocarditis should abstain from exercise for 3-6 months.</li> <li>■ Maximal-effort exercise testing and/or an ambulatory rhythm monitor may be helpful in the evaluation of athletes with: 1) persistent cardiopulmonary symptoms and 2) either normal CMR or CMR that demonstrates other forms of myocardial (or pericardial) involvement. Maximal-effort exercise testing should only be performed, however, after myocarditis has been excluded with CMR.</li> <li>■ CMR to screen athletes who are asymptomatic or with non-cardiopulmonary symptoms is likely to be low yield.</li> <li>■ Repeat cardiac testing is not warranted in athletes with recurrent COVID-19 in the absence of cardiopulmonary symptoms.</li> </ul>

CMR = cardiac magnetic resonance imaging; COVID-19 = novel coronavirus disease 2019; CT = computed tomography; cTn = cardiac troponin; ECG = electrocardiogram; MIS-A = multisystem inflammatory syndrome in adults; mRNA = messenger RNA; NSAID = nonsteroidal anti-inflammatory drug; PASC = post-acute sequelae of SARS-CoV-2 infection; PASC-CVD = post-acute sequelae of SARS-CoV-2 infection-cardiovascular disease; PASC-CVS = post-acute sequelae of SARS-CoV-2 infection-cardiovascular syndrome; RTP = return to play; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

clinical myocarditis <3 months since testing positive for COVID-19, especially if they have had rapid resolution of symptoms and prior demonstration of normal LV systolic function or in those with subclinical myocarditis identified with CMR screening. The best time for this reassessment should likely be individualized, but no sooner than 1 month from the time of initial diagnosis of clinical or subclinical myocarditis. For asymptomatic athletes with complete resolution of myocardial inflammation and no spontaneous arrhythmias, a RTP approach using conservative, graded exercise should be pursued. Finally, screening for myocarditis in the absence of suggestive symptoms following receipt of the COVID-19 mRNA vaccine is not recommended. In addition, although self-limited side effects following vaccination (eg, fatigue, headache, fever, muscle pain) may lead some individuals to stop exercising until symptoms resolve, vaccination per se does not require a set time away from exercise training.

#### 6.3.11. PASC and Return to Exercise

Decision-making regarding RTP in PASC should be informed by whether cardiopulmonary symptoms are present. If they are, a similar approach to that recommended above should be pursued, using: 1) triad testing; 2) CMR (if appropriate); and 3) limitation of strenuous physical activity (see [Figure 9](#)). If PASC-CVD is excluded, further evaluation with CPET and pulmonary function testing may be considered as part of the PASC-CVS evaluation. Although individuals with PASC may be unable to readily resume their prior activity levels, structured and individualized graded exercise, as recommended in the PASC section, should be performed throughout the recovery process.

#### 6.3.12. Future Directions

As our understanding of the cardiovascular effects of COVID-19 evolves, it is anticipated that RTP guidance for athletes will change as well. Several areas of future investigation are noteworthy. First, although it is extremely reassuring that adverse events among infected athletes have been rare, further study is needed to determine how long recovery takes after documented abnormalities and the role that imaging can play in guiding this. Second, the risks and benefits of exercise resumption among patients with PASC remains to be rigorously defined. Given the therapeutic role of training in this population, further investigation into associated risks will be particularly important. Third, our current knowledge stems largely from study of those infected with early variants of SARS-CoV-2. Further research is needed to understand whether the extent and severity of cardiac involvement is different with Delta, Omicron, and

other variants. It will also be important to define the temporal pattern of myocardial involvement, along with predictors of myocarditis progression and resolution with SARS-CoV-2 and other common respiratory viral pathogens. Finally, widespread resumption of competitive sports will come with rare but devastating adverse events, including sudden cardiac death, that well predate COVID-19. Accordingly, it will be important to limit automatic attribution of such events to COVID-19 without further detailed evaluation.

## 7. IMPLICATION OF PATHWAY

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This ECDP provides a framework for evaluation and management of adults with cardiovascular sequelae following SARS-CoV-2 infection. Guidance provided is based on expert consensus, with multiple key takeaways (see [Table 3](#)). Importantly, it is intended to help clinicians understand not only when testing may be warranted, but also when it is not. Given that it reflects the current state of knowledge through early 2022, it is anticipated that recommendations will change over time as our understanding evolves.

For both myocarditis and PASC, there exist significant opportunities to better understand their epidemiology, underlying mechanisms, predisposing risk factors, and preferred approaches for evaluation and management. For RTP, there is a need to more rigorously define how long cardiovascular abnormalities persist and the relative benefits of exercise training in those with PASC.

Beyond the indirect effects and undesirable consequences that COVID-19 has had on care delivery, it also remains to be seen how new variants and vaccine breakthrough infection will affect cardiovascular health. Improved understanding of the associated near- and long-term consequences will be key in helping to improve clinical outcomes.

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**KEY WORDS** ACC Expert Consensus Decision Pathway, athletes, cardiovascular diseases, chest pain, COVID-19, myocarditis, SARS-CoV-2, sports medicine, vaccines

## APPENDIX 1. AUTHOR RELATIONSHIPS WITH INDUSTRY AND OTHER ENTITIES (RELEVANT)— 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

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Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Ty J. Gluckman (Co-Chair)	Providence Heart Institute Providence St. Joseph Health—Medical Director, Center for Cardiovascular Analytics, Research, and Data Science (CARDS)	None	None	None	None	None	None
Nicole M. Bhave (Co-Chair)	University of Michigan Medical School—Associate Professor of Medicine Cardiovascular Medicine	None	None	None	None	None	None
Larry A. Allen (Vice Chair)	University of Colorado School of Medicine—Professor of Medicine; Kenneth Poirier Chair; Associate Head for Clinical Affairs, Cardiology Medical Director, Advanced Heart Failure	<ul style="list-style-type: none"> <li>■ Abbott Laboratories</li> <li>■ Amgen Inc.</li> <li>■ Novartis Corporation</li> </ul>	None	None	None	None	None
Eugene H. Chung (Vice Chair)	University of Michigan Medical School—Professor of Medicine; Director, Sports Cardiology Clinic	None	None	None	None	None	None
Erica S. Spatz (Vice Chair)	Yale University School of Medicine—Associate Professor, Section of Cardiovascular Medicine; Director, Preventive Cardiovascular Health Program	None	None	None	None	None	None
Enrico Ammirati	Niguarda Hospital, Milan, Italy—Cardiologist, Advanced Heart Failure, LVAD and Cardiac Transplant	None	None	None	None	<ul style="list-style-type: none"> <li>■ Myocarditis Foundation</li> </ul>	None
Aaron L. Baggish	Massachusetts General Hospital—Cardiovascular Performance Program Director	None	None	None	None	None	None
Biykem Bozkurt	Baylor College of Medicine—The Mary and Gordon Cain Chair and Professor of Medicine; Associate Provost of Faculty Affairs; Senior Associate Dean of Faculty Development; Director, Winters Center for Heart Failure Research; Associate Director, Cardiovascular Research Institute; Vice- Chair of Medicine	<ul style="list-style-type: none"> <li>■ Amgen</li> </ul>	None	None	None	<ul style="list-style-type: none"> <li>■ Abbott Laboratories*</li> </ul>	None

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APPENDIX 1. CONTINUED

Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
William K. Cornwell, III	University of Colorado Anschutz Medical Campus—Cardiologist, Advanced Heart Failure, LVAD and Cardiac Transplant	None	None	None	None	None	None
Kimberly G. Harmon	University of Washington—Team Physician	None	None	None	None	None	None
Jonathan H. Kim	Emory Clinical Cardiovascular Research Institute, Emory School of Medicine—Associate Professor of Medicine, Director of Sports Cardiology	None	None	None	None	None	None
Anuradha Lala	Icahn School of Medicine at Mount Sinai—Associate Professor, Cardiology & Population Health Science; Program Director, Advanced Heart Failure & Transplant Fellowship	None	None	None	None	None	None
Benjamin D. Levine	Institute for Exercise & Environmental Medicine—Director; Texas Health Presbyterian Dallas—Chair for Wellness and Chair for Cardiovascular Research; The University of Texas Southwestern Medical Center—Professor of Medicine and Cardiology	None	None	■ Amgen Inc*	None	None	None
Matthew M. Martinez	Morristown Medical Center—Director Sports Cardiology and Hypertrophic Cardiomyopathy Center	■ Bristol Myers Squibb	None	None	None	None	None
Oyere Onuma	Yale University School of Medicine—Assistant Professor of Cardiology	None	None	None	None	None	None
Dermot Phelan	Sanger Heart and Vascular Institute, Atrium Health—Director of Sports Cardiology	■ Bristol Myers Squibb	None	None	None	None	None
Valentina O. Puntmann	University Hospital Frankfurt—Associate Professor, Consultant Cardiologist (Cardiovascular Magnetic Resonance Imaging)	■ Bayer AG ■ CMR International	None	None	None	None	None
Saurabh Rajpal	The Ohio State University Wexner Medical Center—Assistant Professor	None	None	None	None	None	None
Pam R. Taub	University of California San Diego Medical Center—Professor of Medicine; Director of Step Family Foundation Cardiovascular Rehabilitation and Wellness Center	■ Amgen	None	None	None	None	None
Amanda K. Verma	Washington University School of Medicine—Assistant Professor of Medicine, Advanced Heart Failure and Transplant Cardiology; Director of COVID Cardiology Clinics	None	None	None	None	None	None

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ACC = American College of Cardiology; LVAD = left ventricular assist device.

**APPENDIX 2. PEER REVIEWER RELATIONSHIPS WITH INDUSTRY AND OTHER ENTITIES (COMPREHENSIVE)—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.**

Reviewer	Representation	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Geoffrey D. Barnes	Content Reviewer—ACC Expert	University of Michigan—Assistant Professor of Internal Medicine; Co-director, Michigan Anticoagulation Quality Improvement Initiative	<ul style="list-style-type: none"> <li>■ Acelis Connected Health</li> <li>■ AMAG Pharmaceuticals, Inc</li> <li>■ Bristol Myers Squibb/Pfizer*</li> <li>■ Janssen Pharmaceuticals, Inc</li> </ul>	None	None	■ Blue Cross Blue Shield of Michigan*	None	None
Diana Berrent	Content Reviewer—Patient Advocate	Survivor Corps—Founder	None	None	None	None	None	None
Devyani Chowdhury	Official Reviewer—ACC Adult Congenital & Pediatric Cardiology Council	Cardiology Care for Children and Ai Dupont Children's Hospital—Director of Cardiology Care for Children; Medical Director of ACHD at Nemour's	■ Tenaya Pharmaceuticals	None	None	<ul style="list-style-type: none"> <li>■ Bill and Melinda Gates Foundation†</li> <li>■ Hitachi Solutions†</li> </ul>	None	None
Leslie T. Cooper	Content Reviewer—ACC Expert	Mayo Clinic—Professor of Medicine	<ul style="list-style-type: none"> <li>■ Bristol Myers Squibb*</li> <li>■ Cantargia, Inc.</li> <li>■ Cardiol, Inc.*</li> </ul>	None	None	■ Moderna, Inc (DSMB)	<ul style="list-style-type: none"> <li>■ Mayo Clinic, Florida Executive Oversight Team†</li> <li>■ The Myocarditis Foundation†</li> </ul>	None
Peter N Dean	Content Reviewer—ACC Expert	University of Virginia— Associate Professor	None	None	None	None	None	None
James L. Januzzi Jr.	Content Reviewer—ACC Expert	Harvard Medical School—Hutter Family Professor of Medicine; Director, Dennis and Marilyn Barry Fellowship in Cardiology Research; Senior Cardiometabolic Faculty, Baim Institute for Clinical Research	<ul style="list-style-type: none"> <li>■ Abbott Laboratories</li> <li>■ Imbria*</li> <li>■ Novartis*</li> <li>■ Roche Diagnostics*</li> </ul>	None	None	<ul style="list-style-type: none"> <li>■ Abbott Laboratories*</li> <li>■ AbbVie, Inc.* (DSMB)</li> <li>■ Amgen* (DSMB)</li> <li>■ Bayer Healthcare Pharmaceuticals* (DSMB)</li> <li>■ Beyer* (DSMB)</li> <li>■ CVRx* (DSMB)</li> <li>■ Janssen Pharmaceuticals, Inc*</li> <li>■ Takeda Pharmaceuticals North America, Inc* (DSMB)</li> </ul>	None	None
Thomas M. Maddox	Content Reviewer—ACC Expert	BJC HealthCare and Washington University School of Medicine—Executive Director, Healthcare Innovation Lab; Professor of Medicine	None	None	None	■ NIH NCATS (1U24TRO02306-01: A National Center for Digital Health Informatics Innovation)*	■ BJC HealthCare/ Washington University School of Medicine*	None
Matthew Oster	Content Reviewer—ACC Expert	Children's Healthcare of Atlanta—Pediatric Cardiologist	None	None	None	None	None	None

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APPENDIX 2. CONTINUED

Reviewer	Representation	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Satish R. Raj	Content Reviewer—ACC Expert	University of Calgary & Alberta Health Services— Professor of Cardiac Sciences	<ul style="list-style-type: none"> <li>■ Medscape</li> <li>■ Spire Learning*</li> </ul>	None	None	<ul style="list-style-type: none"> <li>■ Arena Pharmaceuticals (DSMB)</li> <li>■ Canadian Institutes of Health Research (CIHR)*</li> <li>■ Cardiac Arrhythmia Network of Canada (CANet)*</li> <li>■ Confirm Rx SMART Registry, Abbott Labs‡</li> <li>■ Phase 3 Clinical Effect of TD-9855 for Treating snOH in Subjects With Primary Autonomic Failure, Theravance, Inc‡</li> </ul>	<ul style="list-style-type: none"> <li>■ American Auto-nomic Society†</li> <li>■ Canadian Cardio-vascular Society Academy†</li> <li>■ Dysautonomia International†</li> </ul>	<ul style="list-style-type: none"> <li>■ 2021, Defendan-t, Postural Tachycardia Syndrome</li> </ul>
Ashwin Kumar Ravichandran	Official Reviewer—ACC Heart Failure & Transplant Council	St. Vincent Heart Center—Cardiologist	<ul style="list-style-type: none"> <li>■ Abbott Laboratories*</li> <li>■ Medtronic</li> </ul>	<ul style="list-style-type: none"> <li>■ Actelion*</li> <li>■ Bayer Pharmaceuticals*</li> <li>■ United Therapeutics*</li> </ul>	None	<ul style="list-style-type: none"> <li>■ INCREASE, United Therapeutics‡</li> <li>■ MOMENTUM 3, Abbott Laboratories‡</li> <li>■ SOUTHPAW, United Therapeutics‡</li> <li>■ VICTORIA, Merck &amp; Co., Inc.‡</li> </ul>	None	None
Ashley Schenk	Official Reviewer—American Society of Health System Pharmacists	UK College of Pharmacy; University of Kentucky HealthCare—Acute Care Pharmacy Services; Cardiology Assistant Adjunct Professor	None	None	None	None	None	None
Ravi V. Shah	Content Reviewer—ACC Expert	Massachusetts General Hospital—Cardiologist	<ul style="list-style-type: none"> <li>■ Best doctors*</li> <li>■ Myokardia</li> </ul>	None	None	None	None	None
Cynthia C. Taub	Official Reviewer—American Society of Echocardiography	Dartmouth Hitchcock Medical Center—Chief, Section of Cardiovascular Medicine	None	None	None	None	None	None
David E. Winchester	Official Reviewer—Solution Set Oversight Committee	University of Florida—Associate Professor of Medicine	None	None	None	None	<ul style="list-style-type: none"> <li>■ Alachua County Medical Society Board of Directors†</li> </ul>	None

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ACC = American College of Cardiology; AHA = American Heart Association



**APPENDIX 3. ABBREVIATIONS.**

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ACC = American College of Cardiology

CDC = Centers for Disease Control and Prevention

CMR = cardiac magnetic resonance imaging

CT = computed tomography

cTn = cardiac troponin

COVID-19 = novel coronavirus disease 2019

ECDP = Expert Consensus Decision Pathway

ECG = electrocardiogram

LGE = late gadolinium enhancement

LV = left ventricular

ME/CFS = myalgic encephalomyelitis/chronic fatigue syndrome

MIS-A = multisystem inflammatory syndrome in adults

MIS-C = multisystem inflammatory syndrome in children

mRNA = messenger RNA

PASC = post-acute sequelae of SARS-CoV-2 infection

PASC-CVD = post-acute sequelae of SARS-CoV-2 infection-cardiovascular disease

PASC-CVS = post-acute sequelae of SARS-CoV-2 infection-cardiovascular syndrome

POTS = postural orthostatic tachycardia syndrome

RWI = relationships with industry

RTP = return to play

SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2