Coronavirus Disease 2019 (COVID-19) and the Heart—Is Heart Failure the Next Chapter?

Clyde W. Yancy, MD, MSc; Gregg C. Fonarow, MD

Multiple data sets now confirm the increased risk for morbid and mortal complications due to coronavirus disease 2019 (COVID-19) in individuals with preexisting cardiovascular diseases including hypertension, coronary artery disease, and heart failure.1,2 These salient observations have strengthened preventive strategies and undoubtedly have resulted in lives saved. Although episodes of clinical myocarditis have been suspected and a few cases have been reported in the literature,3 direct cardiac involvement due to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been difficult to confirm.

In this issue of JAMA Cardiology, Lindner and colleagues4 report on 39 autopsy cases of patients with COVID-19 in whom pneumonia was the clinical cause of death in 35 of 39 (89.7%). While histopathologic evaluation did not meet criteria seen in acute myocarditis, there was evidence of virus present in the heart in 24 of 39 patients (61.5%) with a viral load more than 1000 copies per microgram of RNA in 16 of 24 patients (66.7%). Evidence of active viral replication was also noted. In situ hybridization suggested that the most likely localization of the viral infection was in interstitial cells or macrophages infiltrating the myocardial tissue rather than localization in the myocytes themselves. Further using a panel of 6 proinflammatory genes, the investigators demonstrated increased activity among hearts with evidence of viral infection compared with hearts with no SARS-CoV-2 viral infection detected.4 These new findings provide intriguing evidence that COVID-19 is associated with at least some component of myocardial injury, perhaps as the result of direct viral infection of the heart.

The discoveries highlighted in this issue of JAMA Cardiology by Puntmann and colleagues5 are also informative. In 100 recovering patients included in the study, 67% of whom recovered at home, evaluated a mean of 71 days after confirmed COVID-19 diagnosis, 78% had demonstrable cardiac involvement via cardiac magnetic resonance imaging, 76% had detectable high-sensitivity troponin, and 60% had evidence of active myocardial inflammation by abnormal native T1 and T2.

Compared with controls including those with a similar profile of preexisting conditions, left ventricular ejection fraction was lower and volumes higher, as well as 32% manifesting late gadolinium enhancement and 22% with pericardial involvement. There are important residual questions about potential selection bias and generalizability and not all of the patients may have recovered, but the observations cannot be dismissed. Months after a COVID-19 diagnosis, the possibility exists of residual left ventricular dysfunction and ongoing inflammation, both of sufficient concern to represent a nidus for new-onset heart failure and other cardiovascular complications. Moreover, we cannot dismiss important other clinical pathophysiologic observations, including clinical syndromes consistent with acute myocarditis, the cascade of immunologic responses, a prothrombotic milieu with microvascular clot formation, and/or myocardial injury due to supply-demand mismatch. When added to the postmortem pathologic findings from Lindner et al,4 we see the plot thickening and we are inclined to raise a new and very evident concern that cardiomyopathy and heart failure related to COVID-19 may potentially evolve as the natural history of this infection becomes clearer.

We wish not to generate additional anxiety but rather to incite other investigators to carefully examine existing and prospectively collect new data in other populations to confirm or refute these findings. We hope these findings represent that of a select cohort of patients. Yet, if this high rate of risk is confirmed, the pathologic basis for progressive left ventricular dysfunction is validated, and especially if longitudinal assessment reveals new-onset heart failure in the recovery phase of COVID-19, then the crisis of COVID-19 will not abate but will instead shift to a new de novo incidence of heart failure and other chronic cardiovascular complications.

Given the pressing burden of the ongoing COVID-19 crisis, as well as the initiation of longitudinal care models for those recovering from COVID-19, the concerns we are raising are not theoretical but instead practical and require our due diligence to study and prepare for what may be another dimension of the COVID-19 crisis.

ARTICLE INFORMATION

Author Affiliations: Division of Cardiology, Northwestern University Feinberg School of Medicine, Chicago, Illinois (Yancy); Deputy Editor, JAMA Cardiology (Yancy); Ahmanson-UCLA Cardiomyopathy Center, David Geffen School of Medicine, University of California, Los Angeles (Fonarow); Section Editor, JAMA Cardiology (Fonarow).

Corresponding Author: Clyde W. Yancy, MD, MSc, Division of Cardiology Northwestern University, Feinberg School of Medicine, 676 N St Clair, Suite 600, Chicago, IL 60611 (cyancy@nm.org).


Conflict of Interest Disclosures: Dr Fonarow reported receiving personal fees from Abbott Laboratories, Amgen, AstraZeneca, Bayer, CHF Solutions, Edwards Lifesciences, Janssen, Medtronic, Merck, and Novartis outside the

Related articles pages 1281 and 1265
Choosing an Initial Therapeutic Approach for Hypertension—Time for a Fixed-Dose Combination First?

Ann Marie Navar, MD, PhD; Thomas J. Wang, MD

An estimated 1 in 3 outpatient clinic visits are made by adults with hypertension, and most adults with hypertension see their clinician multiple times per year.1 Nonetheless, most adults in the United States with hypertension experience uncontrolled disease.2 Patient-level factors play a role, including medication nonadherence and reluctance for treatment intensification. However, decades of research have shown that therapeutic inertia, or a clinician’s failure to intensify therapy in response to uncontrolled blood pressure (BP), contributes substantially to the ongoing burden of hypertension.3

Combination therapies are one of the most powerful tools available to improve hypertension control, improving adherence, shortening the time to control, and decreasing the number of up titration steps needed. The 2017 Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults4 recommends considering initial therapy with 2 medications for patients with systolic BP greater than 20 mm Hg or diastolic BP of 10 mm Hg over the target. For those with less severely elevated BP, the guideline endorses monotherapy as the appropriate initial approach: “The stepped-care approach defined by the initiation of antihypertensive drug therapy with a single agent followed by the sequential titration of the dose and addition of other agents has been the recommended treatment strategy since the first report....”4(p169)

Several lines of evidence have prompted the current interest in combination therapy, in particular the use of fixed-dose combination (FDC) pills (also called polypills). Observational data suggest that those who initiate treatment with combination therapy are more likely to achieve BP control than those starting with multipill combinations or monotherapy.5 Furthermore, since 2017, multiple trials have shown that FDC therapy may improve BP control compared with usual care.6,7

One of these studies, the Triple Pill Vs Usual Care Management for Patients With Mild to Moderate Hypertension (TRIUMPH) study,8 randomized 700 patients in Sri Lanka to usual care or a once-daily FDC pill containing 20 mg of telmisartan, 2.5 mg of amlodipine, and 12.5 mg of chlorthalidone. Those randomized to FDC were more likely to achieve BP control (70% vs 55%) at 6 months, with an overall difference in systolic BP of 9.8 mm Hg in the treatment arm vs the usual care arm.

While the trial was a success, a notable 30% of patients failed to achieve BP control at the final follow-up visit. In the present analysis published in JAMA Cardiology,9 TRIUMPH investigators evaluated the contribution of therapeutic inertia to persistently poor BP control. The authors identified patients who had BP greater than the target at follow-up and evaluated the frequency of medication changes in each arm. Among those who continued to have uncontrolled BP, the proportion of patients who had their medications uptitrated was lower in the FDC arm compared with usual care at both 6 weeks (13% vs 36%) and 12 weeks (10% vs 35%). This finding suggests that clinicians were less likely to uptitrate therapy in patients receiving FDC. Had uptitration occurred in the FDC arm at the same rate as it did in the usual care arm, the advantage in BP control in the FDC group compared with usual care may have been even greater at the end of the trial.

Other trials also suggest FDC therapy may be associated with a lower inclination for physicians to uptitrate other therapies. In a recent polypill-based BP trial in the United States, there was a significant improvement in BP control in participants randomized to the polypill, although individuals receiving the polypill were less likely to have other BP medications added or increased.7

What might explain higher rates of therapeutic inertia in patients receiving FDC therapy? By design, nearly all patients assigned to FDC therapy (98%) in TRIUMPH9 had immediate treatment intensification, compared with only 73% of those in the usual care arm. The early treatment intensification with FDC therapy was associated with a large reduction in systolic BP (mean, −14.9 mm Hg). This early reduction in BP might have made clinicians less inclined to uptitrate therapy at subsequent visits, even for patients who did not achieve the target BP. The likelihood of medication uptitration at the follow-up

REFERENCES