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# Viral myocarditis: 1917–2020: From the Influenza A to the COVID-19 pandemics ☆☆☆★



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## ABSTRACT

Myocarditis is common during viral infection with cases described as early as the influenza pandemic of 1917, and the current COVID-19 pandemic is no exception. The hallmark is elevated troponin, which occurs in 36% of COVID patients, with electrocardiogram, echocardiogram, and cardiac magnetic resonance being valuable tools to assist in diagnosis. Cardiac inflammation may occur secondary to direct cardiac invasion with the virus, or to intense cytokine storm, often encountered during the course of the disease. Angiotensin converting enzyme inhibitors, angiotensin receptor blockers, and judicious use of beta-blockers are beneficial in management of myocarditis. Corticosteroids may be avoided during the very early phase of viral replication, but can be of clear benefit in hospitalized, critically ill patients. Statins are beneficial to shorten the course of the disease and may decrease mortality.

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## Introduction

Near the end of World War I, a unique disease began to spread across the world. It was mainly characterized by upper respiratory infection with fever. As it progressed, it manifested as bronchopneumonia and could result in severe hypoxemia, ending in mortality [1]. Years later, by analyzing frozen specimens, it was found to be a result of the influenza A virus. In the United States alone, it resulted in 675,000 deaths. In today's terms, considering population growth, it would be equivalent to the death of 2.2 million Americans. Mortality was more common in infants, pregnant women, the elderly, and in people with chronic diseases such as diabetes mellitus [2].

During autopsy studies, the main problems were found in the lungs in the form of bronchopneumonia. Some patients had clearly

identifiable cardiomyopathy, and it was thought that might be secondary to alcohol ingestion used in the treatment of such patients [3]. In those days, electrocardiography was not widely available, and echocardiography had not yet been invented. Later on, it was shown that myocarditis is one of the features of influenza infection.

Further reports confirmed that myocarditis is not uncommon during influenza infection. In most reports, 10% of cases of influenza had a clear acute myocarditis diagnosed clinically, with up to 40% having a definitive diagnosis on autopsy. Patients that were younger than 5-years-old, older than 65, those in nursing homes, and those with underlying chronic diseases were more likely to develop pneumonia. Those with severe illness may have other organ involvement, such as myocarditis [4]. Myocarditis was also described as a result of infection with other viruses such as coxsackievirus, echo virus, and adenovirus infections [5].

## Diagnosis of myocarditis

For proper diagnosis of myocarditis, consider ACE: **A**wareness, **C**linical presentation, and **E**chocardiography. Health care providers need to be aware that acute myocarditis may occur during a viral infection. That myocarditis appears to be present at autopsy at

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a much higher rate than during clinical assessment suggests that myocarditis is often missed during presentation.

Clinically, a patient whose symptoms begin to worsen after initial improvement, or those with sinus tachycardia out of proportion to the degree of fever, should raise suspicion for the disease [6]. Electrocardiogram may show sinus tachycardia, non-specific ST-T wave abnormality, ST elevation, deep T wave inversion, and development of atrial fibrillation [7]. Patients exhibit elevation of troponin enzymes as well as inflammatory markers such as interleukin 6, 8, and 10 [8]. Echocardiography is a valuable tool in detecting viral myocarditis with either global or regional wall motion abnormalities, with myocardial strain patterns adding a special value in early diagnosis [9]. While endomyocardial biopsy is highly specific for diagnosis of myocarditis, its use should be limited to a few cases where diagnosis is challenging and accurate diagnosis is needed to guide medical therapy [10].

Cardiac magnetic resonance has emerged as a valuable tool in the diagnosis of myocarditis. It shows evidence of inflammation, necrosis, or scarring as well as providing a good evaluation of the pericardium, which is often involved in the disease. In addition, it may help exclude other forms of cardiomyopathy [11].

#### *Animal models of myocarditis*

It has been challenging to conduct human studies investigating specific therapies for viral myocarditis. Cases are not commonly encountered in clinical practice or are often missed, making it difficult to have large enough groups of subjects to conduct such studies. This makes utilization of laboratory studies more appealing. Khatib et al [12] established a mouse model for coxsackieviruses B1-B4 myocarditis. The model in mice parallels its human counterpart in both acute and chronic phases of the disease, as well as in histopathologic features. We investigated the effect of non-steroidal anti-inflammatory drugs (NSAIDs) utilizing a group of 82 3-week-old mice infected with coxsackievirus B3, Nancy strain. Both salicylates and indomethacin resulted in more viral replication and worse myocardial inflammation and necrosis when treatment was initiated soon after viral infection [13]. Similar deleterious effects were described by other laboratories using ibuprofen [14]. Only captopril, when tested in the same model, was of tangible benefit. Not only features suggestive of congestive heart failure were improved as expected, but there was also marked improvement in cardiomegaly and myocardial inflammation and necrosis [15]. At a different laboratory in Japan, Matsumori and Kawai [16] studied myocarditis utilizing a mouse model for encephalomyocarditis. Similar benefits were demonstrated using angiotensin converting enzyme (ACE) inhibitors. In addition, aldosterone antagonists, such as eplerenone, improved survival as well as histopathologic lesions in infected mice [17].

Thus, the total experience from laboratory studies suggests that NSAIDs should be avoided in the acute phase of the disease, and ACE inhibitors and aldosterone antagonists should be utilized to have a clear benefit on the disease. It also appears that the earlier therapy is instituted, the more pronounced the benefit will be. Captopril may have an edge over other angiotensin blocker drugs [18].

#### *Human trials*

Human trials for the management of myocarditis are indeed challenging. Some cases will have spontaneous improvement; others will not be diagnosed early enough and will only be recognized at a late phase when respiratory symptoms improve, yet symptoms of clear congestive heart failure manifest, prompting an echocardiogram. Again, cardiac magnetic resonance is currently the best

non-invasive modality to help clinch the diagnosis [19]. In a recent report, Knight et al studied 29 patients with elevated troponin in the setting of COVID-19 viral infections using cardiac magnetic resonance [20]. In addition to left ventricular dysfunction, there were 13 patients with myocarditis-like patterns, according to international criteria. A meta-analysis of the use of immunosuppressive therapy spanned almost 20 years, yet collected a total of 600 cases. Studies included different patient populations with different treatment protocols. Despite short-term benefit, no sustained long-term effects were noted, a conclusion that is hardly enough to draw solid recommendations [21]. In addition, drugs such as angiotensin enzyme inhibitors and aldosterone antagonists with solid clear benefit in laboratory studies and in congestive heart failure patients, precluded conducting ethical randomized clinical studies. We will briefly review human randomized studies exploring use of immunosuppressive therapy, colchicine, and antiviral drugs in human myocarditis. While there is a clear benefit of immunosuppressive therapy in eosinophilic, granulomatous, and giant-cell myocarditis [22], the role in treating viral myocarditis is less clear. A landmark study by Mason et al randomized 111 patients with endomyocardial biopsy-proven myocarditis to conventional therapy only or conventional therapy plus immunosuppressive therapy [23]. The immunosuppressive therapy included prednisone with either cyclosporine or azathioprine for about 7 months. Immunosuppressive therapy did not show benefit in clinical features nor in ejection fraction. No mortality benefit was demonstrated at follow-up for at least 4 years [23]. Meta-analysis of studies of immunosuppressive therapy in adults [24] and in pediatric age groups [25] do not support their use in the management of myocarditis [26]. Only an occasional study of patients with chronic heart failure and no evidence of viral genome suggested a benefit in ejection fraction at 6 months follow-up; however, the group that received prednisone had more fluid retention and an increase in blood sugar levels [27].

Colchicine is another drug used clinically in recurrent pericarditis and primary carditis based on historic case reports. No controlled studies for colchicine in the management of primary myocarditis have been reported; only one randomized study investigated the effect of colchicine as an anti-inflammatory agent in acute myocardial infarction with reported benefit [28]. Newer studies do suggest that colchicine may have a role in chronic coronary artery disease [98].

A recent review discusses the benefit of colchicine as an anti-inflammatory drug in coronary artery diseases, but there are no clear data on perimyocarditis [29]. Only occasional reports suggest a benefit from antiviral drugs such as intravenous ribavirin [30] or interferon-alpha [31]. No clear benefit has been established for intravenous immunoglobulin for the treatment of myocarditis in both children and adults [32]. Despite extensive clinical investigation, no new therapeutic modalities have a proven role in the management of myocarditis, while the mainstay of therapy continues to be ACE inhibitors, angiotensin receptor blocker, and aldosterone antagonists.

#### *Myocarditis in coronaviruses*

Myocarditis is reported to occur in patients infected with coronaviruses. In the severe acute respiratory syndrome (SARS) outbreak in 2002, autopsy studies proved the presence of viral RNA in the myocardium of 35% of patients infected with the virus [33]. Acute myocarditis was also reported during the outbreak of Middle East respiratory syndrome coronavirus (MERS-COV) as well [34]. It may gain access to cardiocytes through angiotensin receptors and may also lead to reduced angiotensin protein expression [33].

The first case of COVID-19 was reported in Wuhan, China in December 2019. By December 2020, globally 217 countries and ter-

ritories have reported about 81.7 million Covid-19 cases and 1.8 million deaths, with numbers continuing to rise. Clinical manifestations of the disease are fever, dry cough, and fatigue with bronchopneumonia, resulting in shortness of breath. Later it became clear that the infection was not limited to the lung, but includes the heart, liver, and kidney, among other organs [35]. Cardiac effects include stress cardiomyopathy, endotheilitis resulting in acute coronary syndromes, cardiac arrhythmias, and myocarditis [36]. This review will focus on myocarditis.

#### COVID-19 myocarditis

It was reported that the intense cytokine storm that may occur during SARS- coronavirus 2 (CoV-2) infection may induce myocardial inflammation without necessarily the presence of virus genome in myocardial biopsy of such patients [37]. Myocardial involvement was first reported from Wuhan, China, and in that initial report, it was suggested that myocardial injury may be related to the effects of the generalized infection with hypotension and hypoxemia, rather than direct cardiac involvement [38].

Cardiac involvement in the current COVID-19 epidemic has been described. The main hallmark of cardiac injury is the elevation of cardiac troponin for either Troponin I or Troponin T [39]. It may include cardiac injury from severe hypoxemia, coagulopathy resulting in acute coronary syndromes [40–44], and endothelial dysfunction [45–48], with a decrease in production of nitric oxide [49]. This report will focus on myocarditis associated with COVID-19 infection.

Cases of cardiac inflammation during the current epidemic are either related to direct viral invasion of the myocardial cells or to intense cytokine storm. Wichmann et al performed autopsy at a single center in Germany [50]. The group included 12 patients with confirmed COVID-19 infection. Five patients demonstrated viral presence in the myocardium. Utilizing endomyocardial biopsy, Tavazzi et al demonstrated the virus invaded the heart, and histologic examination confirmed myocardial inflammation [51].

In COVID-19 patients, another mechanism may be responsible for the development of myocarditis. While reports are still scant, it appears that infection with coronavirus results in elevation of inflammatory cytokines such as IL-1, IL-12, and IL-6. In fact, the higher the level of these cytokines, the higher the chance of severe infection and admission to the intensive care unit (ICU). While the main organ affected by this inflammation is the lung, resulting in acute respiratory distress syndrome (ARDS), other organs such as the heart are affected as well [52].

#### Histopathology of myocardium

Fox et al performed autopsy on 22 hearts in patients with COVID-19 [53]. Gross heart weight was 340–1010 g. The most common finding was enlargement of the right ventricle, probably reflecting the stress imposed from increase pulmonary resistance. Electron microscopy revealed viral particles in the cardiac endothelial cells, scattered myocyte necrosis, and scattered lymphocytes adjacent to small blood vessels. In another series, 21 patients who died from the disease underwent a comprehensive autopsy. Cardiac involvement was present in 55% of patients, with inflammatory cells found in the endocardium, myocardium, and epicardial fat. Fibrin and platelet thrombi were also found in the small intramyocardial blood vessels, but not in larger coronary arteries [54]. While there was no significant coronary atherosclerosis or coronary artery aneurysms described in the autopsy series, evidence of endotheilitis was commonly encountered [55]. Viral particles were detected in cardiomyocytes, interstitial tissue, and endothelial cells [56]. Findings from various autopsy reports suggest direct cardiac involvement, as well as effects from the increase in

cardiac stress from the severe lung involvement. Occasional autopsy reports, however, failed to show larger areas of lymphocytic infiltrates or myocyte necrosis [46].

#### Clinical presentation of myocarditis in COVID-19

Myocardial injury in general is common in patients with COVID-19 infection. While troponin elevation was reported to occur in many patients with COVID-19 as early as March 2020, some patients had significant elevation [57]. The marked increase in the enzyme was noted in critical care units and seems to be associated with increased mortality. In a review of 2,736 patients infected with the virus at Mount Sinai Health System hospitals in New York City, 36% of patients had elevated troponin levels. Patients with underlying cardiovascular disease were more likely to have troponin elevation, and those with elevated troponin were associated with higher mortality rates [58]. Smaller studies from Wuhan, China show at least 20% with cardiac injury [59]. Cardiac injury was defined as elevated cardiac biomarkers. Review of individual case reports described a younger age group where myocarditis was diagnosed utilizing echocardiogram and cardiac magnetic resonance [60–66], and rarely by endomyocardial biopsy [67]. The biopsy showed the characteristic T-lymphocytic inflammatory infiltrates. The symptoms of these patients included—in addition to shortness of breath—fatigue, chest tightness, and palpitation. Examination with 12-lead electrocardiogram showed sinus tachycardia, non-specific ST and T wave abnormality, long QT interval, and ventricular tachycardia. Atrial fibrillation was reported in cases presenting with COVID-19 myocarditis [68]. Laboratory testing included elevation in troponin, creatine kinase, D-dimer, C-reactive protein, N-terminal pro-brain natriuretic peptide, and interleukin [69].

The main diagnostic modalities were 2D echocardiogram and cardiac magnetic resonance. Echocardiogram, as a non-invasive, portable test with immediate interpretation, is the corner stone for diagnosis of myocarditis. In patients with elevated troponin, evidence of congestive heart failure, electrocardiographic abnormalities or cardiac arrhythmias, echocardiogram should be performed [70]. The main findings are dilated cardiac chambers, regional or diffuse left and right ventricular dysfunction, and valvular regurgitation. Pericardial effusion of various degrees may be present. In addition, left ventricular longitudinal strain correlates with myocardial edema detected by cardiac magnetic resonance. Echocardiography also has prognostic implications. Patients with marked reduction in ventricular myocardial strain have a higher mortality rate [71]. In a recent report, structural cardiac abnormalities were noted in up to 65% of infected individuals and was linked to increased mortality [72].

Cardiac magnetic resonance is another diagnostic modality for myocarditis in patients with COVID-19. In addition to structural abnormalities such as dilated cardiac chambers and pericardial effusion, other findings have been detected. Myocardial edema, necrosis, and late gadolinium enhancement are pathognomonic [73]. The magnetic resonance changes may linger after recovery from the viral infection [74]. To confirm diagnosis, and to rule out coronary artery disease as the cause for troponin elevation or echocardiographic abnormality, coronary angiography may be warranted. Clearly cardiac coronary computed tomography angiography (CCTA) may provide the answer, thus avoiding invasive procedures. Positron emission tomography (PET), while rarely used in the clinical arena for diagnosis of myocarditis, may show characteristic inflammation in the myocardium [73]. Endomyocardial biopsy, while definitive for the diagnosis, is only rarely used in COVID-19 patients, probably to limit spread of the infection to medical workers.

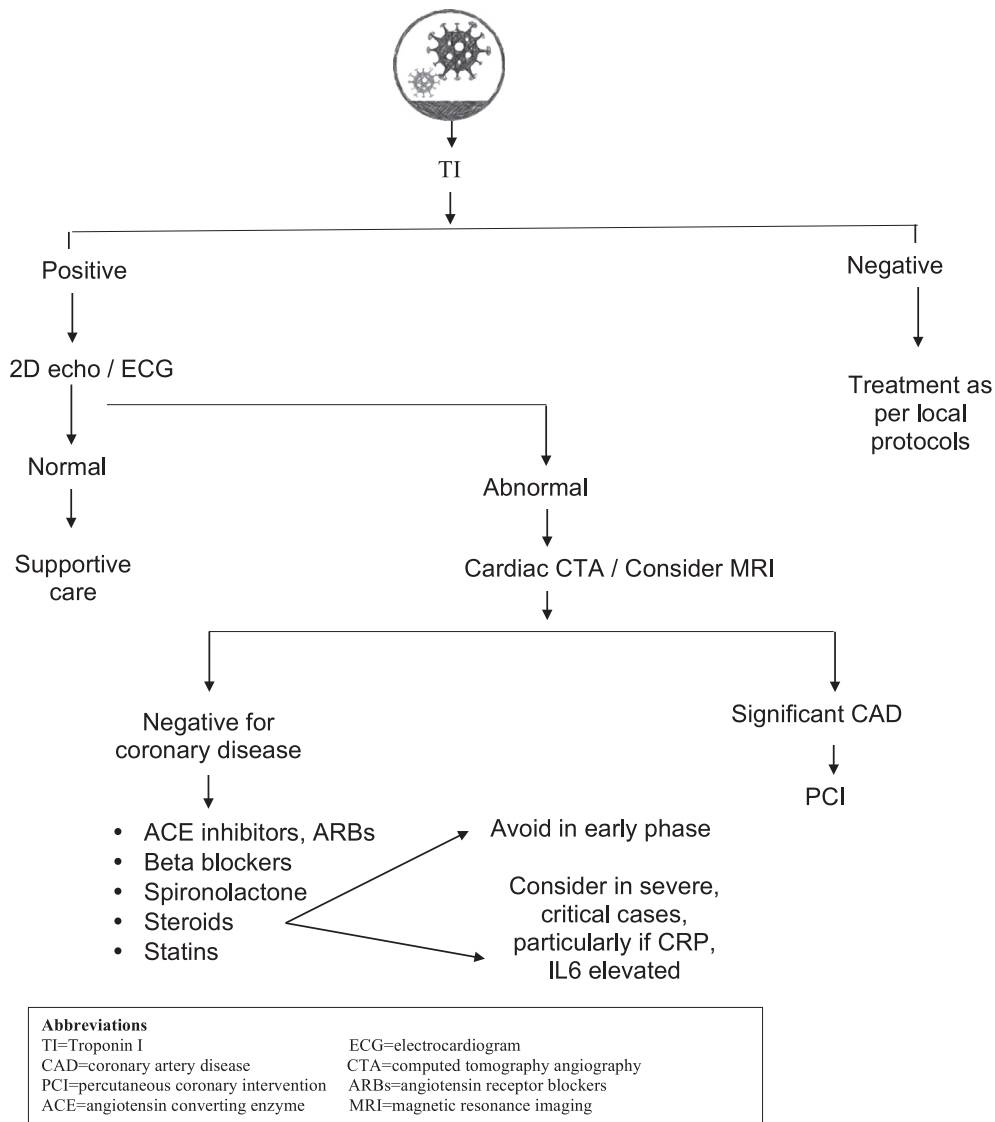


Fig. 1. Suggested algorithm by the authors for diagnosis and management of viral myocarditis.

While it is clear that myocarditis occurs in some patients with the viral infection, there is no agreement on the exact incidence. The spread of the disease across many countries with different health care systems, varying resources, and at times the intensity of the epidemic have made any clear agreement challenging. The American Heart Association recently launched the COVID-19 CVD registry to collect better data about the virus and the extent of cardiovascular disease [75]. Preliminary information presented at the 2020 AHA Scientific Sessions regarding the AHA registry on COVID suggested that the clinical manifestations of myocarditis among hospitalized COVID -19 patients was actually low (< 1%), despite that several studies show higher numbers of patients with elevated troponin levels.

While many cases of myocarditis may have mild symptoms, occasionally fulminant myocarditis was reported [76]. Occasionally, cases similar to Takosubo cardiomyopathy were described [77]. A review of 51 cases of myocarditis showed that recovery was documented in 30% of cases, with a mortality rate of 27% [78].

There are many similarities between infection with COVID-19 and influenza. Viral spread, risk factors for infection, and the range of symptoms are similar. There are, however, clear differences. In-

fluenza myocarditis appears to be related mainly to direct viral invasion of myocytes. In COVID-19, cytotoxin storm plays a prominent role. More recently, autoantibodies against interferon were detected in patients suffering severe infection, and it was associated with life threatening disease [79]. While steroids have shown some effectiveness in COVID-19 infection, they may be of benefit in coronavirus myocarditis; however, large scale controlled studies have not been conducted [80].

Management

Measuring troponin I should be done when COVID-19 infection is suspected. If normal, then the patient should be managed according to accepted local protocols. If elevated, critical evaluation of electrocardiogram, and if coronary artery disease is suspected, proceed with computed coronary angiography. If coronary arteries are normal, then myocarditis is suspected, and imaging with echocardiography and/or cardiac magnetic resonance should be considered. Myocarditis should be initially treated with ACE inhibitors, beta blockers, and aldosterone antagonists.

In the beginning of the pandemic, there were concerns about the use of ACE inhibitors, since it upregulates the ACE2 receptors.



These receptors are the entry point of the virus to both cardiac myocytes and vascular endothelial cells. Despite these earlier concerns, many reports exploring their use in COVID-19 myocarditis proved them to be safe and effective [81]. In a small randomized study, ramipril or placebo were given to a group of patients for 6 months following transcatheter aortic valve replacement. In this study, 11 patients developed COVID-19 infection; ramipril did not affect the incidence or the severity of the infection [82]. Many other reports now show that this group of drugs is not only safe to continue in patients with COVID-19, but are also associated with significant benefits when utilized in management of the disease [83].

Beta blockers may be utilized, but should be started at a lower dose and then gradually increased to full therapeutic dose. Starting with a full dose may precipitate acute heart failure [84]. In fulminant myocarditis, presentation may be cardiogenic shock, in which case administration of inotropes or vasopressors should be considered. Extracorporeal membrane oxygenation, ventricular assist devices, or intra-aortic balloon pump may be used in select cases [85].

While in the beginning of the pandemic, hydroxychloroquine was utilized, with the thought that it may be beneficial, further experience has shown that it resulted in a significant prolongation of the QTc interval on the electrocardiogram [86], which may result in sudden death in Covid-19 patients [87]. A recent meta-analysis of 10,659 patients with COVID-19 did not show any benefit from the use of such drugs [88], putting this controversy to rest. It is now accepted that hydroxychloroquine and related drugs should be avoided in the management of COVID-19.

Initial protocols included the use of NSAIDs. There were no controlled studies to show the benefit in COVID-19 patients [89], and because of many concerns, experts suggest avoiding their use in the course of this infection [90].

Systemic corticosteroids were also considered in the treatment of COVID-19 in sedated patients. In the early phases of viral replications, and in patients with documented intracardiac virus by endomyocardial biopsy, their use should be prohibited. In the late phase, with critically ill patients, they are useful, particularly in the presence of severe inflammation. In a prospective meta-analysis of 1,703 critically ill patients with COVID-19, corticosteroid therapy was clearly beneficial with a lower 28-day all-cause mortality [91].

Recently, strong signals suggest a clear benefit of statins in the severity and recovery of COVID-19 patients [92]. Meta-analysis from multiple reports support such benefit [93]. A mortality benefit was also shown [94,95]. The possible mechanisms for that could be membrane stabilization and inhibition of the cytokine storm that lead to myocarditis and inflammation in the various organs [96]. More recently, a cocktail of neutralizing monoclonal antibodies against SARS-CoV-2 show promising results, although it is still under investigation [97].

No clear role has been demonstrated for anti-viral, immunoglobulins, or anti-leukin G antibodies in the management of coronavirus myocarditis at the time of the writing of this paper [81].

## Conclusion

Myocarditis is a frequently missed complication during viral infections. It occurs in many forms of viruses from influenza virus to the current COVID-19 infection. A presumptive diagnosis is made with elevated cardiac enzymes, echocardiography, and cardiac magnetic resonance. There is a paucity of controlled randomized studies to guide in the management of this disease in humans. Angiotensin converting enzyme inhibitors, angiotensin receptor inhibitors, and spironolactone may be of benefit if there is left ventricular dysfunction. Beta blockers used in low graduating

doses may be utilized. Corticosteroids may be avoided in the early phases during viral replication, but are of clear benefit in hospitalized, critically ill patients. For a suggested algorithm to diagnose and manage COVID-19 myocarditis, see Fig. 1.

## Ethical statement

We the undersigned declare that this manuscript is original, has not been published before and is not currently being considered for publication elsewhere.

Both authors meet the requirements regarding the duties and responsibilities of authorship as set by the International Committee of Medical Journal Editors. Each author participated in the conception and design or analysis and interpretation of the data and in drafting the article or critically revising it. We confirm that all authors are responsible for the content and have read and approved the submitted form of the manuscript to *Trends in Cardiovascular Medicine*; that the manuscript conforms to the Uniform Requirements for Manuscripts Submitted to Biomedical Journals published in *Annals in Internal Medicine*.

Both authors have read and approve and each author accepts responsibility for the manuscript's contents and verifies validity of the results reported. We confirm that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by both of us.

There is no real or potential conflict of interest on the part of any author. Both authors contributed equally to this work and approve the final manuscript.

We understand that the Corresponding Author is the sole contact for the Editorial process. He is responsible for communicating with the other author about progress, submissions of revisions and final approval of proofs.

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