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Familial hypercholesterolemia: The nexus of endothelial dysfunction and lipoprotein metabolism in COVID-19

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Purpose of review
Patients with heterozygous familial hypercholesterolemia (HeFH) are at increased risk for COVID-19 cardiovascular complications in the acute phase of the infection. Elevated levels of LDL-C and often lipoprotein(a) are present from birth and lead to endothelial dysfunction, which is aggravated by a direct viral attack of the endothelial cells and their exposure to the toxic levels of circulating proinflammatory and prothrombotic mediators during the hyperinflammatory reaction typical of COVID-19.

Recent findings
Evidence to date shows the benefit of lipid-lowering therapy in patients with COVID-19. In HeFH patients who are at much higher cardiovascular risk, the focus should, therefore, be on the effective lowering of LDL-C levels, the root cause of the greater cardiovascular vulnerability to COVID-19 infection in these patients. The ongoing use of statins and other lipid-lowering therapies should be encouraged during the ongoing COVID pandemic to mitigate the risk of cardiovascular complications from COVID-19, particularly in HeFH patients.

Summary
Epidemiologic registry data show that the incidence of myocardial infarction is increased in SARS-CoV-2-infected HeFH patients. There is a need to study whether the risk for acute cardiovascular events is increased in the long-term and if there are changes in lipid metabolism after SARS-CoV infection(s) in patients with HeFH.

Keywords
COVID-19, endothelial dysfunction, heterozygous familial hypercholesterolemia, LDL-cholesterol, lipid metabolism, lipid-lowering therapy

INTRODUCTION

After more than 3 years since the first case of coronavirus disease 19 (COVID-19) in man was reported, it is time to accept the fact that COVID-19 is here to stay. The latest massive COVID-19 outbreak is ongoing in China, and the Chinese Center for Disease Control and Prevention (China CDC) estimates that about 18% of the Chines population, which makes up about 250 million people, have already been infected [1]. However, this estimation is probably conservative as other unofficial estimates vary between 50 and 90% of the Chinese population or at least 900 million inhabitants [1,2]. The worldwide prevalence of heterozygous familial hypercholesterolemia (HeFH) has been estimated to be about 1 : 300, and based on this estimate, in China alone, among some 900 million infected inhabitants about 3 million would be expected to be HeFH patients [3]. It can be estimated that of the at least 26 million HeFH patients in the world [4], several million must have been infected with the SARS-CoV-2 virus.

HeFH is the most common autosomal dominant monogenic disorder worldwide which, as a result of a lifelong burden of markedly elevated serum LDL-cholesterol (LDL-C), results in premature atherosclerotic cardiovascular disease (ASCVD) if left untreated [5–7]. In a recent US national database

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KEY POINTS

- Patients with HeFH are at increased risk for COVID-19 cardiovascular complications in the acute phase of the infection and in the longer term.
- Evidence to date shows that in the general population, lipid-lowering therapy is beneficial in patients with COVID-19.
- In HeFH patients who are at even higher cardiovascular risk, the focus should be on the effective lowering of the life-long highly elevated LDL-C levels, the likely root cause of the greater cardiovascular vulnerability to COVID-19 infection in these patients.
- Ongoing use of statins and consideration for other lipid-lowering therapies should be encouraged during the ongoing COVID pandemic to mitigate the risk of cardiovascular complications from COVID-19, particularly also in HeFH patients.

study of over 300 million individuals, it was estimated that patients diagnosed with probable or definite HeFH and SARS-CoV-2 infection had significantly increased Annualized Incidence of Density Rates (AIDRs) for acute myocardial infarction (AMI) when compared with control patients (Myers *et al.*, 2021). In this study, the AIDR for HeFH patients with preexisting ASCVD was 11.3% whereas in controls, it was much lower, that is, 2.3% ($P < 0.0002$). Of note, severe COVID-19 requiring hospital admission increased the risk of myocardial infarction in familial hypercholesterolemia patients whether or not they had been diagnosed with ASCVD.

In addition to the acute impact of SARS-CoV-2 infection on human health, COVID-19 also has long-term cardiovascular consequences because it increases both the burden of dyslipidemia and the ASCVD risk whether the patients had recovered completely or if their symptoms had continued (post-COVID-19 syndrome) [8–11]. The findings demonstrating prolonged dyslipidemia after SARS-CoV-2 infection are very recent and they are based on a very large observational study of the general population with incident dyslipidemia in the post-acute phase of SARS-CoV-2 infection [11]. Accordingly, the study found increased levels of serum total cholesterol (TC), low-density cholesterol (LDL-C), and triglycerides, and decreased levels of high-density cholesterol (HDL-C) among the patients who had had SARS-CoV-2 infection when compared with those who had never been positive for SARS-CoV-2 infection [11,12]. Moreover, the post-COVID lipid burden increase corresponded to the severity of the acute phase of the SARS-CoV-2 infection. Such a prolonged post-COVID burden of dyslipidemia brings special challenges to HeFH patients, who have a genetically determined very high serum LDL-C level, and often also a lower serum HDL-C level when compared with the general population [6,13]. Based on the above observations, it is of particular concern that during the COVID-19 pandemic, ASCVD prevention has diminished not only regarding the management of dyslipidemia in the general population but also in patients with HeFH [14,15].

ACUTE MYOCARDIAL INFARCTION

In the large longitudinal US national database analysis by Myers *et al.* [16▪] covering over 300 million individuals the AIDRs for AMI were retrospectively compared with those individuals with diagnosed or probable HeFH with or without COVID-19. Because COVID-19 patient cases were collected before July 2020, it can be assumed that the patients had not been vaccinated against COVID-19. In this database study, the diagnosed HeFH patients with and without COVID-19 had AIDRs for AMI, which were 3.2 and 0.30%, respectively ($P < 0002$). Comparative AIDRs data for the diagnosed HeFH patients with established ASCVD were 11.3 and 2.3% ($P < 0.0002$). This study shows the high AMI risk of HeFH patients who get infected and particularly of those HeFH patients who have preexisting ASCVD. The findings of this study are very impressive, but we are still lacking epidemiological data to demonstrate the overall increased risk of clinical complications of ASCVD in HeFH patients during the acute phase and during longer follow-ups post-COVID-19 [17].

ENDOTHELIAL DYSFUNCTION

Endothelial dysfunction is already evident in untreated young HeFH children as a result of the high LDL-C burden, often accompanied by an elevated level of serum lipoprotein(a) [Lp(a)], both present from birth [18,19]. Indeed, both factors adversely affect the function of the endothelium. Such dysfunctional endothelium is particularly vulnerable to additional insults such as SARS-CoV-2 infection and ensuing COVID-19, as endothelial cells may become infected by the virus and are also exposed to the toxic levels of circulating proinflammatory and prothrombotic mediators during the hyperinflammatory reaction typical of COVID-19 [20▪▪]. Accordingly, preexisting endothelial dysfunction, such as often found in untreated HeFH patients, renders the endothelium particularly vulnerable, and exposes the COVID-19-infected HeFH patient to a particularly increased risk of vascular complications [20▪▪,21–23]. As the vast majority of

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HeFH patients remain undiagnosed and/or undertreated, they have a steadily increasing burden of premature atherosclerotic lesions, particularly in their coronary arteries. Therefore, the coronary endothelium in an infected HeFH patient even without clinical evidence of ASCVD is exposed to an inflammatory environment both from the luminal side and the abluminal (subendothelial) side, where the chronic inflammatory process of atherosclerosis is ongoing.

The vulnerability of all COVID-19 patients to atherothrombotic complications is also increased during a post-COVID-19 condition because the COVID-19-induced exacerbation of endothelial dysfunction may last several months after the infection [24,25▪]. Furthermore, serum Lp(a) levels (which are often high in HeFH patients) increase further during and post COVID -19 as the LPA gene encoding for Lp (a) contains an interleukin- (IL-6) response element, which is upregulated by elevated IL-6 levels during the acute phase of COVID-19 infection [26]. Hyperactivation of the humoral immune system is also linked to D-dimer elevation reflecting increased thrombotic activity, as shown in a study of 211 hospitalized COVID-19 patients [27].

ATHEROSCLEROTIC CARDIOVASCULAR DISEASE IN THE GENERAL POPULATION

A large prospective cohort study of patients with COVID-19 based on data obtained from the UK Biobank and followed up to 18 months showed increased cardiovascular risk and mortality both during the acute phase of the disease and in the long-term [28]. In this study, encompassing data collected from unvaccinated persons between 16 March 2020 and 30 November 2020, the results showed that during the acute phase (defined as the period up to 21 days after COVID-19 diagnosis), the cardiovascular disease risk was elevated [hazard ratio 4.3 and 95%; confidence interval (CI) 2.6–2.9] and that the long-term risk was also significantly increased (hazard ratio 1.4; 95% CI 1.2–1.8)]. The authors recommend ongoing careful monitoring of signs and symptoms pointing to an increased cardiovascular risk in these patients. A further very large study of the general population in Sweden showed that during the first week after the primary infection, the risks of AMI and acute ischemic stroke were increased (hazard ratio 2.89; 95% CI 1.51–5.55 and hazard ratio 2.97; 95% CI 1.71–5.15, respectively) [29▪▪].

CORONARY MICROCIRCULATION

Endothelial dysfunction plays a major role in the development of coronary microvascular dysfunction (CMD) [30]. Importantly, in a swine familial hypercholesterolemia model, coronary microvascular dysfunction was a primary contributor to both impaired myocardial oxygen balance and impaired cardiac efficiency [31]. The finding of microvascular endothelial dysfunction has also been confirmed in HeFH patients [32]. By analyzing myocardial perfusion reserve (MPR), Drakos *et al.* [33] compared patients who had recently recovered from SARS-CoV-2 infection with those who had classic hypertrophic cardiomyopathy (HCM), and they found a comparable reduction of MPR in both groups of patients. This study concluded that COVID-19 patients had infection-triggered mechanisms, which ultimately resulted in the development of CMD. Although this finding has been confirmed in several studies, especially in hospitalized patients with COVID-19, the severity of CMD among COVID-19 patients appears to vary partly because of the virus variant that caused the disease [34–39]. Importantly, a very recent study in the United Kingdom identified microangiopathic thrombosis as a common cause of myocardial injury in hospitalized COVID-19 patients with troponin elevation [40]. Regarding HeFH patients with COVID-19, both the severe hypercholesterolemia and the SARS-CoV-2 infection jointly cause CMD which, in combination, is likely to be more severe than in normolipidemic individuals [41].

ISCHEMIC STROKE

The meta-analysis by Nannoni *et al.* [42] has shown that acute cerebrovascular events are not unusual among patients with COVID-19, particularly among those with preexisting vascular risk factors who are at greater risk for ischemic stroke [43]. In this meta-analysis, in those patients who had preexisting coronary artery disease, the odds ratio (OR) for the acute cerebrovascular disease was 43.12 (95% CI 1.61–6.02). Preexisting cardiovascular risk factors also predispose to an ischemic stroke in patients with COVID-19 as found in a large multiethnicity registry study and a meta-analysis [44,45]. In addition, the prognosis of stroke is worse in patients with COVID-19 [46–48].

In the prestatin era, HeFH patients had a strongly elevated risk of ischemic stroke, while in the statin era, the risk of ischemic stroke in statin-treated patients has been found to be similar to that in the non-HeFH population [48,49]. However, as most HeFH patients remain undiagnosed and the hypercholesterolemia even in the diagnosed HeFH patients is often undertreated, the risk of a highly deleterious ischemic stroke in the majority of HeFH patients remains elevated [50].

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PRIMARILY LDL-CHOLESTEROL-LOWERING DRUGS

Statins

Although several large randomized controlled studies on the use of statins in patients with COVID-19 are ongoing [51▪], the information accumulated to date is based on systematic reviews, retrospective registry studies, and uncontrolled clinical studies, with the findings from only a few controlled studies having been published [52–60]. These data clearly show that statins are beneficial in SARS-CoV-2 infection, their beneficial effects being derived from their anti-inflammatory, antithrombotic, and endothelial function-enhancing effects, which are partly independent of the extent of lipid-lowering achieved [25▪,61,62]. Furthermore, at least in experimental settings, several statins inhibit viral RNA-dependent RNA polymerase and the SARS-CoV-2 main protease, suggesting that statins may also exert direct antiviral activity [55,63]. Moreover, in experimental settings, both *in vitro* and *in vivo,* simvastatin has been shown to disrupt lipid rafts with ensuing relocation of ACE2 receptors to the nonraft membrane, which again, may hamper the proper interaction of ACE2 and SARS-CoV-2, and so reduce the viral infectivity and ensuing systemic inflammation [64].

PCSK9 inhibitors

In a recent randomized study, 60 hospitalized patients with severe SARS-CoV-2 infection were randomized 1 : 1 to a 140 mg subcutaneous injection of the PCSK9 inhibitor evolocumab or placebo [65▪▪]. Importantly, within 30 days of observation, the patients treated with evolocumab had lower mortality and less need for intubation than those treated with placebo (23.3 vs. 53.3%; 95% CI −53.4 to −6.59%). This study was based on the hypothesis that, as shown for dengue virus infection, a PCSK9 inhibitor could interfere with the production of IL-6, thereby reducing the inflammatory response [66,67]. However, it can be argued that, in addition to preventing the reduction in the expression of antiviral products (type I interferons) by PCSK9, the favorable mechanisms of PCSK9 inhibitors, particularly in patients with HeFH, may also result from the rapid and effective reduction in the levels of LDL-C and, to a lesser extent in Lp(a), with a resultant improvement in endothelial function [68].

Combination therapy

As serum LDL-C levels often remain elevated with statin therapy alone in HeFH patients, ezetimibe with or without a PCSK9 inhibitor may need to be added to the cholesterol-lowering regimen [69,70]. As mentioned, HeFH patients suffer from a lifelong highly elevated serum LDL-C level, which is often accompanied by a high Lp(a) level, both of which cause endothelial dysfunction and expose HeFH patients with COVID-19 to an increased risk of thrombus formation [19]. Accordingly, combination therapy, particularly including a PCSK9 inhibitor, is tenable because it effectively decreases the level of both serum LDL-C and Lp(a), and because it tends to maintain normal endothelial function, which is worsened during SARS-CoV-2 infection. Indeed, all three of these drugs (statins, ezetimibe, and PCSK9 inhibitors) have been shown to have beneficial vascular effects on their own during COVID-19 infection [71,72]. It can be assumed that, in combination, the beneficial effects of these individual drugs are additive. However, this needs to be further studied and confirmed in a clinical setting.

Primarily triglyceride-lowering drugs (fenofibrate)

In a very recent study, Ehrlich *et al.* [73] demonstrated that fenofibrate blocks SARS-CoV-2 replication and the associated lipid accumulation in cultured human lung epithelial cells via a PPAR alpha-dependent mechanism. Interestingly, a large number of patients hospitalized with severe COVID-19 given fenofibrate added to the standard care were found to have lower levels of immuno-inflammation and faster recovery. The authors speculated that COVID-19 progression partly depends on metabolic mechanisms, as obesity, elevated blood glucose, and hyperlipidemia are risk factors for SARS-CoV-induced acute respiratory distress independently of diabetes [74,75]. Moreover, endothelial function-improving effects of fenofibrate in COVID-19 may occur as this drug has been shown to improve endothelial dysfunction in macrovessels and microvessels of diabetic mice, an effect, which was likely independent of its hypolipemic action [11]. In addition to its potential antiviral activity, fenofibrate may exert beneficial immunomodulatory effects in COVID-19 [76]. However, despite the many promises of fenofibrate as a beneficial pharmacological tool for the modulation of SARS-CoV-2 infection, a recent large randomized controlled clinical trial failed to show any improvements in clinical outcomes in patients with COVID-19 [77]. This negative result likely applies also to dyslipidemic HeFH patients during a prolonged post-COVID period and so highlights the importance of a particularly efficient LDL-cholesterol-lowering regimen during this vulnerable period.

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Nirmatrelvir/ritonavir in combination with lipid-lowering therapy

Nirmatrelvir/ritonavir (NMV/r) or Paxlovid has been used to successfully treat SARS-CoV-2 infection [78]. This treatment is most beneficial among patients with preexisting cardiovascular or neurological disease [79]. Although NMV/r treatment is potentially effective for severe COVID-19 among HeFH patients, clinicians need to remember potential drug–drug interactions during concomitant use of NMV/r and certain statins (simvastatin, lovastatin, atorvastatin). As the listed statins are substrates for the hepatic cytochrome P450 (CYP) 3A4, and the ritonavir component of Paxlovid strongly inhibits CYP 3A4, coadministration of Paxlovid with any of the listed statins may increase their concentration to a toxic level [80]. However, it is important to continue statin treatment, particularly in HeFH patients with a high cardiovascular risk [81–83]. Accordingly, during NMV/r treatment, simvastatin or lovastatin should be substituted with either pravastatin or fluvastatin. Additionally, a reduction in the dose of atorvastatin or rosuvastatin is advised. There are no limitations to continuing treatment with ezetimibe and/or evolocumab [80].

CURRENT AND FUTURE PERSPECTIVES

HeFH patients are high-risk patients for COVID-19 complications, notably for acute cardiovascular events, both in the acute phase of the infection and during the years to come after the infection. Elevated levels of LDL-C, often accompanied by an elevated level of Lp(a), are present from birth in HeFH patients, thereby exposing their vascular endothelium to two heritable life-long elevated endothelium damaging factors.

Evidence to date shows a clear benefit of the use of statin therapy as well as other cholesterol-lowering therapies in patients with COVID-19. Particularly in HeFH patients, in addition to all other therapies currently available to treat COVID-19, the focus should be on the effective lowering of the very high LDL-C levels, the root cause of the excess vulnerability of familial hypercholesterolemia patients to COVID-19 infection.

CONCLUSION

HeFH patients with COVID-19 infection, particularly those HeFH patients who have preexisting ASCVD, are at highly elevated risk for cardiovascular events. Unfortunately, we are still lacking epidemiological data to conclusively demonstrate the overall increased risk of clinical complications of ASCVD in HeFH patients during the acute phase and longer follow-up after COVID-19 infection. Further data need to be gathered to confirm whether the risk for and the severity of COVID-19 in HeFH are increased and to confirm that intensification of the lipid-lowering therapy can reduce the cardiovascular event risk in these patients.

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