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Review article

Familial hypercholesterolaemia and COVID-19: A two-hit scenario for endothelial dysfunction amenable to treatment

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ABSTRACT

Patients with familial hypercholesterolemia (FH) are likely at increased risk for COVID-19 complications in the acute phase of the infection, and for a long time thereafter. Because in FH patients the level of low density lipoprotein cholesterol (LDL-C) is elevated from birth and it correlates with the degree of systemic endothelial dysfunction, both heterozygous FH (HeFH) patients and, in particular, homozygous FH (HoFH) patients have a dysfunctional endothelium prone to further damage by the direct viral attack and the hyper-inflammatory reaction typical of severe COVID-19. Evidence to date shows the benefit of statin use in patients with COVID-19. In FH patients, the focus should therefore be on the effective lowering of LDL-C levels, the root cause of the expected excess vulnerability to COVID-19 infection in these patients. Moreover, the ongoing use of statins and other lipid-lowering therapies should be encouraged during the COVID pandemic to mitigate the risk of cardiovascular complications from COVID-19. For the reduction of the excess risk in FH patients with COVID-19, we advocate stringent adherence to the guideline determined LDL-C levels for FH patients, or maybe even to lower levels. Unfortunately, epidemiologic data are lacking on the severity of COVID-19 infections, as well as the number of acute cardiac events that have occurred in FH subjects during the COVID-19 pandemic. Such data need to be urgently gathered to learn how much the risk for, and the severity of COVID-19 in FH are increased.

1. Introduction

In January 2020, there was a global call to action to reduce the atherosclerotic cardiovascular disease (ASCVD) burden caused by the heterozygous form of familial hypercholesterolemia (HeFH), which affects about one out of 200–250 individuals, or over 30 million individuals worldwide [1]. The authors cautioned that lack of awareness of this most common autosomal dominant inherited disease has resulted in an alarmingly low proportion (about 10%) of the HeFH patients being diagnosed and even less being treated. This is despite the World Health Organization (WHO) previously highlighting HeFH as a public health priority back in 1998 [2].

If untreated, HeFH is characterized by a lifelong two-to-three –fold elevation of serum LDL-cholesterol (LDL-C) due to reduced low-density lipoprotein (LDL) receptor-dependent hepatic clearance of circulating LDL particles [3], which leads to early atherosclerosis and about a ten-fold increase in the risk of premature atherosclerotic cardiovascular disease (ASCVD) [4]. Unfortunately, the first symptom of HeFH is often an acute myocardial infarction (AMI) or sudden cardiac death, and it has been estimated that only 20% of untreated HeFH men reach the age of 70 years [5]. On the other hand, early diagnosis and appropriate lowering of LDL-C have been shown to prevent, or at least delay, the onset of ASCVD, and to increase the life expectancy of HeFH patients to the same level as in the general population [6,7].

Coincidentally, at the same time when the global call to action to reduce the HeFH burden was declared, the WHO (December 31, 2019) was informed of cases of pneumonia of unknown cause in Wuhan City, China. Soon this severe respiratory illness was found to be caused by a novel coronavirus named Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), and subsequently called Coronavirus Disease 2019 (COVID-19). Early data from Wuhan showed that severe COVID-19 associates with ASCVD [8]. Indeed, of the COVID-19 patients

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hospitalized in Wuhan and treated in an intensive care unit (ICU), 25% had underlying cardiovascular disease. When WHO declared COVID-19 as a pandemic on March 11, 2020, a potential collision of HeFH, the most common inherited condition leading to ASCVD, and the emerging COVID-19 pandemic was about to begin.

As of December 2020, there were about 75 million COVID-19 cases worldwide and the disease has resulted in over 1.5 million deaths [9], but, as far as we are aware, no data on the association between HeFH and COVID-19 have been reported. However, with a prevalence of 1 in 250, an estimated 300 000 COVID-19 patients should also have had HeFH. Moreover, due to early ASCVD, it is possible among the critically ill and deceased COVID-19 patients with diagnosed acute cardiac events, HeFH is overrepresented, but such data are lacking.

2. Infection as a proatherogenic factor

From the evolutionary point of view, HeFH may have conferred a survival advantage when fatal bacterial infectious diseases were common, widespread, and without cure [10,11]. This hypothesis is supported by the finding that LDL receptor-deficient (*LDLR*$^{-/-}$) mice with high cholesterol concentrations, the murine counterpart of FH, are protected against severe gram-negative infections and lethal endotoxemia [12]. It is even possible that in the past the combination of high cholesterol and relative lack of food benefitted those who got bacterial infections and improved their survival. In modern times, however, the situation is quite the opposite, as a large proportion of undiagnosed HeFH patients (as subjects in the general population) are likely to follow an unhealthy lifestyle, which induces several proatherogenic changes in lipoproteins thereby further increasing their risk for developing premature ASCVD [13].

The progression of atherosclerosis is considered to be non-linear partly because bacterial and viral infections may cause transitory atherogenic changes in lipoproteins, and, among others, through this mechanism intermittently accelerate the development of atherosclerotic lesions [14–16]. Interestingly, HeFH patients with established ASCVD are more often seropositive for *Chlamydia pneumoniae* infection, suggesting that this infection may contribute to the development of advanced atherosclerotic lesions in these patients [17]. Animal data support the above conclusion by showing that *LDLR* $^{-/-}$ mice develop more advanced atherosclerosis after being infected with *Chlamydia pneumonia* [18]. Also, viral infections may accelerate atherogenesis and increase the risk of acute ASCVD events. For example, an association between cytomegalovirus antibodies and atherosclerosis was found in individuals with high levels of lipoprotein(a) [Lp(a)], and fibrinogen [19]. Such prothrombogenic associations maybe even stronger and clinically more significant in HeFH patients who tend to have higher Lp (a) levels and whose platelets show increased aggregation response to fibrinogen [20,21]. Additionally, it has been shown that in acute Epstein-Barr virus infection, the serum concentration of Lp(a) doubles for at least four months [22].

2.1. Pre-existing endothelial dysfunction and acute SARS-CoV-2 infection

Why should a HeFH patient infected with the SARS-CoV-2 virus be more likely to develop complications than a non-HeFH patient? The most obvious reason is the combination of underlying chronic systemic endothelial dysfunction caused by the lifelong hypercholesterolemia present in HeFH patients and the acute direct endothelial attacks by both the virus and the excessive immuno-inflammatory response of the host [23,24]. After all, COVID-19 can be considered an endothelial disease [25,26]. Since most HeFH patients remain undiagnosed and undertreated [27,28], their LDL-C levels remain elevated. Of note, LDL-C levels even in the high normal range may cause endothelial dysfunction [29]. Moreover, HeFH is diagnosed typically only in middle-aged or older patients, by which time their endothelium has been exposed to high LDL-C levels for a great many decades and, like the subendothelial layers of the susceptible segments of the arterial wall, is suffering from an ever-increasing LDL-C burden since birth [30]. Thus, when infected by the SARS-CoV-2, most HeFH patients are likely to have dysfunctional endothelial cells that are oversensitive to further damage by a direct viral attack and by the hyperinflammatory reaction ("cytokine storm") associated with severe COVID-19 [26].

Stenotic coronary lesions may already be evident in the late twenties or early thirties in HeFH males and females, respectively [31], and most middle-aged HeFH patients have subclinical or even clinically significant ASCVD [32]. Importantly, the endothelium covering an inflamed atherosclerotic lesion is vulnerable to erosion [33]. Moreover, a residual inflammatory risk persists both in HeFH and non-HeFH patients even if they are treated with a combination of a statin and a PCSK9 inhibitor [34,35]. Since coronary heart disease mortality remains elevated also in the treated HeFH patients [36], such residual inflammatory risk is probably clinically significant also in optimally treated HeFH patients.

Direct endothelial cell involvement, endotheliitis, in different organs of COVID-19 infected patients has recently been reported [37]. In these patients, widespread endothelial dysfunction results from the viral invasion of endothelial cells or the immune-mediated attack on the endothelium. The endotheliitis is associated with systemic impairment of the microcirculatory function, which then results in activation of the coagulation cascade and, via endothelial-platelet interaction, leads to the formation of multifocal occluding microthrombi, the key elements leading to multi-organ failure and eventual death of the patients with severe COVID-19 [25,26,37]. We can only assume that the prothrombotic reaction to a viral attack of dysfunctional endothelium is more intense than that of a primarily healthy endothelium.

2.2. Lipoprotein(a): a partner in crime

When compared to the general population, HeFH patients tend to have higher levels of Lp(a), which are LDL-like lipoproteins with strong pro-inflammatory and prothrombotic properties, thereby increasing the risk for atherothrombotic events [21]. Of particular concern is that serum Lp(a) levels correlate with the degree of endothelial dysfunction even in children with HeFH [23]. Therefore, in HeFH the vascular endothelium is exposed to a lifelong double insult, both high LDL-C and Lp(a) levels, which together further increase the risk for COVID-19-associated microthrombus formation.

Additionally, with infection, the oxidation of lipids carried in LDL increases [38], which in HeFH patients with markedly elevated serum LDL levels is potentially more harmful than in normocholesterolemic patients. During acute inflammation, also serum Lp(a) levels may further increase [38], so rendering HeFH patients even more vulnerable to vascular complications. As the majority of circulating oxidized phospholipids are carried on Lp(a) particles and are capable of promoting endothelial dysfunction, the oxidized Lp(a) phospholipids likely provide an important mechanistic link between increased Lp(a) level and increased ASCVD risk [39].

2.3. Lower prevalence of type 2 diabetes and obesity in HeFH

Regarding the COVID-19 vulnerability of HeFH patients, there are some potentially mitigating features as well. Subjects with HeFH tend to have a lower prevalence of type 2 diabetes [40], which itself is a major risk factor for complications from COVID-19 infection [41]. Moreover, statin therapy in HeFH does not appear to increase the risk of diabetes to the same degree as in the general population [42]. Finally, because of lifelong adherence to a low saturated fat diet and adoption of a healthier lifestyle, those subjects with diagnosed and well-controlled HeFH tend to be slimmer, which may reduce the risk for developing complications from COVID-19 infection [43,44].

3. Atherothrombotic events in COVID-19 patients

According to a recent meta-analysis, among hospitalized COVID-19 patients, the prevalence of AMI has been 3.3% (0.3–8.5) (95% CI) and the prevalence of ischemic stroke 1.8% (1.3–2.4) (95%, CI) [45]. Only two large studies were included in this meta-analysis, and in both studies, the prevalence of ischaemic stroke and AMI was studied in parallel [46,47]. The findings of these studies are shown in Table 1, and the results allow us to conclude that severe COVID-19 infection increases both arterial thrombotic (cardiac) and thromboembolic (cerebral) ischemic events.

In the SAFEHEART (Spanish Familial Hypercholesterolemia Cohort Study) cohort of 2752 HeFH patients, with median age 44 years and 1045 (38%) being on maximally tolerated statins, 6.5% had suffered a prior AMI and 0.8% an ischaemic stroke [44]. The corresponding numbers and particularly the relative proportions of AMI and ischemic stroke in HeFH patients with COVID-19 are not known. However, one can assume that both numbers would be higher because of the underlying hypercholesterolemia-induced endothelial dysfunction in HeFH.

4. Ischemic stroke in COVID-19

Patients with COVID-19 infection have an increased risk of both ischemic stroke [37,48,49] and intracerebral hemorrhage [50]. Coagulopathy and endothelial dysfunction incurred by COVID-19 may be the mechanisms associated with the increased stroke risk in patients with COVID-19 infection. Moreover, even transient cerebral ischemia induces a local endothelial dysfunction that may contribute to parenchymal injury and worsen the outcome [51]. Stroke is usually a complication of severe COVID-19, the median onset from clinical symptoms of COVID-19 to stroke being 21 days [50,52]. Importantly, a stroke precipitated by COVID-19 is more severe and has a worse functional outcome and higher mortality than a stroke not related to COVID-19 [53]. Early work before the introduction of statins has shown that patients with HeFH have at least a 20-fold higher risk of brain infarction when compared with non-HeFH subjects [54]. Based on these data, we can surmise that, in analogy to the expected increased risk for COVID-19-associated cardiac ischemia in HeFH patients, the risk for COVID-associated cerebral ischemia is increased in this patient population.

5. Statins and COVID-19

As discussed, severe SARS-Cov-2 infection leads to a hyperinflammatory syndrome or “cytokine storm”, which, when severe, also activates the coagulation cascade resulting in a pro-thrombotic state [55,56]. Importantly, elevated levels of IL-6 and/or D-dimer are associated with poor prognosis in COVID-19 patients [57–59] Statins have shown to be beneficial adjuvant drugs to ameliorate components of the proinflammatory cytokine release syndrome, such as the interleukin IL-6 [60]. Moreover, statin use associates with lower D-dimer levels, which may reflect a reduction in the prothrombotic state [61,62].

Table 1
Acute myocardial infarction and stroke among COVID-19 patients in the general population.

Country	No. of patients (total) ICU/ non-ICU	ICU AMI %	ICU stroke %	Non-ICU AMI%	Non-ICU stroke%	Reference
USA	3334 829/2505	3.7[a]	13.9[a]	0.9**	7.3**	[47]
Italy	388 61/327	2.1[a]	6.3[a]	1.0***	1.9***	[46]

ICU = intensive care unit; AMI = acute myocardial infarction.
[a] Of ICU patients; ** of all hospitalized patients; ***of all hospitalized patients in a general ward.

5.1. Clinical benefit of statins in viral infections

Statins have been shown beneficial in patients with the Middle Eastern respiratory syndrome (MERS), another illness caused by a coronavirus [63]. Also, when studying hospitalized influenza patients, it was found that statin therapy either before or during hospitalization associates with a reduction in fatality [64]. In a large study of in-hospital deaths among 8910 COVID-19 patients in different continents, statin use was associated with an improved prognosis [65]. In another recent retrospective study among elderly COVID-19 patients (N = 154) in nursing homes, a significant association between statin use and the absence of symptoms was observed [66].

5.2. Potential mechanisms behind the clinical benefits of statins in COVID-19

The anti-inflammatory effect of statins has been shown in endotoxin-dependent cell culture studies with human vascular smooth muscle and mononuclear cells, in which simvastatin, atorvastatin, fluvastatin, and pravastatin reduced IL-6 production by 53%, 50%, 64%, and 60%, respectively [67]. On the other hand, cholesterol-lowering treatment failed to influence the endotoxin-induced release of proinflammatory cytokines (IL-1β, IL-6, and TNF-alpha) in whole blood from patients with HeFH [68]. Moreover, no clinically significant reduction in the concentration of circulating IL-6 has been observed with statin use [69] Simvastatin use has been associated with a decreased concentration of IL-1β in gingival crevicular fluid among patients with periodontal disease, an interesting finding, but rather remote to COVID-19 [70,71].

On the other hand, statins have been shown to decrease serum D-dimer levels. A study of patients with suspected pulmonary embolism showed that statin use associated with a modest 15% decrease in D-dimer levels, while the use of antiplatelet drugs had no significant effect [72]. In a large cohort study of patients without cardiovascular disease (N = 6814), the D-dimer levels were 9% lower in statin users than in statin non-users [73]. Although statins use does not alter fibrinogen levels [74,75] their use can lead to downregulation of the blood coagulation cascade resulting from decreased tissue factor expression and ensuing reduced thrombin formation [76,77]. Since patients with HeFH exhibit an increased potential for thrombin generation [78], statin-dependent reduction in thrombin generation could be particularly beneficial in HeFH patients with a COVID-19-associated pro-thrombotic state.

5.3. Statins and ischemic stroke

Management of acute ischemic stroke is always a challenge in which time matters [79]. Brain infarctions related to COVID-19 infections should be treated like any ischemic stroke. However, during the COVID-19 pandemic, stroke patients arriving at an emergency room may have contracted SARS-CoV-2 infection and still be clinically asymptomatic regarding COVID-19, so presenting potentially a more demanding therapeutic challenge.

Statin-treated FH patients have a decreased risk of brain infarction [80,81]. Although we still lack evidence of a statin-dependent reduction in the risk of brain infarction associated with COVID-19, the use of statins would be particularly useful in this patient population since patients with COVID-19-associated strokes have an increased risk for poor functional outcome and mortality [53]. When an ischemic stroke patient with FH is discharged from an acute hospital to a rehabilitation clinic or home, statin treatment should be continued. Furthermore, statin therapy should be prescribed to all ischemic stroke patients according to national and international guidelines [82]. This recommendation is based on the fact that every ischemic stroke patient is at increased risk of recurrent stroke and is likely to have an underlying coronary heart disease, which

Table 2
Mortality of COVID-19 patients on statins.

Country	Study type	No. of patients	Age, yrs (range)	Mortality adjusted hazard ratio	Reference
China	Retrospective, multicenter	4305	Statin 66 (59–72) Non-statin 57 (45–67)	0.58 (0.43–0.80)	[84]
Italy	Retrospective, multicenter	3988	63 (58–75)	0.98 (0.81–1.20)	[85]

risks can be reduced by appropriate pharmacologic secondary prevention including the use of statins.

5.4. Statins and mortality in COVID-19

In a meta-analysis of selected COVID-19 studies, the hazard ratio (HR) among statin users for both mortality and severity was significantly reduced (HR = 0.70; 95% CI 0.53–0.94) [83]. Although this preliminary pooled analysis clearly showed a beneficial effect of statins, more data are needed. The two largest studies comparing the mortality among statin-using and non-using COVID-19 patients are shown in Table 2 [84,85]. Of note, Grasseli and co-workers [85] did not report on the dose of statin used, while Zhang and co-workers reported that the median daily statin dose was equivalent to 20 mg atorvastatin. The Massachusetts General Hospital Guidance advises that, if not contraindicated, administration of a daily dose of 40 mg atorvastatin or 20 mg rosuvastatin should be initiated [86].

6. Clinical implications of statin use in HeFH patients with COVID-19

Table 3 reviews the clinical implications of statin use in patients with an established diagnosis of HeFH and those with suspected HeFH. When adjusting for statin treatment or considering HeFH diagnosis in an undiagnosed COVID-19 patient, it is important to use pre-infection lipid values, if known. Table 4 shows two lipid treatment recommendations in COVID-19 by the Heart UK Expert Panel [87] and International Lipid Expert Panel [88]. The purpose of these recommendations is to guide clinicians in their treatment decisions when taking care of FH patients in the pandemic.

From a clinical standpoint, we can infer that regardless of whether or not middle-aged or older HeFH patients have received treatment for hypercholesterolemia, they will have an underlying systemic endothelial dysfunction and, accordingly, are at increased risk for severe COVID-19. Even in the absence of HeFH, concurrent COVID-19 infection in patients with ST-elevation myocardial infarction (STEMI) is associated with a higher thrombus burden and more unfavorable outcomes [89].

We should be mindful of the potential presence of HeFH, either diagnosed or undiagnosed. Accordingly, it has been suggested that all patients with STEMI should undergo COVID-19 testing to identify the possible additional risk in these already high-risk patients. Among such patients, in addition to the intensive care treatment and aggressive antithrombotic therapy, we should initiate, or at least try to avoid any disruption of HeFH-specific lipid-lowering pharmacotherapy.

7. PCSK9 inhibitors and COVID-19

As noted, many HeFH patients have both elevated LDL-C as well as Lp(a) levels, and therefore have a double-inherited athero-inflammatory burden [21]. Unfortunately, however, statins fail to lower serum Lp(a) levels and levels may even increase with statin use [90]. In an attempt to compensate for the excess impairment of endothelial function caused by high Lp(a) level, the level of serum LDL-C should be reduced even more effectively in HeFH patients with known elevated Lp(a) level. This may be achieved with the addition of a PCSK9 inhibitor, which will not only further lower LDL-C by about 60% but will also significantly lower Lp(a) by approximately 30% [21], and, by inhibiting PCSK9 activity, may even enhance the antiviral action of interferon [91]. We recognize, however, while a HeFH patient is being treated for severe COVID-19, maximizing the lipid-lowering therapy in an acute hospital setting may be an overwhelming challenge, at least regarding increasing the statin dose or adding the cholesterol absorption inhibitor ezetimibe to the regimen. Rather, the ongoing lipid-lowering therapy should be continued, having regard to drug-drug interactions between lipid-lowering drugs and the drugs used to treat severe COVID-19 [92]. However, in anticipation of a severe course of the COVID-19 illness, i.e., regarding the high-risk patients, intensification of the lipid-lowering therapy by administering an initial dose of a PCSK-9 inhibitor can be considered already upon admission to the hospital. Since in HeFH patients an increased residual risk for ASCVD events is likely to persist for prolonged periods of time, an adequate lipid-lowering therapy needs to be considered the latest during the recovery period before hospital discharge [87,93].

8. Homozygous FH and COVID-19

Homozygous FH (HoFH) is the most severe form of FH affecting approximately 1 in every 300 000 persons worldwide [94]. As a result of markedly elevated LDL-C levels which are often 4 to 6-fold increased from birth, subjects with HoFH develop severe premature ASCVD which often manifests in childhood or early adolescence. Despite multiple lipid-lowering therapies including lipid apheresis the majority of HoFH patients do not achieve acceptable LDL-C levels and remain at high risk for ASCVD at any age [95].

Patients with pre-existing ASCVD appear to be at heightened vulnerability to develop COVID-19 and tend to have more severe disease with worse clinical outcomes [96]. A predisposition to, and often the presence of ASCVD in subjects with FH, particularly those with HoFH, may therefore significantly increase the risk for and severity of COVID-19 infection [93]. Also, there is some evidence to suggest that the SARS-CoV-2 virus entry into the host cell via the ACE2 receptor is accelerated in the presence of high cholesterol levels [97]. Subjects with HoFH may therefore be even at higher risk of complications of COVID-19 infection than the patients with HeFH if they were to become infected.

HoFH is also characterized by a systemic inflammatory phenotype despite long-term cholesterol-lowering therapy [98] and the even higher Lp(a) levels found in subjects with HoFH (like in HeFH) may put them at

Table 3
Diagnosis and treatment of LDL-C in COVID-19 patients with a definitive diagnosis of HeFH and in COVID-19 patients suspected of having HeFH.

HeFH diagnosis	During COVID-19 (acute)	After COVID-19 (chronic)
Confirmed	Initiate/continue statin and other lipid-lowering medication and ensure that statin dose is effective; consider increasing the dose	Check with a new lipid measurement that lipid-lowering therapy is consistent with the HeFH guidelines
Suspected	Initiate/continue statin and other lipid-lowering medication and ensure that statin dose is effective	Confirm HeFH diagnosis and check with a new lipid measurement that lipid-lowering therapy is consistent with the HeFH guidelines

Table 4
Two lipid treatment recommendations in patients with COVID-19.

Guidance	Statins	Ezetimibe	PCSK9 inhibitors	Reference
Managing hyperlipidemia in patients with COVID-19[a]	Statin therapy should be continued. Note interaction with antiviral medications	Ezetimibe is considered a safe therapeutic option	The continuation of PCSK9 in patients with FH can be considered	An expert panel position statement from HEART UK [87]
Recommendations on the management of adult patients with FH during the COVID-19 pandemic[b]	Statin therapy should be continued. Note potential interactions with antiviral medications	If the target for LDL-C with high-intensity statin therapy not met or statin intolerance, ezetimibe is recommended	If the LDL-C target with high-intensity statin therapy not met or statin intolerance, PCSK9 inhibitor is recommended	The FH Europe and International Lipid Expert Panel [88]

[a] If a patient with homozygous FH (HoFH) is admitted to the hospital, a discussion between the acute hospital team and lipid specialist should occur at the earliest opportunity.
[b] Enable regular apheresis for those HoFH patients who require it. In the absence of apheresis, ensure that HoFH patients get effective therapies within reimbursement programs (lomitapide/PCSK9 inhibitors).

greater risk for atherothrombotic events during viral infection [99]. Lastly, as some treatments for HoFH, such as lipid apheresis and therapy with the ANGPTL3-inhibitor evinacumab which requires a monthly intravenous infusion are hospital-based, disruption of such therapies during the COVID-19 pandemic is of concern.

Epidemiologic data on the severity of COVID-19 infections as well as the number of acute cardiac events that have occurred in HoFH subjects during the COVID-19 pandemic are also sorely lacking and need to be gathered to confirm whether the risk for and severity of COVID-19 in HoFH is indeed increased.

What is important is that the ongoing use of lipid-lowering therapies, including hospital-based therapies like LDL apheresis should be encouraged and continued during the COVID pandemic to mitigate the risk of cardiovascular complications from COVID-19 in these high-risk individuals. Interestingly, plasmapheresis as a means to remove potentially pathogenic factors (e.g., activated complement) from blood has been reported to be an effective empirical therapeutic option to control the SARS-CoV-2 infection in patients requiring intensive care [100].

9. Summary and conclusions

FH patients with COVID-19 appear to belong to the high-risk group of patients for COVID-19 complications in the acute phase of the infection, and in the long term after the infection, they are likely to suffer from accelerated atherogenesis [93]. As elevated levels of LDL-C are already present prenatally [101,102] and since the degree of dysfunction correlates with serum LDL-C level [23], both HeFH and, in particular, HoFH patients are likely to suffer from hypercholesterolemia-induced endothelial dysfunction from birth [103]. Furthermore, levels of serum Lp(a) are elevated in many patients with FH, thereby exposing the vascular endothelium of these patients to two heritable life-long elevated endothelium damaging factors [21] (Fig. 1).

Evidence to date shows a clear benefit of statin use in patients with COVID-19 [104–106]. Also, the NIH guidelines recommend that patients with COVID-19 who use statins for prevention of ASCVD should continue statin therapy [87,107]. This recommendation should apply

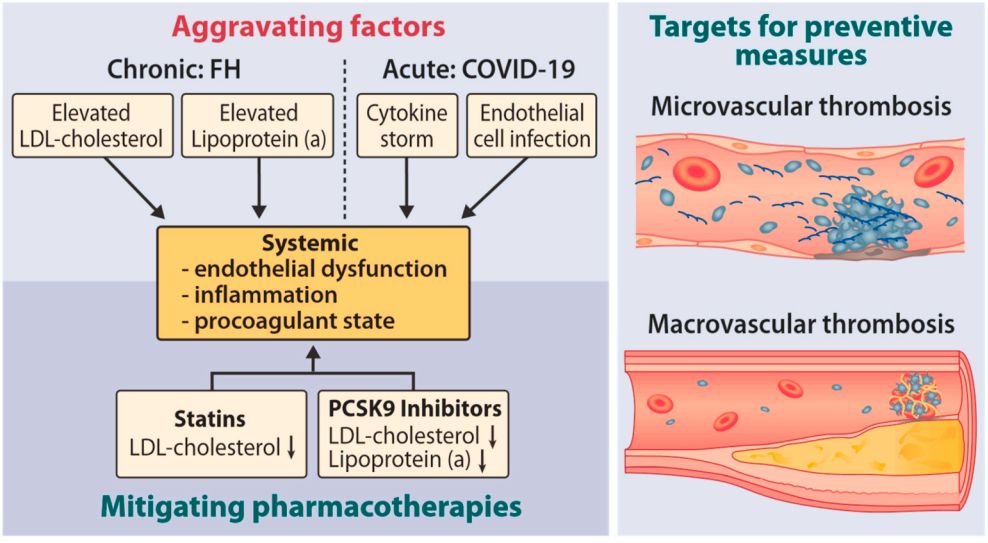

Fig. 1. The diagram shows a two-hit scenario for the development of clinical cardiovascular disease in patients with familial hypercholesterolemia (FH) and COVID-19. Among the aggravating factors are two chronic effectors associated with FH and two acute effectors associated with the SARS-CoV-2 infection. Jointly, these factors induce strong endothelial dysfunction, vascular inflammation, and a procoagulant state, which tend to trigger thrombus formation both at the microvascular level and the macrovascular arterial level (endothelial erosion or plaque rupture). In patients with FH and COVID-19, thrombosis in intramyocardial microvessels or atherosclerotic epicardial coronary arteries would lead to myocardial damage, as already documented in COVID-19 patients with other cardiovascular/cardiometabolic comorbidities. When a thrombus evolves at a critical site of an atherosclerotic extracranial or intracranial cerebral artery, an athero-embolic brain infarction may ensue. In all mentioned patient categories, the endothelial cells are not only among the primary cellular targets of the shown aggravating factors but also among the primary targets for preventive measures. Among such preventive/therapeutic strategies is lowering of the levels of LDL-cholesterol and lipoprotein (a) by hypolipidemic drugs which can act as adjunctive disease-mitigating pharmacotherapies at all stages of COVID-19 in FH patients.

particularly to FH patients. One should consider whether statin treatment should be intensified after the acute phase of the infection, a recommendation we base on the fact that infections can be considered ancillary factors responsible for the acceleration of atherogenesis [93, 108]. Moreover, since statins are safe in children with HeFH aged 8 years and above, statin use in FH children should be continued during the COVID-19 infection, and beyond [109].

Based on the available evidence, the most important mechanism behind the favorable effects of statins in COVID-19 appears to be the reduction in the risk of microthrombus formation. While in severe COVID-19, acute coronary syndromes due to thrombus formation in the epicardial coronary arteries appear to occur during the acute stage of the disease, dysfunction of the myocardial microvascular endothelium (coronary microcirculation) appears to evolve also during the convalescent and chronic stages of the disease [110]. Moreover, in the long term, COVID-19 may trigger a sustained accelerated progression of atherosclerosis [93]. Both the statin-dependent lowering of LDL-C and the pleiotropic effects of statins are systemic, i.e., they attenuate endothelial dysfunction both at the microvascular level (e.g., in intramyocardial microvessels) and at the arterial level (in the epicardial coronary arteries, carotid, and intracranial arteries). Accordingly, statins should be administered in the acute, convalescent, and chronic phases of COVID-19. Ongoing therapy with a statin at effective doses should be encouraged also after full recovery from the COVID-19 infection.

To date, we are lacking data that could unravel the magnitude of the likely elevated risk for atherothrombotic complications of COVID-19 in patients with FH. However, while awaiting such data we need to inform our FH patients that they are likely to be at increased risk of complication from COVID-19 infection. Therefore, FH patients need to be extra vigilant and need to take their lipid-lowering therapy religiously. In FH patients, in addition to all other therapies currently available to treat COVID-19, the focus should also be on the effective lowering of the very high LDL-C levels, the root cause of the expected excess vulnerability of FH patients to COVID-19 infection. Therefore, for the reduction of the excess risk in FH patients with COVID-19, stringent adherence to the guideline-determined LDL-C levels is necessary. The potential long-term additional increment in the ASCVD risk in patients with FH who have suffered the COVID-19 illness may even call for further reduction in the LDL-C levels. The magnitude of the benefit obtained from systemic endothelial protection by efficient LDL-C lowering in SARS-CoV-2-infected FH patients merits further evaluation.

There is a real need to collect data related to the clinical surveillance of hospitalized FH patients with COVID-19 who have received or have not received statin therapy with or without a PCSK9 inhibitor. This will help to test the hypothesis of whether these pharmacotherapies, mainly via mitigating endothelial dysfunction, will decrease atherothrombotic complications (acute myocardial infarction and ischemic stroke) in COVID-19 patients with FH. These data are also valuable for the evaluation of the suggested beneficial effects of statins on the immunothrombotic component of COVID-19 [111].

Declaration of competing interest

FR has received research grants, honoraria, or consulting fees for professional input and/or delivered lectures from Sanofi, Regeneron, Amgen, Novartis, and The Medicines Company.

PTK has received consultancy fees, lecture honoraria, and/or travel fees from Amgen, Novartis, Raisio Group, and Sanofi. The other authors have nothing to disclose.

Author contributions

AV and PTK drafted the manuscript. AV, FR, MK, and PTK wrote the manuscript. All authors approved the final version to be published.

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