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Brief recommendations on the management of adult patients with familial hypercholesterolemia during the COVID-19 pandemic

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The sudden outbreak of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus, which causes coronavirus disease 2019 (COVID-19), occurred in China in late 2019 and was followed by rapid transmission across Europe in early 2020. National healthcare systems experienced immense pressure and stretch in terms of the availability of medical personnel, access to treatments and consequently, the sustainability of outpatient clinics. The treatment of patients affected by COVID-19 has been prioritised, and all resources have been focused on serving that growing population. As a result, the management of familial hypercholesterolaemia (FH), in both the common heterozygous (heFH) and the much more rare homozygous (hoFH) forms is impacted and has been handled differently in different countries. The management of FH already varies between countries due to factors related to population characteristics, practice, resources and policies [1]. The aim of this document is to share practical recommendations about the management of FH patients and optimisation of their treatment during the COVID-19 pandemic.

The pandemic of a new coronavirus is a great challenge for healthcare systems worldwide, with 3.3 million infected individuals, and almost 235,000 deaths (as of May 1st) [2]. Observational data allows us tentatively to identify patients at the highest risk of severe consequences resulting from COVID-19, which includes those over 75 years of age (death rate: 14.2%), with baseline cardiovascular disease (CVD) (>13% for confirmed cases), with diabetes (9.2%), chronic respiratory disease, hypertension and cancer (death rate \geq 7.5% for all) [3]. Therefore, in order to reduce the risk of a severe disease course in individuals with COVID-19, it is critically important to improve the treatment of all concomitant diseases, for both healthy people and those already infected. Moreover, physicians need to know whether a patient's baseline therapy regimen should be continued concomitantly with antiviral, antiretroviral, anti-parasitic, antirheumatic, and antibiotics (mainly macrolides) that may be administered to individuals with symptoms of COVID-19 [4]. An equally important challenge is to provide

accessible healthcare to those patients with concomitant diseases, including ambulatory and in-patient care, and continued access to laboratory measurements, imaging tests, and medicines.

FH patients are a group with important healthcare needs who require frequent and continued medical attention. It is estimated that more than 30 million individuals worldwide have FH, and this large number of patients is of special importance at the time of a global pandemic of SARS-CoV-2 [5]. Both heFH and hoFH patients (especially the latter) have a genetic predisposition to very high circulating concentrations of low-density lipoprotein cholesterol (LDL-C). Recent recommendations suggest that all FH patients should be considered to have (at least) a high CVD risk [6]. If they have any additional risk factors, FH patients are at very high risk. The most recent recommendations suggest that FH patients should be considered to have an extremely high risk of repeated events if they have had an occurrence of acute coronary syndrome (ACS) [7]. Consequently, all these patient groups should be treated in order to achieve a circulating concentration of LDL-C below 70 mg/dL (1.8 mmol/L), and those at very high risk below 55 mg/dL (1.4 mmol/L), according to the principle of '*the lower, the better*'. This is critically important in order to stabilize and potentially even reduce the burden of atherosclerotic plaque, and consequently to lower CVD events' risk as well as mortality [8,9]. Lipid-lowering therapy (LLT) with statins, fixed combinations of statins with ezetimibe, and/or triple therapy with proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors results in stabilization of plaques and prevention of CVD events [8,9]. However, these drugs have additional mechanisms of action. Statins may substantially reduce inflammation and oxidative stress beyond that attributable to LDL-C reduction (and the reduction of oxidized LDL-C), through pleiotropic (anti-inflammatory) effects. PCSK9 inhibitors potentially reduce inflammation as a result of (among other effects) downregulation of LDL receptors, reduction of proinflammatory mediators, reduced infiltration of monocytes into the subendothelial layer and monocyte migration, and amelioration of vascular

inflammation [10-12]. These mechanisms are critically important in the context of COVID-19, because available data suggests that the disease results in a cytokine storm in susceptible patients, which would be expected to promote instability of the atherosclerotic plaque and consequent myocardial infarction with a very poor prognosis [13]. Therefore, because FH patients are at high, or extremely high risk of CVD, they need to be treated optimally and it is vital for them to have access to drugs and procedures (such as lipid apheresis in the case of severe HeFH and HoFH). Physicians need to know how to optimally manage FH patients who become infected with coronavirus, and to be aware of any interactions between drugs used to treat COVID-19, and drugs used in the management of FH.

Equally important is the effective organization of healthcare systems at this difficult time in order to continue the treatment of patients with FH and to enable the diagnosis of new cases, and consequent initiation of suitable treatments including PCSK9 inhibitors. Healthcare systems should be organized in such a way to allow the effective therapy of patients with COVID-19 (including those with FH), but also to allow the optimal treatment of uninfected FH patients, especially those with life-threatening CV complications, to avoid an increase in morbidity and mortality unrelated to COVID-19. Meeting these two objectives simultaneously is difficult because of the large number of SARS-CoV-2 cases being admitted to hospital and also changes the out-patients' routine practices.

When implementing lockdown procedures, which limit access to healthcare, and developing legislation relating to COVID-19, Ministries of Health (or equivalent organizations responsible for healthcare administration) should consider allowing temporary access to drugs, which are effective in FH but are not currently widely available. Lomitapide may effectively prevent CVD events when lipid apheresis is unavailable [14]. Reimbursement for PCSK9 inhibitors could be extended for those at very high and extremely high-risk patients of CVD events, who do not meet the current criteria in given countries. Access to these drugs for new

and already treated patients could be improved by allowing GPs to prescribe them. In this way, it would be possible to have most FH patients on optimal LLT, resulting in fewer CVD events, and better prognosis should these patients become infected with SARS-CoV-2. [13,15]. Finally, it is essential that educational activities for patients at the highest risk of CVD (including those with FH) are continued. These include joint activities of governmental organizations, scientific societies and patient organizations, which provide regular and extensive information on drug accessibility. It is also essential to maintain the availability of necessary procedures for FH patients in specialized centers (e.g. drug programs, lipid apheresis).

Based on the information summarised above, experts from the International Lipid Expert Panel (ILEP) and the European FH Patient Network (FH Europe) have taken part in online meetings and discussions with the representatives of the European countries. These meetings resulted in the preparation of recommendations on how to manage FH patients during the coronavirus pandemic. Taking into account the similar way of management they might be also extended for non-FH patients with severe hypercholesterolemia being at high/very high CV risk. The recommendations are presented in a ‘question and answer’ (Q&A) format (**Table 1**).

Table 1. Q&A recommendations for the management with patients with FH during the COVID-19 pandemic.

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| 1. | <p><i>Are there any additional beneficial effects of LLT on SARS-Cov-2 infection?</i></p> <p>This still needs to be confirmed with further research on SARS-CoV-2. However, in one study with infectious bronchitis coronavirus (IBV-CoV), it was demonstrated that cholesterol reduction disrupted lipid rafts and prevented binding of coronavirus with the host cells. In another study with porcine deltacoronavirus (PD-CoV), the authors observed that cholesterol present in the cell membrane and viral envelope contributed to virus replication by acting as a key component in viral entry. Therefore, the pharmacological reduction of cellular or viral cholesterol with effective LLT might block both virus attachment and internalization [16,17]. There is also data suggesting that statins might enhance angiotensin converting enzyme 2 (ACE2), which could mitigate the invasion of SARS-CoV-2 through the ACE2 receptor, potentially having a beneficial effect in attenuating risk of infection [18]; another data, based on <i>in-silico</i> study, showed that pitavastatin, rosuvastatin, lovastatin, and fluvastatin could be efficient SARS-CoV-2 main protease inhibitors [19].</p> |
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| 2. | <p><i>Are patients with FH at increased risk of COVID-19 complications?</i></p> <p>At every age FH patients have an increased risk of experiencing a severe course of COVID-19. This is because of their elevated lifelong risk of CVD (which may be as much as 100x higher at the age of 20-40 in comparison to healthy subjects, and is at least similar to that of patients with baseline CVD) [6]. Therefore, FH patients should strictly follow the directions of social distancing and isolation, wear masks and gloves when outside, and should wash their hands as often as possible. Detailed advice is available elsewhere, e.g., https://www.nhs.uk/conditions/coronavirus-covid-19/advice-for-people-at-high-risk/</p> |
| 3. | <p><i>Can FH patients be suitably monitored and treated when ambulatory clinics visits and scheduled hospitalizations are cancelled?</i></p> <p>FH patients should receive all the necessary medical information <i>via</i> electronic resources (e-advice) and/or e-consultations (with a physician or nurse). Drugs should be prescribed electronically (e-prescription). In the case of ongoing therapy, LDL-C measurements can be postponed. For newly diagnosed patients, the intensification of the therapy should be based on CVD risk stratification and the last two available LDL-C measurements (also necessary for further monitoring of LLT effectiveness). When tools for telemedicine are unavailable in hospitals, phone consultations can be used to provide advice to patients. Drugs should be prescribed for at least 3 months. This also applies when appointments are postponed or cancelled due to staff unavailability.</p> |
| 4. | <p><i>What about ongoing screening and identification as well as treatment of newly confirmed patients?</i></p> <p>In most countries, active searching and diagnosis of new FH patients has been put on hold. However, based on the above recommendations, when a new phenotypic and/or genetic diagnosis is made (e.g. during hospitalization) patients should be immediately directed to a specialized lipid center and should receive an e-consultation in order to start effective therapy (with e-prescription) as quickly as possible. For further details see above.</p> |
| 5. | <p><i>Are statins safe in FH patients with coronavirus infection?</i></p> <p>Lipid-lowering drugs are generally safe in patients with coronavirus infections and should be continued. When COVID-19 is treated with antiretroviral drugs (lopinavir/ritonavir) it is recommended that prescribers discontinue atorvastatin, simvastatin, and lovastatin. It is possible to continue therapy with rosuvastatin, with preference for starting a low dose (5-10 mg) and titrating up (with careful monitoring of muscle symptoms and creatine kinase levels). It is also reasonable to lower the dose of rosuvastatin and prescribe it in fixed combination with ezetimibe, or to continue therapy with pravastatin or fluvastatin (with or without ezetimibe, as necessary) [10,20]. Caution is necessary when treating patients with some macrolides (erythromycin, clarithromycin, and telithromycin) [9]. However, there is no data on severe or serious interactions of rosuvastatin and fluvastatin with azithromycin (inconsistent data refers to the potential interactions with atorvastatin; moderate to severe interactions were observed for simvastatin, lovastatin and pitavastatin) [21]. In case of muscle symptoms occurrence patients should be managed based on available recommendations for statin intolerance [22]. There are no contraindications to use</p> |

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| | <p>statins with chloroquine and hydroxychloroquine [9]. There is also no data on any interactions of statins with remdesivir [23]. In case of therapy with tocilizumab, rosuvastatin is recommended, as simvastatin and atorvastatin concentrations may be reduced when used concomitantly with this drug [24].</p> |
| 6. | <p><i>What about therapy with ezetimibe and PCSK9 inhibitors?</i></p> <p>In patients not meeting the therapeutic target for LDL-C with high intensity statin therapy, as well as in those with statin intolerance, therapy with ezetimibe and PCSK9 inhibitors is recommended [9,25,26]. In addition to significantly reducing the risk of CVD events and mortality, PCSK9 inhibitors may exert some additional anti-inflammatory effects. There is no data on any interactions of ezetimibe and PCSK9 inhibitors with any drugs that might be used during coronavirus infections [9,10,25].</p> |
| 7. | <p><i>What about patients requiring lipid apheresis when the treatment is not accessible?</i></p> <p>All patients requiring regular (every 1-2 weeks) lipid apheresis, including very high risk HoFH patients, should be enabled to access this procedure. Where this is not possible, treatment might be postponed safely by as much as 2 months while using intensive LLT, and strict monitoring of symptoms. When clinical symptoms arise, patients should be admitted to hospitals as urgent cases. In the absence of apheresis appropriate health organizations shall consider alternative therapies. There is therefore a need to lobby governments to ensure FH patients are able to access effective therapies within reimbursement programs (lomitapide/PCSK9 inhibitors).</p> |
| 8. | <p><i>What can patients do in order to monitor their disease?</i></p> <p>With the help of the national scientific societies and patients' organizations, it is important to continuously advise and educate FH patients on self-monitoring and the self-reporting of symptoms. Education and advice on continuing lifestyle changes, exercise and dietary treatment should be provided, as they can be severely compromised by stay-at-home directives. It may be critically important to enable e-consultations with physicians to prevent undesirable events.</p> |

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