Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Review article

Managing hyperlipidaemia in patients with COVID-19 and during its pandemic: An expert panel position statement from HEART UK

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ABSTRACT

The emergence of the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which causes Coronavirus Disease 2019 (COVID-19) has resulted in a pandemic. SARS-CoV-2 is highly contagious and its severity highly variable. The fatality rate is unpredictable but is amplified by several factors including advancing age, atherosclerotic cardiovascular disease, diabetes mellitus, hypertension and obesity. A large proportion of patients with these conditions are treated with lipid lowering medication and questions regarding the safety of continuing lipid-lowering medication in patients infected with COVID-19 have arisen. Some have suggested they may exacerbate their condition. It is important to consider known interactions with lipid-lowering agents and with specific therapies for COVID-19. This statement aims to collate current evidence surrounding the safety of lipid-lowering medications in patients who have COVID-19. We offer a consensus view based on current knowledge and we rated the strength and level of evidence for these recommendations. Pubmed, Google scholar and Web of Science were searched extensively for articles using search terms: SARS-CoV-2, COVID-19, coronavirus, Lipids, Statin, Fibrates, Ezetimibe, PCSK9 monoclonal antibodies, nicotinic acid, bile acid sequestrants, nutraceuticals, red yeast rice, Omega-3-Fatty acids, Lomitapide, hypercholesterolaemia, dyslipidaemia and Volanesorsen. There is no evidence currently that lipid lowering therapy is unsafe in patients with COVID-19 infection. Lipid-lowering therapy should not be interrupted because of the pandemic or in patients at increased risk of COVID-19 infection. In patients with confirmed COVID-19, care should be taken to avoid drug

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interactions, between lipid-lowering medications and drugs that may be used to treat COVID-19, especially in patients with abnormalities in liver function tests.

1. Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes Coronavirus Disease 2019 (COVID-19), infects cells of the respiratory tract via receptor-mediated endocytosis after interaction with the angiotensin converting enzyme receptor 2 (ACE2) protein [1]. Lipid lowering therapy is generally considered safe; however, there are theoretical concerns regarding their contribution to infectivity and safety in patients with COVID-19 pneumonia or acute respiratory distress syndrome (ARDS). Baseline characteristics of patients who required critical care unit admission due to COVID-19 from Lombardy, Italy, revealed that there was an 18% prevalence of hypercholesterolaemia as a co-morbid condition [2]. In a case series of patients suffering from COVID-19, 35.3% of patients were found to have underlying atherosclerotic cardiovascular disease and this was associated with a 50% fatality rate [3]. Similarly, data from New York showed that 26% of patients hospitalised because of COVID-19 were reported to have hyperlipidaemia as a co-morbid condition and 10% were known to have coronary artery disease [4]. In non-hospitalised COVID-19 patients, however, the prevalence of hyperlipidaemia and coronary artery disease (CAD) was 11% and 2%, respectively. Of the hospitalised patients, there was a similar prevalence of hyperlipidaemia (27% *vs.* 24%) and CAD (12% *vs.* 9%) in those admitted to critical care *vs.* discharged from hospital (and thereby not requiring any ventilatory or other supportive therapy). In a multivariate regression analysis assessing risk factors for hospitalisation, including age, cancer, chronic kidney disease, CAD, hypertension, hyperlipidaemia, heart failure, obesity, pulmonary disease, race, male sex and tobacco use, the odds ratio (OR) for hyperlipidaemia (OR 0.67; $p = 0.003$) suggested a relative reduction in the individual proportional risk for hospital admission [4]. However, the authors did not mention how many of the hyperlipidaemic patients were on statins or other lipid lowering therapies. Hu et al. recently reported lower serum cholesterol levels amongst COVID-19 patients [5], leading some to suggest temporary cessation of lipid lowering therapy [6]. However, lipid parameters often fall in cytokine-mediated inflammation as a consequence of the acute phase response rather than having a causative or pathological contribution towards infection [7–9]. It is reasonable to assume that patients with a previous history of myocardial injury are at higher risk for further events, thereby justifying the need for maintaining their lipid lowering therapy as far as possible [3].

2. Aim

The aim of this consensus statement is to provide recommendations on the continuation, alteration or cessation of lipid-lowering therapies in patients with COVID-19 infection based on the currently available evidence, especially when considering concurrent novel therapeutic options for COVID-19 used in clinical trials. We aim to provide, in the absence of a high-quality clinical trial evidence, a consensus statement by HEART UK (Hyperlipidaemia Education and Atherosclerosis Research Trust in United Kingdom) largely based on experts' opinion to provide a guide for managing hyperlipidaemia during the SARS-CoV-2 pandemic. Considering the differences between health care systems in different countries, this consensus statement is not intended to be didactic but rather it aims to provide advice to clinicians on the safe use of lipid lowering therapies during this pandemic.

3. Method and search strategy

Pubmed, Google scholar and Web of Science were searched extensively for articles using search terms: SARS-CoV-2, COVID-19, Lipids, Statin, Fibrates, Ezetimibe, PCSK9 monoclonal antibody, Omega-3-Fatty acids, hypercholesterolaemia, dyslipidaemia, Lomitapide and Volanesorsen. A core team assessed the data and presented an outline to the group. After initial discussions, the core group produced the first draft followed by extensive discussion and editing via teleconferences, video links and electronic mail until a consensus was reached. We did not include lipid lowering drugs in development because of marked paucity of data. Patients who are taking such medications, as part of a clinical trial, should be discussed with the respective clinical trials team. We rated the strength and level of evidence for these recommendations based on the American College Cardiology/American Heart Association (ACC/AHA) system (Table 1A and B) [10].

4. Recommendations

4.1. General advice

Patients with no symptoms or diagnosis of COVID-19 should continue their lipid-lowering medications, as well as other cardioprotective therapies, as usually prescribed. Our general advice is consistent with previous assessments and recommendations [11–13].

There is no need to withhold lipid-lowering medications during the COVID-19 pandemic. This is especially important in patients who are at high risk of cardiovascular disease, in whom stopping lipid-lowering therapy can increase the risk of an atherosclerotic vascular event.

4.1.1. Recommendation 1

- Patients treated for hyperlipidaemia should continue with their advised diet and lifestyle measures and should not interrupt their pharmacologic treatment because of the COVID-19 pandemic (I, A).
- Lipid lowering medications can be suspended temporarily in patients with confirmed COVID-19, who are too unwell to receive medications orally (I, E-EO).
- Creatine kinase measurements should be considered when clinically indicated and in patients who are critically ill. We recommend stopping statin therapy if creatine kinase rises 10-fold to levels above 2000 IU/L in asymptomatic patients or at a lower level of 5-fold upper limit of normal in symptomatic patients (I, B-R).
- It is important to reassess and recommence oral lipid lowering medications in patients who recover before or soon after they leave hospital (I, B-NR).
- In rare and inherited disorders such as homozygous familial hypercholesterolemia (HoFH) (see below), heterozygous familial hypercholesterolemia (HeFH), familial chylomicronaemia syndrome (FCS). it would be good practice to consult with a lipid specialist to assess specific risks and therapeutic (see recommendations 10 and 11 below) challenges (Ia, E-EO).

4.2. Abnormal liver functions tests in COVID-19 patients

Abnormal liver function tests are increasingly recognised as a feature of COVID-19 infection with a prevalence as high as 37.2% at admission [14]. There is some evidence to suggest that men are affected more than women, and older age and higher initial viral load increase predisposition [15]. It is not clear if COVID-19 causes direct liver injury or if this is part of the wider systemic inflammatory response syndrome. Nonetheless, it is important to recognise hepatic injury in COVID-19 patients as the majority of lipid lowering therapies are metabolised in the liver.

Table 1
ACC/AHA guideline recommendation system: applying class of recommendation and level of evidence to clinical strategies, intervention, treatments, or diagnostic testing in patients care.* Adapted from Halperin et al. [10].

Table 1A

Class (strength) of recommendation (COR)	Description	Benefit *vs* risk
Class I - Strong	- Is recommended, indicated and useful - Should be performed - Is indicated, effective and beneficial - Comparative-effectiveness phrases** • Treatment/strategy A is recommended/indicated in preference to B • Treatment A should be chosen over treatment B	Benefit ≫ Risk
Class IIa – Moderate	- Is reasonable - Can be effective and beneficial - Comparative-effectiveness phrases** • Treatment/strategy A is probably recommended/indicated in preference to B • It is reasonable to choose treatment A over treatment B	Benefit ≫ Risk
Class IIb – Weak	- May be reasonable but usefulness may be unclear or not well established	Benefit ≥ Risk
Class III – No benefit	- Is not recommended - Not indicated - Should not be performed	Benefit = Risk
Class III - Harm	- Potentially harmful - Should not be performed	Benefit < Risk

Table 1B

Level (quality) of evidence (LOE)	Description	Supporting evidence
Level A	- High quality evidence*** from >1 RCT - Meta-analysis of high quality RCTs -One or more RCTs corroborated by high quality registry studies	RCTs/meta-analysis/ registries
Level B – R	- Moderate quality evidence*** from 1 or more RCT - Meta-analysis of moderate quality RCTs	RCTs/meta-analysis
Level B - NR	- Moderate quality evidence*** from 1 or more well designed, well executed non-randomised, observational or registry studies - Meta-analyses of such studies	Non-randomised clinical trials
Level C - LD	- Randomised or non-randomised, observational or registry studies with limitations of design or execution - Meta-analyses of such studies - Physiological mechanistic studies	RCT or non-RCT but with limited data
Level A – EO	Consensus expert opinion based on clinical experience	Non-randomised clinical trials

COR and LOE are determined independently (any COR may be paired with any LOE).
A recommendation with LOE C does not imply that the recommendation is weak. Many important clinical questions addressed in guidelines do not lend themselves to clinical trials. Although RCTs are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.
*The outcome or result of the intervention should be specified (an improved clinical outcome or increased diagnostic accuracy or incremental prognostic information).
**For comparative-effectiveness recommendations (COR I and IIa; LOE A and only), studies that support the use of comparator verbs should involve direct comparisons of treatments or strategies being evaluated.
***The method of assessing quality is evolving, including the application of standardised, widely used, and preferably validated evidence grading tools; and for systematic reviews, the incorporation of an Evidence Review Committee.
RCT: randomised clinical trial; COR: class of recommendation; LOE: level of evidence; NR: non-randomised; R: randomised; LD: limited data; EO: expert opinion.

4.2.1. Recommendation 2

- Continue lipid lowering therapy in patients with confirmed diagnosis of COVID-19 and abnormal liver functions tests (LFTs) unless alanine Transaminase (ALT) or Aspartate Transaminase (AST) rises progressively (1, B-R).
- Stop therapy and monitor if ALT or AST is greater than 3 times the upper limit of normal (I, B-R).
- Reassess and consider recommencing oral lipid lowering medications in patients who recover before or soon after they leave hospital (1, B-NR).

4.3. Statins

Statins are 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors. They have shown great efficacy in treating a variety of lipid disorders whilst also providing mortality benefits against cardiovascular disease [16,17]. Studies on the pharmacodynamic properties of statins have shown they have pleiotropic properties with effects that may modulate inflammation [18], sepsis [19], immunity [20], and vasomotor tone [21]. Of relevance in the current COVID-19 pandemic is the effect of statins on ACE2 receptor expression. Pharmacologic blockade of the renin-angiotensin-aldosterone system has generally been shown to upregulate ACE2 expression in a variety of tissues [22]. This has led some to question the safety of such therapies in patients who test positive for COVID-19 with advocates for both sides [23–25]. Shin et al. showed that a combination of fluvastatin and insulin upregulated ACE2 expression in murine cardiac muscle cells [26]. A study by Tikoo et al. found that atorvastatin can upregulate ACE2 expression in cardiac tissue when animals were fed high cholesterol diets [27]. Similar findings were reported by Aguilar et al. in a murine model [28] and Li et al. found rosuvastatin upregulated ACE2 expression in murine vascular smooth muscle cells [29]. Conclusions from these data highlight the beneficial role of statins in mediating attenuation of cardiovascular risk, however, amidst the current COVID-19 pandemic, there is concern about pharmacologic upregulation of the ACE2 receptor, for example with ACE-inhibitor treatment. A joint statement by the Council on Hypertension and the European Society of Cardiology has advised physicians to continue treatment with their current regimen, even though these drugs can raise ACE2 levels [30]. The safety of the ACE-inhibitor therapy has been subsequently been evaluated in observational studies, which did not show any adverse outcome [31,32]. Given the current lack of sufficient convincing evidence to confirm adverse outcomes and benefits of these drugs, the American Society for Preventive Cardiology advised that patients should continue their cardioprotective drugs [13]. Emerging evidence suggests that ACE2 blockade may indeed be beneficial [25,33]. Importantly, no human or animal data exist on the relationship between pulmonary ACE2 receptors and statin therapy. Furthermore, statins could be efficient SARS-CoV-2 main protease inhibitors and, in theory, may alleviate COVID-19 symptoms [34].

One study has demonstrated endothelial cell involvement across vascular beds of different organs in a series of patients with COVID-19, suggesting that SARS-CoV-2 infection facilitates the induction of inflammation of the endothelium as a direct consequence of viral involvement and of the host inflammatory response [35]. In addition, induction of apoptosis and pyroptosis may have important roles in endothelial cell injury in patients with COVID-19. Inflammation of the endothelium could explain the systemic impaired microcirculatory function in different vascular beds and their clinical sequelae in patients with COVID-19. This hypothesis provides a rationale for therapies to stabilise the endothelium while tackling viral replication, particularly with anti-inflammatory anti-cytokine drugs, ACE inhibitors, and statins.

Bilateral diffuse alveolar damage with cellular fibromyxoid exudates has been found in COVID-19 infection [36]. These changes may cause acute respiratory distress syndrome (ARDS), with a reported prevalence in COVID-19 of 8.2% [37]. A systematic review from 2019 concluded

that in ARDS patients, statins make little or no difference to early mortality or duration of ventilation, suggesting their safety in this setting [38]. A UK-based observational study of 2067 patients suggested that statins may impart a mortality benefit in patients with community acquired pneumonia [39]. In contrast, however, a multicentre cohort study from the United States found no evidence of protection conferred by statins on clinical outcomes in a similar cohort [40]. A meta-analysis found that although statin treatment was associated with decreased mortality after pneumonia, there was attenuation of this effect in certain subgroups and it was indicated that no robust conclusions could be drawn without a dedicated randomised clinical trial [41]. Data on protectiveness of statins in viral pneumonias are also inconsistent with studies reporting benefit [42–44] or no benefit [45]. Pertinently, in another coronavirus related disease, Middle Eastern Respiratory Syndrome (MERS), statins were postulated to protect against mortality [46]. There are also some studies which have shown a beneficial role of statins in sepsis [47], and this is not unfounded given their anti-oxidant, anti-inflammatory and immunomodulatory properties [48,49]. Longer-term data are required, however, before such claims can be substantiated. Notwithstanding the somewhat conflicting data on the benefits of statin use in pneumonia, no studies so far have demonstrated a negative effect on outcome. Patients with tuberculosis, receiving statin

Table 2
Statins' potential drug-drug interactions with medications used for COVID-19 or assessed in clinical trials and recommendations.

	Statins					
	Atorvastatin	Simvastatin	Rosuvastatin[a]	Fluvastatin	Pitavastatin[a]	Pravastatin
Metabolism [124]	CYP34A [124,125]	CYP34A [126]	CYP2C9 [125]	CYP2C9 [124, 125]	CYP2C9 minimal [125]	CYP34A [125]
Remdesivir – in part metabolised by CYP3A4 [127]	May compete for metabolism [127] **Recommend**: Switch to low dose Rosuvastatin	May compete for metabolism [127] **Recommend**: Switch to low dose Rosuvastatin	NSI **Recommend:** Continue	NSI **Recommend:** Continue	NSI **Recommend:** Continue	May compete for metabolism [127] **Recommend**: Switch to low dose Rosuvastatin
Hydroxychloroquine[b] [128]	NSI **Recommend:** Continue	NSI **Recommend:** Continue	NSI **Recommend:** Continue	NSI **Recommend:** Continue	NSI **Recommend:** Continue	NSI **Recommend:** Continue
Lopinavir [129]	Caution- increased risk of hepatotoxicity & rhabdomyolysis **Recommend**: reduce the dose to 10 mg daily or switch to low dose Rosuvastatin	Caution- increased risk of hepatotoxicity & rhabdomyolysis **Recommend**: Switch to low dose Rosuvastatin	Caution- increased risk of hepatotoxicity & rhabdomyolysis **Recommend**: Reduce dose to 10 mg OD	NSI **Recommend:** Continue	Caution- increased risk of hepatotoxicity & rhabdomyolysis **Recommend**: Switch to low dose Rosuvastatin	NSI **Recommend:** Continue
Ritonovir [129]	Caution- increased risk of hepatotoxicity & rhabdomyolysis: **Recommend**: Switch to low dose Rosuvastatin	Caution- increased risk of hepatotoxicity & rhabdomyolysis: **Recommend**: Switch to low dose Rosuvastatin	Caution- increased risk of hepatotoxicity & rhabdomyolysis: **Recommend**: Reduce dose to 10 mg OD	NSI **Recommend:** Continue	Caution- increased risk of hepatotoxicity & rhabdomyolysis: **Recommend**: Switch to low dose Rosuvastatin	NSI **Recommend:** Continue
Ribavirin [130]	NSI **Recommend:** Continue	NSI **Recommend:** Continue	NSI **Recommend:** Continue	NSI **Recommend:** Continue	NSI **Recommend:** Continue	NSI **Recommend:** Continue
Inteferon-Beta-1-Alpha [130]	Increased risk of hepatoxicity **Recommend:** Temporarily stop treatment	Increased risk of hepatoxicity **Recommend:** Temporarily stop treatment	Increased risk of hepatoxicity **Recommend:** Temporarily stop treatment	Increased risk of hepatoxicity **Recommend:** Temporarily stop treatment	Increased risk of hepatoxicity **Recommend:** Temporarily stop treatment	Increased risk of hepatoxicity **Recommend:** Temporarily stop treatment
Melatonin [131]**- previously suggested to be hepato-protective against statins**	NSI **Recommend:** Continue	NSI **Recommend:** Continue	NSI **Recommend:** Continue	NSI **Recommend:** Continue	NSI **Recommend:** Continue	NSI **Recommend:** Continue
Dexamethasone	NSI **Recommend:** Continue	NSI **Recommend:** Continue	NSI **Recommend:** Continue	NSI **Recommend:** Continue	NSI **Recommend:** Continue	NSI **Recommend:** Continue
Azithromycin[c] [132–135]	Caution- interaction with macrolide **Recommend**: Temporarily stop treatment	Caution- interaction with macrolide **Recommend**: Temporarily stop treatment	Caution- interaction with macrolide **Recommend**: Temporarily stop treatment	Caution- interaction with macrolide **Recommend**: Temporarily stop treatment	Caution- interaction with macrolide **Recommend**: Temporarily stop treatment	Caution- potential interaction with macrolide **Recommend:** Temporarily stop treatment
Tocilizumab [136] **– impacts both CYP34A and CYP2C9** [137]	Caution- interaction with metabolising enzymes [138] **Recommend**: Temporarily stop treatment	Caution- interaction with metabolising enzymes **Recommend**: Temporarily stop treatment	Caution- interaction with metabolising enzymes **Recommend**: Temporarily stop treatment	Caution- interaction with metabolising enzymes. **Recommend**: Temporarily stop treatment	Caution- interaction with metabolising enzymes. **Recommend**: Temporarily stop treatment	Caution- interaction with metabolising enzymes. **Recommend**: Temporarily stop treatment

NSI: no significant interactions.
Refer to individual drugs summary of product characteristics (SmPC).
[a] Pitavastatin is minimally metabolised by the cytochrome P450 enzymes are therefore is not subject to interactions involving enzyme inhibitors and inducers [125].
[b] There is disquiet regarding the risk of ventricular arrythmias with hydroxychloroquine use in COVID-19 patients. A study showing increased risk published in the Lancet was recently retracted [139].
[c] We like to emphasise the risk of myositis with all statins and all macrolide antibiotics.

treatment responded more rapidly to anti-tuberculous drugs and had lower rates of reactivation [50]. This effect is likely to be due to the decrease in circulating low-density lipoprotein cholesterol (LDL-C) rather than to a direct effect on the bacterium itself or the macrophage foam cells which are its host in the tuberculoma, because very little statin survives its first pass through the liver to reach the lungs [51].

Red yeast rice (RYR), a nutraceutical that inhibits HMG-CoA reductase and reduces LDL-C [52], is used by some patients who are intolerant to statins [53]. It is enzymatically hydrolysed in the small intestine and liver by cytochrome P450. There is little if any data on RYR interactions with drugs potentially used for COVID-19. The pharmaceutical properties of different RYR preparations varies. If the patient is on RYR and no evidence of COVID-19, there is no need to stop treatment, however, it is recommended to avoid RYR if medications interfering with its metabolism are started.

Lipid metabolism changes in patients with acute illness and sepsis; high density lipoprotein cholesterol (HDL-C) tends to lose its anti-inflammatory effect and LDL-C tends to be more susceptible to atherosclerotic modifications [51]. Furthermore, atherosclerotic plaques may become more vulnerable to rupture predisposing to an acute cardiovascular event, so it is important to continue with lipid modifying agents except in cases where risks outweigh benefits.

4.3.1. Recommendation 3

Statin therapy should be continued in patients with confirmed diagnosis of COVID-19 (1, C-LD) but should be stopped, or dose reduced if:

- ALT or AST rises progressively. Stop statin therapy and monitor if ALT or AST is greater than 3 times the upper limit of normal (1, B-R).
- There is a significant drug-drug interaction identified (Table 2). Consider reducing the dose or change to another statin (Table 2) (1, C-LD).
- We recommend stopping statin therapy if creatine kinase rises 10-fold to levels about 2000 IU/L or more in asymptomatic patients or at a lower level of 5-fold upper limit of normal in symptomatic patients (1, B-R).
- If there is evidence of myositis, renal function should be monitored (1, B-NR).
- If treatment is suspended, a further individualised risk *vs.* benefit assessment should be conducted to restart treatment soon after the patient's condition has stabilised (1, B-NR).

4.4. Fibrates

Fibrates are peroxisome proliferator-activated receptor alpha (PPAR-α) agonists and are used primarily in the treatment of hypertriglyceridemia [54]. Elevated triglyceride levels are associated with inflammation [55], and used as part of the H-Score, which determines the presence of secondary haemophagocytic lymphohistiocytosis, an under-recognised hypercytokinaemia syndrome thought to occur in COVID-19 infection [56]. Similar to statins, fibrates are also known to have anti-inflammatory properties and have been suggested as a potential anti-viral agent [44]. Indeed, it has been shown that gemfibrozil confers survival benefits in mice infected with severe H2N2 influenza [57], and prolonged survival has been demonstrated in mice when combined with oseltamivir [58]. Despite these animal data, there are no studies on the effects of fibrates on respiratory viral infections in humans. A case report described an association between eosinophilic pneumonia and clofibrate [59]. Fibrates are generally well tolerated with the major concerns being muscle-related side effects [60]. Although the absolute risk is very small, there is an aggregated risk of myopathy and myositis when used in combination with statins, in particular gemfibrozil (which is no longer recommended in combination with statin therapy) [61,62]. Notwithstanding their good tolerability, evidence suggests that they may cause a mildly reversible elevated creatinine [63], a slight increase propensity towards cholelithiasis [64] and an augmented response of anti-coagulants such as warfarin [65].

Fibrates are primarily used for hypertriglyceridaemia [66]. Fibrates are metabolised by cytochrome P450 isoenzyme 2C9 (CYP2C9) whilst may also mildly inhibit this enzyme [67], they are renally excreted, and therefore doses should be reduced in patients with an eGFR <60 ml/min/1.73 m^2 and stopped if the eGFR drops below 15 ml/min/1.73 m^2 [62]. No drug interactions have been reported between the commonly used fibrates and the proposed drugs on trial for treating COVID-19 (Table 3).

4.4.1. Recommendation 4

Fibrate therapy should be continued in patients with and without a confirmed diagnosis of COVID-19 (1, C-LD) unless:

- There is a significant drug-drug interaction identified (Table 3) (1, C-LD).
- ALT or AST rises progressively, when fibrate therapy should be stopped if ALT or AST is greater than 3 times the upper limit of normal (1, B-R).
- There is clinical evidence and/or biochemical evidence of myopathy or if creatine kinase is greater than five times upper limit of normal (1, B-R).
- Acute kidney injury with deteriorating estimated glomerular filtration rate (eGFR) (1, B-NR).
- Assess drug interactions if oral anticoagulants are initiated (1, C-LD).
- If treatment is suspended, further assessment should be conducted to restart treatment soon after the patient's condition has stabilised (1, B-NR).

4.5. Ezetimibe

Ezetimibe selectively blocks the Niemann-Pick C1-like Protein (NPC1L1) in the jejunal brush border, resulting in the inhibition of dietary cholesterol absorption [68] and was shown to reduce LDL-C and ASCVD risk [68–70]. Ezetimibe is considered a safe therapeutic option with few side effects and no known drug interactions with the proposed medications being trialled for COVID-19. No trials reporting long-term outcome of ezetimibe use in viral or bacterial pneumonia have been conducted.

4.5.1. Recommendation 5

Ezetimibe therapy should be continued in patients with confirmed diagnosis of COVID-19 (1, C-LD) unless:

- There is a significant drug-drug interaction identified (Table 4) (1, C-LD).
- ALT and/or AST rises above 3 times the upper limit of normal (1, B-R).
- If treatment is suspended, further assessment should be conducted to restart treatment soon after the patient's condition has stabilised (1, B-NR).

4.6. PCSK9 monoclonal antibodies

Proprotein convertase subtilisin/kexin type 9 (PCSK9) monoclonal antibodies are novel drugs that reduce LDL-C to previously unprecedented levels [71]. They reduce cardiovascular events [72–74], are well tolerated and safe [75]. However, given their novelty, longer term safety data are still required. The PCSK9 protein is often upregulated during sepsis and inflammation and is postulated to have a detrimental effect on host response and survival [76,77]. This has led some to argue for a possible role of PCSK9 monoclonal antibodies in treating the dysregulated immune response during infection [78]. However, a review by Ruscica et al. found no significant reductions in high-sensitivity C-reactive protein in patients receiving PCSK9 monoclonal antibodies

Table 3
Fibrates' drug-drug interactions with medications used for COVID-19 or assessed in clinical trials and recommendations.

	Fibrates			
	Fenofibrate	Bezafibrate	Gemfibrozil	Clofibrate
Remdesivir [127]	Not directly studied but likely safe **Recommend:** Continue	Not directly studied but likely safe **Recommend:** Continue	Not directly studied but likely safe **Recommend:** Continue	Not directly studied but likely safe **Recommend:** Continue
Hydroxychloroquine [140]	NSI **Recommend:** Continue	NSI **Recommend:** Continue	NSI **Recommend:** Continue	NSI **Recommend:** Continue
Lopinavir	NSI **Recommend:** Continue [141, 142]	Not studied directly but likely safe **Recommend**: Continue with monitoring [141,142]	NSI - recommend to continue, however, efficacy of Gemfibrozil may be reduced [143] **Recommend:** Continue	Not studied – but likely safe **Recommend**: Continue with monitoring
Ritonovir	NSI **Recommend:** Continue [141, 142,144]	Not studied directly but likely safe **Recommend**: Continue with monitoring [141,142]	NSI - recommend to continue, however, efficacy of Gemfibrozil may be reduced [143] **Recommend:** Continue	Not studied – but likely safe **Recommend**: Continue with monitoring
Ribavirin	Not studied directly but likely safe **Recommend**: Continue with monitoring	NSI **Recommend:** Continue	Not studied directly but likely safe **Recommend**: Continue with monitoring	Not studied directly but likely Safe- **Recommend**: Continue with monitoring
Inteferon-Beta 1 -Alpha	Increased risk of hepatoxicity **Recommend**: Stop	Increased risk of hepatoxicity **Recommend**: Stop	Increased risk of hepatoxicity **Recommend**: Stop	Increased risk of hepatoxicity **Recommend**: Stop
Melatonin	Not directly studied but likely safe **Recommend:** Continue with LFT monitoring	Not directly studied but likely safe **Recommend:** Continue with LFT monitoring	Not directly studied but likely safe **Recommend:** Continue with LFT monitoring	Not directly studied but likely safe **Recommend:** Continue with LFT monitoring
Dexamethasone [145]	Not directly studied but likely safe **Recommend:** Continue	Not directly studied but likely safe **Recommend:** Continue	Not directly studied but likely safe **Recommend:** Continue	Not directly studied but likely safe **Recommend:** Continue
Azithromycin [146]	Not directly studied but likely safe **Recommend:** Continue with LFT monitoring	Not directly studied but likely safe **Recommend:** Continue with LFT monitoring	Not directly studied but likely safe **Recommend:** Continue with LFT monitoring	Not directly studied but likely safe **Recommend:** Continue with LFT monitoring
Tocilizumab	Caution- interaction with metabolising enzymes [138] **Recommend**: Stop	Caution- interaction with metabolising enzymes **Recommend**: Stop	Caution- interaction with metabolising enzymes [138] **Recommend**: Stop	Caution- interaction with metabolising enzymes [138] **Recommend**: Stop
Ivermectin	Not directly studied but likely safe **Recommend:** Continue with LFT monitoring	Not directly studied but likely safe **Recommend:** Continue with LFT monitoring	Not directly studied but likely safe **Recommend:** Continue with LFT monitoring	Not directly studied but likely safe **Recommend:** Continue with LFT monitoring

Fibrates are contraindicated as GFR declines. To reassess if there is a decline in renal function and consider stopping (please refer to recommendation 4).
Fibrates can interact with anticoagulants. This should be taken in consideration if oral anticoagulants used.
Refer to individual drugs SmPC and the University of Liverpool's Drug interaction site (www.COVID-19-druginteractions.org).
NSI: no significant interactions.

from clinical trial data [79]. Whilst there is some evidence that PCKS9 inhibitors may modulate the inflammatory response in atherosclerosis, their utility in dampening inflammation and benefit during sepsis is a matter of debate. Although an increased frequency of nasopharyngeal symptoms and flu-like syndrome have been reported amongst recipients in PCSK9 monoclonal antibody studies [75], it is unclear whether this translates into an increased susceptibility to respiratory viruses such as COVID-19. Flu-like symptoms are a class effect of monoclonal antibodies and therefore such results are unsurprising [80].

Whilst very limited drug-drug interaction data are available, pharmacokinetic data indicate that likely they are safe, as drug elimination occurs via saturable binding to PCSK9, with no clinically significant differences in patients with hepatic or renal impairment or with other concomitant drug use [81]. Vuorio et al. recommended the continuation of these drugs in patients who have familial hypercholesterolaemia (FH) and have contracted COVID-19 [12]. The rationale for this was that patients with FH are at higher risk of atherosclerotic cardiovascular events.

4.6.1. Recommendation 6

PCSK9 monoclonal antibodies should be continued in all patients with a confirmed diagnosis of COVID-19 (Table 4).

- In critically ill patients, treatment can be paused until recovery and discharge from the critical care unit (1, E-EO).
- If treatment is suspended or delayed, a further individualised risk *vs.* benefit assessment should be conducted to restart treatment soon after patient's condition has stabilised (1, B-NR).

4.7. Omega-3 fatty acids

Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in sufficient amounts reduce triglyceride levels [82–84], and have been associated with favourable effects on various markers of cardiovascular risk such as reduced blood pressure [85,86], and decreased platelet aggregation [87]. Their anti-inflammatory properties [88], and potential role in atherosclerotic plaque stability, have also been described [89, 90]. Despite this, there remains some controversy surrounding the evidence for cardiovascular outcome benefits [91–94]. Most recently, the REDUCE-IT (Reduction of Cardiovascular Events with EPA-Intervention Trial) study demonstrated a significant decrease in residual risk of cardiovascular events in patients with atherosclerotic cardiovascular disease and elevated triglyceride levels [95]. There is no available evidence on the use of omega-3 fatty acids in acute infection or illness although there are no clear mechanistic reasons that raise safety concerns.

There are no significant drug interactions between possible trial therapies for COVID-19 and omega-3 fatty acids (Table 4). It has been suggested that they may prolong bleeding time [96], however, clinical trials have not shown adverse outcomes in relation to this [97,98].

Table 4
Other lipid lowering medications' drug-drug interactions with medications used for COVID-19 or assessed in clinical trials and recommendations.

	Ezetimibe [147,148]	PCSK9 inhibitors [75]	Omega-3- fatty acids	Lomitapide [116]
Remdesivir	Not directly studied but likely safe **Recommend**: Continue	Not directly studied but likely safe **Recommend**: Continue	Not directly studied but likely safe **Recommend**: Continue	Not directly studied **Recommend:** to withhold treatment temporarily
Hydroxychloroquine	Not directly studied but likely safe **Recommend**: Continue	Not directly studied but likely safe **Recommend**: Continue	NSI **Recommend**: Continue [149]	Not directly studied **Recommend:** to withhold treatment temporarily
Lopinavir	Not directly studied but likely safe **Recommend**: Continue	Not directly studied but likely safe **Recommend**: Continue	NSI **Recommend**: Continue [150]	Lopinavir is predicted to markedly increase the exposure to lomitapide and risk of hepatotoxicity **Recommend:** to withhold treatment temporarily
Ritonavir	Not directly studied but likely safe **Recommend**: Continue	Not directly studied but likely safe **Recommend**: Continue	NSI **Recommend**: Continue [150]	Ritonavir is predicted to markedly increase the exposure to lomitapide and risk of hepatotoxicity **Recommend:** to withhold treatment temporarily
Ribavirin	Not directly studied but likely safe **Recommend**: Continue	Not directly studied but likely safe **Recommend**: Continue	NSI **Recommend**: Continue [151–153]	Not directly studied. **Recommend:** to withhold treatment temporarily
Interferon-Beta 1 -Alpha	Not directly studied but likely safe **Recommend**: Continue	Not directly studied but likely safe **Recommend**: Continue	NSI **Recommend**: Continue [154,155]	Increased risk of hepatoxicity. **Recommend:** to withhold treatment temporarily
Melatonin	Not directly studied but likely safe **Recommend**: Continue	Not directly studied but likely safe **Recommend**: Continue	Not directly studied but likely safe **Recommend**: Continue	Not directly studied **Recommend:** to withhold treatment temporarily
Dexamethasone	Not directly studied but likely safe **Recommend**: Continue	Not directly studied but likely safe **Recommend**: Continue	NSI **Recommend**: Continue	Not directly studied **Recommend:** to withhold treatment temporarily.
Azithromycin	Not directly studied but likely safe **Recommend**: Continue	Not directly studied but likely safe **Recommend**: Continue	NSI **Recommend**: Continue [156]	Azithromycin is a weak CYP3A4 inhibitor and is predicted to increase exposure to lomitapide **Recommend**: to withhold treatment temporarily
Tocilizumab	Not directly studied but likely safe **Recommend**: Continue	Not directly studied but likely safe **Recommend**: Continue	Not directly studied but likely safe **Recommend**: Continue	Not directly studied **Recommend**: to withhold treatment temporarily
Ivermectin	Not directly studied but likely safe **Recommend**: Continue	Not directly studied but likely safe **Recommend**: Continue	Not directly studied but likely safe **Recommend**: Continue	Not directly studies. Some references suggest that lomitapide may slightly increase levels of ivermectin **Recommend:** to withhold treatment temporarily

We recommend stopping niacin in acutely ill patients with COVID-19.
For other drugs potential interactions please visit https://www.hiv-druginteractions.org/ also BNF, Stockley's Drug Interactions, individual drugs SmPC and consult with your pharmacy department.
NSI: no significant interactions.

4.7.1. Recommendation 7

Omega-3 fatty acids can be continued in patients with confirmed diagnosis of COVID-19 unless:

- The patient is critically ill (1, C-EO).
- If treatment is suspended, a further individualised risk *vs.* benefit assessment should be conducted to restart treatment when patient's condition has improved (1, B-NR).

4.8. Bile acid sequestrants

The bile acid sequestrants such as cholestyramine, colesevalam and colestipol are highly positive charged molecules, which interact with negatively charged bile acids preventing their absorption in the intestines [99]. They are not absorbed themselves and therefore do not interact pharmacologically with other agents; however, they may inhibit the absorption of a number of orally administered drugs [100].

4.8.1. Recommendation 8

In the absence of cardiovascular outcome data and given the potential for interfering with drug absorption, it would be reasonable that bile acid sequestrants are discontinued in patients diagnosed with COVID-19 (1, C-LD).

4.9. Nicotinic acid (niacin)

Niacin positively impacts apo-B containing lipoproteins whilst favourably increasing apo A1 [101,102]. This translates into reductions in LDL-C and triglycerides whilst concomitantly raising HDL-C [103,104]. Despite the lack of cardiovascular efficacy when added to background statin therapy [105], its ubiquitous use continues worldwide [101,106]. Niacin often causes facial flushing as a side effect, which sometimes limits its use [107]. Niacin undergoes conjugation with glycine in the liver producing its major metabolite, nicotinuric acid, which is excreted in urine [103]. Niacin has been shown to attenuate endotoxemic lung inflammation in animal models [108], however, hard data in human viral infections are lacking. No reports questioning its safety profile have been reported during the previous SARS and MERS outbreaks.

Recommendation 9: Niacin therapy can be continued in patients without COVID-19, however, in the absence of consistent clinical trials evidence to support cardiovascular events prevention, we recommend discontinuing niacin temporarily in patients diagnosed with COVID-19 (1, C-LD).

4.10. Homozygous familial hypercholesterolaemia

Homozygous familial hypercholesterolemia confers high cardiovascular risk from a very young age [109,110]. Atherosclerotic plaque burden is high and there is particular concern about stopping lipid lowering therapies. Treatment is based on maximum tolerated oral lipid lowering agents, PCSK9 inhibitors and lipoprotein apheresis [109–111]. In addition, lomitapide has been developed specifically for the condition [111].

Lomitapide inhibits microsomal triglyceride transfer protein (MTP) in hepatocytes and enterocytes, reducing apoB-containing lipoprotein particles secreted into the circulation [112]. It is currently used as adjunctive therapy for HoFH, achieving LDL-C reductions of 35.6%–45.5% in Phase III and extension trials [113,114]. This is consistent with real world clinical experience reported so far, with 68% and 42% of

patients achieving LDL-C <100 mg/dl (2.5 mmol/l) and <70 mg/dl (1.8 mmol/l), respectively [115]. Its mechanism of action also explains the adverse events of hepatic steatosis and elevated transaminases.

Lomitapide is metabolised in the liver through CYP3A4 and lomitapide is also an inhibitor of CYP3A4 [116]. Its excretion occurs through both renal and intestinal routes. There are therefore significant potential drug interactions, with strong and moderate CYP3A4 inhibitors being contraindicated. Macrolide antibiotics, potent enzyme inhibitors, are common antimicrobial options in the treatment of pneumonia and therefore likely the most frequent drug interaction to be encountered in the management of COVID-19. Similarly, the concurrent use of protease inhibitors lopinavir and ritonavir, both predicted to markedly increase exposure to lomitapide through potent CYP3A4 inhibition, is contraindicated.

Due to the rarity of HoFH, there are currently no available data on the effect of lomitapide on outcomes in acute infection or illness. Monitoring is required with the use of lomitapide because of possible liver injury. This is dose related and, if interacting drugs are necessary, it should be discontinued.

4.10.1. Recommendation 10

Patients with HoFH are at high risk of cardiovascular events and any proposed changes to therapy in these patients should be discussed with a lipid specialist familiar with the management of the condition. If a patient with HoFH is admitted into hospital, a discussion between the acute hospital team and lipid specialist should occur at the earliest opportunity. For specific treatment strategies we recommend:

- For statins, evolocumab, ezetimibe, fibrates, omega-3 fatty, bile acids sequestrants please refer to the recommendations above.
- Lipoprotein apheresis is safe and should be continued if logistically possible (1a, C-LD).
- Lomitapide should be continued in patients with confirmed diagnosis of COVID-19 (1a, C-EO) unless:
  - There is a drug-drug interaction identified (Table 4). Lomitapide can be temporarily discontinued in acutely ill patients and/or those who are started on anti-microbial medication with significant drug-drug interactions (Table 4) (1, C-LD).
  - The patient develops significant gastrointestinal symptoms (1, C-LD).
  - The patient is critically ill and/or unable to take oral medications (1, C-EO).
  - Stop treatment if progressive rise in ALT and/or AST or if ALT any above 3 times the upper limit of normal (1, C-LD).
  - If treatment is withheld for any reason, further individualised risk vs. benefit assessment should be conducted to restart treatment when the patient has recovered (1, B, NR).

4.11. Familial chylomicronaemia syndrome

Familial chylomicronaemia syndrome (FCS) is characterised by very high triglyceride levels and increased risk of acute pancreatitis [117]. The cornerstone of current management is a low-fat intake. Volanesorsen is a newly licensed antisense oligonucleotide inhibitor of apolipoprotein CIII (Apo CIII) [118]. [119]. It is delivered on a 2-weekly basis via a subcutaneous injection and its major side effects include injection site reactions and thrombocytopaenia [119]. Emerging evidence suggests that low platelet count is associated with an increased risk of severe disease and mortality in patients with COVID-19 [120–122]. Whether this is directly causative is unknown; however, mechanisms for COVID-19-induced thrombocytopaenia have been suggested [123]. Based on these data, it is currently felt that the safest option would be to withhold treatment until the patient recovers.

4.11.1. Recommendation 11

Any proposed changes to therapy in patients with FCS should be discussed with a lipid specialist familiar with the management of the condition. If a patient with FCS is admitted into hospital, a discussion between the acute hospital team, lipid specialist and dietitians should occur at the earliest opportunity. For specific treatment strategies, we recommend:

- Very-low fat diet should be maintained in all patients including those on par-enteral feeding (1, C-LD).
- Oil based medications drugs, like propofol, should be avoided in patients who need assisted ventilation and sedation (1, C-LD).
- For statins, fibrates and other lipid lowering medications, please refer to the recommendations above.
- We recommend Volanesorsen is temporarily withheld in FCS patients with confirmed diagnosis of COVID-19 (1, C-EO).
- Further assessment should be conducted to restart treatment when the patient has recovered (1, C-LD).
- Low platelet count during COVID-19 infection should not be used to permanently withhold treatment (C-LD).

5. Conclusion

Many studies show a favourable effect of statin therapy in acutely ill patients and some studies show no statistically significant impact on outcome; reassuringly, however, no study to date has demonstrated harm. Lipid-lowering therapy has a well-established role in both the primary and secondary prevention of atherosclerotic cardiovascular disease and therefore, in the absence of much needed trial data, it follows that these drugs should be continued wherever possible. Importantly, COVID-19 is a new disease with a scarce evidence base upon which to make recommendations; however, with the rapid evolution of clinical studies, inevitably guidelines may need further revision.

Author contributions

HS conceived the topic for discussion and designed the outline of the article. ZI, JHH, SA, MF, DN & HS researched articles and put forward initial recommendations. ZI wrote the first draft and collated drug data into tables. ZI, SA, JHH, PND, HS, MF, AS, DM, AR, RK, JC, CB, NQ, JDS, NC, GF, JS, KN, DD, AP, JH, AK & JP reviewed the manuscript, tables and continued discussions until a consensus was reached. All authors revised and approved of the final draft.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. HS received research and education grants from AMGEN, AKCEA, AMRYT and SANOFI. There are no other conflicts of interest related to this article to declare.

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Appendix A. Supplementary data

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