Atherosclerosis

Managing Hyperlipidaemia in Patients with COVID-19 and During its Pandemic: An Expert Panel Position Statement from HEART UK

--Manuscript Draft--

Manuscript Number:	ATH-D-20-00695R2
Article Type:	Review article
Keywords:	Keywords: Covid-19; statins; Fibrates; lipid lowering therapy; PCS9 monoclonal antibodies; Ezetimibe; Bile Acid sequestrants; Omega-3-fatty acids; Volanesorsen; Lomitapide

Corresponding Author:	Handrean Soran Central Manchester University Hospitals NHS Trust Manchester, UNITED KINGDOM
First Author:	Zohaib Iqbal, MB ChB, MSc, MRCP(UK)
Order of Authors:	Zohaib Iqbal, MB ChB, MSc, MRCP(UK)
	Jan Hoong Ho
	Safwaan Adam
	Michael France
	Akheel Syed
	Dermot Neely
	Alan Rees
	Rani Khatib
	Jaimini Cegla
	Christopher Byrne
	Nadeem Qureshi
	Nigel Capps
	Gordon Ferns
	Jules Payne
	Jonathan Schofield
	Kirsty Nicholson
	Dev Datta
	Alison Pottle
	Julian Halcox
	Paul Durrington
	Handrean Soran

Abstract:

<div class="abstract"> <p> <div><div class="abstract"> <p> <div><div class="abstract"> <p> <div><div class="abstract"> <p> <div><div class="abstract"> <p> <div><div class="abstract"> <p> <div><div class="abstract"> <div><p>Background & Aims: 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 worldwide 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. In a rapidly emerging field new therapies will need to be assessed in the same way.</p> <p>Methods: 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 sequestrate, nutraceuticals, red yeast rice, Omega-3-Fatty acids, Lomitapide, hypercholesterolaemia, dyslipidaemia and Volanesorsen.</p> <p>Results &Conclusions:</p> <p>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 interactions, between lipid-lowering medications and drugs that may be used to treat COVID-19, especially in patients with abnormalities in liver function tests. </p> </div> </div></div> </p> </div></div> </p> </div></div> </p> </div></div> </p> </div></div> </p> </div></div> </p> </div> </p>

Highlights

- Patients with known atherosclerotic cardiovascular disease and related comorbidities are at increased risk of severe illness and mortality if infected with COVID-19.

- There is no convincing evidence to suggest harm from lipid lowering therapy or on-treatment low LDL cholesterol if patients develop acute illnesses or SARS-CoV-2. In fact, available evidence suggests that statin therapy is associated with benefits.

- Patients treated for hyperlipidaemia should not interrupt their treatment because of COVID-19 pandemic.

- Continue lipid lowering therapy in patients with confirmed diagnosis of COVID-19 unless possible risks outweigh benefits.

- In patient treated for COVID-19 with pharmacologic agents, drug interactions with lipid lowering therapies should be investigated and assessed.

Graphical Abstract

Statins

Continue unless:

- ALT or AST rises progressively or ALT and/or AST is greater than 3 times the upper limit of normal (1, B-R).
- Clinical or biochemical evidence of myopathy or myositis (1, B-R).
- Dose reduction or alternative statin if significant drug-drug interaction identified (1, C-LD).

Ezetimibe

Continue unless:

- A significant drug-drug interaction identified (1, C-LD).
- ALT and/or AST rises above 3 times the upper limit of normal (1, B-R).

Fibrates

Continue unless:

- A significant drug-drug interaction identified (1, C-LD).
- ALT or AST rises progressively, or ALT and/or AST is greater than 3 times the upper limit of normal (1, B-R).
- Clinical evidence and/or biochemical evidence of myopathy or myositis (1, B-R).
- Acute kidney injury (1, B-NR).

Managing hyperlipidaemia in patients with COVID-19 and during its pandemic:

An Expert Panel Position Statement from HEART UK

Other Medications

Bile Acid Sequestrants:
Discontinue temporarily in patients diagnosed with COVID-19 (1, C-LD).

Niacin:
Discontinue temporarily in patients diagnosed with COVID-19.

PCSK9 Inhibitors

Continue unless:

- Critically ill patients -(1, E-EO).
- Individualised risk vs. benefit assessment to restart treatment after patient's condition has improved (1, B-NR).

Omega-3-Fatty Acids

Continue unless:

- Critically ill (1, C-EO).
- Individualised risk vs. benefit assessment to restart treatment when patient's condition has improved (1, B-NR).

HoFH and FCS

Lipoprotein apheresis is safe and should be continued if logistically possible (1a, C-LD).
For other medications including Lomitapide and Volanesorsen please refer to recommendations 10 and 11.

General advice

- Patients should continue with their advised diet and lifestyle measures and should not interrupt their pharmacologic treatment because of the COVID-19 pandemic (I, A).
- Oral lipid lowering medications can be suspended temporarily in patients with confirmed COVID who are too unwell for oral administration (I, E-EO).
- In rare and inherited disorders such as Homozygous Familial Hypercholesterolemia (HoFH), 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 challenges (Ia, E-EO).
- 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 lipid lowering therapy and monitor if ALT or AST is greater than 3 times the upper limit of normal (I, B-R).
- Creatine kinase measurements should be considered when clinically indicated and in patients who are critically ill. Discontinue statin therapy temporarily if creatine kinase rises 10-fold to levels about 2,000 IU/L or more in asymptomatic patients or at a lower levels of 5-fold upper limit of normal in symptomatic patients (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).

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

Zohaib Iqbal[1,2], Jan Hoong Ho[1,2], Safwaan Adam[2,3], Michael France[1], Akheel Syed[4], Dermot Neely[5], Alan Rees[6], Rani Khatib[7,8], Jaimini Cegla[9], Christopher Byrne[10], Nadeem Qureshi[11], Nigel Capps,[12] Gordon Ferns[13], Jules Payne[6], Jonathan Schofield[1,2], Kirsty Nicholson[1], Dev Datta[14], Alison Pottle[15], Julian Halcox[16], Paul Durrington[2], and Handrean Soran[1,2*], on behalf of Heart UK's Medical Scientific and Research Committee

[1] Cardiovascular Trials Unit, Manchester University NHS Foundation Trust, Manchester, United Kingdom

[2] Faculty of Biology, Medicine and Health, University of Manchester, Manchester, United Kingdom

[3]The Christie NHS Foundation Trust, Manchester, United Kingdom

[4] Department of Diabetes, Endocrinology and Obesity Medicine, Salford Royal NHS Foundation Trust, Salford, United Kingdom

[5]Department of Blood Sciences and NIHR MedTech and IVD Centre, Newcastle Upon Tyne Hospitals, Newcastle Upon Tyne, United Kingdom

[6]HEART UK, Maidenhead, United Kingdom

[7]Departments of Cardiology & Pharmacy, Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom

[8] Leeds Institute of Cardiovascular and Metabolic Medicine, University of Leeds, Leeds, United Kingdom

[9]Division of Diabetes, Endocrinology and Metabolism, Imperial College London, 6th Floor Commonwealth Building, Hammersmith Hospital, Du Cane Road, W12 0NN, London, United Kingdom

[10]Department of Nutrition and Metabolism, Faculty of Medicine, University of Southampton, United Kingdom

[11]Division of Primary Care, University of Nottingham, Nottingham, United Kingdom

[12]The Shrewsbury and Telford Hospital NHS Trust, United Kingdom

[13]Department of Medical Education, Brighton and Sussex Medical School, Brighton, United Kingdom

[14]Department of metabolic Medicine, University Hospital of Wales, Cardiff, United Kingdom

[15]Department of Cardiology, Harefield Hospital, United Kingdom

[16]Department of Medicine, Swansea University, Swansea, United Kingdom

Keywords: Covid-19; Hyperlipidaemia; Statins; Fibrates; Lipid lowering therapy; PCSK9 monoclonal antibodies; Ezetimibe; Bile Acid sequestrants; Omega-3-fatty acids; Volanesorsen; Lomitapide.

Correspondence to:

Handrean Soran

University Department of Medicine, Manchester University NHS Foundation Trust, Manchester, United Kingdom

E-mail: handrean.soran@mft.nhs.uk OR hsoran@aol.com

Abstract

Background & aims: 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 worldwide 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.

Methods: 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 sequestrate, nutraceuticals, red yeast rice, Omega-3-Fatty acids, Lomitapide, hypercholesterolaemia, dyslipidaemia and Volanesorsen.

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

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 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].

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.

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, Lomitapide, 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].

Recommendations

General advice

Patients with no symptoms or diagnosis of COVID-19 should continue their lipid-lowering medications, as well as other cardio-protective 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.

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 2,000 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).

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.

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).

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 in several organs as a direct consequence of viral involvement and of the host inflammatory response [35]. In addition, induction of apoptosis and pyroptosis may have an important role 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. Indeed, a recent study reported that use of ACE inhibitors or statins was associated with better survival among patients with Covid-19 [10].

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 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 cellsm 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 importance to continue with lipid modifying agents except in cases where risks outweigh benefits.

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 2,000 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).

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/1.73m^2 and stopped if the eGFR drops below 15 ml/min/1.73m^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).

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).

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.

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).

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 is 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 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 is available, pharmacokinetic data indicates 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.

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).

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 COVID19 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].

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).

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].

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).

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 in general practice [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 is 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).

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% to 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 is 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.

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).

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.

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).

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

Table 1A

much needed trial data, it follows that these drugs should be continued wherever possible. Importantly, COVID19 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.

Conflicts of interests

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.

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 & JP reviewed the manuscript, tables and continued discussions until a consensus was reached. All authors revised and approved of the final draft.

Acknowledgements

We acknowledge HEART UK for providing logistic support and support from Lipid Disease Fund, Manchester Comprehensive Local Research Network, and The National Institute for Health Research/Wellcome Trust Clinical Research Facility.

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

Table 1A and B: 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].

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

Table 2	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 – 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 10mg 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 10mg 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

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 COVID19 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.

NSI- No Significant interactions.

Refer to individual drugs summary of product characteristics (SmPC).

Table 3	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.covid19-druginteractions.org).

NSI- No Significant interactions.

Table 4	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 temporaril
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.

References

[1] Ou X, Liu Y, Lei X *et al.* Characterization of spike glycoprotein of SARS-CoV-2 on virus entry and its immune cross-reactivity with SARS-CoV. Nature Communications 2020; 11:1620.

[2] Grasselli G, Zangrillo A, Zanella A *et al.* Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy. JAMA 2020.

[3] Guo T, Fan Y, Chen M *et al.* Cardiovascular Implications of Fatal Outcomes of Patients With Coronavirus Disease 2019 (COVID-19). JAMA Cardiology 2020; 5(7):811-818

[4] Petrilli CM, Jones SA, Yang J *et al.* Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. BMJ 2020; 369:m1966.

[5] Hu X, Chen D, Wu L *et al.* Low Serum Cholesterol Level Among Patients with COVID-19 Infection in Wenzhou, China. China (February 21, 2020). http://dx.doi.org/10.2139/ssrn.3544826

[6] Greenhalgh T, Koh GCH, Car J. Covid-19: a remote assessment in primary care. BMJ 2020; 368 368:m1182

[7] Herbert KE, Erridge C. Regulation of low-density lipoprotein cholesterol by intestinal inflammation and the acute phase response. Cardiovasc Res 2018; 114:226-232.

[8] Feng Q, Wei WQ, Chaugai S *et al.* Association Between Low-Density Lipoprotein Cholesterol Levels and Risk for Sepsis Among Patients Admitted to the Hospital With Infection. JAMA Netw Open 2019; 2:e187223.

[9] Golucci A, Marson FAL, Ribeiro AF, Nogueira RJN. Lipid profile associated with the systemic inflammatory response syndrome and sepsis in critically ill patients. Nutrition 2018; 55-56:7-14.

[10] Halperin JL, Levine GN, Al-Khatib SM *et al.* Further evolution of the ACC/AHA clinical practice guideline recommendation classification system: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation 2016; 133:1426-1428.

[11] Banach M, Penson PE, Fras Z *et al.* Brief recommendations on the management of adult patients with familial hypercholesterolemia during the COVID-19 pandemic. Pharmacol Res 2020; 158:104891.

[12] Vuorio A, Watts GF, Kovanen PT. Familial hypercholesterolemia and COVID-19: triggering of increased sustained cardiovascular risk. J Intern Med 2020; 287: 746-747
.

[13] Khera A, Baum SJ, Gluckman TJ *et al.* Continuity of care and outpatient management for patients with and at high risk for cardiovascular disease during the COVID-19 pandemic: A scientific statement from the American Society for Preventive Cardiology. American Journal of Preventive Cardiology 2020; 1:100009.

[14] Fan Z, Chen L, Li J *et al.* Clinical Features of COVID-19-Related Liver Damage. Clin Gastroenterol Hepatol 2020; 18: 1561-1566

[15] Feng G, Zheng KI, Yan Q-Q *et al.* COVID-19 and liver dysfunction: Current insights and emergent therapeutic strategies. Journal of Clinical and Translational Hepatology 2020; 8:18.

[16] Stone NJ, Robinson JG, Lichtenstein AH *et al.* 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Journal of the American College of Cardiology 2014; 63:2889-2934.

[17] Soran H, Schofield JD, Durrington PN. Cholesterol, not just cardiovascular risk, is important in deciding who should receive statin treatment. European heart journal 2015; 36:2975-2983.

[18] Schönbeck U, Libby P. Inflammation, immunity, and HMG-CoA reductase inhibitors: statins as antiinflammatory agents? Circulation 2004; 109:II-18-II-26.

[19] Almog Y. Statins, inflammation, and sepsis: hypothesis. Chest 2003; 124:740-743.

[20] Zeiser R. Immune modulatory effects of statins. Immunology 2018; 154:69-75.

[21] Koh KK. Effects of statins on vascular wall: vasomotor function, inflammation, and plaque stability. Cardiovascular research 2000; 47:648-657.

[22] South AM, Diz D, Chappell MC. COVID-19, ACE2 and the Cardiovascular Consequences. Am J Physiol Heart Circ Physiol 2020; 318:5, H1084-H1090

[23] Patel AB, Verma A. COVID-19 and Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers: What Is the Evidence? JAMA 2020;323(18):1769-1770.

[24] Vaduganathan M, Vardeny O, Michel T *et al.* Renin–Angiotensin–Aldosterone System Inhibitors in Patients with Covid-19. New England Journal of Medicine 2020; 382:1653-1659.

[25] Bean DM, Kraljevic Z, Searle T *et al.* Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers are not associated with severe COVID-19 infection in a multi-site UK acute hospital trust. Eur J Heart Fail 2020; 22:967-974.

[26] Shin YH, Min JJ, Lee JH *et al.* The effect of fluvastatin on cardiac fibrosis and angiotensin-converting enzyme-2 expression in glucose-controlled diabetic rat hearts. Heart Vessels 2017; 32:618-627.

[27] Tikoo K, Patel G, Kumar S *et al.* Tissue specific up regulation of ACE2 in rabbit model of atherosclerosis by atorvastatin: role of epigenetic histone modifications. Biochem Pharmacol 2015; 93:343-351.

[28] Aguilar C, Ventura F, Rodríguez-Delfín L. [Atorvastatin induced increase in homologous angiotensin I converting enzyme (ACE2) mRNA is associated to decreased fibrosis and

decreased left ventricular hypertrophy in a rat model of diabetic cardiomyopathy]. Rev Peru Med Exp Salud Publica 2011; 28:264-272.

[29] Li Y-H, Wang Q-X, Zhou J-W *et al.* Effects of rosuvastatin on expression of angiotensin-converting enzyme 2 after vascular balloon injury in rats. J Geriatr Cardiol 2013; 10:151-158.

[30] de Simone G. Position statement of the ESC council on hypertension on ACE-inhibitors and angiotensin receptor blockers. European Society of Cardiology 2020.

[31] Mancia G, Rea F, Ludergnani M *et al.* Renin–angiotensin–aldosterone system blockers and the risk of Covid-19. New England Journal of Medicine 2020; 2020; 382:2431-2440

[32] Reynolds HR, Adhikari S, Pulgarin C *et al.* Renin–angiotensin–aldosterone system inhibitors and risk of Covid-19. New England Journal of Medicine 2020; 382:2441-2448

[33] Meng J, Xiao G, Zhang J *et al.* Renin-angiotensin system inhibitors improve the clinical outcomes of COVID-19 patients with hypertension. Emerging Microbes & Infections 2020; 9:757-760.

[34] Reiner Ž, Hatamipour M, Banach M *et al.* Statins and the COVID-19 main protease: in silico evidence on direct interaction. Archives of Medical Science 2020; 16:490-496.

[35] Varga Z, Flammer AJ, Steiger P *et al.* Endothelial cell infection and endotheliitis in COVID-19. The Lancet 2020; 395:1417-1418

[36] Xu Z, Shi L, Wang Y *et al.* Pathological findings of COVID-19 associated with acute respiratory distress syndrome. The Lancet respiratory medicine 2020; 8:420-422

[37] Ñamendys-Silva SA. ECMO for ARDS due to COVID-19. Heart Lung 2020; 49:348-349

[38] Lewis SR, Pritchard MW, Thomas CM, Smith AF. Pharmacological agents for adults with acute respiratory distress syndrome. Cochrane Database of Systematic Reviews 2019.

[39] Grudzinska FS, Dosanjh DP, Parekh D *et al.* Statin therapy in patients with community-acquired pneumonia. Clin Med (Lond) 2017; 17:403-407.

[40] Yende S, Milbrandt EB, Kellum JA *et al.* Understanding the potential role of statins in pneumonia and sepsis. Crit Care Med 2011; 39:1871-1878.

[41] Chopra V, Rogers MAM, Buist M *et al.* Is Statin Use Associated with Reduced Mortality After Pneumonia? A Systematic Review and Meta-analysis. The American Journal of Medicine 2012; 125:1111-1123.

[42] Kwong JC, Li P, Redelmeier DA. Influenza morbidity and mortality in elderly patients receiving statins: a cohort study. PLoS One 2009; 4:e8087-e8087.

[43] Schlienger RG, Fedson DS, Jick SS *et al.* Statins and the risk of pneumonia: a population-based, nested case-control study. Pharmacotherapy 2007; 27:325-332.

[44] Fedson DS. Treating influenza with statins and other immunomodulatory agents. Antiviral Res 2013; 99:417-435.

[45] Dublin S, Jackson ML, Nelson JC *et al.* Statin use and risk of community acquired pneumonia in older people: population based case-control study. Bmj 2009; 338:b2137.

[46] Yuan S. Statins May Decrease the Fatality Rate of Middle East Respiratory Syndrome Infection. mBio 2015; 6:e01120-01115.

[47] Hackam DG, Mamdani M, Li P, Redelmeier DA. Statins and sepsis in patients with cardiovascular disease: a population-based cohort analysis. The Lancet 2006; 367:413-418.

[48] Halcox JP, Deanfield JE. Beyond the laboratory: clinical implications for statin pleiotropy. Circulation 2004; 109:II-42-II-48.

[49] Soran H, Adam S, Ho JH, Durrington PN. Evidence for more intensive cholesterol lowering. Current opinion in lipidology 2017; 28:291-299.

[50] Lai C-C, Lee M-tG, Lee S-H *et al.* Statin treatment is associated with a decreased risk of active tuberculosis: an analysis of a nationally representative cohort. Thorax 2016; 71:646-651.

[51] Soran H, Ho JH, Durrington PN. Acquired low cholesterol: diagnosis and relevance to safety of low LDL therapeutic targets. Current opinion in lipidology 2018; 29:318-326.

[52] Banach M, Patti AM, Giglio RV *et al.* The Role of Nutraceuticals in Statin Intolerant Patients. Journal of the American College of Cardiology 2018; 72:96-118.

[53] Dujovne CA. Red Yeast Rice Preparations: Are They Suitable Substitutions for Statins? Am J Med 2017; 130:1148-1150.

[54] Schofield JD, France M, Ammori B *et al.* High-density lipoprotein cholesterol raising: does it matter? Current opinion in cardiology 2013; 28:464-474.

[55] Machowicz R, Janka G, Wiktor-Jedrzejczak W. Similar but not the same: Differential diagnosis of HLH and sepsis. Crit Rev Oncol Hematol 2017; 114:1-12.

[56] Mehta P, McAuley DF, Brown M *et al.* COVID-19: consider cytokine storm syndromes and immunosuppression. The Lancet 2020; 395:1033-1035

[57] Budd A, Alleva L, Alsharifi M *et al.* Increased survival after gemfibrozil treatment of severe mouse influenza. Antimicrobial agents and chemotherapy 2007; 51:2965-2968.

[58] Xu L, Bao L, Li F *et al.* Combinations of oseltamivir and fibrates prolong the mean survival time of mice infected with the lethal H7N9 influenza virus. J Gen Virol 2015; 96:46-51.

[59] Hendrickson RM, Simpson F. Clofibrate and Eosinophilic Pneumonia. JAMA 1982; 247:3082-3082.

[60] Gaist D, Rodríguez LAG, Huerta C *et al.* Lipid-lowering drugs and risk of myopathy: a population-based follow-up study. Epidemiology 2001; 12:565-569.

[61] Pierce LR, Wysowski DK, Gross TP. Myopathy and rhabdomyolysis associated with lovastatin-gemfibrozil combination therapy. JAMA 1990; 264:71-75.

[62] Davidson MH, Armani A, McKenney JM, Jacobson TA. Safety considerations with fibrate therapy. Am J Cardiol 2007; 99:3c-18c.

[63] Hottelart C, El Esper N, Rose F *et al.* Fenofibrate increases creatininemia by increasing metabolic production of creatinine. Nephron 2002; 92:536-541.

[64] Leiss O, von Bergmann K, Gnasso A, Augustin J. Effect of gemfibrozil on biliary lipid metabolism in normolipemic subjects. Metabolism 1985; 34:74-82.

[65] Ascah KJ, Rock GA, Wells PS. Interaction between fenofibrate and warfarin. Annals of Pharmacotherapy 1998; 32:765-768.

[66] Piepoli MF, Hoes AW, Agewall S *et al.* 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). European heart journal 2016; 37:2315-2381.

[67] Okopień B, Bułdak Ł, Bołdys A. Benefits and risks of the treatment with fibrates—a comprehensive summary. Expert Review of Clinical Pharmacology 2018; 11:1099-1112.

[68] Phan BAP, Dayspring TD, Toth PP. Ezetimibe therapy: mechanism of action and clinical update. Vasc Health Risk Manag 2012; 8:415-427.

[69] Savarese G, De Ferrari GM, Rosano GM, Perrone-Filardi P. Safety and efficacy of ezetimibe: A meta-analysis. Int J Cardiol 2015; 201:247-252.

[70] Cannon CP, Blazing MA, Giugliano RP *et al.* Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. New England Journal of Medicine 2015; 372:2387-2397.

[71] Hess CN, Low Wang CC, Hiatt WR. PCSK9 inhibitors: mechanisms of action, metabolic effects, and clinical outcomes. Annual review of medicine 2018; 69:133-145.

[72] Giugliano RP, Pedersen TR, Park J-G *et al.* Clinical efficacy and safety of achieving very low LDL-cholesterol concentrations with the PCSK9 inhibitor evolocumab: a prespecified secondary analysis of the FOURIER trial. The Lancet 2017; 390:1962-1971.

[73] Sabatine MS, Giugliano RP, Keech AC *et al.* Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. New England Journal of Medicine 2017; 376:1713-1722.

[74] Ridker PM, Revkin J, Amarenco P *et al.* Cardiovascular Efficacy and Safety of Bococizumab in High-Risk Patients. New England Journal of Medicine 2017; 376:1527-1539.

[75] Iqbal Z, Dhage S, Mohamad JB *et al.* Efficacy and safety of PCSK9 monoclonal antibodies. Expert Opinion on Drug Safety 2019:1-11.

[76] Paciullo F, Fallarino F, Bianconi V *et al.* PCSK9 at the crossroad of cholesterol metabolism and immune function during infections. Journal of Cellular Physiology 2017; 232:2330-2338.

[77] Khademi F, Momtazi-Borojeni AA, Reiner Ž *et al.* PCSK9 and infection: A potentially useful or dangerous association? J Cell Physiol 2018; 233:2920-2927.

[78] Momtazi AA, Banach M, Sahebkar A. PCSK9 inhibitors in sepsis: a new potential indication? Expert Opin Investig Drugs 2017; 26:137-139.

[79] Ruscica M, Tokgözoğlu L, Corsini A, Sirtori CR. PCSK9 inhibition and inflammation: A narrative review. Atherosclerosis 2019; 288:146-155.

[80] Hansel TT, Kropshofer H, Singer T *et al.* The safety and side effects of monoclonal antibodies. Nat Rev Drug Discov 2010; 9:325-338.

[81] Kasichayanula S, Grover A, Emery MG *et al.* Clinical Pharmacokinetics and Pharmacodynamics of Evolocumab, a PCSK9 Inhibitor. Clin Pharmacokinet 2018; 57:769-779.

[82] Harris WS. n-3 fatty acids and serum lipoproteins: human studies. The American journal of clinical nutrition 1997; 65:1645S-1654S.

[83] Leslie MA, Cohen DJ, Liddle DM *et al.* A review of the effect of omega-3 polyunsaturated fatty acids on blood triacylglycerol levels in normolipidemic and borderline hyperlipidemic individuals. Lipids in health and disease 2015; 14:53.

[84] Brinton EA, Ballantyne CM, Bays HE *et al.* Effects of icosapent ethyl on lipid and inflammatory parameters in patients with diabetes mellitus-2, residual elevated

triglycerides (200–500 mg/dL), and on statin therapy at LDL-C goal: the ANCHOR study. Cardiovascular diabetology 2013; 12:100.

[85] Mozaffarian D, Wu JH. Omega-3 fatty acids and cardiovascular disease: effects on risk factors, molecular pathways, and clinical events. Journal of the American College of Cardiology 2011; 58:2047-2067.

[86] Miller PE, Van Elswyk M, Alexander DD. Long-chain omega-3 fatty acids eicosapentaenoic acid and docosahexaenoic acid and blood pressure: a meta-analysis of randomized controlled trials. American journal of hypertension 2014; 27:885-896.

[87] Von Schacky C, Fischer S, Weber PC. Long-term effects of dietary marine omega-3 fatty acids upon plasma and cellular lipids, platelet function, and eicosanoid formation in humans. The Journal of clinical investigation 1985; 76:1626-1631.

[88] Li K, Huang T, Zheng J *et al.* Effect of marine-derived n-3 polyunsaturated fatty acids on C-reactive protein, interleukin 6 and tumor necrosis factor α: a meta-analysis. PLoS One 2014; 9(2): e88103

[89] Thies F, Garry JM, Yaqoob P *et al.* Association of n-3 polyunsaturated fatty acids with stability of atherosclerotic plaques: a randomised controlled trial. The Lancet 2003; 361:477-485.

[90] Konishi T, Sunaga D, Funayama N *et al.* Eicosapentaenoic acid therapy is associated with decreased coronary plaque instability assessed using optical frequency domain imaging. Clinical cardiology 2019; 42:618-628.

[91] Marik PE, Varon J. Omega-3 dietary supplements and the risk of cardiovascular events: a systematic review. Clinical Cardiology: An International Indexed and Peer-Reviewed Journal for Advances in the Treatment of Cardiovascular Disease 2009; 32:365-372.

[92] Kwak SM, Myung S-K, Lee YJ *et al.* Efficacy of omega-3 fatty acid supplements (eicosapentaenoic acid and docosahexaenoic acid) in the secondary prevention of

cardiovascular disease: a meta-analysis of randomized, double-blind, placebo-controlled trials. Archives of internal medicine 2012; 172:686-694.

[93] Del Gobbo L, Imamura F, Aslibekyan S *et al.* Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Fatty Acids and Outcomes Research Consortium (FORCe). ω-3 Polyunsaturated fatty acid biomarkers and coronary heart disease: pooling project of 19 cohort studies. JAMA Intern Med 2016; 176:1155-1166.

[94] Chowdhury R, Warnakula S, Kunutsor S *et al.* Association of dietary, circulating, and supplement fatty acids with coronary risk: a systematic review and meta-analysis. Annals of internal medicine 2014; 160:398-406.

[95] Bhatt DL, Steg PG, Miller M *et al.* Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. New England Journal of Medicine 2019; 380:11-22.

[96] Harris WS. Expert opinion: omega-3 fatty acids and bleeding-cause for concern? Am J Cardiol 2007; 99:44c-46c.

[97] Jeansen S, Witkamp RF, Garthoff JA *et al.* Fish oil LC-PUFAs do not affect blood coagulation parameters and bleeding manifestations: Analysis of 8 clinical studies with selected patient groups on omega-3-enriched medical nutrition. Clin Nutr 2018; 37:948-957.

[98] Group ASC. Effects of n−3 Fatty Acid Supplements in Diabetes Mellitus. New England Journal of Medicine 2018; 379:1540-1550.

[99] Soran H, Adam S, Mohammad JB, et al. Hypercholesterolaemia - practical information for non-specialists. *Arch Med Sci*. 2018;14(1):1-21.

[100] Feingold KR. Cholesterol Lowering Drugs. In: Endotext. Edited by: Feingold KR, Anawalt B, Boyce A *et al.* South Dartmouth (MA): MDText.com, Inc.

Copyright © 2000-2020, MDText.com, Inc.; 2000.

[101] Kamanna VS, Kashyap ML. Mechanism of Action of Niacin. The American Journal of Cardiology 2008; 101:S20-S26.

[102] Yadav R, Liu Y, Kwok S *et al.* Effect of extended-release niacin on high-density lipoprotein (HDL) functionality, lipoprotein metabolism, and mediators of vascular inflammation in statin-treated patients. Journal of the American Heart Association 2015; 4:e001508.

[103] Mullangi R, Srinivas NR. Niacin and its metabolites: role of LC-MS/MS bioanalytical methods and update on clinical pharmacology. An overview. Biomed Chromatogr 2011; 25:218-237.

[104] Yadav R, Kwok S, Ammori BJ *et al.* Safety and tolerability of extended-release niacin with laropiprant. Expert opinion on drug safety 2012; 11:151-159.

[105] Schandelmaier S, Briel M, Saccilotto R *et al.* Niacin for primary and secondary prevention of cardiovascular events. Cochrane Database Syst Rev 2017; 6:Cd009744.

[106] Jackevicius CA, Tu JV, Ko DT *et al.* Use of niacin in the United States and Canada. JAMA internal medicine 2013; 173:1379-1381.

[107] Farnier M. Safety review of combination drugs for hyperlipidemia. Expert Opinion on Drug Safety 2011; 10:363-371.

[108] Kwon WY, Suh GJ, Kim KS, Kwak YH. Niacin attenuates lung inflammation and improves survival during sepsis by downregulating the nuclear factor-κB pathway. Crit Care Med 2011; 39:328-334.

[109] France M, Rees A, Datta D *et al.* HEART UK statement on the management of homozygous familial hypercholesterolaemia in the United Kingdom. Atherosclerosis 2016; 255:128-139.

[110] Cuchel M, Bruckert E, Ginsberg HN *et al.* Homozygous familial hypercholesterolaemia: new insights and guidance for clinicians to improve detection and clinical management. A position paper from the Consensus Panel on Familial Hypercholesterolaemia of the European Atherosclerosis Society. European heart journal 2014; 35:2146-2157.

[111] Raal FJ, Hovingh GK, Blom D *et al.* Long-term treatment with evolocumab added to conventional drug therapy, with or without apheresis, in patients with homozygous familial

hypercholesterolaemia: an interim subset analysis of the open-label TAUSSIG study. The lancet Diabetes & endocrinology 2017; 5:280-290.

[112] Gordon DA. Recent advances in elucidating the role of the microsomal triglyceride transfer protein in apolipoprotein B lipoprotein assembly. Current opinion in lipidology 1997; 8:131-137.

[113] Blom DJ, Averna MR, Meagher EA *et al.* Long-term efficacy and safety of the microsomal triglyceride transfer protein inhibitor lomitapide in patients with homozygous familial hypercholesterolemia. Circulation 2017; 136:332-335.

[114] Cuchel M, Meagher EA, du Toit Theron H *et al.* Efficacy and safety of a microsomal triglyceride transfer protein inhibitor in patients with homozygous familial hypercholesterolaemia: a single-arm, open-label, phase 3 study. The Lancet 2013; 381:40-46.

[115] Underberg J, Cannon C, Larrey D *et al.* LONG-TERM SAFETY AND EFFICACY OF LOMITAPIDE IN PATIENTS WITH HOMOZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA: THREE-YEAR DATA FROM THE LOMITAPIDE OBSERVATIONAL WORLDWIDE EVALUATION REGISTRY (LOWER). Journal of the American College of Cardiology 2018; 71:A168.

[116] Goulooze SC, Cohen AF, Rissmann R. Lomitapide. British journal of clinical pharmacology 2015; 80:179.

[117] Moulin P, Dufour R, Averna M *et al.* Identification and diagnosis of patients with familial chylomicronaemia syndrome (FCS): Expert panel recommendations and proposal of an "FCS score". Atherosclerosis 2018; 275:265-272.

[118] Paik J, Duggan S. Volanesorsen: First Global Approval. Drugs 2019; 79:1349-1354.

[119] Witztum JL, Gaudet D, Freedman SD *et al.* Volanesorsen and Triglyceride Levels in Familial Chylomicronemia Syndrome. N Engl J Med 2019; 381:531-542.

[120] Lippi G, Plebani M, Henry BM. Thrombocytopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: A meta-analysis. Clin Chim Acta 2020; 506:145-148.

[121] Yang X, Yang Q, Wang Y *et al.* Thrombocytopenia and Its Association with Mortality in Patients with COVID-19. J Thromb Haemost 2020; 18:1469-1472

[122] Liu Y, Sun W, Guo Y *et al.* Association between platelet parameters and mortality in coronavirus disease 2019: Retrospective cohort study. Platelets 2020:1-7.

[123] Xu P, Zhou Q, Xu J. Mechanism of thrombocytopenia in COVID-19 patients. Ann Hematol 2020; 99:1205-1208

[124] Durrington P. Hyperlipidaemia 3Ed: Diagnosis and Management. CRC Press; 2007.

[125] Hirota T, Ieiri I. Drug–drug interactions that interfere with statin metabolism. Expert Opinion on Drug Metabolism & Toxicology 2015; 11:1435-1447.

[126] Miller DB, Spence JD. Clinical pharmacokinetics of fibric acid derivatives (fibrates). Clin Pharmacokinet 1998; 34:155-162.

[127] European Medicines Agency. Summary on compassionate use: Remdesivir Gilead. April 3, 2020

[128] Pareek A, Chandurkar N, Thulaseedharan NK *et al.* Efficacy and safety of fixed dose combination of atorvastatin and hydroxychloroquine: a randomized, double-blind comparison with atorvastatin alone among Indian patients with dyslipidemia. Curr Med Res Opin 2015; 31:2105-2117.

[129] Driggin E, Madhavan MV, Bikdeli B *et al.* Cardiovascular considerations for patients, health care workers, and health systems during the coronavirus disease 2019 (COVID-19) pandemic. Journal of the American College of Cardiology 2020; 75 (18) 2352-2371

[130] Zhu Q, Li N, Han Q *et al.* Statin therapy improves response to interferon alfa and ribavirin in chronic hepatitis C: a systematic review and meta-analysis. Antiviral Res 2013; 98:373-379.

[131] Chojnacki C, Błońska A, Chojnacki J. The Effects of Melatonin on Elevated Liver Enzymes during Statin Treatment. Biomed Res Int 2017; 2017:3204504.

[132] Strandell J, Bate A, Hägg S, Edwards IR. Rhabdomyolysis a result of azithromycin and statins: an unrecognized interaction. Br J Clin Pharmacol 2009; 68:427-434.

[133] Abu Mellal A, Hussain N, Said AS. The clinical significance of statins-macrolides interaction: comprehensive review of in vivo studies, case reports, and population studies. Ther Clin Risk Manag 2019; 15:921-936.

[134] Patel AM, Shariff S, Bailey DG *et al.* Statin toxicity from macrolide antibiotic coprescription: a population-based cohort study. Ann Intern Med 2013; 158:869-876.

[135] Bakheit AH, Al-Hadiya BM, Abd-Elgalil AA. Azithromycin. Profiles Drug Subst Excip Relat Methodol 2014; 39:1-40.

[136] Castagne B, Viprey M, Martin J *et al.* Cardiovascular safety of tocilizumab: A systematic review and network meta-analysis. PLoS One 2019; 14(8): e0220178

[137] Bellosta S, Corsini A. Statin drug interactions and related adverse reactions: an update. Expert Opinion on Drug Safety 2018; 17:25-37.

[138] Schmitt C, Kuhn B, Zhang X *et al.* Disease–drug–drug interaction involving tocilizumab and simvastatin in patients with rheumatoid arthritis. Clinical Pharmacology & Therapeutics 2011; 89:735-740.

[139] Mehra MR, Desai SS, Ruschitzka F, Patel AN. Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis. The Lancet 2020.

[140] Lozada A, Dujovne CA. Drug interactions with fibric acids. Pharmacol Ther 1994; 63:163-176.

[141] Gordon LA, Malati CY, Hadigan C *et al.* Lack of an Effect of Ritonavir Alone and Lopinavir-Ritonavir on the Pharmacokinetics of Fenofibric Acid in Healthy Volunteers. Pharmacotherapy 2016; 36:49-56.

[142] Calza L, Manfredi R, Chiodo F. Use of fibrates in the management of hyperlipidemia in HIV-infected patients receiving HAART. Infection 2002; 30:26-31.

[143] Busse KH, Hadigan C, Chairez C *et al.* Gemfibrozil Concentrations are Significantly Decreased in the Presence of Lopinavir/ritonavir. Journal of acquired immune deficiency syndromes (1999) 2009; 52:235.

[144] Penzak SR, Chuck SK. Management of protease inhibitor-associated hyperlipidemia. Am J Cardiovasc Drugs 2002; 2:91-106.

[145] Rao MS, Subbarao V. Effect of dexamethasone on ciprofibrate-induced cell proliferation and peroxisome proliferation. Fundam Appl Toxicol 1997; 35:78-83.

[146] Periti P, Mazzei T, Mini E, Novelli A. Pharmacokinetic drug interactions of macrolides. Clin Pharmacokinet 1992; 23:106-131.

[147] Pappa E, Rizos CV, Filippatos TD, Elisaf MS. Emerging Fixed-Dose Combination Treatments for Hyperlipidemia. J Cardiovasc Pharmacol Ther 2019; 24:315-322.

[148] Arita Y, Kihara S, Ouchi N *et al.* Paradoxical decrease of an adipose-specific protein, adiponectin, in obesity. Biochemical and biophysical research communications 1999; 257:79-83.

[149] Proudman SM, James MJ, Spargo LD *et al.* Fish oil in recent onset rheumatoid arthritis: a randomised, double-blind controlled trial within algorithm-based drug use. Ann Rheum Dis 2015; 74:89-95.

[150] Bednasz C, Luque AE, Zingman BS *et al.* Lipid-Lowering Therapy in HIV-Infected Patients: Relationship with Antiretroviral Agents and Impact of Substance-Related Disorders. Curr Vasc Pharmacol 2016; 14:280-287.

[151] Popa SG, Moţa M. Impact of obesity and omega-3 polyunsaturated fatty acids on fibrogenesis and responsiveness to antiviral therapy in chronic hepatitis C. Rom J Intern Med 2007; 45:165-170.

[152] Morsy KH, Zaghloul A, Mahmoud M. Can eicosapentaenoic acid maintain the original ribavirin dose or affect the response during the treatment course of chronic hepatitis C virus (HCV) patients? Turk J Gastroenterol 2016; 27:55-61.

[153] Suzuki M, Inage E, Minowa K *et al.* Prophylaxis for ribavirin-related anemia using eicosapentaenoic acid in chronic hepatitis C patients. Pediatr Int 2012; 54:528-531.

[154] Su KP, Lai HC, Yang HT *et al.* Omega-3 fatty acids in the prevention of interferon-alpha-induced depression: results from a randomized, controlled trial. Biol Psychiatry 2014; 76:559-566.

[155] Chang JP, Lai HC, Yang HT *et al.* Polyunsaturated fatty acids levels and initial presentation of somatic symptoms induced by interferon-alpha therapy in patients with chronic hepatitis C viral infection. Nutr Neurosci 2017; 20:291-296.

[156] Hanssens L, Thiébaut I, Lefèvre N *et al.* The clinical benefits of long-term supplementation with omega-3 fatty acids in cystic fibrosis patients - A pilot study. Prostaglandins Leukot Essent Fatty Acids 2016; 108:45-50.

Reply to editors comments: Minor Revision
Aug 2020

Atherosclerosis

Editors' comments:

The paper was revised accordingly, is clear, well written using the available evidence at its best and certainly will guide physicians in dealing with dyslipidemic patients with COVID-19. My only suggestion is that please add an extra table explaining the recommendation grading used in it since many physicians may not be aware of the adopted criteria proposed by the ACC/AHA.

Many thanks for the comments. We have now added table 1a and 1b as per the editor's request. These tables have been incorporated into the main body of the manuscript however we are equally happy to make these added table as supplementary tables if the reviewer or the editor prefer.

Submission declaration statement

The article is not under consideration for publication elsewhere.

Publication of the article is approved by all authors and tacitly or explicitly by the responsible authorities where the work was carried out.

If the article is accepted, it will not be published elsewhere by the authors, including electronically in the same form, in English or in any other language, without the written consent of the copyright-holder.

Yours Sincerely

Dr Handrean Soran MSc, MD, FRCP

Consultant Physician and Endocrinologist, University Departmen t of Medicine, Manchester University NHS Foundation Trust, Manchester, United Kingdom

E-mail: handrean.soran@mft.nhs.uk OR hsoran@aol.com

Secretary Tel: +44 (0) 161 276 4066, Fax: +44 (0) 161 276 3630

Declaration of interests

☒ 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.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Yours Sincerely

Dr Handrean Soran MSc, MD, FRCP

Consultant Physician and Endocrinologist, University Departmen t of Medicine, Manchester University NHS Foundation Trust, Manchester, United Kingdom

E-mail: handrean.soran@mft.nhs.uk OR hsoran@aol.com

Secretary Tel: +44 (0) 161 276 4066, Fax: +44 (0) 161 276 3630

Atherosclerosis style guide checklist

Atherosclerosis applies format guidelines to all accepted papers, with the aim of improving their readability.

Manuscripts that do not conform to the format guidelines of the *Atherosclerosis* Journal will be returned to the authors for reformatting.

Please find below a questionnaire to guide authors to comply with the formatting requirements for revised submissions. For more detailed information, visit our website.

Please note that when you answer "No" to a question, editing of your manuscript is required before submission to *Atherosclerosis*.

Manuscript structure and style

Does your manuscript contain all the below essential elements, in this order? Yes No
(please stick to the headers as indicated below)

- Title
- Authors, Affiliations, Contact Information
- Abstract in the Atherosclerosis format (*Background and aims*, *Methods*, *Results*, *Conclusions*)
- Introduction
- Materials and methods (or Patients and methods)
- Results
- Discussion
- Conflict of interest (mandatory)
- Financial support (if applicable)
- Author contributions (mandatory)
- Acknowledgements (if applicable)
- References
- Figures and Tables (with legends in the suitable style)

Abstract style

Is the Abstract structured in the below sections? Yes No

- *Background and aims*
- *Methods*
- *Results*
- *Conclusions*

Figure and table legends

Are figure and table legends formatted as described below? Yes No

Each figure and table legend should have a brief overarching title that describes the entire figure without citing specific panels, followed by a description of each panel, and all symbols used.

If a figure or table contains multiple panels, the letter describing each panel should be capitalized and surrounded by parenthesis: i.e. (A)(B)(C)(D).

Please make sure to apply the formatting requirements to figures and tables where necessary (e.g. style of *p* values, gene and protein nomenclature).

Footnotes to tables

Are footnotes to tables formatted as described below? Yes No

Footnotes to tables should be listed with superscript lowercase letters, beginning with "[a]."
Footnotes must not be listed with numbers or symbols.

Abbreviations

Are abbreviations defined when first used in the text? Yes No

Use of abbreviations should be kept at a minimum.

Units

Are units expressed following the international system of units (SI)? **Yes** **No**

If other units are mentioned, please provide conversion factors into SI units.

DNA and protein sequences

Are gene names italicized? **Yes** **No**

Gene names should be italicized; protein products of the loci are not italicized.

For murine models, the gene and protein names are lowercase except for the first letter.
(e.g., gene: *Abcb4;* protein: Abcb4)

For humans, the whole gene name is capitalized.
(e.g., gene: *ABCB4;* protein ABCB4)

Mouse strains and cell lines

Are knock-out or transgenic mouse strains and cell lines italicized and the symbol superscripted? Yes No

(e.g. *ob/ob* , $p53^{+/+}$, $p53^{-/-}$)

p values

Are *p* values consistently formatted according to the below style throughout the manuscript (including figures and tables)? **Yes** **No**

p <X
p >X
p=X

Language

Is your manuscript written in good English? **Yes** **No**

Please make sure that you consistently use either American or British English, but not a mixture of them.

Please make sure that words are written consistently in the same way throughout the manuscript.
e.g. non-significant or nonsignificant
e.g. down-regulation or downregulation

Artwork

Have you submitted high-resolution versions of your original artwork? **Yes** **No**

Please make sure to use uniform lettering and sizing in your original artwork, including letters to indicate panels, consistently throughout all figures.