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THE PRESENT AND FUTURE

JACC STATE-OF-THE-ART REVIEW

Investigating Lipid-Modulating Agents for Prevention or Treatment of COVID-19

JACC State-of-the-Art Review

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ABSTRACT

Coronavirus disease-2019 (COVID-19) is associated with systemic inflammation, endothelial activation, and multiorgan manifestations. Lipid-modulating agents may be useful in treating patients with COVID-19. These agents may inhibit viral entry by lipid raft disruption or ameliorate the inflammatory response and endothelial activation. In addition, dyslipidemia with lower high-density lipoprotein cholesterol and higher triglyceride levels portend worse outcomes in patients with COVID-19. Upon a systematic search, 40 randomized controlled trials (RCTs) with lipid-modulating agents were identified, including 17 statin trials, 14 omega-3 fatty acids RCTs, 3 fibrate RCTs, 5 niacin RCTs, and 1 dalcetrapib RCT for the management or prevention of COVID-19. From these 40 RCTs, only 2 have reported preliminary results, and most others are ongoing. This paper summarizes the ongoing or completed RCTs of lipid-modulating agents in COVID-19 and the implications of these trials for patient management. (J Am Coll Cardiol 2021;78:1635–1654)

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ABBREVIATIONS AND ACRONYMS

ACE = angiotensin-converting enzyme

ARDS = acute respiratory distress syndrome

CETP = cholesterol ester transfer protein

COVID-19 = coronavirus disease-2019

CRP = C-reactive protein

DHA = docosahexaenoic acid

EPA = eicosapentaenoic acid

HDL = high-density lipoprotein

ICU = intensive care unit

NAD = nicotinamide adenine dinucleotide

PCR = polymerase chain reaction

RCT = randomized controlled trial

SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

SOC = standard of care

Severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) cellular entry is mediated by attachment to angiotensin-converting enzyme 2 (ACE2). Lipid rafts are plasma membrane microdomains, mainly composed of cholesterol, glycosphingolipids, and phospholipids, capable of changing their composition in response to stimuli that may play a critical role in this process (1). SARS-CoV-2 can trigger an uncontrolled innate inflammatory response (cytokine storm) leading to local and systemic tissue damage commonly seen in advanced coronavirus disease-2019 (COVID-19) (2). Inflammation and resultant endothelial injury might lead to a hypercoagulable state and predispose patients to microthrombosis and macrothrombosis (3,4).

Lipid-modulating agents may limit inflammation and thromboinflammation in COVID-19 by exerting antiviral, anti-inflammatory, immunomodulatory, and antithrombotic effects (5). Moreover, lower high-density lipoprotein (HDL) cholesterol and higher triglyceride levels are associated with worse outcomes in patients with COVID-19 (6). Through lipid raft disruption (7), lipid profile improvement, and other effects, lipid-modulating agents may affect the outcomes of patients with COVID-19. Moreover, as previously seen in other SARS infections, SARS-CoV-2 infection could lead to the *MYD88* gene being highly induced, with resultant activation of the nuclear factor kappa-light-chain-enhancer of the activated B-cell pathway (8,9). Statins have inhibitory effects on this pathway (and a reduction in type 1 interferon) and hyper-inflammation (10,11).

The current paper systematically summarizes the randomized controlled trials (RCTs) evaluating lipid-modulating therapies for the prevention or treatment of COVID-19. The presumed mechanisms of action and existing knowledge of RCTs, as well as knowledge gaps that may influence the design of future trials, are highlighted.

HIGHLIGHTS

- Lipid-modulating agents have pleiotropic effects, including antiviral, immunomodulatory, and antithrombotic properties that might help treat COVID-19.
- Thirty-six randomized controlled trials are evaluating lipid-modulating agents, including statins, omega-3 fatty acids, fibrates, niacin, and cholesteryl ester transfer protein inhibitors, for the treatment of COVID-19.
- Four ongoing randomized controlled trials are investigating omega-3 fatty acid preparations for prevention of COVID-19, and 2 are evaluating niacin in patients beyond the acute phase of illness with COVID-19.

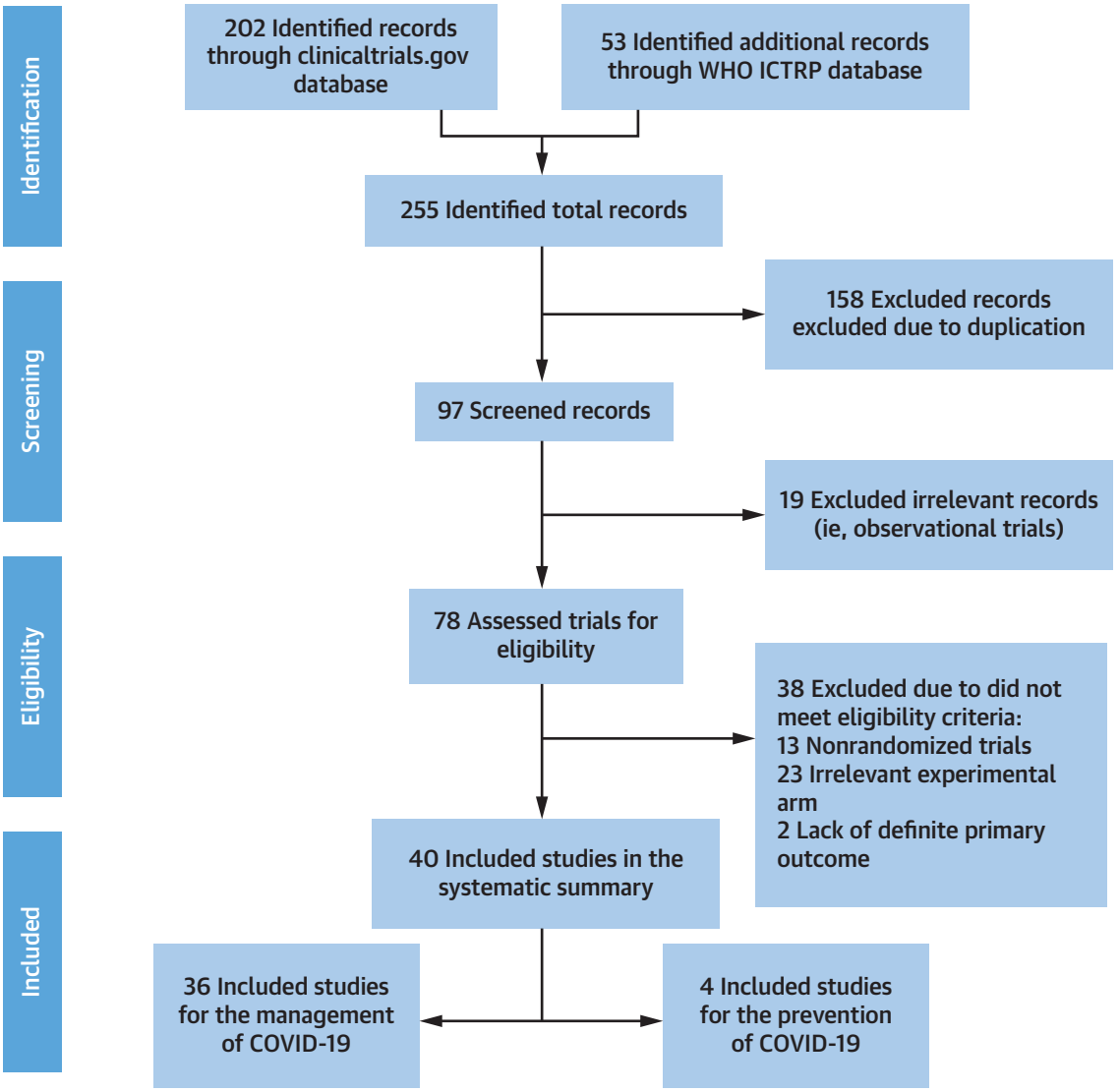
METHODS

DATA SOURCE AND SEARCH STRATEGY. ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform were searched to identify RCTs investigating trials of lipid-modulating agents in COVID-19 (date of last search, March 31, 2021). We used key words for COVID-19 or SARS-CoV-2 or coronavirus disease-2019 and statins (including atorvastatin, rosuvastatin, simvastatin, fluvastatin, lovastatin, pitavastatin, and pravastatin), fibrates (including fenofibrate, clofibrate, bezafibrate, gemfibrozil, and pemafibrate), ezetimibe, bile acid sequestrants (colesevelam, cholestyramine, and colestipol), proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors (including alirocumab, evolocumab, and inclisiran), omega-3 fatty acids (including icosapent ethyl, eicosapentaenoic acid [EPA], and docosahexaenoic acid [DHA]), niacin, nicotinic acid, nicotinamide, vitamin B_3, evinacumab, mipomersen, lomitapide, bempedoic acid, and cholesteryl ester transfer protein (CETP) inhibitors (anacetrapib, dalcetrapib, evacetrapib, torcetrapib, and TA-8995).

We separated the RCTs between those with agents used for the treatment of patients with COVID-19 versus those used for preventing the development (or severity) of COVID-19. Study eligibility criteria for inclusion in this review were RCT design with a lipid-modifying agent and description of inclusion and exclusion criteria and the primary outcome at ClinicalTrials.gov or the World Health Organization International Clinical Trials Registry Platform. Figure 1 describes the search strategy and screening of the studies. For RCTs that met the aforementioned eligibility criteria, we searched MEDLINE with PubMed Interface, Google Scholar, and pre-print servers for published design papers or final result manuscripts.

SUMMARY OF THE SEARCH RESULTS. A total of 255 records were screened; 97 required further manual

FIGURE 1 **PRISMA Flow Diagram**



Key words used for the literature search included: COVID-19 or SARS-CoV-2 with statin, atorvastatin, rosuvastatin, simvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, fibrate, fenofibrate, bezafibrate, gemfibrozil, pemafibrate, ezetimibe, bile acid sequestrant, colesevelam, cholestyramine, colestipol, omega-3, icosapent ethyl, eicosapentaenoic acid, docosahexaenoic acid, PCSK9 inhibitors, Proprotein Convertase Subtilisin/Kexin type 9, alirocumab, evolocumab, inclisiran, niacin, nicotinic acid, nicotinamide, evinacumab, bempedoic acid, mipomersen, lomitapide, cholesterol ester transfer protein inhibitors, CETP inhibitors, anacetrapib, dalcetrapib, evacetrapib, and torcetrapib. COVID-19 = coronavirus disease-2019; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-analyses; WHO ICTRP = World Health Organization International Clinical Trials Registry Platform.

review. Ultimately, 40 RCTs met the eligibility criteria, of which 36 were related to the management of COVID-19: 17 for statins, 10 for omega-3 fatty acids, 3 for fibrates, 5 for niacin, and 1 for dalcetrapib. In addition, 4 RCTs of omega-3 fatty acids were identified for the prevention of COVID-19. No RCTs were identified for ezetimibe, bile acid sequestrants, proprotein convertase subtilisin/kexin type 9 inhibitors, evinacumab, mipomersen, lomitapide, bempedoic acid, or CETP inhibitors other than dalcetrapib for the management or prevention of COVID-19.

A summary of the methodological features of the ongoing RCTs categorized according to drug class is provided in Table 1. Factors such as number of enrollees, comparator types, blinding, type of primary outcomes (clinical or surrogate outcomes),

TABLE 1 Methodological Features of the Ongoing RCTs Categorized According to Drug Class

			Sample Size		Enrolling Sites		Comparator Types		Blinding						
	Total No. of Patients	Total No. of RCTs	<150 Participants	>150 Participants	Single-Center	Multicenter	Placebo	SOC/No Intervention	Open Label	Single	Double	Primary Clinical Outcome	Primary Surrogate Outcome	Blinded Outcome Adjudication	Design Paper Published
Statins	18,215	17	7	10	10	7	5	12	11	1	5	14	3	2	4
Fibrates	1,050	3	1	2	1	2	3	-	-	-	3	3	0	1	-
Niacin	1,200	5	4	1	4	1	5	-	-	-	5	4	1	-	-
Omega-3 fatty acids	21,898	14	8	6	9	5	7	7	2	5	7	8	6	-	3
Dalcetrapib	227	1	-	1	-	1	1	-	-	-	1	1	-	-	-

SOC = standard of care; RCTs = randomized controlled trials.

blinded outcome adjudication, and the existence of published design paper are included. For 7 studies, a design paper or study protocol was available (12-18). Of all RCTs, only 1 has reported the results (at the National Lipid Association Virtual Scientific Sessions) (19).

POTENTIAL MECHANISMS OF ACTION OF LIPID-MODULATING AGENTS IN PATIENTS WITH COVID-19. Figure 2 illustrates the potential pathways through which lipid-modulating drugs that have ongoing RCTs may affect outcomes in COVID-19. These agents include statins, omega-3 fatty acids, fibrates, niacin, and dalcetrapib.

Statins inhibit 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (20) and the production of isoprenoid intermediates that are critical for viral entry, immune signaling, and the inflammatory cascade (21). These agents also induce transcription factors such as Krüppel-like factor-2, limiting inflammation and prothrombotic functions of activated endothelial cells (22). Statins exert antioxidant and antiapoptotic effects, potentiate the production of nitric oxide (3,23), and up-regulate transforming growth factor beta receptor III, thereby reducing collagen deposition and pulmonary fibrosis (24).

Data in observational studies, RCTs, and meta-analyses in patients with sepsis are controversial. Two RCTs showed no improvement in acute respiratory distress syndrome (ARDS) versus placebo (25,26). However, some studies suggest a benefit associated with statin use (27). Secondary analysis of the HARP-2 (Hydroxymethylglutaryl-CoA Reductase Inhibition with Simvastatin in Acute Lung Injury to Reduce Pulmonary Dysfunction) trial suggested potential improved survival in patients with a high inflammatory status (28). In a meta-analysis of cohort studies and RCTs of patients with ARDS, statin use was not associated with reduced mortality in patients with acute lung injury but correlated with increased ventilator-free days and reduced Sequential Organ Failure Assessment scores (29). In COVID-19, a recent single-center retrospective study suggested lower adjusted mortality rates in patients with antecedent statin use compared with nonusers (30).

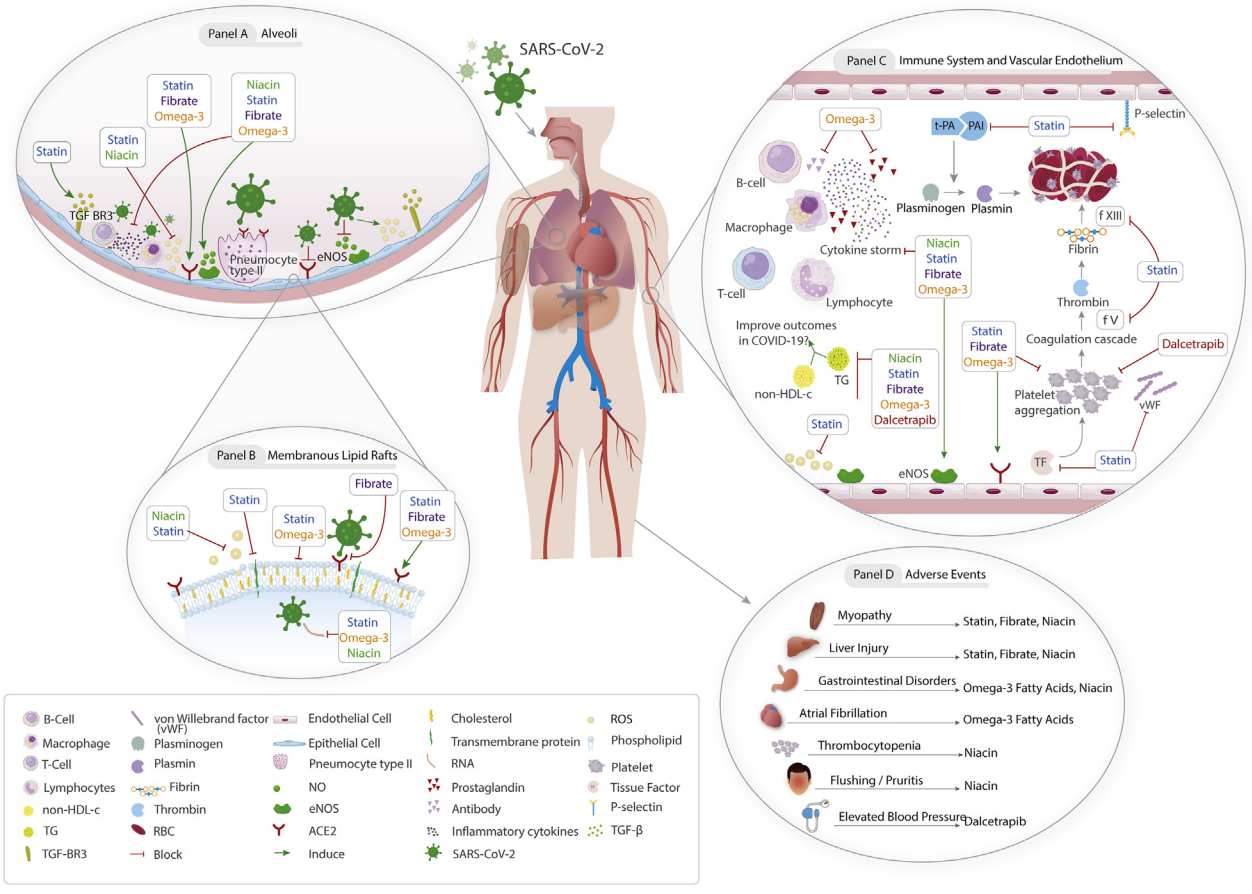
Omega-3 polyunsaturated fatty acids act as a precursor to lipid mediators that reduce inflammation and may prove beneficial in the COVID-19 inflammatory response (14). Icosapent ethyl, an ethyl ester of EPA, has exhibited anti-inflammatory properties (15). Multiple RCTs have evaluated omega-3 polyunsaturated fatty acids in ARDS. Although individual trial results have been mixed, a meta-analysis found favorable outcomes with regard to ventilator-free days, length of stay in the intensive care unit (ICU), organ failure, and mortality in patients receiving a diet enriched with EPA and gamma-linolenic acid (31,32).

In vitro studies suggest that fenofibrate, a fibric acid derivative, destabilizes the receptor-binding domain of the SARS-CoV-2 spike protein and inhibits the receptor-binding domain that binds to ACE2. This may reduce viral infectivity by up to 70% (33).

Niacin (nicotinic acid, nicotinamide) increases HDL cholesterol levels and may reduce inflammatory mediators. Niacin may also possess antiviral activity through increasing nicotinamide adenine dinucleotide (NAD), as nicotinamide restores poly-adenosine diphosphate-ribose polymerase functions, which inhibit the viral replication and support innate immunity to SARS-CoV-2 (34).

CETP inhibitors (eg, dalcetrapib) raise HDL cholesterol levels, which may have anti-inflammatory properties and inhibit platelet activation (35). However, off-target effects should be considered. In the ILLUMINATE (Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events) trial, torcetrapib (another CETP inhibitor) had favorable effects on lipids but showed an increase in death due to sepsis and increased systolic blood pressure (36).

FIGURE 2 **Posited Mechanisms of Action of Lipid-Modulating Agents in COVID-19**



(A) Binding of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) to pneumocytes results in cytokine release. Statins, fibrates, and omega-3 fatty acids can maintain the alveolar epithelial integrity. Statins may alleviate pulmonary fibrosis. **(B)** Fibrates, statins, and omega-3 fatty acids can inhibit viral entry. **(C)** Omega-3 fatty acids can inhibit the excessive antibody release. Statins, fibrates, omega-3 fatty acid, and dalcetrapib may have antiplatelet activities. Statins may also have antithrombotic properties. **(D)** Possible adverse effects of lipid-modulating agents. ACE = angiotensin-converting enzyme; COVID-19 = coronavirus disease-2019; CYP = cytochrome P450; RBD = receptor-binding domain; TG = triglyceride.

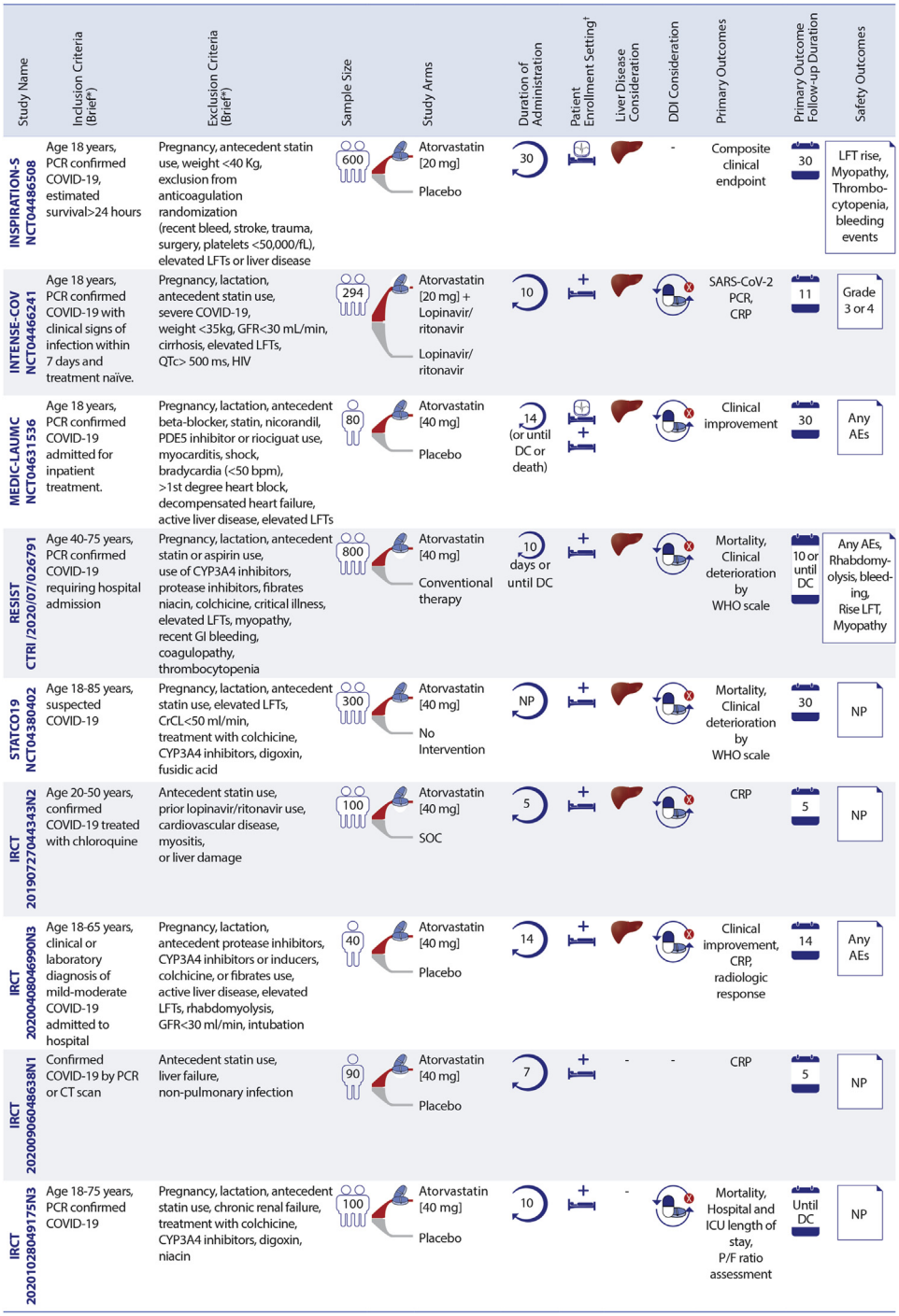
SUMMARY OF THE ONGOING RCTS

A graphical summary of design features of all RCTs for statins, omega-3 fatty acid preparations, fibrates, and niacin for the management of COVID-19 is illustrated in **Figures 3, 4, 5, and 6**, respectively. Also, the section on RCTs for the management of patients with diagnosed COVID-19 begins with statin therapy RCTs, followed by RCTs of omega-3 fatty acid preparations, fibrates, niacin, and dalcetrapib. This sequence does not describe treatment preference. **Figure 7** presents a graphical summary of design features of RCTs for the prevention of COVID-19 (only omega-3 fatty acid had such RCTs). The **Central Illustration** summarizes all ongoing trials per each class of drug. In each section, discussion of these trials is provided according to the clinical setting.

RCTs FOR MANAGEMENT OF PATIENTS WITH DIAGNOSED COVID-19. Ongoing RCTs of statin therapy. Seventeen RCTs of statin therapy have been registered: 16 in the hospitalized setting and 1 in a post-discharge setting. These trials assess either moderate-intensity statin therapy (with simvastatin 40 to 80 mg daily or atorvastatin 20 mg daily or rosuvastatin 5 mg daily) or high-intensity statin therapy (with atorvastatin 40 to 80 mg daily or rosuvastatin 40 mg daily) (37).

Ongoing RCTs of statin therapy in hospitalized non-ICU patients. Statins are being evaluated in 14

FIGURE 3 Ongoing Statin Therapy RCTs in Patients With COVID-19



Statin trials are evaluating patients in different settings. *See full list of inclusion/exclusion criteria in the original trial records. †Enrollment setting includes hospitalized and post-discharge. AEs = adverse events; CK = creatine kinase; CrCl = creatinine clearance; CRP = C-reactive protein; CT = computed tomography; DC = discharge; DDI = drug-drug interaction; FRAIL = Fatigue Resistance, Ambulation, Illnesses, and Loss of weight questionnaire; GFR = glomerular filtration rate; HBV = hepatitis B virus; HCV = hepatitis C virus; LFT = liver function tests; MI = myocardial ischemia; NP = not pointed; P/F ratio = arterial oxygen partial pressure/fractional inspired oxygen; PDE5 = phosphodiesterase type 5; SOC = standard of care; RCTs = randomized controlled trials; C-19-ACS = Preventing cardiac complications of COVID-19 disease with early acute coronary syndrome therapy: a randomized controlled trial; COLSTAT = Colchicine/Statins for the prevention of COVID-19 complications; RESIST = A randomized control trial of statin and aspirin as adjuvant therapy in patients with SARS-CoV-2 infection; STATCO19 = Atorvastatin as adjuvant therapy in COVID-19. All other full study names are provided in the text.

Continued on the next page

FIGURE 3 Continued

Study Name	Inclusion Criteria (Brief*)	Exclusion Criteria (Brief*)	Sample Size	Study Arms	Duration of Administration	Patient Enrollment Setting†	Liver Disease Consideration	DDI Consideration	Primary Outcomes	Primary Outcome Follow-up Duration	Safety Outcomes
NCT04813471	Age 18-99 years, PCR confirmed COVID-19	Pregnancy, lactation, antecedent statin or nicorandil use, concomitant use of levodopa, PDE-5 inhibitors, riociguat, pulmonary edema, active liver disease, elevated LFTs	70	Atorvastatin [40 mg] SOC	14 days or until DC	+		X	Clinical Improvement	28	Any AEs
C-19-ACS NCT04333407	Age 40 years or diabetes or known coronary disease or hypertension, PCR confirmed COVID-19	Age <18 years or >85 years, pregnancy, acute coronary syndrome, myocarditis, bleeding diathesis, life expectancy <3 months	3170	Atorvastatin [80 mg] Placebo	28	+	-	X	Mortality	30	Any AEs, Bleeding and thrombotic events
HEAL-COVID NCT04801940	Age 18 years, confirmed COVID-19 by laboratory assessment, estimated hospital discharge within 5 days	Pregnancy, lactation, antecedent statin use or complications with statins, use of protease inhibitors or cyclosporine life expectancy < 14 days post-discharge, elevated LFTs, CK> 10 ULN, Child-Pugh C, or chronic liver disease	2631	Atorvastatin [40 mg] SOC	365	+		X	Hospital free survival	365	Serious AEs
COLSTAT NCT04472611	Age 18 years, PCR confirmed COVID-19	Pregnancy, lactation, chronic colchicine or corticosteroid use, acute liver disease, GFR < 30mL/min, QTc >500ms, WHO ordinal scale 5-8, rhabdomyolysis, cytopenia	466	Rosuvastatin [40 mg] + Colchicine SOC	During hospitalization	+		-	COVID 19 Severity by WHO scores	30	NP
NCT04359095	Age 18 years, PCR confirmed COVID-19	Pregnancy, cirrhosis or elevated LFTs, GFR < 30mL/min, advanced or metastatic cancer, FRAIL score of fragility >3	1200	Rosuvastatin [40 mg]+ Colchicine Rosuvasta-tin[40 mg]+ Colchicine+ Truvada SOC	14 (Truvada for 10 days)	+		-	Mortality	28	Severe AEs
Ruxo-Sim-20 NCT04348695	Age 18 years, clinical diagnosis of COVID-19 or confirmed PCR or antibodies, grade 3-4 of the WHO 7-point scale of severity, platelets> 50,000/uL, neutrophils> 500/uL	Pregnancy, lactation, impaired gastrointestinal function with impairment of the absorption of simvastatin, concomitant severe bacterial or fungal infection, Co-infection with HIV, HBV, HCV	94	Simvastatin [40 mg] + Ruxolitinib SOC	14	+		-	COVID 19 Severity by WHO scores	7	Any AEs
REMAP-CAP NCT02735707	Age 18 years, acute illness due to suspected or proven COVID-19	Estimated survival < 24 hours, expected discharge within 48 hours of admission, >14 prior days of inpatient admission	7100	Simvastatin [80 mg] No intervention	28 days or until DC	+	-	-	Mortality	90	NP
FJD-COVID-ESTATINAS EUCTR2020-001319-26-ES	Age > 45 years, positive COVID-19 requiring hospital admission and discharged within 3 months	Pregnancy, lactation, antecedent statin use, history of statin intolerance, GFR <30mL / min, prognosis <1-year, liver or heart transplant, myopathy, concomitant cyclosporine use, elevated LFTs	1080	Rosuvastatin [5 mg] No Intervention	NP			X	Mortality	365	NP

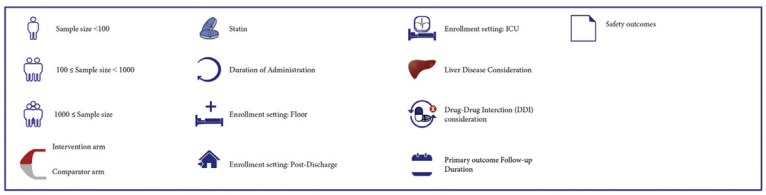


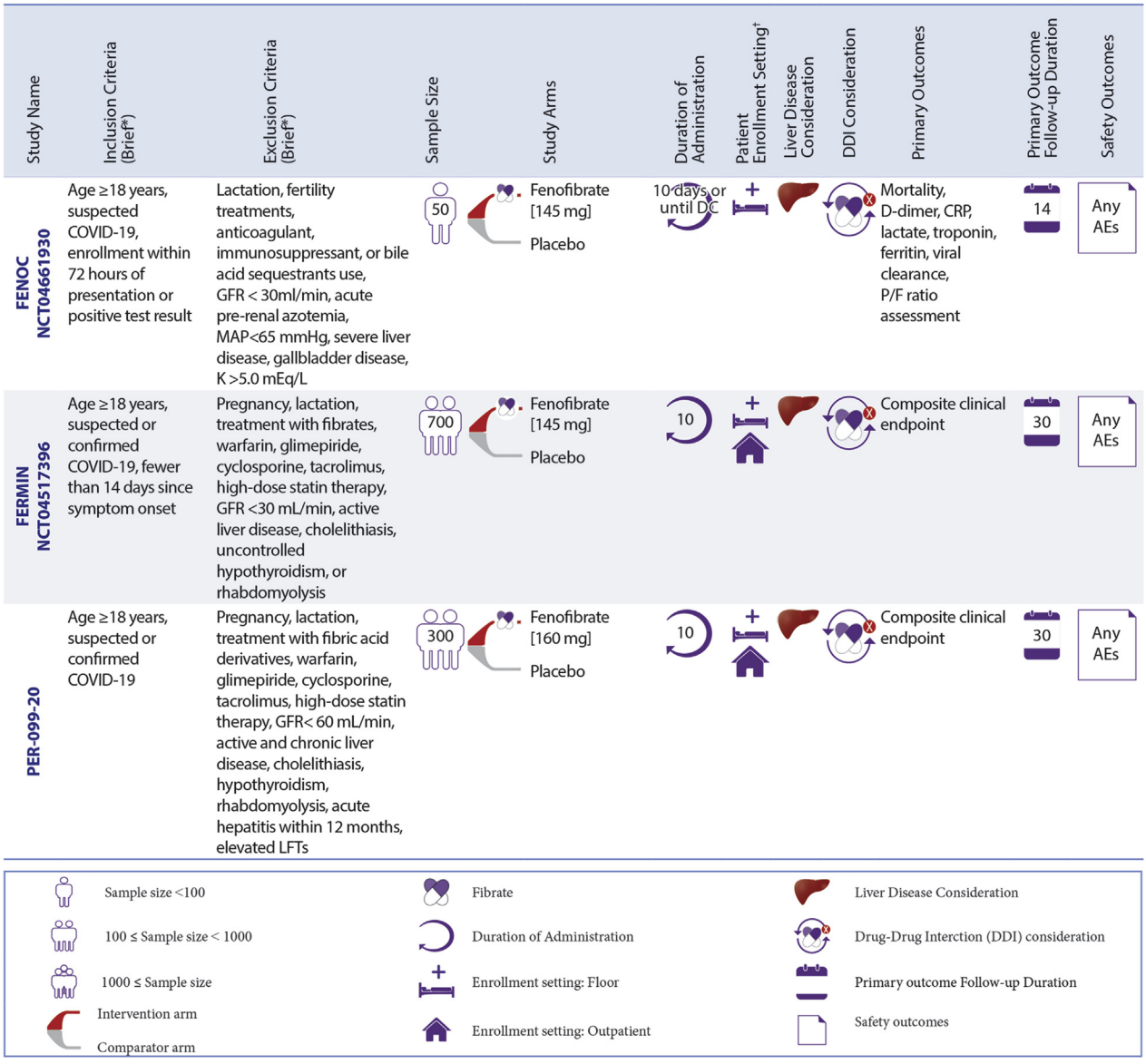
FIGURE 4 Ongoing RCTs of Omega-3 Fatty Acids in Patients With COVID-19

Study Name	Inclusion Criteria (Brief*)	Exclusion Criteria (Brief*)	Sample Size	Study Arms	Duration of Administration	Patient Enrollment Setting†	Liver Disease Consideration	DDI Consideration	Primary Outcomes	Primary Outcome Follow-up Duration	Safety Outcomes
KONS-COVID19 NCT04357990	Age ≥18 years, confirmed COVID-19, symptoms of upper respiratory infection	Pregnancy, asymptomatic infection, severe pneumonia, antecedent medication by inhalation or naso- and oropharyngeal route, asthma	128	Omega3 Viruxide [Oral and Nasal Spray TDS] Placebo	14	Home	-	-	Time to clinical improvement, hospital admission	28	Any AEs
PREPARE-IT 2 NCT04460651	Age ≥40 years, confirmed COVID-19 by RT-PCR with clinical signs of infection within 7 days	Pregnancy or breastfeeding, lack of access to adequate means of communication via the web, contraindication to EPA, anticoagulant use, hemorrhagic diathesis	4000	Icosapent ethyl [4 g BID for 3 days, then 2 g BID for days 4-28] Placebo	28	Home	-	-	Percentage of patients requiring hospitalization	28	Any AEs
VASCE-PA-COVID-19 NCT04412018	Age 18-75 years, confirmed COVID-19 within 72 hours with at least one of the following: fever, cough, sore throat, shortness of breath, myalgia	Pregnancy, lactation, life expectancy <3 months, history of MI, stroke, hospitalization for acute lung, liver or kidney disease within last month, active liver disease, acute or chronic pancreatitis	100	Icosapent ethyl [4 g BID for 3 days, then 2 g BID for the subsequent 11 days] Usual care	14	Home	Liver	-	hs-CRP	14	NP
IRCT 20200511047399N1	Age≥18 years, BMI ≥18.5, diabetic patients with confirmed COVID-19	Pregnancy, lactation, Liver, kidney or thyroid abnormalities, pancreatitis, malignancy, menopause, smoking or alcohol use, any abnormality in coagulation study	30	EPA+ DHA [2010 mg] + HCQ HCQ	NP	Floor	Liver	-	ESR, CRP	14	LFT rise, fatigue, body pain
NCT04335032	Age ≥18 years, confirmed moderate-severe COVID-19 within 7 days	Pregnancy, lactation, use of immunomodulators, mechanical ventilation, oxygen delivered by high flow nasal cannula, noninvasive positive pressure ventilation, ECMO, multi-organ failure, estimated survival < 48 hours	284	EPA-FFA [1 g BD] Placebo	NP	Floor	-	Yes	Mortality, time to treatment failure, P/F ratio assessment	28	Any AEs
NCT04495816	Age ≥18 years, PCR confirmed COVID-19, self-reported new-onset olfactory dysfunction	COVID-19 without self-reported anosmia, severe COVID-19, pre-existing olfactory dysfunction, chronic nasal/sinus infections (rhinosinusitis), endoscopic sinus surgery, nasal steroid spray or irrigation use	126	EPA +DHA [1 g BD] Placebo	42	Home	-	-	Brief Smell Identification Test	42	NP
NCT04507867	Age 30-75, PCR confirmed COVID-19, O2sat <90% and respiratory distress, with concomitant diseases such as CVD, diabetes mellitus 2, hypertension, obesity with BMI <35	PO intolerance	240	Concentrated omega 3 fatty acids [10 g BD] SOC	5	Floor	-	-	Mortality, hospital stay, qSOFA, ICU admission, LFT, bilirubin, coagulation study, lipid profile, fibrinogen, D-dimer, homocysteine, ferritin, CRP, P/F ratio assessment	21days or until DC	Any AEs
NCT04553705	Age 25-40 years, suspected COVID-19, CT evidence of viral pneumonia, respiratory rate < 25 /min, O2sat>95%	Pregnancy, lactation, Child-Pugh C, estimated survival <24 hours, end-stage lung disease	200	DHA+ EPA [1 g] SOC	30	Floor	Liver	-	Clinical improvement, PCR levels, hospital length of stay, lipid profile, CRP, Ferritin, LDH, P/F ratio assessment	30	NP
NCT04647604	Age ≥18 years, suspected or confirmed COVID-19	Pregnancy, lactation, Bleeding diathesis, shock, myocardial infarction, stroke, acute emboli, coma	40	DHA+ EPA [2 mL/kg, IV] Placebo (NaCl)	5	Floor	-	-	CRP, lipid profile, inflammatory biomarkers	5	NP
RBR-7jrxqm	Age 18-65 years, PCR confirmed COVID-19	Pregnancy, artificial nutrition within 15 days, hyperglycemia, hypertriglyceridemia, neutropenia, immunodeficiency/suppression including AIDS, cirrhosis, NYHA class IV heart failure, terminal neurological processes, short life expectancy, shock	50	Fatty acids omega-3 [200 ml] SOC	7	Floor	-	-	CRP, TNF-α, IL-6	NP	Any AEs

Sample size <100
100 ≤ Sample size < 1000
1000 ≤ Sample size
Intervention arm
Comparator arm
Omega3 pearl
Omega3 (Oral/Nasal Spray)
Omega-3 injection
Omega-3 Sachet
Omega-3 Liquid
Duration of Administration
Enrollment setting: Outpatient
Enrollment setting: Floor
Liver Disease Consideration
Drug-Drug Interction (DDI) consideration
Primary outcome Follow-up Duration
Safety outcomes

Omega-3 fatty acid preparations are being assessed among non-intensive care unit (ICU) inpatients, and outpatients. *See full list of inclusion/exclusion criteria in the original trial records. †Enrollment setting includes hospitalized non-ICU patients and outpatient settings. BMI = body mass index; CVD = cardiovascular disease; DHA = docosahexaenoic acid; ESR = erythrocyte sedimentation rate; EPA = eicosapentaenoic acid; FFA = free fatty acid; HCQ = hydroxychloroquine; hs-CRP = high-sensitivity C-reactive protein; IL = interleukin; IV = intravenous; LDH = lactate dehydrogenase; NYHA = New York Heart Association; O_2sat = oxygen saturation; qSOFA = quick Sequential Organ Failure Assessment; TNF = tumor necrosis factor; other abbreviations as in Figure 3. Full study names are provided in the text.

FIGURE 5 **Ongoing RCTs of Fibrates in Patients With COVID-19**

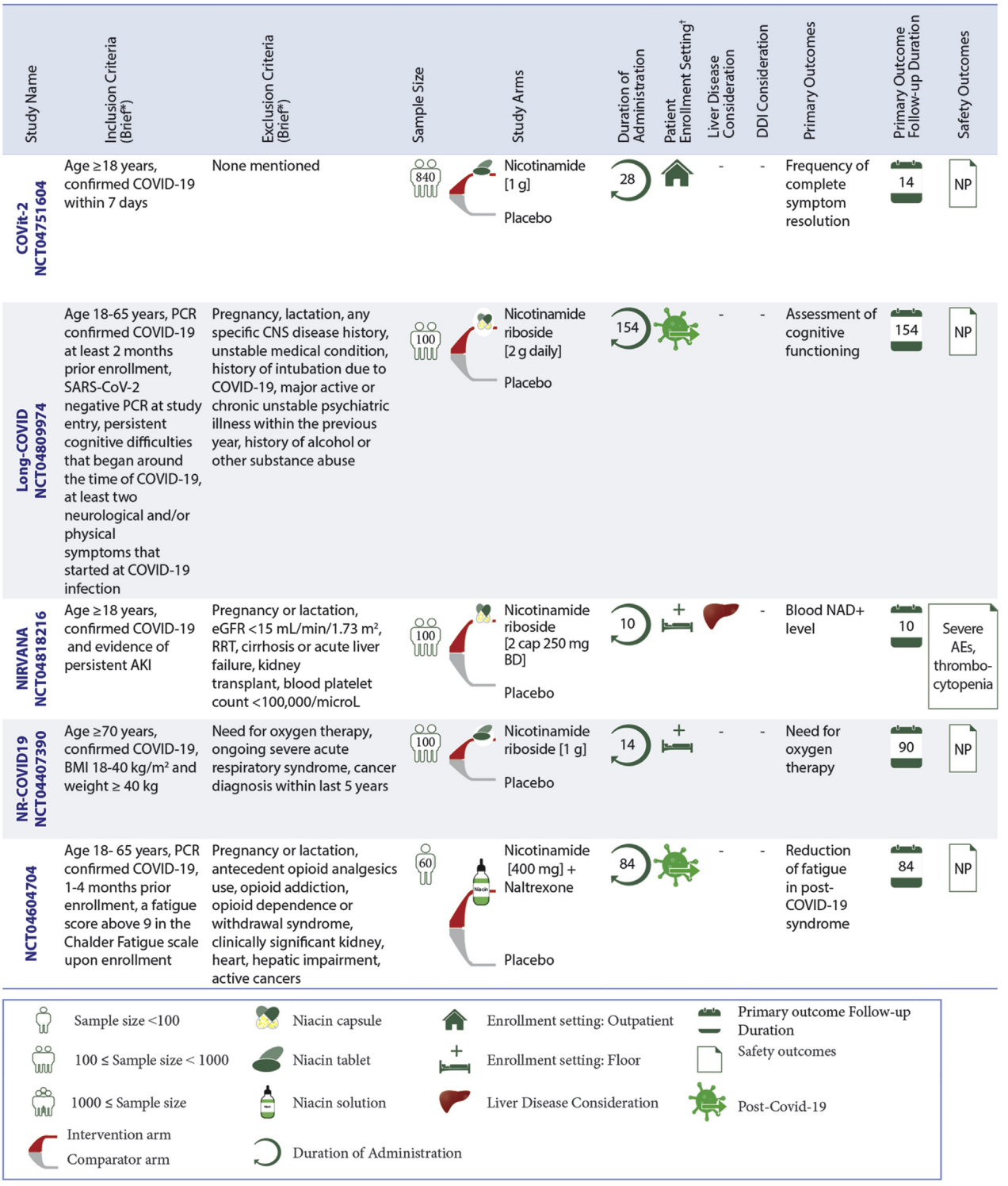


Fenofibrate is being evaluated in different settings, including inpatient non-ICU, and outpatient settings. *The full list of inclusion and exclusion criteria should be found in the original trial records. †Patient enrollment setting includes hospitalized non-ICU patients and outpatient settings. MAP = mean arterial pressure; other abbreviations as in Figures 3 and 4. Full study names are provided in the text.

RCTs, with the number of participants ranging from 40 to 7,100 patients in the non-ICU hospital settings. These RCTs include 12 for hospitalized non-ICU patients and 2 that enroll both ICU and non-ICU patients (MEDIC-LAUMC [Managing Endothelial Dysfunction in COVID-19: A Randomized Controlled Trial at LAUMC] and Effectiveness and Safety of Medical Treatment for SARS-CoV-2 [COVID-19] in Colombia; NCT04359095).

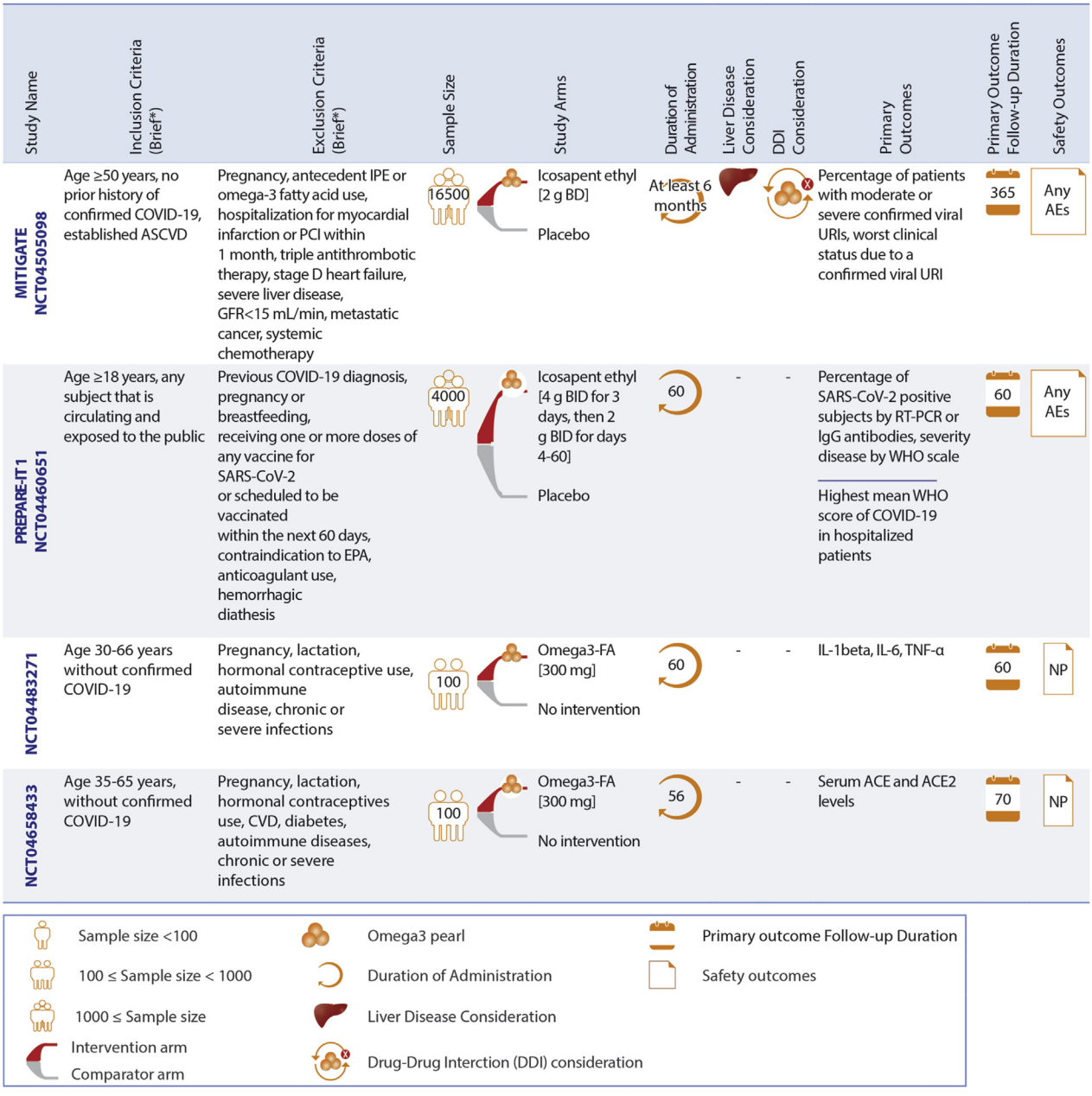
Moderate-intensity statin therapy is being tested in 3 of these 14 RCTs for hospitalized non-ICU patients. The primary outcomes include mortality within 90 days in the REMAP-CAP (Randomized, Embedded, Multifactorial Adaptive Platform Trial for

FIGURE 6 Ongoing RCTs of Nicotinamide in Patients With COVID-19



Niacin is being evaluated in different settings, including inpatient non-ICU, outpatient, and post-acute COVID-19 settings. *The full list of inclusion and exclusion criteria should be found in the original trial records. †Patient enrollment setting includes hospitalized non-ICU patients, outpatient, and post-acute COVID-19 settings. AKI = acute kidney injury; CNS = central nervous system; eGFR = estimated glomerular filtration rate; NAD = nicotinamide-adenine dinucleotide; RRT = renal replacement therapy; other abbreviations as in Figures 3 and 4. Full study names are provided in the text.

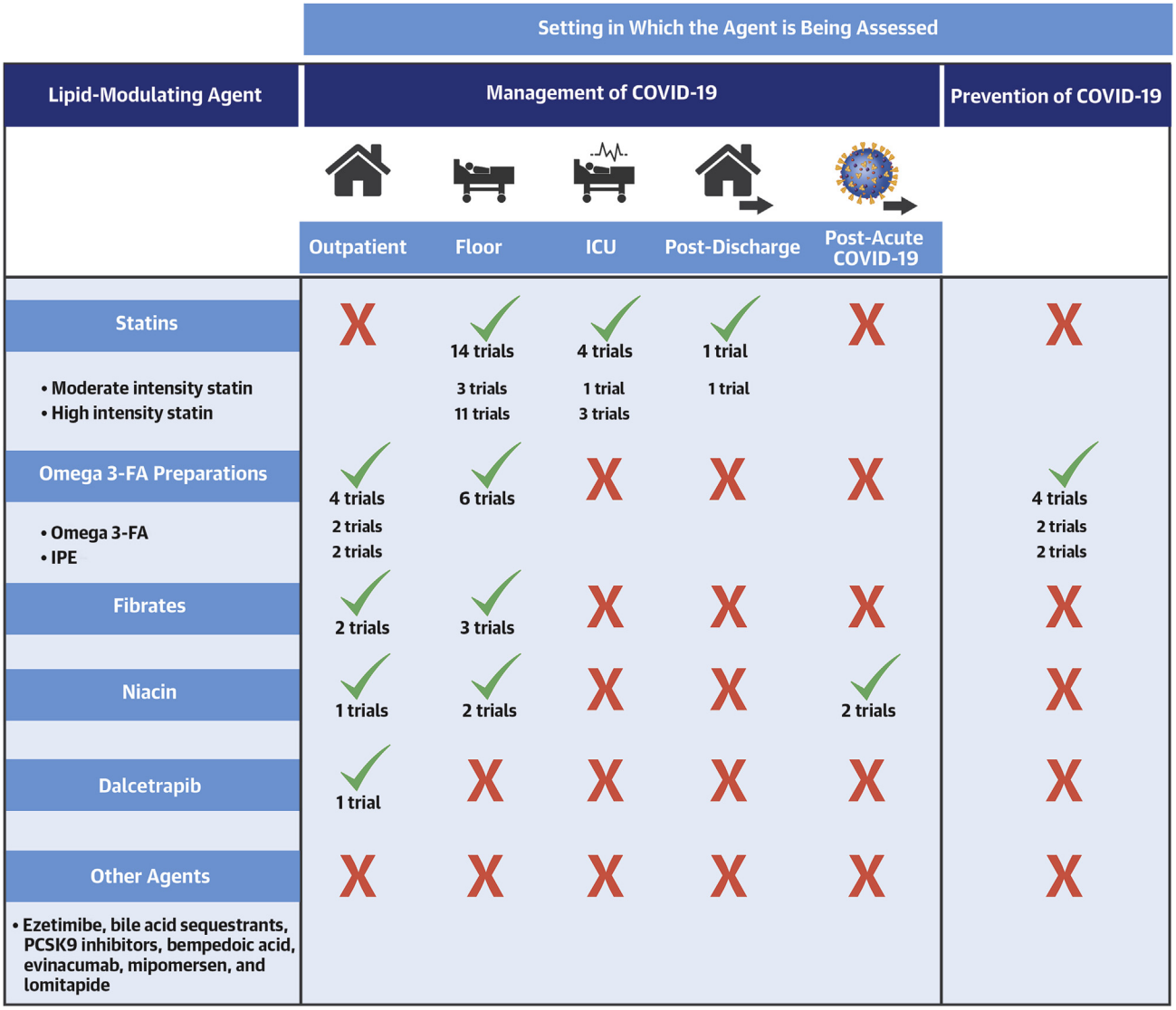
FIGURE 7 **Ongoing RCTs of Omega-3 Fatty Acids for Prevention of COVID-19**



Omega-3 fatty acid preparations are being evaluated in those with moderate to high risk of COVID-19. *The full list of inclusion and exclusion criteria should be found in the original trial records. AF = atrial fibrillation; ASCVD = atherosclerotic cardiovascular disease; IgG = immunoglobulin G; IL = interleukin; IPE = icosapent ethyl; PCI = percutaneous coronary intervention; RT-PCR = reverse transcription polymerase chain reaction; TNF = tumor necrosis factor; URI = upper respiratory tract infection; other abbreviations as in Figures 2 to 4.

Community-Acquired Pneumonia) study for 7,100 hospitalized non-ICU patients (17) and assessment of COVID-19 severity according to World Health Organization scores within 7 days in the Ruxo-Sim-20 (Study of Ruxolitinib Plus Simvastatin in the Prevention and Treatment of Respiratory Failure of COVID-19) trial for 94 participants. The comparators of these trials are no intervention and standard of care (SOC), respectively. The third RCT of moderate-intensity statin therapy, INTENSE-COV

CENTRAL ILLUSTRATION **Summary of Ongoing Trials of Lipid-Modulating Agents in Coronavirus Disease-2019**



Talasaz, A.H. et al. J Am Coll Cardiol. 2021;78(16):1635-1654.

Statins are the most frequently studied lipid-modulating agents in randomized controlled trials of patients with coronavirus disease 2019 (COVID-19). Omega-3 fatty acid preparations are the only studied lipid-modulating agents in the prevention of COVID-19. Niacin is the only lipid-modulating agent being studied for post-acute COVID-19. Additional details are provided in Figures 3, 4, and 5.

(Combination therapies to reduce carriage of SARS-Cov-2 and improve outcome of COVID-19 in Ivory Coast: a phase randomized IIb trial), plans to randomize 294 patients to atorvastatin plus lopinavir/ritonavir versus lopinavir/ritonavir for the co-primary outcomes of the proportions of patients with undetectable SARS-CoV-2 polymerase chain reaction (PCR) and C-reactive protein (CRP) <27 mg/L at day 11.

High-intensity statin therapy is being assessed in 11 of 14 ongoing RCTs, with a total of 8,977 hospitalized non-ICU patients with COVID-19. These 11 RCTs are studying high-intensity statin therapy compared with no treatment (2 of 11) or SOC (5 of 11) or placebo (4 of 11). Mortality during hospitalization or within 10 to 30 days is the most common primary outcome in 5 of 11 RCTs with high-intensity statins

for hospitalized non-ICU patients (13,18). The HEAL-COVID (Helping Alleviate the Longer-term Consequences of COVID-19) trial plans to enroll 2,631 participants to explore the effect of high-intensity statin therapy on hospital-free survival within 12 months from enrollment.

Patients with liver disease are excluded in 2 of 3 RCTs with moderate-intensity statins and 8 of 11 trials with high-intensity statins. Considerations of drug-drug interactions at the time of enrollment were evaluated in 1 of 3 RCTs and 8 of 11 RCTs with moderate- and high-intensity statins, respectively.

Ongoing RCTs of statin therapy in critically ill patients. Statins are being assessed in 4 RCTs in ICU patients, of which 2 enroll both ICU and non-ICU patients (MEDIC-LAUMC [Managing Endothelial Dysfunction in COVID-19: A Randomized Controlled Trial at LAUMC] and NCT04359095). Two other RCTs include ICU patients only (INSPIRATION-S [The Intermediate versus Standard-dose Prophylactic Anticoagulation and Statin In Critically-ill Patients with COVID-19: An Open Label Randomized Controlled Trial] with 600 participants [12] and Managing Endothelial Dysfunction in Critically Ill COVID-19 Patients at LAUMCRH [NCT04813471]) with 70 patients with COVID-19.

INSPIRATION-S is the only trial of moderate-intensity statin therapy versus placebo in ICU patients (12). A composite of all-cause mortality, venous or arterial thrombotic events, and treatment with extracorporeal membrane oxygenation within 30 days is the study's primary outcome. The INSPIRATION-S trial completed patient enrollment in April 2021. Thirty-day preliminary results were presented at the 2021 American College of Cardiology Annual Scientific Sessions. Among 587 randomized patients, atorvastatin 20 mg once daily compared with placebo did not result in a significant reduction in the primary composite outcome of venous or arterial thrombosis, treatment with extracorporeal membrane oxygenation, or all-cause death with an odds ratio of 0.84 (95% confidence interval [CI]: 0.58-1.21; $P = 0.35$). In the prespecified analysis of patients hospitalized within 7 days of symptom onset, there was a hypothesis-generating reduction in the odds of the primary outcome (odds ratio: 0.60; 95% CI: 0.37-0.99; P interaction = 0.05) (38).

The remaining RCTs in critically ill patients (3 of 4 trials) are investigating high-intensity statin therapy; 2 of these trials (NCT04813471 and NCT04359095) are studying high-intensity statin therapy compared with SOC. The MEDIC-LAUMC is assessing the effects of high-intensity atorvastatin versus placebo among 80 participants. In addition, 2 of 3 trials of high-intensity statin therapy (MEDIC-LAUMC and NCT04813471) consider drug-drug interactions before enrollment, and clinical improvement within 1 month is being assessed as the primary outcome in these 2 trials. The other trial, NCT04359095, is assessing the influence of high-intensity statin therapy on mortality within 28 days as the primary outcome among 1,200 ICU or non-ICU patients. Patients with liver disease are excluded in all of the RCTs with moderate- or high-intensity statins for critically ill patients.

Ongoing RCTs of statin therapy in post-discharge patients. Rosuvastatin (5 mg daily) is the only statin-based intervention under investigation in the post-discharge setting. The FJD-COVID-ESTATINAS RCT (Multicenter, randomized, controlled, open-label clinical trial to assess the prognostic implications of rosuvastatin treatment in patients discharged after hospitalization for COVID-19) is evaluating rosuvastatin compared with no treatment in 1,080 patients discharged from hospitalization for COVID-19. The primary outcome is a composite of mortality, myocardial infarction, or ischemic stroke within 12 months. Patients with liver disease or concomitant treatment with cyclosporine are excluded. Additional details about ongoing clinical trials of statin therapy are provided in Figure 3.

Ongoing RCTs of omega-3 fatty acid preparations. There are 10 ongoing RCTs evaluating the role of omega-3 fatty acid preparations for the management of COVID-19: 6 RCTs in hospitalized non-ICU patients and 4 ongoing RCTs in the outpatient setting.

Ongoing RCTs of omega-3 fatty acid preparations in hospitalized non-ICU patients. Omega-3 fatty acids are being evaluated in 6 RCTs, with the number of participants ranging from 30 to 284 patients in the non-ICU hospital settings. Most RCTs (5 of 6) assess the oral use of omega-3 fatty acid preparations compared with SOC (3 of 5) or with placebo (1 of 5). The oral use of omega-3 fatty acid preparations plus hydroxychloroquine compared with hydroxychloroquine alone is assessed in the Comparison of the Effectiveness of Omega-3 and Hydroxychloroquine on Inflammatory Factors, Liver Enzymes, and Clinical symptoms in Diabetic COVID-19 Patients (IRCT20200511047399N1) study. Only one RCT (Resolving Inflammatory Storm in COVID-19 Patients by Omega-3 Polyunsaturated Fatty Acids; NCT04647604) explores intravenous administration of omega-3 fatty acid preparations versus placebo (14). Moreover, 3 of 6 RCTs of hospitalized non-ICU patients have co-primary outcomes, including inflammatory markers and lipid levels. Elevated liver enzymes are being evaluated as the safety outcome only in the

IRCT20200511047399N1 trial. Patients with liver disease are excluded in 2 of the 6 RCTs of omega-3 fatty acid in hospitalized non-ICU patients.

Ongoing RCTs of omega-3 fatty acid preparations in outpatient setting. Omega-3 fatty acid preparations are being evaluated in 4 ongoing RCTs for the treatment of COVID-19: KONS-COVID19 (Viruxal Oral and Nasal Spray for Treating the Symptoms of COVID-19), VASCEPA-COVID-19 (An Investigation on the Effects of Icosapent Ethyl [Vascepa] on Inflammatory Biomarkers in Individuals With COVID-1), PREPARE-IT 2 (Prevention of COVID19 With EPA in Healthcare Providers at Risk–Intervention Trial 2), and the COVID-19 Anosmia Study (NCT04495816) (16).

The KONS-COVID19 trial tests omega-3 inhaled use versus placebo among 128 outpatient participants. The primary outcome is time to clinical improvement within 28 days. The VASCEPA-COVID-19 trial assesses the oral use of icosapent ethyl compared with usual care in a total of 100 outpatient participants. High-sensitivity CRP level is the primary outcome in VASCEPA-COVID-19. Patients with active severe liver disease are excluded in this trial. Initial findings from the VASCEPA-COVID-19 were presented at the National Lipid Association Scientific Sessions (19). The investigators found that the use of icosapent ethyl for 14 days reduced high-sensitivity CRP (3.2 vs 1.6 mg/L; $P = 0.011$) and led to symptom improvement, assessed by using the InFLUenza Patient-Reported Outcome score in outpatients with COVID-19 after 14 days. The PREPARE-IT 2 trial is assessing the effects of icosapent ethyl versus placebo in 2,000 outpatient participants. The impact of oral use of omega-3 fatty acid preparations versus placebo on olfactory performance within 6 weeks among outpatients is under evaluation in the NCT04495816 trial with 126 participants. Additional details about ongoing RCTs of omega-3 fatty acid preparations for treatment of COVID-19 are described in Figure 4.

Ongoing RCTs of fibrates. Three RCTs are investigating fibrates in patients with COVID-19. These RCTs are testing fenofibrate versus placebo in hospitalized non-ICU patients: FENOC (Fenofibrate for Patients With COVID-19 Requiring Hospitalization), FERMIN (Fenofibrate as a Metabolic Intervention for COVID-19), and Fenofibrate as a Metabolic Intervention for Coronavirus Disease 2019 [COVID-19]: A Randomized Controlled Trial [PER-099-20]). FERMIN and PER-099-20 also enrolled outpatients. The sample size of these studies ranges from 50 to 700 patients.

The main outcomes in the FENOC study include improvement in laboratory markers, the ratio of arterial oxygen partial pressure to fractional inspired oxygen, and mortality. The composite endpoint as the primary outcome for the FERMIN and PER-099-20 trials will be a global rank score that grades patients based on survival, need for respiratory/mechanical support, the fraction of inspired oxygen/percent oxygen saturation, the number of days out of the hospital for outpatient participants who are hospitalized after enrollment, and the modified Borg dyspnea scale for the outpatient subset not hospitalized. All these trials consider drug-drug interactions before the enrollment. Patients with active liver disease are excluded in all 3 of these trials. Additional information about these RCTs is summarized in Figure 5.

Ongoing RCTs of niacin. Five RCTs of niacin therapy were identified: 2 in hospitalized non-ICU patients, 1 in the outpatient setting, and 2 ongoing RCTs in post-acute COVID-19. All of these trials are studying niacin compared with placebo.

Ongoing RCTs of niacin in hospitalized non-ICU patients. Niacin is being assessed in 2 ongoing RCTs for 100 hospitalized non-ICU patients in each trial: NIRVANA (Nicotinamide Riboside in SARS-CoV-2 [COVID-19] Patients for Renal Protection) and NR-COVID19 (Effects of Nicotinamide Riboside on the Clinical Outcome of Covid-19 in the Elderly). The primary outcomes of these trials are the alteration of blood NAD+ level within 10 days and the need for oxygen therapy with a follow-up duration of 90 days, respectively. In NIRVANA, thrombocytopenia is being evaluated as the safety outcome, and patients with liver disease are being excluded.

Ongoing RCTs of niacin in outpatient setting. The COVit-2 (Improvement of the Nutritional Status Regarding Nicotinamide [Vitamin B3] and the Disease Course of COVID-19) trial is the only study of niacin therapy versus placebo in an outpatient setting; 840 patients plan to be enrolled. The frequency of complete symptom resolution within 2 weeks is the primary outcome.

Ongoing RCTs of niacin in post–COVID-19 setting. Niacin is being evaluated in 2 RCTs in the post-COVID-19 setting: Long-COVID (Clinical Trial of Niagen to Examine Recovery in People with Persistent Cognitive and Physical Symptoms After COVID-19 Illness) and Pilot Study Into Low Dose Naltrexone (LDN) and Nicotinamide Adenine Dinucleotide (NAD+) for Treatment of Patients With Post-COVID-19 Syndrome (NCT04604704). These RCTs assess the oral use of niacin in 100 participants and iontophoresis patches for 60 patients with COVID-19, respectively.

The Long-COVID trial is studying the impact of niacin on the cognitive function of patients with a positive PCR at least 2 months before enrollment. The primary outcome follow-up duration is 22 weeks.

NCT04604704 plans to enroll 60 patients with PCR-confirmed COVID-19 1 to 4 months before enrollment. This trial assesses the reduction in fatigue in post-COVID-19 syndrome within 12 weeks as the primary outcome. Patients with liver disease are excluded in the NCT04604704 trial. Additional details about the RCTs of niacin are illustrated in **Figure 6**.

Ongoing RCT of CETP inhibitors. The dal-COVID (Effect of Dalcetrapib in Patients with Confirmed Mild to Moderate COVID-19) trial is the only study of dalcetrapib (900 mg, 1,800 mg, and 3,600 mg daily) versus placebo and includes 208 outpatients with mild to moderate COVID-19. The primary outcome is time to sustained symptom resolution within 28 days. Patients with liver disease are excluded from the NCT04676867 trial. Drug-drug interactions are being considered before enrollment.

RCTs FOR PREVENTION OF CONTRACTING COVID-19. Use of omega-3 fatty acid preparations as a preventive measure against COVID-19 is being investigated in 4 RCTs: MITIGATE (A Pragmatic Randomized Trial of Icosapent Ethyl for High-Cardiovascular Risk Adults) (15), PREPARE-IT 1 (Prevention of COVID19 With EPA in Healthcare Providers at Risk-Intervention Trial 1), the Effect of Omega-3 on Selected Cytokines Involved in Cytokine Storm (NCT04483271), and the Effect of Omega-3 Supplements on the Serum Levels of ACE/ACE2 Ratio as a Potential Key in Cardiovascular Disease and COVID-19 (NCT04658433).

The MITIGATE and PREPARE-IT 1 trials are studying the effects of icosapent ethyl versus SOC and placebo, respectively. NCT04483271 and NCT04658433 assess omega-3 fatty acid supplements compared with no treatment for 100 patients in each trial. The number of confirmed viral infections and worst clinical status due to a viral upper respiratory infection are the co-primary outcomes for MITIGATE with 16,500 participants. The number of confirmed viral infections is the primary outcome in PREPARE-IT 1 with 2,000 participants. The primary outcomes for the NCT04483271 and NCT04658433 trials are inflammatory markers such as interleukin-1beta, interleukin-6, tumor necrosis factor-alpha, and serum ACE and ACE2. Patients with severe liver disease are excluded only in MITIGATE. Additional details about these RCTs are summarized in **Figure 7**.

DISCUSSION

The perspective of the COVID-19 disease state has broadened from pneumonia to a systemic multi-organ disease, with systemic inflammation and thrombosis as key features (2,39). The current review identified 34 RCTs that evaluate the role of lipid-modulating agents in the management of acute COVID-19, 2 RCTs in patients with post-acute COVID-19, and 4 RCTs for prevention of contracting (or severity of) COVID-19. Results from these trials may expand the armamentarium for management of COVID-19. The neutral results of recent RCTs of escalated-dose anticoagulation in critically ill patients with COVID-19 (40,41) may indicate the significance of the maladaptive immune response in severe COVID-19 (42). It is in this context that lipid-modulating agents with pleotropic effects offer possible therapeutic potential (43). The moderate immunomodulating effect of these agents lessens the chance of excessive immunosuppression and superinfection, commonly seen with other anti-inflammatory agents.

Despite such hope, certain methodological limitations of some of the ongoing RCTs deserve attention. These include small sample size, use of primary surrogate outcomes, and lack of blinded outcome adjudication, which hamper the rigor of the trials. More than 1 year into the pandemic, 40 RCTs of lipid-modifying therapies were identified, with only 21 (with total estimated sample size of 7,675) having a double-blind design. The results from only 2 trials have been communicated in preliminary form and none in the peer-reviewed published form. In addition, despite the scientific rationale summarized in this paper, translation to clinical benefit is not assured. Among the immune-modulating therapies, only steroids have shown consistent efficacy in patients with COVID-19 (44-48). The neutral results with ivermectin (49) and hydroxychloroquine (50), and the mixed results with colchicine (51,52) and tocilizumab (53,54), remind us that biological plausibility may not translate into meaningful treatment. Hence, the ongoing lipid-modulating therapy RCTs are of particular interest.

STATINS AS MULTIPURPOSE DRUGS? Despite initial concern that statins might increase expression of ACE2 and facilitate SARS-CoV-2 entry with potential deleterious effects, observational studies suggest an association between antecedent statin use and improved survival. In a population-based propensity-matched study of 10,448 patients with COVID-19, Lee et al (55) reported a significant reduction in hazard of death in statin users compared with nonusers (hazard ratio: 0.64; 95% CI: 0.43-0.95; $P = 0.02$). In a retrospective propensity matching analysis of 1,296 patients with COVID-19, Gupta et al (30) reported similar reduction in the odds of death with antecedent statin use (odds ratio: 0.47; 95% CI: 0.36-0.62; $P < 0.001$). Such nonrandomized observational studies are

subject to confounding, including confounding by indication, and require confirmation in ongoing RCTs. There are several limitations to the ongoing statin investigations. Several RCTs do not include thrombotic events among their prespecified outcomes. Quality of life is evaluated in only 3 RCTs. The role of statin therapy in the post-discharge setting for patients with COVID-19 is being studied in only 1 RCT with 1,080 patients but not in the outpatient setting.

OMEGA-3 POLYUNSATURATED FATTY ACIDS: HOPE OR HYPE? Anti-inflammatory effects (56) and potential impact on ARDS progression (57) make omega-3 fatty acids worthwhile agents for investigation. Functional limitations and quality of life are evaluated exclusively in outpatient trials, whereas mortality and clinical improvement are evaluated in hospitalized patients. Two trials with considerable sample size evaluate the role of icosapent ethyl in the prevention of contracting COVID-19.

Several limitations apply to the omega-3 fatty acid RCTs. There are relatively few total numbers of patients enrolled in trials of omega-3 fatty acids for the management of COVID-19 (**Figure 4**). Heterogeneity in use of various formulations (EPA, DHA, or EPA-DHA; ethyl esters vs free fatty acids) and impurities and/or oxidative alterations in unregulated supplement preparations make it more difficult to determine the specific effects of each. Icosapent ethyl will be studied in 2 large outpatient trials (PREPARE-IT 1 and MITIGATE) as a preventive agent but not in the inpatient setting.

FIBRATES: NEW SPARK FOR A DYING CANDLE? Despite the declining use for cardiovascular risk reduction (58), fibrates may decrease viral entry and SARS-CoV-2 infectivity by increasing sulfatide levels (59) and inhibiting the receptor-binding domain to ACE2 (33). Strengths of the ongoing fibrate trials include endpoint selection; death, ARDS-related outcomes, inflammatory markers, and invasive mechanical support are the primary outcomes under evaluation. Drug interactions were generally considered with fenofibrate initiation. However, fenofibrate is the only fibrate under investigation in RCTs including patients with COVID-19, and its lack of benefit in cardiovascular disease prevention may raise skepticism regarding its utility in COVID-19.

NIACIN: TIME FOR A COMEBACK? Anti-inflammatory effects (34) and potential protection against lung injury (60) have made niacin a target for investigation in COVID-19. Niacin is under evaluation in both acute and post-acute settings. Clinical improvement and symptom resolution are primary outcomes in the majority of the RCTs. RCTs in the post-COVID-19 setting will evaluate fatigue and cognitive function for 3 to 6 months.

As with fenofibrate, lack of benefit and presence of adverse effects with nicotinic acid seen in prior cardiovascular RCTs (61,62) may dampen enthusiasm for use in COVID-19. The ongoing trials of niacin in COVID-19 are evaluating the role of nicotinamide, another form of niacin that is not typically used as a lipid-modifying agent. Trials in the inpatient and post-acute setting are limited by small sample size, and variability in niacin dosing may lead to heterogeneous results.

CETP INHIBITORS: ROOM FOR POTENTIAL BENEFIT? Low HDL levels are associated with increased severity of COVID-19 and correlate with approved biomarkers such as ferritin and D-dimer levels (6). Dalcetrapib will be the first CETP inhibitor to be tested in patients with mild to moderate COVID-19, with time to symptom resolution as the primary outcome. Of note, dalcetrapib did not improve clinical outcomes in those with acute coronary syndromes (63). Among CETP inhibitors, only anacetrapib showed a modest cardiovascular benefit (9% relative risk reduction) (64), whereas torcetrapib (36,65) led to increases in systolic blood pressure and worse cardiovascular outcomes. Findings from dal-COVID will help clarify whether dalcetrapib merits further testing in COVID-19.

EXPECTING THE UNEXPECTED: POSSIBLE ADVERSE EFFECTS FOR LIPID-MODULATING AGENT TRIALS. Based on the knowledge from RCTs in cardiovascular diseases, important adverse effects should be monitored when the results of these RCTs accrue. Myopathy is the most common adverse effect of statin use and is managed by conversion to other statin formulations. Severe muscle complications (ie, rhabdomyolysis) are exceedingly rare (66). Rise in liver enzyme levels is another potential but infrequent adverse effect. Fibrates may also increase the risk of myopathy and hepatocyte injury (67). Drug-drug interactions play an important role in this increased risk and are considered in the ongoing COVID-19 RCTs (68). Other risks associated with statin use, including hemorrhagic stroke in those with previous stroke, are not of clinically important magnitude (69-71). New-onset or worsening of atrial fibrillation is a concern with omega-3 fatty acids (72-74), and increased bleeding due to the effects on platelet aggregation should be monitored in the RCT results.

The adverse effects of niacin, specifically nicotinic acid, include flushing, pruritus, gastrointestinal

disorder, thrombocytopenia, hyperuricemia, hyperglycemia, myopathy, and hepatotoxicity (75). However, only nicotinamide is used in COVID-19 studies. The NIRVANA trial assesses thrombocytopenia as a safety outcome and excluded patients with liver disease.

These potential risks are limited by the short duration of treatment in most trials. Of note, the adverse events in massive event-driven cardiovascular trials result from multiple months to years of treatment, whereas the current COVID-19 trials generally have much shorter treatment duration. The possible adverse effects of lipid-modulating agents are illustrated in **Figure 2**.

CONCLUSIONS

Lipid-modulating agents may mitigate the multiorgan damage associated with COVID-19 through anti-inflammatory, antiviral, and pleiotropic effects. Findings from ongoing rigorously conducted and adequately powered RCTs can assess the possible efficacy of lipid-modulating agents in the prevention or treatment of various stages of COVID-19 and may open new horizons for research and clinical practice.

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Dr Vaduganathan has received research grant support or served on advisory boards for American Regent, Amgen, AstraZeneca, Bayer AG, Baxter Healthcare, Boehringer Ingelheim, Cytokinetics, Lexicon Pharmaceuticals, and Relypsa; participates in speaker engagements with Novartis and Roche Diagnostics; and participates on clinical endpoint committees for studies sponsored by Galmed, Novartis, and the National Institutes of Health. Dr Fanikos has served as a consultant for Portola, Inc and Pfizer, Inc. Dr Piazza has received research grant support from BSC, Bayer, Bristol Myers Squibb/Pfizer Alliance, Portola, Amgen, and Janssen; and has received consulting fees from Amgen, Pfizer, and BSC. 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