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Can N-3 polyunsaturated fatty acids be considered a potential adjuvant therapy for COVID-19-associated cardiovascular complications?



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ABSTRACT

Coronavirus disease 2019 (COVID-19), caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), has currently led to a global pandemic with millions of confirmed and increasing cases around the world. The novel SARS-CoV-2 not only affects the lungs causing severe acute respiratory dysfunction but also leads to significant dysfunction in multiple organs and physiological systems including the cardiovascular system. A plethora of studies have shown the viral infection triggers an exaggerated immune response, hypercoagulation and oxidative stress, which contribute significantly to poor cardiovascular outcomes observed in COVID-19 patients. To date, there are no approved vaccines or therapies for COVID-19. Accordingly, cardiovascular protective and supportive therapies are urgent and necessary to the overall prognosis of COVID-19 patients. Accumulating literature has demonstrated the beneficial effects of n-3 polyunsaturated fatty acids (n-3 PUFA) toward the cardiovascular system, which include ameliorating uncontrolled inflammatory reactions, reduced oxidative stress and mitigating coagulopathy. Moreover, it has been demonstrated the n-3 PUFAs, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are precursors to a group of potent bioactive lipid mediators, generated endogenously, which mediate many of the beneficial effects attributed to their parent compounds. Considering the favorable safety profile for n-3 PUFAs and their metabolites, it is reasonable to consider n-3 PUFAs as potential adjuvant therapies for the clinical management of COVID-19 patients. In this article, we provide an overview of the pathogenesis of cardiovascular complications secondary to COVID-19 and focus on the mechanisms that may contribute to the likely benefits of n-3 PUFAs and their metabolites.

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Abbreviations: AA, Arachidonic acid; ACE, Angiotensin converting enzyme; ALA, α -Linolenic acid; ALI, Acute lung injury; ARB, Angiotensin II receptor blocker; ARDS, Acute respiratory distress syndrome; Ang, Angiotensin; COVID-19, Coronavirus disease 2019; COX, Cyclooxygenase; CRP, C-reactive protein; CYP, Cytochrome P450; CVD, Cardiovascular disease; DHA, Docosahexaenoic acid; EDP, Epoxydocosapentaenoic acid; EEQ, Epoxyeicosatetraenoic acid; EPA, Eicosapentaenoic acid; GPR, G-protein coupled receptor; HF, Heart failure; HDHA, Hydroxydocosahexaenoic acid; HDL-c, High density lipoprotein cholesterol; ICU, Intensive care unit; IFN, Interferon; IL, Interleukin; LA, Linoleic acid; LPS, Lipopolysaccharide; LOX, Lipoxygenase; LT, Leukotriene; MERS-CoV, Middle East respiratory syndrome-related coronavirus; MI, Myocardial infarction; nCoVs, Novel coronaviruses; NF- κ B, Nuclear factor kappa-light-chain-enhancer of activated B cells; NLRP3, NOD, LRR and pyrin domains-containing protein 3; PG, Prostaglandin; PMN, Polymorphonuclear neutrophils; PPAR, Peroxisome proliferator-activated receptor; PUFA, Polyunsaturated fatty acid; RAAS, Renin-angiotensin aldosterone system; RNA, Ribonucleic acid; ROS, Reactive oxygen species; SARS-CoV, Severe acute respiratory syndrome coronavirus; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; SPM, Specialized pro-resolving mediators; TLR, Toll-like receptor; TNF- α , Tumor necrosis factor- α ; TX, Thromboxane.

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1. Introduction

The first outbreak of the novel coronaviruses was triggered by severe and acute respiratory syndrome coronavirus (SARS-CoV) in China in 2002, which was followed in 2012 by the Middle East respiratory syndrome-related coronavirus (MERS-CoV). Both SARS-CoV and MERS-CoV are infectious, lethal and accounted for thousands of deaths over the past two decades (de Wit, van Doremalen, Falzarano, & Munster, 2016; Zaki, van Boheemen, Bestebroer, Osterhaus, & Fouchier, 2012). The Coronavirus Study Group of the International Committee on Taxonomy of Viruses evaluated the novelty of the coronavirus responsible for the recent outbreak in 2019 (COVID-19) and formally considered it related to SARS-CoV, as they share about 79% nucleotide identity and accordingly named it as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or 2019-novel coronavirus (Coronaviridae Study Group of the International Committee on Taxonomy of, 2020; Ren et al., 2020; Zhou et al., 2020). The recent eruption of COVID-19 was first reported in Wuhan, Hubei Province, China in late December 2019 when a series of pneumonia cases of unknown cause were detected (Wang et al., 2020). Highly contagious, COVID-19 spread rapidly throughout China and most countries across the world. On March 11th, the spread of COVID-19 was declared by the World Health Organization as a global pandemic and by October 9, 2020, the cumulative number of diagnosed patients internationally was 36,577,872 with 1,062,677 global deaths (<https://coronavirus.jhu.edu/map.html>, 2020).

Coronaviruses infect both animals and humans affecting their respiratory, gastrointestinal, cardiovascular and central nervous systems (Cui, Li, & Shi, 2019). Consistently, SARS-CoV-2 primarily targets the lungs but it can affect many other organs and systems, including the kidneys, heart, blood vessels, gastrointestinal tract and brain (Wadman, Couzin-Frankel, Kaiser, & Maticic, 2020). Symptoms of COVID-19 are manifested as myalgia, fatigue, fever and dry cough, together with lower respiratory tract disease. In some cases, the severe progression of the disease leads to acute lung injury (ALI), acute respiratory distress syndrome (ARDS), respiratory failure, sepsis, heart failure (HF) and sudden cardiac arrest within a few days. Importantly, there is significant morbidity and mortality in the elderly and individuals with underlying health conditions (Chen et al., 2020; Huang et al., 2020). Although treatment with corticosteroids, antiviral therapy and mechanical respiratory support have been employed, there is still no specific treatment for COVID-19 and therefore supportive care is of paramount importance (Huang et al., 2020; Wu & McGoogan, 2020) (Table 1).

2. COVID-19 and cardiovascular complications

The correlation between pneumonia, an inflammatory condition of lung alveoli with a compromised ability for gas exchange, and cardiovascular complications has been well established (Cilli et al., 2018; Corrales-Medina et al., 2011). For example, patients with underlying cardiovascular disease are more likely to develop community-acquired pneumonia (Corrales-Medina et al., 2015) and about 8 to 25% of patients with community acquired pneumonia develop at least one cardiac complication during their hospital stay. The exaggerated cardiovascular episodes after pneumonia have been associated with increased mortality (Corrales-Medina et al., 2012; Viasus et al., 2013). In line with these observations, cardiac complications have been reported in patients with novel coronavirus infections such as tachycardia and hypotension, which are common in SARS patients.

Moreover, arrhythmia, cardiomegaly and diastolic dysfunction have been reported in SARS patients (Li et al., 2003; Yu et al., 2006). In addition, infection with MERS-CoV was associated with acute myocarditis, myocardial edema and severe left ventricular dysfunction (Alhagbani, 2016).

In the context of COVID-19, both patients with and without underlying cardiovascular comorbidities can develop cardiovascular complications secondary to SARS-CoV-2 infection. For example, Wang et al., reported that among 138 hospitalized patients with COVID-19 in Wuhan, China, cardiac injury, as evidenced by new ECG or echocardiographic abnormalities or elevated high-sensitivity cardiac troponin I, was present in 7.2% of all patients and 22% of patients who required intensive care unit (ICU) hospitalization (Wang, Hu, et al., 2020). Moreover, the National Health Commission of China reported that 12% of patients infected with SARS-CoV-2 and without known cardiovascular disease (CVD) had elevated troponin levels or cardiac arrest during hospitalization, 17% had coronary heart disease and 35% of patients had hypertension (Zheng, Ma, Zhang, & Xie, 2020; Zhou et al., 2020). However, there is accumulating evidence that COVID-19 patients with underlying CVD are at higher risk for developing severe complications (Huang et al., 2020; Wang, Hu, et al., 2020). For instance, older patients with underlying CVD who are infected with SARS-CoV-2 are more prone to become severely ill, develop cardiac injury or require intensive care (Guo et al., 2020; Shi et al., 2020). The death rate among patients with underlying CVD has been stated as 10.5%, which is much higher than that of the general population (Epidemiology Working Group for Ncip Epidemic Response & Prevention, 2020; Wu & McGoogan, 2020). Furthermore, according to an epidemiological study conducted in China, 4.2% of the confirmed cases and 22.7% of mortalities have cardiovascular comorbidities (Epidemiology Working Group for Ncip Epidemic Response & Prevention, 2020). Many COVID-19 patients suffer from persistent hypotension, myocardial injury, myocarditis, left ventricular dysfunction, arrhythmia and HF (Guan, et al., 2020; Guo et al., 2020; Inciardi et al., 2020; Zhou, Yu, et al., 2020). Importantly, cardiac biopsy samples collected from patients with COVID-19 demonstrated increased interstitial infiltration of mononuclear inflammatory cells providing extra evidence of myocarditis in COVID-19 patients (Xu et al., 2020). Therefore, cardiovascular damage secondary to COVID-19 is now drawing growing attention in clinical practice (Table 2) and the American College of Cardiology recently issued a clinical report to address the cardiovascular consequences of SARS-CoV-2 infection (Mohammad Madjid et al., 2020).

3. Potential mechanisms of cardiovascular complications in COVID-19 patients

To date, there have been few reports about the pathologic features of COVID-19 and consequently the exact pathophysiological mechanisms of myocardial injury secondary to COVID-19 remain elusive. However, direct damage by the virus, exaggerated uncontrolled inflammatory responses, instability of coronary plaques, thrombosis and hypoxia have been proposed as possible mechanisms (Guo et al., 2020; Zheng et al., 2020; Zhou, Yu, et al., 2020). Importantly, the severity of infection, patient characteristics and host reaction all participate in the development of cardiac complications. The main proposed mechanisms for cardiovascular deterioration in patients with COVID-19 can be summarized as follows (Fig. 1).

Table 1
Overview of some proposed pharmacological agents with potential beneficial effects in COVID-19 patients.

Pharmacological intervention	Conclusion	Reference
Antioxidants including Vitamin C and E	<ul style="list-style-type: none"> Antioxidant effects may ameliorate cardiac injuries of critically ill COVID-19 patients 	(Wang, Zhang, & Bai, 2020)
Melatonin	<ul style="list-style-type: none"> May have preventive effect against septic cardiomyopathy Has benefits in myocardial infarction, cardiomyopathy, hypertensive heart diseases, and pulmonary hypertension 	(Zhang et al., 2020)
Anti-interleukin-6	<ul style="list-style-type: none"> Tocilizumab (anti-IL-6 receptor), siltuximab (anti-IL-6), and sirukumab (anti-IL-6) are proposed as possible treatments to manage cytokine storm and elevated IL-6 levels 	(Akhmerov & Marban, 2020; Hendren, Drazner, Bozkurt, & Cooper Jr., 2020; Rizk et al., 2020)
Anti-TNF α	<ul style="list-style-type: none"> Infliximab, adalimumab, etanercept, golimumab, certolizumab as TNFα neutralizing therapies suggested as potential agents for COVID-19 hyperinflammatory state which may ameliorate organ damage including acute cardiac injury 	(Convertino et al., 2020)
Janus kinase (JAK) inhibitors	<ul style="list-style-type: none"> Ruxolitinib, tofacitinib, baricitinib are proposed to be beneficial in controlling excessive IL-6 signaling through STAT-1 and STAT-3 pathways 	(Alijotas-Reig et al., 2020; Convertino et al., 2020; Richardson et al., 2020; Rizk et al., 2020)
Anti-interleukin-1	<ul style="list-style-type: none"> Anakinra, a modified IL-1 receptor antagonist protein, is suggested to have therapeutic potential in cytokine storm, given its effectiveness on patient survival in severe sepsis 	(Alijotas-Reig et al., 2020; Rizk et al., 2020)
Granulocyte-macrophage-colony stimulating factor (GM-CSF) inhibition	<ul style="list-style-type: none"> GM-CSF can play a pro-inflammatory role signaling to macrophages COVID-19 patients have been demonstrated to have elevated GM-CSF levels Literature proposes that targeting GM-CSF upstream of inflammatory cytokines ex. gimsilumab, may be useful to blunt cytokine storm 	(Rizk et al., 2020)
Statins	<ul style="list-style-type: none"> Anti-inflammatory properties, including reduction in cytokines, may benefit in COVID-19 hyperinflammatory states in addition to their conventional cardioprotective properties 	(Alijotas-Reig et al., 2020; Rizk et al., 2020)

Table 1 (continued)

Pharmacological intervention	Conclusion	Reference
ACEi/ARBs	<ul style="list-style-type: none"> Proposed that treatment with RAAS antagonists may theoretically be beneficial by upregulating ACE2 and compensating for ACE2 receptors lost due to COVID-19 	(Akhmerov & Marban, 2020)
N-acetylcysteine (NAC)	<ul style="list-style-type: none"> Anti-oxidant and anti-inflammatory properties of NAC proposed as an adjuvant therapy for COVID-19 and secondary cardiovascular complications Suggested role for NAC in prevention of hypertension, atherosclerosis--associated inflammation, acute heart failure, thrombo--inflammation, and myocardial ischemia 	(De Flora, Balansky, & La Maestra, 2020; Guglielmetti et al., 2020)
Eicosanoids and soluble epoxide hydrolase (sEH) inhibitors	<ul style="list-style-type: none"> Epoxyeicosatrienoic acids (EETs) are cardioprotective, anti-inflammatory and pro-resolving Inhibition of their metabolizing enzyme, sEH, may be beneficial by maintaining eicosanoid levels and reducing endoplasmic reticulum (ER) stress Potential to limit inflammatory storm and resolve inflammation in addition to their established cardioprotective properties Co-treatment with sEH inhibitors and omega-3 fatty acids may provide synergistic effects 	(Hammock, Wang, Gilligan, & Panigrahy, 2020)

3.1. Direct pathogen invasion

Direct invasion of pathogens to the cardiac tissue has been confirmed in patients with severe pneumonia. For example, *Streptococcus pneumoniae* was identified in the myocardium of patients with severe pneumococcal disease, leading to local inflammatory reactions and consequently cardiac injury (Xu, Shi, et al., 2020). Oudit et al. reported SARS-CoV RNA was detected in 35% (7/20) of autopsied human heart samples obtained from SARS patients during the Toronto SARS outbreak, suggesting the likelihood of direct damage to cardiomyocytes by the virus (Oudit et al., 2009). In the same report, a study in mice infected with the human strain of the SARS-CoV demonstrated that pulmonary infection with SARS-CoV also precipitated myocardial infection (Oudit et al., 2009). As SARS-CoV-2 is genetically related to SARS-CoV, there is a high potential that it shares a similar mechanism and the same functional host-cell receptor, angiotensin-converting enzyme 2 (ACE2) for cell entry (Gheblawi et al., 2020). Importantly, ACE2 is highly expressed in both the heart and the lung (Patel, Zhong, Grant, & Oudit, 2016) and evidence indicates the affinity of SARS-CoV-

Table 2
Overview of COVID-19-associated cardiovascular complications.

COVID-19-induced cardiovascular injury	Proposed mechanism of injury
<ul style="list-style-type: none"> Acute myocarditis 	<ul style="list-style-type: none"> Direct pathogen invasion Indirect cytokine storm
<ul style="list-style-type: none"> Instability of coronary atherosclerotic plaques Coagulopathy Acute MI Hypertension Left ventricular dilation, hypertrophy and dysfunction Arrhythmias (long QT-syndrome, torsade de pointes) Worsening of heart failure 	<ul style="list-style-type: none"> Indirect inflammatory response (Cytokine storm) Volume overload due to impaired sodium and water metabolism Disturbance of endothelial function Hypoxemia Activation of the NLRP3 inflammasome Pneumonia-induced increase in sympathetic activity
<ul style="list-style-type: none"> Pyroptosis of cardiomyocytes 	
<ul style="list-style-type: none"> Severe tachycardia, increased peripheral resistance, hypertension, increased myocardial oxygen requirements and ischemia 	

2 to ACE2 is approximately 10- to 20-fold higher than that for SARS-CoV-2 which may account for both the greater pathogenicity of SARS-CoV-2 and the rapid spread (Gheblawi et al., 2020; Hoffmann et al., 2020). Altogether, SARS-CoV-2 might directly infect the myocardial tissue leading to severe cardiac injury (Wu et al., 2020). However, large-scale biopsy studies are still warranted to further confirm the direct myocardial infection by SARS-CoV-2.

3.2. Indirect inflammatory response - cytokine storm

Inflammation plays an important role in the development of cardiovascular impairment in the setting of COVID-19. Similar to SARS-CoV and MERS-CoV infection, SARS-CoV-2 infection can also trigger excessive host immune responses, leading to extensive and uncontrolled release of proinflammatory cytokines termed as cytokine storm (Restrepo & Reyes, 2018; Zumla, Hui, Azhar, Memish, & Maeurer, 2020). Cytokines play a pivotal role in the immune response to defend against different bacterial and viral infections. However, it has also been established that dysregulated, amplified and uncontrolled immune responses may cause immunopathology leading to systematic self-attack contributing to multiple organ damage and cardiovascular injury secondary to SARS-CoV-2 infection (Zhang et al., 2020). A plethora of studies have shown increased amounts of cytokines, such as interleukin-6 (IL-6), IL-7, IL-8, IL-9, IL-10, IL-1 β , IL-1RA, tumor necrosis factor-alpha (TNF- α), granulocyte-macrophage colony-stimulating factor, fibroblast growth factor, macrophage inflammatory protein 1 alpha, platelet-derived growth factor, monocyte chemoattractant protein and vascular endothelial growth factor in the serum of COVID-19 patients, especially in ICU patients (Chen, Zhou, et al., 2020; Conti et al., 2020; Huang et al., 2020; Wang, Hu, et al., 2020; Zhang, Zhao, Zhang, et al., 2020). Importantly, there is a strong correlation between serum cytokine levels and mortality rates in patients with COVID-19. The amplified and uncontrolled inflammatory response induces cellular apoptosis or necrosis of the affected cells. This is followed by increased permeability of blood vessels leading to the accumulation of inflammatory monocytes, macrophages and neutrophils in different body organs fueling the inflammatory cascade (Channappanavar et al., 2016). The vicious circle intensifies the situation as the cytokine storm is further stimulated and the regulation of immune response is lost resulting in severe consequences. Collectively, this indicates the uncontrolled inflammatory

response is a major factor in the adverse response observed in COVID-19 patients. In that sense, it would seem reasonable that ameliorating the exaggerated immune response would improve the clinical outcomes in patients with COVID-19 (Table 3).

The innate immune system detects viral infections by using pattern recognition receptors, particularly Toll-like receptors (TLR), to recognize pathogen-associated molecular patterns of the virus including lipids, lipoproteins, proteins and nucleic acids (Li et al., 2020). Activation of the TLR increases the expression of the transcription factors nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B), interferon (IFN) regulatory factor 3 and mitogen-activated protein kinases, which subsequently induce the expression of a myriad of inflammatory factors (Akira, 2009). For example, the binding of SARS-CoV-2 to TLR activates the NF- κ B inflammatory pathway triggering the transcription of the different components of the NLRP3 (NOD-, LRR-, and pyrin domain-containing 3) inflammasome (Chen, Moriyama, Chang, & Ichinohe, 2019; Siu et al., 2019). The NLRP3 inflammasome is a large multiple protein platform consisting of main 3 components, the NLRP3 scaffold, the adapter component apoptosis-associated speck-like protein carrying a caspase activation and recruitment domain and the inactive zymogen procaspase-1 (Elliott & Sutterwala, 2015; Latz, Xiao, & Stutz, 2013). Upon activation of the NLRP3 inflammasome and once assembled, procaspase-1 is converted into the active effector protease caspase-1, which then causes cleavage and maturation of proinflammatory cytokines pro-interleukin-1 β (pro-IL-1 β) and pro-IL-18 into their corresponding active forms, inflammatory IL-1 β and IL-18. This, in turn, triggers a cascade of other downstream mediators of inflammation such as TNF- α , IL-6, prostaglandins and leukotrienes which induces more tissue damage, fever, and fibrosis (Conti et al., 2020; Yue et al., 2018). Based on the robust inflammatory response triggered by the NLRP3 inflammasome cascade, targeting the pathway has potential therapeutic value, which can reduce the detrimental consequences of uncontrolled inflammation from SARS-CoVs infections.

Inflammation is well known to participate in various CVDs, such as atherosclerosis, coagulopathy, coronary artery disease and HF (Libby, Ridker, & Maseri, 2002). In the majority of severe cases of COVID-19, the cytokine storm has been coupled with elevated levels of erythematous sedimentation rate and C-reactive protein (CRP). Subsequently, hypercoagulation and disseminated intravascular coagulation would present as thrombosis, thrombocytopenia and gangrene of the limbs (Siddiqi & Mehra, 2020; Zhang, Zhao, Zhang, et al., 2020). The identification of key cytokines such as TNF α in patients with HF demonstrated a strong positive correlation between cytokines and the severity of left ventricular dilation/hypertrophy and left ventricular dysfunction (Dibbs et al., 2003; Janczewski et al., 2003). Other evidence indicates increased IL-1 β and IL-6 levels detected in patients with acute myocarditis and acute MI (Xu, Shi, et al., 2020). Increased IL-6 levels have been associated with long QT-syndrome in patients with systemic inflammation, leading to higher risks for arrhythmias such as torsade de pointes (Aromolaran et al., 2018). As well, the level of IL-6 can be used as a predictor of adverse cardiovascular events after acute coronary syndrome and chronic HF (Fanola et al., 2017; Held et al., 2017). The serum levels of IL-8 are increased in patients with acute MI and is associated with higher mortality rates (Cavusoglu et al., 2015). Collectively, we can conclude there is a strong correlation between elevated inflammatory markers and the adverse cardiovascular outcomes observed in patients with COVID-19 suggesting the potential role of an inflammatory storm in the development and progression of cardiac injury.

Importantly, it has been reported that populations at high risk to develop the more severe forms of cardiac complications secondary to COVID-19 are patients with advanced age, obesity, metabolic syndrome, hypertension and diabetes. These conditions share a common feature where immune changes favour a hyperinflammatory state and compromised inflammatory resolution (Bruunsgaard & Pedersen, 2003; Goldstein, 2010; Lawrence & Gilroy, 2007; Rius et al., 2012). Therefore, traditional cardiovascular treatment plus anti-inflammatory therapy

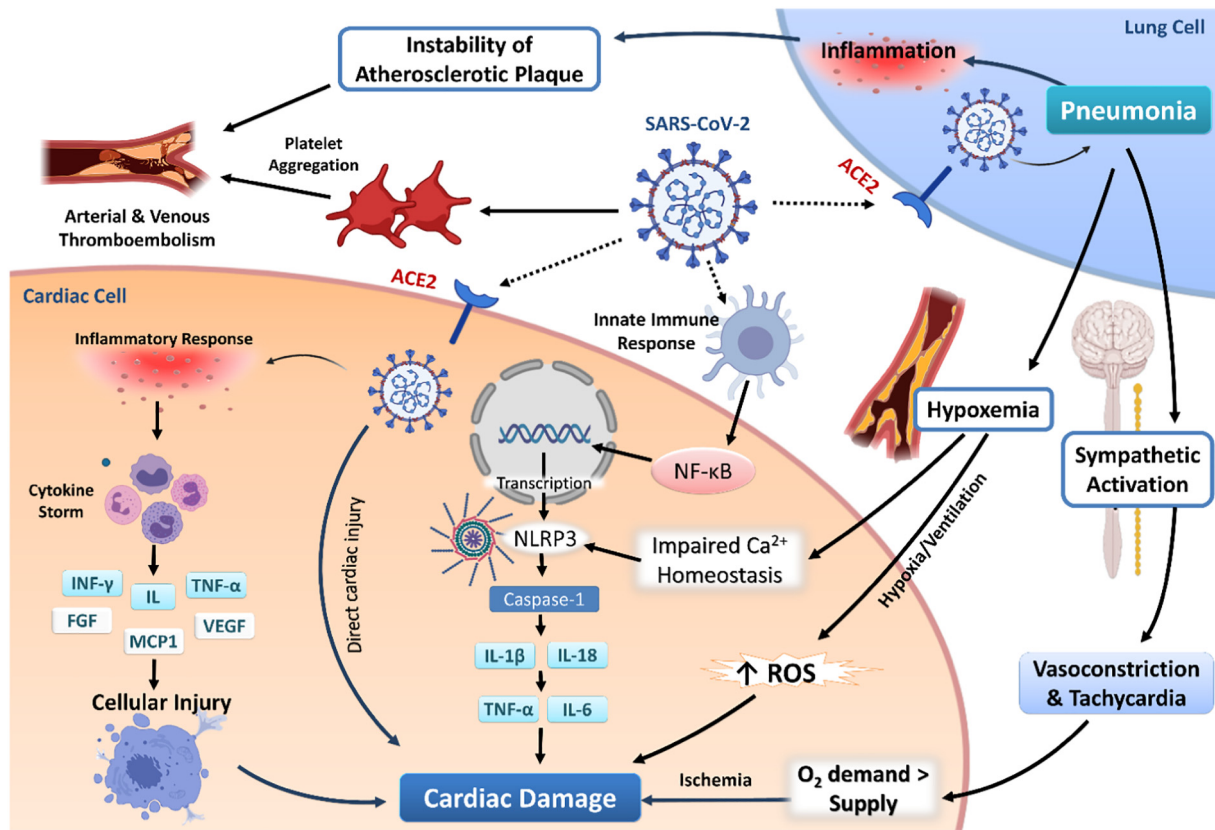


Fig. 1. Potential mechanisms of SARS-CoV-2-induced cardiovascular complications. SARS-CoV-2 may be taken up by cardiac cells using different routes, such as via ACE2 receptors expressed on the cell surface. Following entry, SARS-CoV-2 may exert cardiac injury by direct action and/or induction of immune responses resulting in release of pro-inflammatory cytokines ("Cytokine storm") such as IL, TNF- α , INF- γ , FGF, MCP1 and VEGF. SARS-CoV-2 can trigger the innate immune response involving NLRP3 inflammasomes which lead to activation of pro-inflammatory cytokines, IL-1 β and IL-18 and the inflammatory cascade (IL-6 and TNF- α) resulting in tissue damage and fibrosis. SARS-CoV-2-induced pneumonia results in the development of hypoxemia which can impair Ca²⁺ homeostasis, increase ROS production and activate NLRP3 inflammasomes leading to cardiac damage. Activation of the sympathetic nervous system in response to pneumonia leads to vasoconstriction and tachycardia compromising coronary perfusion. This results in a mismatch of myocardial O₂ demand and supply precipitating ischemia. SARS-CoV-2 can destabilize coronary atherosclerotic plaques and mediate platelet aggregation resulting in arterial and venous thrombosis. Altogether, these SARS-CoV-2 mediated effects may be contributing to the observed cardiovascular injury. ACE2, Angiotensin-converting enzyme-2; Ca²⁺, Calcium; FGF, Fibroblast growth factor; IL, Interleukin; INF, Interferon; MCP-1, Monocyte chemoattractant protein-1; NF- κ B, Nuclear factor kappa-light-chain enhancer activated B-cells; NLRP3, NACHT, LRR and PYD domains-containing protein 3; O₂, Oxygen; ROS, Reactive oxygen species; SARS-CoV-2, Severe and acute respiratory syndrome coronavirus; TNF- α , Tumor necrosis factor- α ; VEGF, Vascular endothelial growth factor.

targeting key steps and components of the cytokine storm could be hypothesized as a therapeutic strategy and management of cardiovascular impairment in severe cases of COVID-19. As the inflammatory response in different organs share common pathways, ameliorating the systematic inflammatory response will benefit the cardiovascular system and have potential advantages for other organs.

3.3. Miscellaneous mechanisms

Other proposed mechanisms of COVID-19-associated cardiovascular impairment include instability of coronary atherosclerotic plaques (Madjid, Vela, Khalili-Tabrizi, Casscells, & Litovsky, 2007) and increased platelet-aggregating activity (Modica, Karlsson, & Mooe, 2007) leading to excessive and uncontrolled coagulation and thrombosis (Milbrandt et al., 2009). The systemic inflammatory response to pneumonia induces endothelial dysfunction, increases the procoagulant activity of the blood and consequently triggers inflammatory reactions within coronary atherosclerotic plaques, making them unstable and susceptible to rupture. Together, this contributes to the formation of an occlusive thrombus over a ruptured coronary plaque. It is documented that COVID-19 patients are prone to arterial and venous thromboembolisms due to hypoxia, excessive inflammation and diffuse intravascular coagulation. In a Dutch study of 184 ICU patients with proven COVID-19 pneumonia, one-third of patients exhibited blood clots and thrombotic

complications. These findings, consequently, reinforced the recommendation to use antiplatelets and other pharmacological thrombosis prophylaxis drugs in all COVID-19 patients (Klok et al., 2020) (Table 4).

A 12-year follow-up study conducted by Wu et al. of 25 patients who recovered from SARS-CoV infection demonstrated patients were affected by various metabolic disturbances altering lipid metabolism and the cardiovascular system. These patients suffered from hyperlipidemia, increased serum concentrations of free fatty acids, abnormal glucose metabolism and other cardiovascular abnormalities (Wu et al., 2017). Considering the genetic similarities between SARS-CoV and SARS-CoV-2, Zhang et al. recently proposed the use of the lipid-lowering statins, which also possess anti-inflammatory properties, as a therapeutic option for patients with COVID-19. This study reported that amongst 13,981 cases of COVID-19, in-hospital use of statins was associated with a lower risk of death and a significantly lower inflammatory response during the entire hospitalization period (Zhang et al., 2020). Thus, suggesting the use of lipid-lowering drugs with anti-inflammatory properties can improve the cardiovascular outcomes in patients with COVID-19.

COVID-19 patients are susceptible to hypoxemia due to reduced lung performance, impaired gas exchange across the inflamed alveoli and abnormal ventilation/perfusion. This will lead to decreased myocardial oxygen supply, myocardial ischemia and impaired calcium homeostasis. The disturbance in calcium balance will trigger the activation of

Table 3

Overview of the pharmacological approaches under investigation for ameliorating cytokine storm, hyperinflammatory state and the associated secondary organ complications in COVID-19 patients.

Pharmacological intervention	Sample size and criteria	Treatment protocol	Key findings	Conclusion	Reference
• Tocilizumab for IL-6 cytokine release syndrome	<ul style="list-style-type: none"> Multicenter Randomized controlled trial (RCT) Severe COVID-19 infections 18–85 years of age Elevated serum IL-6 N = 94 standard therapy + tocilizumab N = 94 standard therapy 	<ul style="list-style-type: none"> 4–8 mg/kg tocilizumab i.v. once Additional dose if fever persists in 24 h after first dose 	<ul style="list-style-type: none"> First phase showed normalization of fever within 24 h of tocilizumab Improved respiratory function, oxygenation, and pulmonary lesions 	<ul style="list-style-type: none"> Phase 4 study completed in May 2020 Results pending Tocilizumab may be a promising investigative therapy to reduce cytokine release syndrome and associated multi-organ damage 	(ChiCTR2000029765, 2020)
• Tocilizumab to mitigate cytokine storm and associated complications	<ul style="list-style-type: none"> Retrospective cohort study >18 years of age Intensive care unit (ICU) COVID-19 hospitalization Primary endpoint of hospital-related mortality N = 210 standard care + tocilizumab N = 420 standard care 	<ul style="list-style-type: none"> 400 mg single dose or 8 mg/kg tocilizumab 88% required 1 infusion, 12% received a second infusion 	<ul style="list-style-type: none"> Hazard ratio (HR) 0.71 for hospital related mortality (95% confidence interval (CI) 0.56–0.89) Treatment was more effective in patients with C-reactive protein (CRP) >15 mg/dL HR 0.48 (95% CI 0.30–0.77) than those with CRP <15 mg/dL HR 0.92 (95% CI 0.57–1.48) 	<ul style="list-style-type: none"> Tocilizumab treatment is associated with a lower rate of mortality, particularly in those with enhanced inflammatory state Double blind RCT recently completed with results pending NCT04320615 	(Biran et al., 2020)
• Tocilizumab to mitigate cytokine storm	<ul style="list-style-type: none"> Prospective observational study Severe or critical COVID-19 infection 25 to 88 years of age N = 210 tocilizumab + standard therapy 42.9% had CVD 	<ul style="list-style-type: none"> 4–8 mg/kg or 400 mg tocilizumab i.v. once 85.7% received single dose of tocilizumab, 14.3% required second dose within 12 h of first dose 	<ul style="list-style-type: none"> Fever normalized within 24 h Reduced O₂ therapy requirements Minimal improvement in IL-6 levels CT lung lesion improvement All patients discharged 	<ul style="list-style-type: none"> Limited sample size and no control group Tocilizumab treatment in severe COVID-19 cases may improve clinical symptoms in hyperinflammatory state 	(Xu et al., 2020)
• Intensive methylprednisolone regimen +/- tocilizumab for management of cytokine storm	<ul style="list-style-type: none"> Prospective observational study O₂ sat ≤ 94% OR tachypnea, elevated CRP, high D-dimer Primary outcome of hospital discharge or clinical improvement N = 86 methylprednisolone +/- tocilizumab N = 86 standard care 	<ul style="list-style-type: none"> Stage 1: Immediate methylprednisolone 250 mg i.v. on day 1, then 80 mg on days 2–5 Stage 2 (lack of clinical improvement or worsening respiratory status): Add tocilizumab 8 mg/kg i.v. once between days 2–5 	<ul style="list-style-type: none"> Improvement in respiratory status HR 1.79 (95% CI 1.20–2.67) Improvement reached in a shorter time vs. control Reduced hospital mortality and need for mechanical ventilation 	<ul style="list-style-type: none"> Short duration of intensive immunosuppressive therapy is associated with improved clinical outcomes in patients with hyperinflammatory state 	(Ramiro et al., 2020)
• Ruxolitinib treatment for elevated cytokine levels and inflammatory response	<ul style="list-style-type: none"> Prospective RCT 18 to 75 years of age with severe infection Primary outcome of time to clinical improvement N = 20 ruxolitinib + standard care N = 21 placebo + standard care 	<ul style="list-style-type: none"> Ruxolitinib 5 mg twice daily Placebo vitamin C 100 mg twice daily 	<ul style="list-style-type: none"> No difference in primary endpoint HR 1.669 (95% CI 0.836–3.335) Improvement in lung computerized tomography (CT) scans Significantly reduced cytokine levels and CRP by day 3 	<ul style="list-style-type: none"> Ruxolitinib may hasten time of chest CT scan improvement and mitigate systemic inflammation 	(Cao et al., 2020)
• Anakinra for targeting the cytokine inflammatory cascade through IL-1 blockade	<ul style="list-style-type: none"> Open label case series Elevated CRP N = 9 6/9 with CVD risk factors (diabetes, obesity) 3/9 with hypertension 	<ul style="list-style-type: none"> Anakinra 100 mg every 12 h s.c. on days 1–3 Anakinra 100 mg once daily s.c. on days 4–10 	<ul style="list-style-type: none"> Fever subsided by day 3 CRP normalized in 5 patients by day 11 Halted progression of CT lung lesions 100% survival Significantly reduced need for 	<ul style="list-style-type: none"> Small case series, potential for confounding factors Potential therapy to target inflammatory cascade Positive results in patients with hypertension and other CVD risk factors 	(Aouba et al., 2020)
• Ana-COVID study • Anakinra for	<ul style="list-style-type: none"> Prospective/retrospective cohort study 	<ul style="list-style-type: none"> Anakinra 100 mg s.c. twice daily for 3 days 	<ul style="list-style-type: none"> Significantly reduced need for 	<ul style="list-style-type: none"> Anakinra may be associated with improved outcomes in patients 	(Huet et al., 2020)

Table 3 (continued)

Pharmacological intervention	Sample size and criteria	Treatment protocol	Key findings	Conclusion	Reference
COVID-19 hyperinflammatory state	<ul style="list-style-type: none"> Hospitalized adults with critical lung function Cohort with CVD (hypertension, stroke, cardiopathy) Primary outcome of ICU admission with mechanical ventilation or death N = 52 anakinra + standard care N = 44 standard care 	<ul style="list-style-type: none"> Then anakinra 100 mg s.c. once daily for 7 days 	mechanical ventilation or death HR 0.22 (0.11–0.41)	<ul style="list-style-type: none"> with severe COVID-19 infection, including those with CVD and history of cardiovascular events May be due to mitigation of inflammatory cascade 	

the NLRP3 inflammasome and different inflammatory components which consequently lead to the death of cardiomyocytes (Moccia et al., 2020; Zheng et al., 2020). Additionally, the systemic response to pneumonia includes an increase in sympathetic activity causing severe tachycardia and increased peripheral resistance. Subsequently, a rapid heart rate together with vasoconstriction may result in elevated myocardial oxygen requirements and a shortened diastolic interval, the period during which coronary perfusion occurs. The mismatch between myocardial oxygen demand and supply can lead to cardiac ischemia and infarction, especially in the presence of pre-existing coronary artery disease (Corrales-Medina, Musher, Shachkina, & Chirinos, 2013). Volume overload due to impaired sodium and water metabolism

(Dreyfuss, Leviel, Paillard, Rahmani, & Coste, 1988), transient disturbance of endothelial function and vascular tone (Benson, Akbarian, Adler, & Abelmann, 1970; Kumar, Wallace, Ramirez, Benson, & Abelmann, 1970) and cardiac arrhythmias (Cilli et al., 2018) may also contribute to decreased left ventricular function or worsening of HF in patients with COVID-19.

Collectively, these effects can all result in the aggravation of existing CVDs and trigger severe events, such as acute coronary syndromes, thrombosis, myocardial ischemia or exacerbation of HF. Indeed, cardiovascular protective strategies are needed for the prevention and management of severe adverse cardiovascular events to improve the prognosis of COVID-19 patients (Tables 5 and 6).

Table 4

Overview of the pharmacological interventions under investigation targeting hypercoagulability and platelet activation in COVID-19 patients.

Pharmacological intervention	Sample size and criteria	Treatment protocol	Key findings	Conclusion	Reference
• Heparin anticoagulant treatment in sepsis-induced coagulopathy	<ul style="list-style-type: none"> Retrospective cohort study ≥ 18 years of age Severe COVID-19 infection Evaluation of 28-day mortality in heparin and non-heparin users 48.5% comorbid hypertension and/or heart disease N = 99 heparin N = 350 no heparin 	<ul style="list-style-type: none"> Unfractionated (10,000–15,000 U/day) or low molecular weight heparin (40–60 mg enoxaparin/day) for 7 days or longer 	<ul style="list-style-type: none"> No difference in 28-day mortality endpoint between heparin and non-heparin users. Lower 28-day mortality in patients with sepsis-induced coagulopathy (SIC) score of ≥4 in stratified analysis Odd Ratio (OR) 0.372 (95% CI 0.154–0.901) 	<ul style="list-style-type: none"> Heparin may be associated with a lower 28-day mortality rate only in patients with enhanced coagulopathy risk such as SIC score of 4 or greater 	(Tang, Bai, et al., 2020)
• Antiplatelet and anticoagulant combination therapy for hypoxemia, respiratory failure, and cardiac adverse events	<ul style="list-style-type: none"> Case control, proof-of-concept study Adult patients with hypoxemic respiratory failure N = 5 ASA + clopidogrel + tirofiban + fondaparinux + standard care N = 5 matched controls given low molecular weight heparin Secondary outcome included major and minor cardiac adverse events 	<ol style="list-style-type: none"> Single dose of acetylsalicylic acid (ASA) 250 mg i.v. and single loading dose of oral clopidogrel 300 mg ASA and clopidogrel continued at 75 mg orally for 30 days Tirofiban 25 µg/kg as bolus i.v. injection, then 0.15 µg/kg/min continuous i.v. infusion for 48 h Fondaparinux 2.5 mg/day s.c. for the duration of the hospital stay 	<ul style="list-style-type: none"> Significant improvement in alveolar--arterial oxygen gradient Significant improvement in CRP and lymphocyte count Patients in treatment group did not experience any cardiac adverse events 	<ul style="list-style-type: none"> Small study and not a randomized controlled trial (RCT) Intensive antithrombotic therapy may be useful in patients with severe respiratory distress with prothrombotic state at risk for acute cardiac events 	(Viecca, Radovanovic, Forleo, & Santus, 2020)

Table 5
Overview of proposed pharmacological approaches to attenuate COVID-19 associated cardiovascular injury.

Pharmacological intervention	Sample size and criteria	Treatment protocol	Key findings	Conclusion	Reference
• Colchicine for the improvement of cardiac biomarkers, inflammation, and clinical outcomes	<ul style="list-style-type: none"> • Prospective, open-label randomized controlled trial (RCT) • N = 55 colchicine + standard care • N = 50 standard care • Primary endpoints included maximum cardiac troponin level, time for C-reactive protein (CRP) to reach 3× upper limit normal, time to deterioration by at least 2 points on clinical status scale 	<ul style="list-style-type: none"> • Colchicine 1.5 mg loading dose, 0.5 mg after 60 min, and then 0.5 mg twice daily + standard care for up to 3 weeks 	<ul style="list-style-type: none"> • No difference in cardiac troponin or CRP levels • Clinical deterioration less common with colchicine treatment odd ratio (OR) 0.11 (95% CI 0.01–0.96) • Abdominal pain and diarrhea significantly more common with colchicine treatment 	<ul style="list-style-type: none"> • Colchicine may not have a significant effect on cardiac or inflammatory biomarkers, however it may be useful in stabilizing patients with severe COVID-19 infection and preventing clinical deterioration 	(Deftereos et al., 2020)
• Statin therapy and impact on inflammation and patient prognosis	<ul style="list-style-type: none"> • Retrospective cohort study • Primary endpoint of 28-day all-cause mortality • Secondary endpoint included acute cardiac injury • N = 1219 statin use • N = 12, 762 no statin 	<ul style="list-style-type: none"> • In-hospital statin use • Atorvastatin 83.2%, Rosuvastatin 15.6% • Dose differences between statins were converted to a daily equivalent dose of atorvastatin ranging from 18.9–20.0 mg/day 	<ul style="list-style-type: none"> • Reduced all-cause mortality with statin use hazard ratio (HR) 0.63 (95% CI 0.48–0.84) • Patients on ACEi/ARB therapy in addition to statin did not have increased mortality compared to statin alone • Statin therapy not associated with acute cardiac injury • Inflammatory markers CRP, IL-6 were lower in statin treated patients while in hospital 	<ul style="list-style-type: none"> • Reduced mortality and improved prognosis associated with in-hospital statin use may be due to the anti-inflammatory and immunomodulatory effects of statins 	(Zhang, Qin, Cheng, et al., 2020)
• ACEi/ARB impact on mortality in COVID-19 patients with comorbid hypertension	<ul style="list-style-type: none"> • Retrospective, multi-centre cohort study • Patients with comorbid hypertension hospitalized with COVID-19 • Age 18 to 74 years • Primary endpoint of 28-day all-cause mortality • N = 188 ACEi/ARB therapy • N = 940 no ACEi/ARB 	<ul style="list-style-type: none"> • ACEi/ARB for treatment of hypertension • individual patient dosing regimens not specified 	<ul style="list-style-type: none"> • Risk of all-cause mortality lower in ACEi/ARB treated group HR 0.42 (95% CI 0.19–0.92). • Use of ACEi/ARB in comparison to other anti-hypertension therapies was associated with lower mortality HR 0.30 (95% CI 0.12–0.70). • No difference in acute cardiac injury outcome between groups 	<ul style="list-style-type: none"> • Chronic ACEi/ARB therapy may not increase mortality of COVID-19 patients • May not have much benefit in acute heart injury due to COVID-19 inflammation 	(Zhang, Cai, et al., 2020)
• Statin use impact on acute myocardial injury patient outcomes	<ul style="list-style-type: none"> • Retrospective observational cohort study • Patients with elevated troponin • History of CVD in 24% of patients • N = 3069 • Objective to characterize myocardial injury and associated outcomes 	<ul style="list-style-type: none"> • 36% of patients using statins • Doses and regimens not specified 	<ul style="list-style-type: none"> • Statin use amongst patients with acute myocardial injury was associated with improved survival HR 0.57 (95% CI 0.47–0.69) 	<ul style="list-style-type: none"> • Statin treatment may be associated with a survival benefit in patients with CVD and elevated troponin levels • Exact beneficial mechanism(s) associated with statins in COVID-19 remain to be studied 	(Lala et al., 2020)

4. Adverse cardiovascular effects of the proposed empirical/supportive treatments

Currently, there is no approved vaccination or effective drug for protecting against or treating COVID-19; only symptomatic therapy and empirical/supportive treatments are available. Many of the mortalities related to COVID-19 have been primarily attributed to original patient comorbidities instead of pneumonia (Wang et al., 2020). This highlights the importance of focusing on pre-existing comorbidities of COVID-19 patients, particularly those of the cardiovascular system. Attention to therapies with cardiovascular side effects being proposed and applied to patients with COVID-19, especially those with underlying CVD is important. Notably, many of the therapies proposed to ameliorate the poor prognosis of COVID-19 patients are associated with cardiovascular adverse effects. For example, treatment of patients with COVID-19 with non-steroidal anti-inflammatory drugs, glucocorticoids and anti-viral agents, such as ribavirin, lopinavir/ritonavir, INF- α and the antibiotic azithromycin, could further increase the cardiovascular risk of COVID-19 patients.

Excessive use of non-steroidal anti-inflammatory drugs and glucocorticoids is associated with deleterious effects on the cardiovascular

system increasing the risk of events including, ischemia, MI, arrhythmias and HF (England, Thiele, Anderson, & Mikuls, 2018; Roubille et al., 2015). Although corticosteroids are sometimes prescribed for the treatment of patients with severe SARS-CoV infection for the possible relief of inflammation (Wong et al., 2004), recent evidence suggests corticosteroids may exacerbate lung injury associated with SARS-CoV-2 due to delayed viral clearance (Mehta, et al., 2020; Russell, Millar, & Baillie, 2020). The antiviral agents lopinavir and ritonavir have been tested in a randomized controlled, open-label trial in hospitalized adult patients with COVID-19 and concluded that no benefit was observed with lopinavir–ritonavir treatment beyond standard care. Moreover, about 14% of lopinavir–ritonavir recipients were unable to complete the full 14-day course of administration due primarily to the adverse events including the risks of QT prolongation (Cao et al., 2020). It is important to highlight that the adverse effects of these antivirals involve altering the cardiac electrical conduction system causing QTc and/or PR interval prolongation, which can lead to atrioventricular block and torsade de pointes arrhythmias increasing the risk of MI (Worm et al., 2010). Further, the use of these protease inhibitors can lead to metabolic disturbances such as hyperglycemia, hyperlipidemia and lipodystrophy, which may also contribute to adverse cardiovascular

Table 6

Summary of the ongoing trials investigating pharmacological agents targeting a cytokine storm and acute cardiac injury secondary to SARS-CoV-2 infection.

Pharmacological intervention	Sample size and criteria	Treatment protocol	Reference
<ul style="list-style-type: none"> TACTIC-E Trial Immunomodulatory agents 	<ul style="list-style-type: none"> Multi-arm randomized trial Pre-intensive care unit (ICU) COVID-19 patients Immunomodulatory drug EDP1815 vs. dapagliflozin + ambrisentan vs. standard care Primary outcome includes need for cardiovascular organ support 	<ul style="list-style-type: none"> EDP1815 as 2 capsules twice daily (1.6×10^{11} cells) for up to 7 days Dapagliflozin 10 mg + ambrisentan 5 mg once daily 	(NCT04393246, 2020)
<ul style="list-style-type: none"> High dose IV Vitamin C to ameliorate cytokine storm and associated organ dysfunction 	<ul style="list-style-type: none"> Prospective placebo controlled randomized controlled trial (RCT) N = 308 High dose i.v. vitamin C (HIVC) vs. placebo Primary outcome of ventilator-free days 	<ul style="list-style-type: none"> 12 g/50 ml vitamin C infusion 12 ml/h twice daily for 7 days vs. 50 ml sterile water for injection infused at 12 ml/h 	(Liu, Zhu, Zhang, Li, & Peng, 2020)
<ul style="list-style-type: none"> TOC-COVID Trial 	<ul style="list-style-type: none"> Prospective placebo controlled RCT N = 100 tocilizumab + standard treatment N = 100 placebo + standard treatment Primary outcome of ventilation-free days 	<ul style="list-style-type: none"> Tocilizumab 8 mg/kg single i.v. dose 	(Rilinger et al., 2020)
<ul style="list-style-type: none"> TACTIC-R Trial Immunomodulatory agents 	<ul style="list-style-type: none"> Randomized parallel 3-arm open label trial N = 125 Baricitinib N = 125 Ravulizumab N = 125 standard of care Primary outcome includes need for cardiovascular organ support 	<ul style="list-style-type: none"> Baricitinib 4 mg orally once daily on days 1–14 Ravulizumab single i.v. weight-based dose regimen 	(Kulkarni et al., 2020)
<ul style="list-style-type: none"> CytoResc Trial Cytokine storm in hyperinflammation and shock 	<ul style="list-style-type: none"> Prospective, open-label, pilot study 'CytoSorb' polystyrene-based hemoabsorber to adsorb circulating cytokines N = 40–50 'CytoSorb' N = 40–50 standard care Primary outcome is time to resolution of vasoplegic shock 	<ul style="list-style-type: none"> 'CytoSorb' therapy administered via a shaldon catheter for 3–7 days 	(Stockmann et al., 2020)
<ul style="list-style-type: none"> MelCOVID Trial 	<ul style="list-style-type: none"> Double blind placebo controlled RCT ICU COVID-19 patients N = 12 melatonin + standard of care N = 6 placebo control + standard care Secondary outcome includes CRP, IL-6 levels 	<ul style="list-style-type: none"> Melatonin 5 mg/kg/day i.v. divided every 6 h for 7 days Placebo dose of 5 mg/kg/day i.v. divided every 6 h for 7 days 	(Rodriguez-Rubio et al., 2020)
<ul style="list-style-type: none"> Siltuximab for patients diagnosed with severe respiratory complications due to COVID-19 Anti-IL-6 mitigation of cytokine storm 	<ul style="list-style-type: none"> Observational retrospective cohort study Cohort A: continuous positive airway pressure followed by siltuximab Cohort B: intubation followed by siltuximab Control group receiving continuous positive airway pressure or intubation only N = 220 Primary outcome of mortality over 30 days 	<ul style="list-style-type: none"> Detailed siltuximab dosing regimen not specified. Treatment procedure was based on clinicians judgement Study completed May 8, 2020. Results pending 	(NCT04322188, 2020)
<ul style="list-style-type: none"> COV-AID Trial Use of anti-interleukin agents for cytokine storm 	<ul style="list-style-type: none"> Phase 3 prospective RCT Patients with signs of cytokine storm N = 38 Anakinra alone (anti-IL-1 receptor) N = 76 Siltuximab alone (anti-IL-6) N = 38 Anakinra + siltuximab N = 76 Tocilizumab alone (anti-IL-6 receptor) N = 38 Anakinra + tocilizumab N = 76 standard care alone Primary outcome as time to clinical improvement 	<ul style="list-style-type: none"> Anakinra 100 mg s.c. daily for 28 days Siltuximab single i.v. infusion 11 mg/kg Tocilizumab single i.v. infusion 8 mg/kg max 800 mg 	(Maes et al., 2020)
<ul style="list-style-type: none"> Sarilumab for hospitalized COVID-19 infections Cytokine storm syndrome 	<ul style="list-style-type: none"> Phase 2/3 RCT Phase 2: Sarilumab in hospitalized patients regardless of disease severity vs. placebo Primary outcome of % change in CRP in patients with serum IL-6 > upper limit normal Phase 3 Cohort 1: Sarilumab in hospitalized critical infection receiving mechanical ventilation vs. placebo Cohort 2: Sarilumab in hospitalized infection receiving mechanical ventilation vs. placebo N = 1912 Primary outcome of at least 1 point improvement on 7 point clinical scale 	<ul style="list-style-type: none"> Phase 2: Low dose sarilumab i.v. Phase 2: Mid-dose sarilumab i.v. Phase 3 Cohort 1: Low dose sarilumab i.v. Phase 3 Cohort 1: Mid-dose sarilumab i.v. Phase 3 Cohort 2: High dose sarilumab i.v. Placebo given to match sarilumab administration 	(NCT04315298, 2020)
<ul style="list-style-type: none"> CORIMUNO-SARI Trial Sarilumab to mitigate enhanced IL-6 signalling 	<ul style="list-style-type: none"> RCT Moderate, severe, or critical COVID-19 pneumonia Sarilumab vs. standard of care N = 239 	<ul style="list-style-type: none"> Sarilumab 400 mg single i.v. infusion over 1 h on day 1 	(NCT04324073, 2020)
<ul style="list-style-type: none"> Baricitinib for hospitalized COVID-19 patients 	<ul style="list-style-type: none"> Non-randomized clinical trial Any adult patient hospitalized with moderate/severe COVID-19 Baricitinib + standard care vs. standard care alone Primary outcome of clinical status after 15 days 	<ul style="list-style-type: none"> Baricitinib 2 mg orally daily for 10 days 	(NCT04321993, 2020)
<ul style="list-style-type: none"> RUXCOVID Trial 	<ul style="list-style-type: none"> Phase 3 placebo-controlled RCT Patients age ≥ 12 with cytokine storm Ruxolitinib + standard care vs. placebo + standard care 	<ul style="list-style-type: none"> Ruxolitinib 5 mg orally twice daily for 14 days May extend treatment to 28 days 	(NCT04362137, 2020)

(continued on next page)

Table 6 (continued)

Pharmacological intervention	Sample size and criteria	Treatment protocol	Reference
<ul style="list-style-type: none"> Losartan (ARB) in patients hospitalized for COVID-19 	<ul style="list-style-type: none"> N = 402 randomized in 2:1 ratio treatment: placebo Phase 2 RCT Losartan vs. placebo + standard care N = 200 Secondary outcome includes cardiovascular organ failure/dysfunction 	<ul style="list-style-type: none"> Losartan 50 mg orally once daily 	(NCT04312009, 2020)
<ul style="list-style-type: none"> Losartan (ARB) in patients not requiring hospitalization for COVID-19 	<ul style="list-style-type: none"> Phase 2 RCT Losartan vs. placebo + standard care N = 500 Primary outcome of patients admitted to hospital within 15 days of randomization 	<ul style="list-style-type: none"> Losartan 25 mg orally once daily 	(NCT04311177, 2020)
<ul style="list-style-type: none"> Eicosapentaenoic acid (EPA) free fatty acid for hospitalized COVID-19 patients 	<ul style="list-style-type: none"> Phase 3 interventional trial Treatment with EPA gastro-resistant capsules vs. standard care 28-day treatment period Primary outcome of time to treatment failure i.e. need for additional therapy, intubation, transfer to ICU, or death Secondary outcome includes reduction of IL-6 levels 	<ul style="list-style-type: none"> Eicosapentaenoic acid free fatty acid (EPA-FFA) 1 g gastro-resistant capsules twice daily (2 g total) 	(NCT04335032, 2020)
<ul style="list-style-type: none"> COLCORONA Trial Colchicine and inflammatory cytokine storm 	<ul style="list-style-type: none"> Phase 3 multi-centre placebo-controlled randomized controlled trial (RCT) Age 40 years or older Patients must have at least one high-risk factor i.e. uncontrolled hypertension, HF, coronary artery disease (CAD), diabetes, obesity, etc. Colchicine vs. placebo 30-day treatment N = 6000 Primary composite endpoint of need for hospitalization or death 	<ul style="list-style-type: none"> Colchicine 0.5 mg orally twice daily for 3 days, then 0.5 mg once daily for 27 days Placebo will match colchicine administration 	(NCT04322682, 2020)

outcomes (Hill, Sawyer, & Gazzard, 2009; Tsiodras, Mantzoros, Hammer, & Samore, 2000). Recently, IFN- α 2b was used in an uncontrolled exploratory study including 77 hospitalized adults with confirmed COVID-19 in Wuhan, China (Zhou et al., 2020). The trial showed that treatment with IFN- α 2b markedly decreased the duration of detectable virus in the upper respiratory tract and also reduced the interval of the elevated inflammatory markers IL-6 and CRP in the blood. However, treatment with IFN- α has been associated with hypertension, hypertriglyceridemia and direct cardiotoxicities, including arrhythmias, MI and cardiomyopathy, which could exacerbate underlying cardiac dysfunction (Page 2nd et al., 2016). An open-label randomized trial has been conducted to test the efficacy of IFN beta-1b, lopinavir-ritonavir and ribavirin for treating patients admitted to hospital with COVID-19 and concluded early triple antiviral therapy was effective in alleviating symptoms and shortening the duration of hospital stay in patients with mild to moderate infections (Hung, et al., 2020). However, it is worth noting ribavirin has a US boxed warning issued for hemolytic anemia associated with use that may worsen underlying cardiac disease and lead to fatal and non-fatal MI (Durante-Mangoni et al., 2011). Numerous recent studies proposed the use of hydroxychloroquine and azithromycin as a treatment of COVID-19 in open-label non-randomized clinical trials, however, no positive results were produced (Arshad et al., 2020; Cavalcanti, et al., 2020; Gautret et al., 2020; Tang et al., 2020). Well known adverse effects associated with azithromycin or hydroxychloroquine include development of severe QT prolongation (Gibson et al., 2017), which worsened when azithromycin is combined with hydroxychloroquine to treat COVID-19 patients (Choi, Lim, Chung, Choi, & Yoon, 2018; Mercurio et al., 2020).

Currently, there are multiple *in vitro* experiments and preclinical studies being performed around the world to test novel COVID-19 therapies, which are quickly moving into clinical trials. Importantly, the early efficacy results have been limited to small-scale clinical studies in which the safety profiles have not been well-identified. The safety profiles will be critical for COVID-19 patients with underlying comorbidities such as cardiovascular dysfunction. Therefore, as there is a

need for rapid clinical translation and a wide use of novel therapies for COVID-19, continued attention to safety profiles is important. The rapid spread of COVID-19 globally continues to impact susceptible populations, like elderly patients and individuals with underlying comorbidities. While underlying cardiovascular issues are impacted by COVID-19 infection, many existing and novel therapeutic strategies have direct adverse cardiovascular effects, highlighting the importance for consideration in new drug research and development.

5. Overview of the n-3 polyunsaturated fatty acids

The long-chain n-3 polyunsaturated fatty acids (n-3 PUFAs) are essential fatty acids obtained from both dietary and non-dietary sources. The simplest n-3 PUFA is α -linolenic acid (ALA, 18:3 n-3). Once inside the body, ALA can be converted through a series of elongation and desaturation reactions into other n-3 PUFAs. For instance, ALA is metabolized into eicosapentaenoic acid (EPA, C20:5n-3) which can be further metabolized into docosahexaenoic acid (DHA, C22:6n-3), the two most abundant n-3 PUFAs in mammalian tissues (Wiktorowska-Owczarek, Berezinska, & Nowak, 2015). Mammals lack the necessary enzymes (δ -12 and δ -15 desaturase) required to synthesize ALA *de novo*. As such, these fatty acids are described as "essential" and must be obtained from the diet such as fish, other marine sources, plants or supplements (Burdge & Calder, 2015; Sprecher, 1981). Conversely, linoleic acid (LA, 18:2 n-6) is considered the primary source of the essential n-6 PUFAs. LA can be further metabolized into arachidonic acid (AA, 20:4n-6) by the same series of elongase and δ -4,-5,-6 desaturase enzymes. As n-3 PUFAs can compete for the same metabolic pathways with n-6 PUFAs, n-3 PUFAs supplementation may reduce the synthesis of n-6 PUFA-derived metabolites, thus, altering the metabolite profile and impacting numerous signaling pathways within the body, including the immune system, leading to disparate effects (Arterburn, Hall, & Oken, 2006).

6. Role of n-3 polyunsaturated fatty acids in patients with respiratory infections and/or sepsis

A plethora of human and animal studies have investigated the beneficial effects of EPA and DHA in patients with ALI and ARDS which are common characteristics observed in severe SARS-CoV-2 patients (Messina et al., 2020; Nelson et al., 2003; Shirai, Yoshida, Matsumaru, Toyoda, & Ogura, 2015; Singer et al., 2006). Mancuso et al. demonstrated Long-Evans rats fed enteral diets containing fish oil as a source of n-3 PUFAs for 21 days were subjected to acute inflammation caused by an intravenous injection of *Salmonella* endotoxin. N-3 PUFA fed rats had a lower severity of pulmonary microvascular protein permeability and decreased pulmonary neutrophil accumulation compared to rats fed the n-6 PUFA enriched diet (Mancuso et al., 1997a; Mancuso et al., 1997b). Furthermore, stimulated alveolar macrophages had lower concentrations of AA-derived metabolites, such as thromboxane B2 (TxB2) and prostaglandin E2 (PGE2) suggesting a beneficial effect of n-3 PUFAs over n-6 PUFAs in attenuation of ALI (Mancuso et al., 1997a; Mancuso et al., 1997b). Saedisomeolia et al. demonstrated in Calu-3 epithelial cells infected with Rhinovirus RV-43 and RV-1B that pre-incubating with DHA significantly reduced the release of IL-6 and IFN- γ -inducible protein, suppressing RV-induced inflammation (Saedisomeolia, Wood, Garg, Gibson, & Wark, 2009). Collectively, these studies demonstrate that the anti-inflammatory properties of n-3 PUFAs play a pivotal role in attenuating the uncontrolled immune response in the lungs secondary to bacterial or viral infections which could be helpful in the setting of COVID-19.

Clinical evidence from trials assessing the role of n-3 PUFAs in ameliorating ALI, ARDS and sepsis has been limited. Pontes-Arruda et al. investigated the effect of a diet enriched with EPA, γ -linolenic acid and antioxidants in patients with severe sepsis or septic shock who required mechanical ventilation (Pontes-Arruda, Aragao, & Albuquerque, 2006). The data suggested the diet contributed to improved ICU and hospital clinical outcomes and was associated with lower mortality rates when compared to the control groups. Meta-analysis reported a significant reduction in ventilator-free days, organ failures, length of stay in ICU, mortality rates as well as relevant improvements in oxygenation and clinical outcomes of ventilated patients with ALI/ARDS given EPA and γ -linolenic acid (Pontes-Arruda, Demichele, Seth, & Singer, 2008). The efficacy and safety of a diet supplemented with a high-dose EPA and DHA (9 g/d added to 1 g/d ascorbic acid, 400UI/12 h α -tocopherol and 100 μ g/d selenium) was assessed in patients with early-stage sepsis for 7 days. The investigators found patients had lower levels of CRP, IL-6 and procalcitonin, as well as less need for mechanical ventilation and reduced development of severe sepsis (Hosny, Nahas, Ali, Elshafei, & Khaled, 2013). Evidence for beneficial effects of n-3 PUFA-containing diets in patients with severe ARDS demonstrated similar outcomes such as reduced duration of mechanical ventilation, shorter ICU length and improved oxygenation (Langlois, D'Aragon, Hardy, & Manzanares, 2019). These effects are highlighted in a recent systematic review with a meta-analysis demonstrated critically ill patients receiving parenteral nutrition therapy enriched with fish oil lipid emulsion had reduced risk for infection and sepsis (40% and 56%, respectively) as well a reduction of hospital and ICU stay by about two days (Pradelli et al., 2020). Together, these studies demonstrate n-3 PUFA supplementation has favorable results in terms of multiple inflammatory, respiratory and clinical outcomes.

Recently, Bistrrian proposed the use of parenteral supplementation of fish-oil emulsions, containing substantial amounts of EPA and DHA (4–6 g/d), to treat patients with severe SARS-CoV-2, in order to inhibit cytokine secretion and mitigate the inflammatory response (Bistrrian, 2020). In agreement with this idea, Torrinhas et al. suggested the immune modulatory properties of n-3 PUFAs will provide important and beneficial effects to improve clinical outcomes of COVID-19 particularly in hospitalized high-risk populations with severe underlying conditions including the elderly, obese, hypertensive, oncologic and diabetic

patients (Torrinhas, Calder, & Waitzberg, 2020). Furthermore, they suggested n-3 PUFAs could provide additional benefits by attenuating the aggravated inflammatory state observed with pre-existing health conditions which might have a role in triggering detrimental outcomes associated with severe COVID-19 phenotypes.

Currently, there is an open-label, randomized control study to investigate the effect of n-3 PUFAs in hospitalized subjects with confirmed SARS-CoV-2 (NCT04335032) (NCT04335032, 2020). The study comprises 240 participants, with one group receiving standard care, the other additionally being provided 2 g daily of EPA capsules. Interventions will be carried out between 28 and 90 days and the efficacy of EPA in the treatment of the disease, oxygen saturation, levels of pro-inflammatory IL-6, mortality rate, ICU stays, hospitalization days and need for mechanical ventilation will be determined. While the results from this study are not available, the evidence suggests oral or intravenous administration of bioactive lipids could potentially reduce the severity and/or enhance the recovery of those infected with COVID-19 (Das, 2020a). However, further research is undoubtedly required.

7. Cardiovascular benefits of n-3 polyunsaturated fatty acids

N-3 PUFAs and many of their endogenously generated metabolites act as bioactive lipid molecules with a wide array of properties against numerous disorders including CVD (Lordan, Redfern, Tsoupras, & Zabetakis, 2020; Lordan, Tsoupras, & Zabetakis, 2017; Moro, Nagahashi, Ramanathan, Takabe, & Wakai, 2016). Numerous studies have suggested higher consumption of n-3 PUFAs lowers the number of mortalities related to CVD (Darwesh, Sosnowski, Lee, Keshavarz-Bahaghighat, & Seubert, 2019; Kris-Etherton, Harris, Appel, & Nutrition, 2003; Lee, O'Keefe, Lavie, & Harris, 2009; Mozaffarian, 2007). For instance, Mozaffarian et al. demonstrated higher plasma levels of n-3 PUFA biomarkers in a U.S. adults cohort study was associated with lower total mortality attributable with fewer cardiovascular compared to non-cardiovascular deaths (Mozaffarian et al., 2013). Currently, the intake of n-3 PUFAs is still recommended by the American Heart Association to prevent clinical CVD episodes in individuals with predominant coronary heart disease, such as a recent MI, to reduce death rates as well as individuals with prevalent HF to reduce hospitalizations and number of mortalities (Sacks et al., 2017; Siscovick, et al., 2017).

The cardiovascular benefits of n-3 PUFAs could be attributed to their pleiotropic effects on the different elements of the cardiovascular system. Evidence suggests a higher intake of n-3 PUFAs has a beneficial effect on lipid profiles by replacing saturated fatty acids and lowering triglyceride levels, thereby stabilizing atherosclerotic plaques and reducing the incidence of thrombus formation (Plutzky, 1999; Thies et al., 2003). Furthermore, n-3 PUFAs can enrich cell membranes and alter the lipid raft structure and function leading to improved organelle and cellular function (Din et al., 2008), autonomic tone (Abuissa, O'Keefe Jr., Harris, & Lavie, 2005; O'Keefe Jr., Abuissa, Sastre, Steinhaus, & Harris, 2006), elevated arrhythmic thresholds (Anand, Alkadri, Lavie, & Milani, 2008) and ameliorating hypertension (Geleijnse, Giltay, Grobbee, Donders, & Kok, 2002; O'Keefe Jr. et al., 2006). Importantly, several experimental, clinical and epidemiological studies hypothesize that the cardioprotective effects of n-3 PUFAs and their metabolites are attributed mainly to their immunomodulatory properties. Notably, emerging evidence demonstrates the ability of n-3 PUFAs to reduce circulating levels of inflammatory chemokines, cytokines, and the pro-inflammatory metabolites derived from n-6 PUFAs (Calder, 2013, 2017).

8. Potential cardioprotective mechanisms of n-3 PUFAs in the setting of COVID-19

Based on several clinical reports, COVID-19 patients with severe ALI/ARDS may also suffer from increased risk of sepsis and cardiac arrest (Huang et al., 2020). Accumulating reports have indicated that n-3

PUFAs could improve resolution of inflammation, sepsis survival and precondition the heart against septic cardiomyopathy (Korner et al., 2018; Leger et al., 2019). In this review, we propose that n-3 PUFAs can protect against and ameliorate cardiovascular complications associated with COVID-19 mainly due to their immunomodulatory features, antioxidant potential as well as their ability to maintain tissue homeostasis. This section will highlight the cardioprotective mechanisms of n-3 PUFAs and their metabolites hypothesizing how n-3 PUFAs might have a supportive adjuvant utility in treating and protecting against cardiac complications associated with COVID-19 (Fig. 2).

8.1. The anti-inflammatory properties of n-3 PUFAs

As mentioned earlier, an exacerbated immune system response and uncontrolled inflammation are fundamental mechanisms in the development of cardiovascular impairment in patients with COVID-19. Accordingly, a plethora of experimental studies and clinical trials demonstrate that targeting different inflammatory components may be considered promising strategies to control cardiovascular impairment during the acute and remission phases of COVID-19 (Fig. 3).

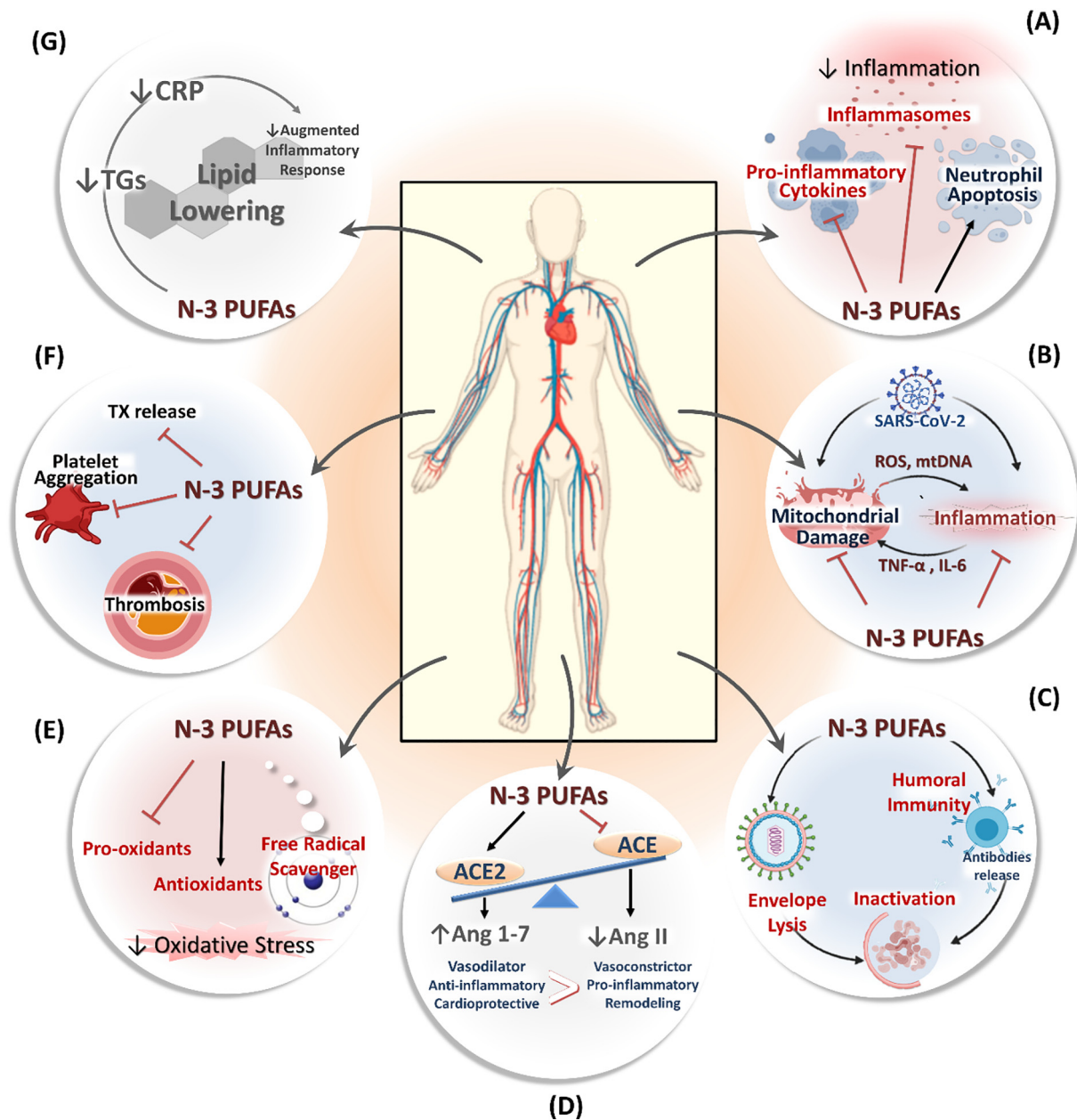


Fig. 2. Potential cardioprotective mechanisms of n-3 PUFAs in the setting of COVID-19. (A) N-3 PUFAs ameliorate uncontrolled immune responses and exert anti-inflammatory effects via several mechanisms. (B) N-3 PUFAs attenuate the vicious cycle/interaction of mitochondrial dysfunction and aggravated immune response. (C) N-3 PUFAs have the capability to attenuate viral infections via both direct effects on membrane integrity and indirect mechanisms through activating the humoral response to decrease overall viral load. (D) N-3 PUFAs have the ability to regulate the RAAS system in the favor of the vasodilatory, the anti-inflammatory and the cardioprotective ACE2/Ang (1–7) effectors. (E) N-3 PUFAs enhance antioxidant capacity and attenuate oxidative stress in the tissue. (F) N-3 PUFAs ameliorate coagulopathy by exerting anti-thrombotic effects. (G) The triglyceride-lowering effect of n-3 PUFAs may play a key role in blunting the exaggerated inflammation observed in patients with COVID-19. ACE, Angiotensin-converting enzyme; Ang, Angiotensin; CRP, C-reactive protein; IL, Interleukin; mtDNA, Mitochondrial DNA; PUFA, Poly unsaturated fatty acid; ROS, Reactive oxygen species; TGs, Triglycerides; TNF- α , Tumor necrosis factor alpha; TX, Thromboxane.

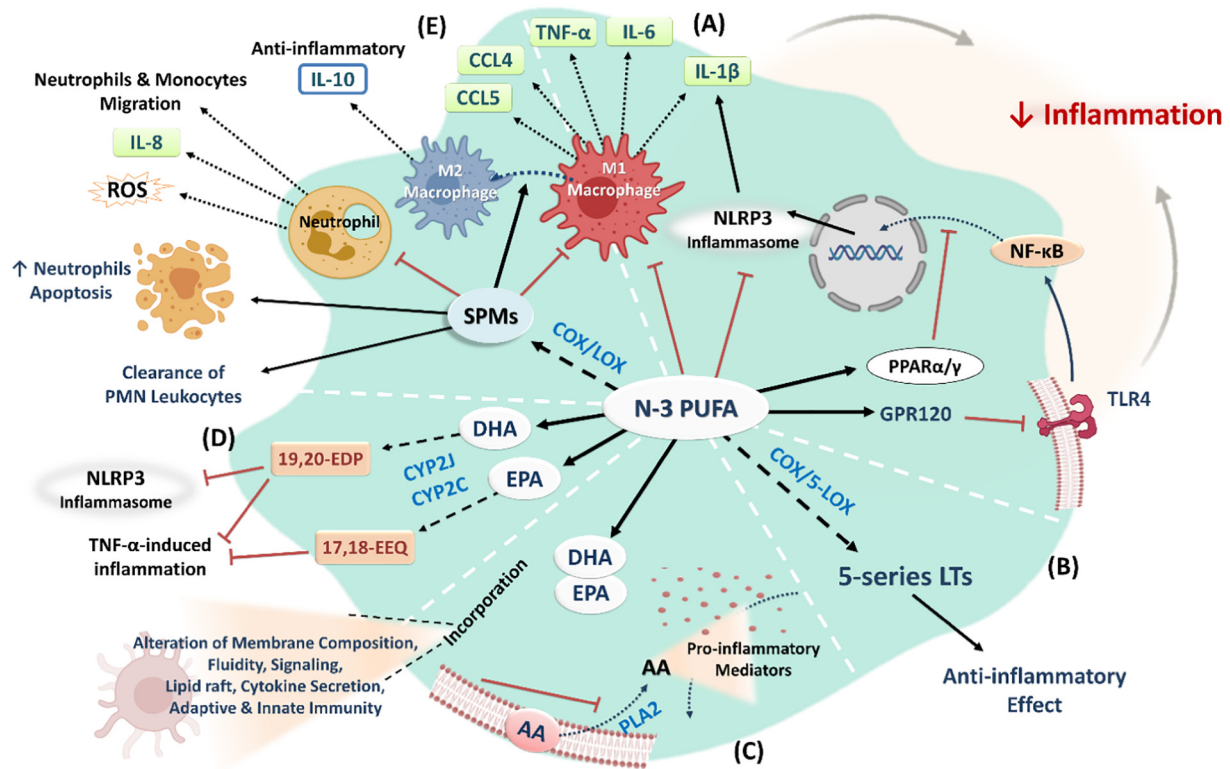


Fig. 3. A summary of the anti-inflammatory mechanisms of n-3 PUFAs. (A) N-3 PUFAs can regulate expression of inflammatory cytokines, chemokines and adhesion molecules, inhibit NLRP3 inflammasomes, activate anti-inflammatory transcription factors (PPAR α/γ) and activate GPR120 receptors which inhibit TLR4-mediated activation of NF- κ B. (B) N-3 PUFAs are metabolized by COX/5-LOX into 5-series LTs which exert anti-inflammatory effects. (C) N-3 PUFAs can replace n-6 PUFAs, such as AA, altering the inflammatory response. N-3 PUFA will alter cell membrane composition, fluidity and mediated signaling. (D) N-3 PUFAs, DHA and EPA, are metabolized by CYP epoxygenases into bioactive epoxy lipids with anti-inflammatory properties. (E) N-3 PUFAs are metabolized by COX/LOX into SPMs which act as potent anti-inflammatory modulators. AA, Arachidonic acid; CCL, Chemokine ligand; COX, Cyclooxygenase; CYP, Cytochrome P450; DHA, Docosahexaenoic acid; EDP, Epoxydocosapentaenoic acid; EEQ, Epoxyeicosatetraenoic acid; EPA, Eicosapentaenoic acid; GRP, G-protein coupled receptor; IL, Interleukin; LOX, Lipoxygenase; LT, Leukotriene; PUFA, Poly unsaturated fatty acid; NF- κ B, Nuclear factor kappa-light-chain enhancer activated B-cells; NLRP3, NACHT, LRR and PYD domains-containing protein 3; PLA2, Phospholipase A2; PMN, Polymorphonuclear neutrophils; PPAR, Peroxisome proliferator-activated receptor; ROS, Reactive oxygen species; SPMs, Specialized pro-resolving mediators; TLR, Toll like receptor; TNF- α , Tumor necrosis factor- α .

8.1.1. N-3 PUFAs regulate the expression of several proinflammatory innate immune components and modulate macrophage response

A 'cytokine storm' and activation of the central innate immune pathway linking the NLRP3 inflammasome, IL-1 β , TNF- α and IL-6 response is a primary cause of excessive inflammation reported in COVID-19 that negatively impacts cardiovascular system. Therefore, targeting the different components is a promising approach to ameliorate cardiac complications secondary to COVID-19 (Huang et al., 2020). While there is no direct clinical evidence related to the use of n-3 PUFAs in COVID-19 patients, the application of n-3 PUFAs in several inflammatory settings, including cardiovascular disorders, has been demonstrated to ameliorate detrimental immune reactions by several mechanisms (Rogerio et al., 2020). The anti-inflammatory effect of n-3 PUFAs seems to be consistent across several previous clinical findings (Calder, Carr, Gombart, & Eggersdorfer, 2020; Fritsche, 2006; Kiecolt-Glaser et al., 2012; Vedin et al., 2008). Intriguingly, Tan et al. recently demonstrated in a randomized controlled study that high-dose n-3 PUFA supplementation (1.5 g/day EPA and 1.0 g/day DHA) markedly reduces plasma levels of IL-6, IL-1 β and TNF- α after 4 weeks of therapy in middle or late-aged patients with chronic venous leg ulcers suggesting n-3 PUFAs as an effective low-risk dietary intervention to modulate inflammation (Tan, Sullenbarger, Prakash, & McDaniel, 2018). This study indicates that n-3 PUFAs could have direct modulatory effects on the main components of the cytokine storm IL-6, IL-1 β and TNF- α .

N-3 PUFAs can modulate the transcription and expression of inflammatory genes including cytokines, chemokines and adhesion molecules in cardiomyocytes, fibroblasts, endothelial cells, monocytes and

macrophages (Collie-Duguid & Wahle, 1996; De Caterina, Cybulsky, Clinton, Gimbrone, & Libby, 1994; Hughes, Southon, & Pinder, 1996; Miles, Wallace, & Calder, 2000; Sanderson & Calder, 1998). This is primarily achieved through the regulation of key transcription factors, such as inhibiting NF- κ B (Kumar, Takada, Boriek, & Aggarwal, 2004; Lo, Chiu, Fu, Lo, & Helton, 1999; Novak, Babcock, Jho, Helton, & Espot, 2003; Zhao, Joshi-Barve, Barve, & Chen, 2004) or activating peroxisome proliferator-activated receptors- α/γ (PPAR α/γ) (Gani & Sylte, 2008; Zapata-Gonzalez et al., 2008). Activation of PPAR α/γ can directly interfere with the activation of NF- κ B and prevent its shuttling to the nucleus reducing the inflammatory burst (Matsumoto et al., 2008; Mishra, Chaudhary, & Sethi, 2004; Poynter & Daynes, 1998; Ricote, Huang, Welch, & Glass, 1999; Vanden Berghe et al., 2003). Interestingly, direct activation of PPAR, using PPAR agonists, was proposed as a therapeutic target for blunting and regulating cytokine storm in COVID-19 patients suggesting n-3 PUFAs could have a promising effect (Ciavarella, Motta, Valente, & Pasquinelli, 2020). Another important immunomodulatory mechanism induced by n-3 PUFAs involves activation of G protein-coupled receptor 120 (GPR120), which mediates strong and wide-ranging anti-inflammatory effects. Research from Oh et al. indicates n-3 PUFAs stimulate GPR120 in both monocytic RAW 264.7 cells and primary intraperitoneal macrophages inhibiting TLR4-mediated inflammatory responses. Knockdown of GPR120 attenuates the protective effects attributed to n-3 PUFA consumption (Oh et al., 2010). These studies together provide evidence that n-3 PUFAs mediate anti-inflammatory effects through different mechanistic pathways.

Cardiac macrophages are primarily derived and replenished from inflammatory monocytes in response to an infection with resident macrophages also having a role. Briefly, macrophages will differentiate into classical M1 inflammatory cells to clean cellular and matrix debris (Epelman et al., 2014). Subsequently, M1 macrophages may undergo polarization and transformation to the alternatively activated or reparatory M2 stage which secrete IL-10 to promote resolution and contribute to wound healing and tissue repair (Murray, 2017). Controlling the migration and the polarization of macrophages to the myocardium in the context of COVID-19 is a tentative approach to limit cardiac injury (Frantz & Nahrendorf, 2014; Fujii, Wang, & Nagai, 2014; Leblond et al., 2015; van Amerongen, Harmsen, van Rooijen, Petersen, & van Luyn, 2007). In COVID-19, an excessive cardiac recruitment and accumulation of pro-inflammatory M1 macrophages potentially aggravates cardiovascular injury. Notably, as M1 macrophages secrete a large variety of chemokines and cytokines such as TNF- α and IL-1 β to recruit and activate other immune cells from both the innate and the adaptive immune system. The effect will impede the reparative phase mediated by M2 macrophages and thus aggravates adverse cardiac remodeling (Dewald et al., 2005; Gordon, Pluddemann, & Martinez Estrada, 2014; Murray & Wynn, 2011; ter Horst et al., 2015).

Interestingly, evidence demonstrates n-3 PUFAs and/or their biologically active metabolites have the ability to blunt the expression, production and release of IL-1 β , TNF- α , and IL-6 by M1 macrophages (Allam-Ndoul, Guenard, Barbier, & Vohl, 2017; Liu et al., 2014; Mildenerger et al., 2017). Schoeniger et al., showed n-3 PUFAs have the ability to down-regulate inflammatory processes and reduce the production and secretion of pro-inflammatory cytokines from RAW 264.7 macrophages infected with microorganisms, *R. equi* and *P. aeruginosa* (Schoeniger, Adolph, Fuhrmann, & Schumann, 2011). Moreover, the inhibitory effects of EPA and DHA on the pro-inflammatory NLRP3 inflammasome pathway has also been well-documented in macrophage cell lines as well as in primary human and mouse macrophages (Iverson et al., 2018; Kumar et al., 2016). Kumar et al., investigated the effects of 15-lipoxygenase (LOX) metabolites of ALA on lipopolysaccharide (LPS)-induced inflammation in RAW 264.7 cells and peritoneal macrophages. The findings revealed the anti-inflammatory effects of these metabolites involve inactivation of the NLRP3 inflammasome complex through the PPAR- γ pathway (Kumar et al., 2016). N-3 PUFAs can increase the phagocytic capacity of macrophages, which has been shown through the engulfment of zymosan particles (Chang, Lee, Kim, & Surh, 2015), *Pseudomonas aeruginosa*, *Rhodococcus equi* (Adolph, Fuhrmann, & Schumann, 2012), *E.coli* (Davidson, Kerr, Guy, & Rotondo, 1998) and apoptotic cells (Chang et al., 2015). It has been suggested the increase in phagocytic capacity of macrophages upon n-3 PUFA treatment could be attributed to changes in the cellular membrane composition and structure caused by the incorporation of the n-3 PUFAs (Hellwing, Tigistu-Sahle, Fuhrmann, Kakela, & Schumann, 2018; Schoeniger, Fuhrmann, & Schumann, 2016). Importantly, n-3 PUFAs have been found to promote M2 polarization in macrophage cell lines and primary mouse macrophages enhancing resolution of inflammation and tissue repair after infection (Chang et al., 2015; Ohue-Kitano et al., 2018). Collectively, the modulatory properties of n-3 PUFAs on the immune system could impart a promising beneficial effect on the cardiovascular system in the context of COVID-19, an effect which needs further exploration and confirmation in larger clinical trials.

8.1.2. Shifting to the anti-inflammatory COX- and LOX-derived metabolites of n-3 PUFAs

Accumulating literature demonstrates potent immunomodulatory properties of metabolites generated from n-3 PUFAs and consequently their impact on cardiovascular health (Jamieson, Endo, Darwesh, Samokhvalov, & Seubert, 2017; Schunck, Konkel, Fischer, & Weylandt, 2018). The metabolism of n-3 and n-6 PUFAs is closely interconnected as parent compounds compete for the same metabolic enzymes but

result in the production of a wide array of either pro- or anti-inflammatory metabolites. For example, cyclooxygenase (COX) converts the n-6 PUFA arachidonic acid (AA) to the 2-series of prostaglandins (PGs) and the 2-series of thromboxanes (TX), while lipoxygenase (LOX) enzymes metabolize AA to the 4-series leukotrienes (LTs) and the hydroxyicosatetraenoic acids. These lipid mediators are considered pro-inflammatory and are involved in various pathological processes including cardiovascular disorders (Innes & Calder, 2018; Kalinski, 2012; Lewis, Austen, & Soberman, 1990). The synthesis and production of PGE₂ occurs in several cells, including dendritic cells, macrophages, fibroblasts and endothelial cells. PGE₂ not only mediates vasodilation, endothelial permeability and increase of pain (Ricciotti & FitzGerald, 2011) but also contributes to the tissue influx of neutrophils, mast cells and macrophages and can affect the differentiation of these cells (Kalinski, 2012).

N-3 PUFAs can also act as a substrate for COX and 5-LOX enzymes resulting in production of the 3-series of PGs and TxAs as well as 5-series LTs, which are a set of less inflammatory or even anti-inflammatory metabolites in comparison to the metabolite family derived from AA (Corey, Shih, & Cashman, 1983; Lee et al., 1984; Surette, 2008). These eicosanoids are responsible for producing several physiological responses related to inflammation, and their imbalance has been observed in several diseases (Calder, 2006; Falck et al., 2011). For example, the production of PGE₂ and LTB₄ by human inflammatory cells was significantly decreased in a diet rich in fish oil (Caughey, Mantzioris, Gibson, Cleland, & James, 1996; Lee et al., 1985; Prescott, 1984; von Schacky, Kiefl, Jendraschak, & Kaminski, 1993). Therefore, the metabolism of n-3 PUFAs by COX and LOX enzymes not only reduce the AA-derived pro-inflammatory metabolites but also alter the metabolic profile towards more biologically active anti-inflammatory mediators (Goldman, Pickett, & Goetzl, 1983; Lee et al., 1984; Lee, Mencia-Huerta, et al., 1984). This may represent one of the central anti-inflammatory and consequently cardioprotective mechanisms of n-3 PUFAs against cardiac complications associated with COVID-19.

8.1.3. Anti-inflammatory features of the n-3 PUFAs-derived specialized pro-resolving mediators (SPMs)

Metabolism of n-3 PUFAs also generates another group of highly specialized pro-resolving mediators (SPMs) which include resolvins 'resolution phase interaction products' produced from both EPA (E-series, RvE1-2) and DHA (D-series, RvD1-6) as well as protectins and maresins produced from DHA (Serhan et al., 2002; Serhan, Chiang, & Van Dyke, 2008). Both the COX and LOX pathways are involved in the synthesis of these metabolites with distinct epimers being produced in the presence and absence of aspirin (Mas, Croft, Zahra, Barden, & Mori, 2012).

SPMs possess potent anti-inflammatory and inflammation resolving properties which is essential to terminate ongoing inflammatory processes, accelerate the cleaning process and aid in tissue regeneration and wound healing allowing tissue homeostasis to return (Serhan et al., 2000; Serhan et al., 2002; Spite et al., 2009; Titos et al., 2011). Several mechanistic pathways contribute to the anti-inflammatory effects of resolvins, protectins and maresins. This includes preventing the migration of neutrophils and monocytes across epithelial cells and promoting clearance of polymorphonuclear (PMNs) leukocytes, apoptotic cells and debris from the site of inflammation (Campbell et al., 2007; Serhan et al., 2002). Krishnamoorthy et al. showed resolvins inhibit tissue migration of neutrophils by lowering the expression of surface adhesion receptors on neutrophils, such as CD11b or CD18, and reducing the production of the chemokine IL-8 (Krishnamoorthy et al., 2010). Additionally, the partial agonist/antagonist activity of RvE1 toward LTB₄ receptors on PMNs will inhibit NF- κ B activation, abolish pro-inflammatory cytokine production and reduce PMN leukocyte infiltration (Arita et al., 2007; Serhan et al., 2002; Serhan et al., 2008). Resolvins can blunt reactive oxygen species (ROS) production from neutrophils, induce neutrophil apoptosis and clearance by macrophages, as well

contribute to inhibiting chemokine signaling (Ariel et al., 2006; Schwab, Chiang, Arita, & Serhan, 2007; Serhan & Chiang, 2004). Furthermore, Morin et al. demonstrated a diet enriched with DHA and monoglycerides can significantly increase the levels of RvD2 and RvD3, which correlate with reduced levels of proinflammatory mediators CRP, IL-6, TNF- α , and IL-1 β in a rat model of hypertension (Morin, Rousseau, Blier, & Fortin, 2015). Additionally, there is growing evidence for a role of SPMs in regulating the humoral immune response. A study conducted by Ramon et al., showed 17-hydroxydocosahexaenoic acid (17-HDHA), the precursor of the D-series SPMs (RvD1, 17R-RvD1, RvD2), can reduce IL-6 secretion in human B cells, increase B cell antibody production and promote B cell differentiation to an antibody secreting cell (Ramon, Gao, Serhan, & Phipps, 2012). These new findings highlight the potential applications of SPMs as non-toxic, supportive adjuvants and as anti-inflammatory therapeutic molecules particularly during infection as in the case of COVID-19.

Resolvins, protectins and maresins play a pivotal role regulating the function of macrophages. Sulciner et al. demonstrates RvD1, RvD2 or RvE1 can inhibit debris-stimulated cancer progression by enhancing clearance of debris via macrophage phagocytosis in multiple tumors. These resolvins suppressed the release of the proinflammatory cytokines/chemokines, including TNF α , IL-6, IL-8, chemokine ligand 4, and chemokine ligand 5, by human macrophages cocultured with tumor cell debris (Sulciner et al., 2018). Maresins are conjugates of sulfides synthesized by macrophages, which are also participants in acute inflammation resolution and seem to promote tissue regeneration (Serhan et al., 2009). Maresin-1 biosynthesis involves an active intermediate (13S,14S-epoxi-DHA) that stimulates macrophage conversion from M1 (pro-inflammatory) to M2 (anti-inflammatory) phenotype (Dalli, Ramon, Norris, Colas, & Serhan, 2015). It is noteworthy that M2 macrophages secrete resolvins, protectins and maresins to dampen inflammation and restore homeostasis (Bouchery & Harris, 2017; Ramon et al., 2016) and at the same time augment phagocytic capacity of macrophages and other cells to remove debris from the site(s) of infection and injury and enhance microbial clearance (Dalli et al., 2013; Norris et al., 2018; Poorani, Bhatt, Dwarakanath, & Das, 2016).

The role of resolvins in the resolution of inflammation has been demonstrated in several animal models of ALI and ARDS (Gao et al., 2017; Uddin & Levy, 2011; Wang, Yan, Hao, & Jin, 2018; Zhang et al., 2019). These studies carried out using rat and mouse models infected with the *E.coli* endotoxin, LPS, suggested the pro-resolving effects of these molecules could be attributed, for example, to the suppression of neutrophil infiltration due to reduced expression and release of pro-inflammatory cytokines from alveolar macrophages (Uddin & Levy, 2011; Zhang et al., 2019). Further, it has been demonstrated protectins may reduce the replication of influenza (Morita et al., 2013) and potentially affect the inflammatory manifestations of respiratory viral diseases (Russell & Schwarze, 2014).

Importantly, pro-inflammatory cytokines, TNF- α and IL-6, will inhibit the activities of desaturases, which are essential for the generation of AA, EPA and DHA from their precursors LA and ALA (Das, 2013). Hence, in instances where there is a substantial degree of inflammation due to high levels of IL-6 and TNF- α , such as following COVID-19 infection, a deficiency of EPA and DHA and subsequent decreased generation of resolvins, protectins and maresins can occur (Das, 2018). Thus, administration of PUFAs and/or their metabolites, resolvins, protectins and maresins can suppress inappropriate production of IL-6 and TNF- α to resolve inflammation, enhance recovery and limit cytokine storm (Das, 2019) in COVID-19. Together, the studies imply administration of n-3 PUFA may enhance recovery from infections and further, if present in adequate amounts, may modulate the response to infections.

8.1.4. Role of CYP-mediated metabolites in ameliorating inflammation

CYP2J and CYP2C isoforms, the constitutively expressed cytochrome P450 (CYP) epoxygenases found in the cardiovascular system, metabolize EPA into 5 regioisomeric epoxyeicosatetraenoic acids (5,6-, 8,9-, 11,12-,

14,15-, 17,18-EEQ) and DHA into 6 regioisomeric epoxydocosapentaenoic acids (4,5-, 7,8-, 10,11-, 13,14-, 16,17-, 19,20-EDP) (Arnold et al., 2010; Konkel & Schunck, 2011; Westphal, Konkel, & Schunck, 2015). Recent evidence suggests that 17,18-EEQ and 19,20-EDP mediate several anti-inflammatory effects of n-3 PUFAs in various models of tissue injury (Arnold et al., 2010; Ulu et al., 2014; Wang, Chai, Lu, & Lee, 2011). For example, Fang et al. demonstrated a n-3 PUFA-rich diet attenuates MI injury in mice by producing a protective eicosanoid pattern, which results in shifting the metabolite profile to a more anti-inflammatory state by increasing the levels of the 19,20-EDP and 17,18-EEQ and decreasing the pro-inflammatory PGE₂ (Fang et al., 2018). The cardioprotective effects of n-3 PUFAs are also attributed to their ability to attenuate the NLRP3 inflammasome complex cascade (Darwesh, Jamieson, Wang, Samokhvalov, & Seubert, 2019). Importantly, the anti-inflammatory features of CYP-derived epoxy metabolites have been reported in numerous models. For example, in TNF α -induced retinal vascular inflammation, Capozzi et al. demonstrated 19,20-EDP can ameliorate vascular adhesion molecule and intracellular adhesion molecule expression and reduce leukocyte adherence to human retinal microvascular endothelial cell monolayers (Capozzi, Hammer, McCollum, & Penn, 2016). Additionally, evidence demonstrates intraperitoneal infusions of 17,18-EEQ and 19,20-EDP protect against allergic intestinal inflammation and kidney fibrosis in corresponding mouse models (Kunisawa et al., 2015; Sharma et al., 2016). 17,18-EEQ was able to inhibit TNF α -induced inflammation in human lung tissue obtained from patients undergoing surgery for lung carcinoma via inhibition of NF- κ B and activation of the transcription factor PPAR- γ (Morin, Sirois, Echave, Albadine, & Rousseau, 2010). The anti-inflammatory properties of DHA epoxides were also well demonstrated using animal models of inflammatory pain. For example, Morisseau et al. demonstrated that direct injection of the DHA epoxides, EDPs, together with the pro-inflammatory carrageenan into the paw or spinal cord of male Sprague-Dawley rats resulted in significant antihyperalgesic activity. Surprisingly, both the parent free fatty acid DHA and the corresponding diols were inactive, supporting the hypothesis that the epoxy lipids mediate many of the beneficial effects of the parent compounds (Morisseau et al., 2010). The bacterial endotoxin, LPS, has a marked role in triggering inflammatory injury which can result in several cardiovascular complications. In a study using HL-1 cardiac cells, 19,20-EDP protected against LPS-stimulated inflammatory injury by activating the histone deacetylase Sirtuin-1 inhibiting the activation of the pro-inflammatory transcription factor NF- κ B (Samokhvalov, Jamieson, Vriend, Quan, & Seubert, 2015). The accumulating evidence suggests the anti-inflammatory properties of CYP-epoxygenase metabolites of n-3 PUFAs have a substantial role in activating protective responses in models of cardiovascular injury. However, further investigation is required to elucidate whether the protective properties limit cardiovascular injury secondary to COVID-19 infection.

8.1.5. N-3 PUFAs alter cell membrane structure and function - modulation of the lipid raft

Within a cell, n-3 PUFAs can be found incorporated into phospholipid membranes where elevating levels will replace existing n-6 PUFAs thereby altering the composition and properties of lipid rafts (Lordan et al., 2017; Lordan et al., 2020). The increased incorporation of n-3 PUFAs into membrane bilayers can have a role in mediating immunomodulatory effects by altering membrane composition, fluidity and function. These changes will impact membrane-mediated signaling, protein trafficking, generation of bioactive lipids, cytokine secretion and gene activation in both innate and adaptive immune responses. For example, a change in fluidity can interfere with the dimerization and expression of the TLR4 subunits, blocking the downstream inflammatory reaction (Ciesielska & Kwiatkowska, 2015; Takashima et al., 2016). Evidence of these effects by n-3 PUFAs have been demonstrated to impact the maturation of dendritic cells, macrophage function and T and B cell polarization/activation (Katagiri, Kiyokawa, & Fujimoto, 2001; Kim

et al., 2010; McMurray, Bonilla, & Chapkin, 2011; Rockett, Salameh, Carraway, Morrison, & Shaikh, 2010; Shaikh & Edidin, 2006, 2008). Interestingly, DHA appears to be better than EPA in replacing n-6 PUFAs and cholesterol in plasma membranes of aortic endothelial cells enhancing the fluidity of the phospholipid membrane (Hashimoto, Hossain, Yamasaki, Yazawa, & Masumura, 1999).

In most cell types, AA is the predominant n-6 PUFA in membrane phospholipids (Yaqoob, Pala, Cortina-Borja, Newsholme, & Calder, 2000). Inflammatory immune cells such as monocytes, neutrophils, macrophages and lymphocytes often contain a large amount of AA in their membrane. The high membrane AA composition is important during normal inflammatory responses. Under stress conditions activation of phospholipase A2 liberates AA from the cell membrane leading to metabolism and production of many pro-inflammatory metabolites (Ford, Hazen, Saffitz, & Gross, 1991; Hazen, Ford, & Gross, 1991; Leslie, 2015; Mancuso et al., 2003). Supplementation with n-3 PUFAs leads to the substitution of AA with EPA and DHA in the cell membrane which can alter immune cell reaction in response to stress stimuli by shifting the metabolic profile to less proinflammatory or even anti-inflammatory metabolite predominance (Brouard & Pascaud, 1990; Faber et al., 2011; Gibney & Hunter, 1993; Grando et al., 2009). Therefore, increasing n-3 PUFAs, such as EPA and DHA, in the phospholipids has a potential benefit of ameliorating detrimental effects during uncontrolled inflammatory responses (Lordan et al., 2020).

8.2. N-3 PUFAs have the potential to ameliorate mitochondrial dysfunction in the pathogenesis of COVID-19

Under normal physiological conditions, it is essential for all body organs and physiological systems, particularly the cardiovascular system, to maintain a large number of functional mitochondria to provide energy, as well as preserve and regulate different cellular functions (Murphy, et al., 2016). Maintaining a healthy pool of mitochondria depends upon a delicate balance between the formation of newly generated mitochondria termed as "mitochondrial biogenesis", to meet the increased energy demand, and the efficient elimination of irreversibly damaged mitochondria through mitophagy (Bayeva, Gheorghide, & Ardehali, 2013; Meyers, Basha, & Koenig, 2013). Mitochondrial damage, decreased biogenesis and impaired mitophagy has been implicated in several pathologies including diabetes, CVDs, aging, as well as viral and bacterial infections (Cho, Kim, & Jo, 2020; Kim, Ahn, Syed, & Siddiqui, 2018; Rovira-Llopis et al., 2017; Srivastava, 2017; Wu, Zhang, & Ren, 2019). While the intrinsic mechanism(s) involved in the pathogenesis of cardiovascular insult secondary to COVID-19 are not fully understood, altered mitochondrial homeostasis could be a major contributing factor (Grivennikova, Kareyeva, & Vinogradov, 2010; Melsner, Lavie, & Benard, 2015; Murphy, et al., 2016; Saleh, Peyssonnaud, Singh, & Edeas, 2020). Notably, symptoms such as sleep and appetite disturbance, loss of energy, fatigue and muscle weakness, observed in COVID-19 patients, are cardinal signs of mitochondrial distress (Filler et al., 2014).

Recent studies identified a level of interaction or interplay between mitochondria and innate immune inflammatory responses. Mitochondrial dysfunction is considered both a trigger and target of uncontrolled inflammatory responses (Gurung, Lukens, & Kanneganti, 2015; Mohanty, Tiwari-Pandey, & Pandey, 2019; Yu et al., 2014). As such, this implicates the potential role of impaired mitochondrial homeostasis in the aggravation of cardiovascular injury secondary to COVID-19 (Darwesh, Jamieson, et al., 2019; Darwesh, Keshavarz-Bahaghighat, Jamieson, & Seubert, 2019; Keshavarz-Bahaghighat, Darwesh, Sosnowski, & Seubert, 2020; Samokhvalov et al., 2018). Inflammatory mediators are well documented to trigger several intracellular cascades that alter mitochondrial metabolism and function. For example, the pro-inflammatory cytokines TNF- α , IL-1 β and IL-6, found in the serum from COVID-19 patients, can impede mitochondrial oxidative phosphorylation, inhibit ATP production and mitochondrial ROS production

exacerbating injury (Jo, Kim, Shin, & Sasakawa, 2016; Naik & Dixit, 2011). Furthermore, IFN- γ and IL-6 can increase mitochondrial ROS production and directly affect the activity of the electron transport chain, which may cause mitochondrial membrane permeabilization, altered mitochondrial dynamics and cell death (Li et al., 2013).

Conversely, direct mitochondrial damage was found to aggravate the production of proinflammatory cytokines and worsen disease prognosis. Briefly, the pathological changes observed in patients infected with SARS-CoV-2 such as pneumonia, hypoxia and impaired calcium homeostasis can indirectly induce mitochondrial dysfunction. Moreover, a very recent study conducted by Singh et al. interestingly showed both RNA and DNA transcripts of SARS-CoV-2 can directly target and localize to mitochondria hijacking the host cell's mitochondrial function to viral advantage (Singh, Chaubey, Chen, & Suravajhala, 2020). Subsequently, SARS-CoV-2 will manipulate the host cell's mitochondrial function to evade removal and facilitate virus replication and progression. These effects lead to the release of mitochondrial DNA and ROS in the cytosol (Herst, Rowe, Carson, & Berridge, 2017; Kozlov, Lancaster Jr., Meszaros, & Weidinger, 2017; Mittal, Siddiqui, Tran, Reddy, & Malik, 2014; Starkov, 2008; Twig & Shirihai, 2011; West et al., 2015), which drives the activation and release of central pro-inflammatory cytokines such as NLRP3 inflammasomes, IL-1 β and IL-6 (Jo et al., 2016; Naik & Dixit, 2011; Nakahira et al., 2011; West et al., 2015), the hallmark cytokines of the COVID-19 severity. Thus, highlighting a vicious cycle of mitochondrial damage and inflammation that has a critical role in aggravating cardiovascular injury. Accordingly, mitochondria are considered a strategic therapeutic target to improve the outcomes in the context of COVID-19.

Numerous studies have demonstrated cardioprotective properties of n-3 PUFA, and their epoxy lipid metabolites, involve an ability to preserve a healthy mitochondrial pool and attenuate exaggerated inflammatory responses under stress conditions. For example, n-3 PUFAs could impart a cardioprotective effect via enriching mitochondrial membrane phospholipid composition, which enhances mitochondrial function promoting efficient ATP generation (Duda, O'Shea, & Stanley, 2009; Samokhvalov, Jamieson, Fedotov, Endo, & Seubert, 2016). In a mouse model of ischemia reperfusion injury, both DHA and its epoxy metabolite, 19,20-EDP, were able to improve postischemic functional recovery by preserving mitochondrial function and attenuating NLRP3 inflammasome response (Darwesh, Jamieson, et al., 2019). Moreover, recent data indicates a synthetic EDP analogue imparts cardioprotective effects against ischemia reperfusion injury via preservation of mitochondrial homeostasis and anti-oxidant defenses, which blunted a detrimental innate NLRP3 inflammasome response (Darwesh et al., 2020). Earlier data demonstrated 19,20-EDP protected HL-1 cardiac cells from the bacterial endotoxin, LPS, cell injury by preserving mitochondrial biogenesis and integrity (Samokhvalov et al., 2015). These data suggest n-3 PUFAs and their metabolites provide beneficial protective responses in models of cardiovascular injury via maintaining mitochondrial quality and ameliorating detrimental immune responses. However, further research is required to investigate the proposed hypothesis in the context of COVID-19.

8.3. Direct and indirect effects of n-3 PUFAs on the viral load

Although EPA and DHA have been widely used to ameliorate chronic inflammatory diseases their effect on viral infections remains limited (Das, 2018; Husson et al., 2016; Ingram, Eaton, Erdos, Tedder, & Vreeland, 1982; Juers, Rogers, McCurdy, & Cook, 1976; Territo & Golde, 1979). Some evidence indicates EPA, DHA and other dietary unsaturated fatty acids can inactivate viruses by directly causing leakage or lysis of the viral envelopes, which will disrupt the membrane integrity or activate the humoral immune system to produce antibodies against these pathogens (Das, 2018, 2020a; Hilmarsson, Larusson, & Thormar, 2006; Kohn, Gitelman, & Inbar, 1980). Morita et al. demonstrated n-3 PUFA-derived lipid mediator, protectin D1, exhibits antiviral activity,

markedly attenuates influenza A virus replication and improves survival in severe influenza infection in male C57Bl/6J mice. This study highlighted the importance of the endogenous protectin D1 as an innate suppressor of influenza virus replication attenuating lethal infection (Morita et al., 2013). In another study, Ramon et al. evaluated the ability of 17-HDHA, a SPM derived from DHA, for improving the immune response to H1N1 influenza virus. The results showed 17-HDHA was able to enhance the humoral immunity against viruses by increasing the number of antibody-secreting cells and the levels of H1N1 antibodies, which resulted in greater protection against live H1N1 influenza infection in mice (Ramon et al., 2014). More recently, Braz-De-Melo highlighted the beneficial effects of n-3 PUFAs against viral infections by showing that DHA pre-treatment to neuroblastoma SH-SY5Y cells infected with Zika virus increased their viability and proliferation, restored mitochondrial function, reduced viral load and triggered an anti-inflammatory response identifying n-3 PUFAs as useful therapeutic tools in combating viruses (Braz-De-Melo et al., 2019). Additionally, Yan et al. has shown that EPA and DHA can inhibit the replication of both enterovirus A71 and coxsackievirus A16 the most common causes of hand, foot, and mouth disease (Yan et al., 2019). Collectively, we can conclude that n-3 PUFAs have the capability to attenuate viral infections via both direct effects on membrane integrity and indirect mechanisms activating the humoral response to decrease overall viral load.

In contrast, the immunosuppressive effects of EPA and DHA supplementation can decrease the immune response against viral infections and thus compromising removal from the body. C57Bl/6J mice supplemented with fish oil and infected with H1N1 influenza virus showed a 40% higher mortality rate and 70% higher viral load compared to the corresponding control. Moreover, the treated mice had markedly reduced numbers of CD8⁺ T lymphocytes and reduced mRNA expression of inflammatory mediators IL-6 and TNF- α (Schwerbrock, Karlsson, Shi, Sheridan, & Beck, 2009). Similarly, BALB/c mice fed a high-fat diet rich in EPA and DHA had reduced levels of IFN- γ , serum immunoglobulin G and lung immunoglobulin A-specific antibodies following infection with the influenza virus, indicating a virus-specific lung T cell cytotoxicity. These results suggested supplementation with a diet rich in EPA and DHA could impair immune response by delaying virus clearance. However, differences noticed during the course of infection did not affect the ultimate outcome as n-3 PUFA-fed mice were finally able to clear the virus and returned to pre-infection food consumption and body weight similar to the control group (Byleveld, Pang, Clancy, & Roberts, 1999; Byleveld, Pang, Clancy, & Roberts, 2000). Importantly, other factors contribute to these opposite results, for example, an initial weight loss is typically observed when mice are supplemented with fish oil (Byleveld et al., 1999). In addition, thoroughly controlled animal studies have not been conducted with the SARS-CoV-2 virus and significant variations between viruses should be considered. Therefore, further research is needed to understand the role of EPA and DHA in the immune response related specifically to SARS-CoV-2 viral infections.

8.4. Role of n-3 PUFAs in modulating the renin-angiotensin aldosterone system in the setting of COVID-19

The renin-angiotensin aldosterone system (RAAS) is a key regulator of vascular function modulating natriuresis, blood volume and blood pressure. Briefly, angiotensin I (Ang I) is metabolized by angiotensin-converting enzyme (ACE) to form the vasoconstrictor angiotensin II (Ang II). Accumulation, prolonged and excessive binding of Ang II to the angiotensin 1 receptor in the heart and blood vessels mediates several effects which include vasoconstriction, hypertension, cardiac hypertrophy, increased ROS production and adverse fibrosis (Fyhrquist, Metsarinne, & Tikkanen, 1995; Perazella & Setaro, 2003). Earlier literature demonstrated Ang II may act as a proinflammatory cytokine potentially having a significant role in cardiac remodeling (Gibbons, Pratt, & Dzau, 1992; Griendling, Minieri, Ollerenshaw, & Alexander, 1994). Conversely, the master regulator ACE2, a type 1 integral membrane

glycoprotein expressed in most tissues including the lungs, kidneys, heart and vascular endothelium layers, can metabolize Ang II to produce the vasodilator angiotensin (Ang 1–7) which protects the cardiovascular system against the actions of Ang II (Das, 2018; Kumar & Das, 1997; Yan et al., 2020). Beside its vasodilatory properties, Ang-(1–7) promotes resolution of inflammation by decreasing TNF- α , IL-6, vascular adhesion molecule, monocyte chemoattractant protein-1 and macrophage infiltration enhancing the survival of cardiomyocytes and endothelial cells during severe immune responses (Simoes e Silva, Silveira, Ferreira, & Teixeira, 2013; Zhang et al., 2015). Accordingly, several clinical and experimental studies reported dysregulation of RAAS due to increased Ang II and decreased ACE2 can lead to detrimental inflammatory responses and worsening of cardiovascular disorders. Therefore, maintaining the activity of ACE2 is essential in preserving the balance of the RAAS and effects on vasoconstriction, sodium retention and fibrosis and may elicit protective effects against hypertension, HF, MI and other CVDs (Crackower et al., 2002; Patel et al., 2016; Wang, Gheblawi, & Oudit, 2020).

Recent evidence has demonstrated SARS-CoV-2 uses ACE2 as an internalization receptor to enter the target cells. The spike (S) glycoprotein of SARS-CoV-2 recognizes and interacts with its target ACE2 receptor on the host cell surface, mediating viral entry during the infection cycle (Letko, Marzi, & Munster, 2020; Yan et al., 2020). Excessive binding of spike protein to ACE2 leads to downregulation of the ACE2 receptor (Jung et al., 2020). This finding is consistent with reports in the animal models infected with SARS-CoV (Crackower et al., 2002; Imai et al., 2005; Kuba et al., 2005). The reduction in ACE2 levels leads to excessive proinflammatory responses adversely affecting both lung and cardiovascular systems (Crackower et al., 2002; Imai et al., 2005; Kuba et al., 2005). These detrimental effects can be explained as the partial decrease in ACE2 function leads to dominant angiotensin II effects, including augmented cytokine storm, inflammation, vasoconstriction and susceptibility for thrombosis. These effects further increase the cardiovascular burden by worsening hypertension, HF and other cardiovascular disorders in predisposed patients (Liu, Blet, Smyth, & Li, 2020; Oudit et al., 2009). Importantly, the accumulation of Ang II was positively associated to viral load and lung injury (Liu et al., 2020). Moreover, reduction in the activity and/or number of ACE2 leads to deficiency of Ang-(1–7) production and consequently loss of its anti-inflammatory, vasodilatory, and cardiovascular protective effects (Lelis, Freitas, Machado, Crespo, & Santos, 2019; Patel et al., 2016). Therefore, it is hypothesized that inhibition of RAAS may be helpful to attenuate the inflammatory storm and ameliorate end-organ damage. Interestingly, recent data indicates individuals with COVID-19 who are being treated with ACE inhibitors or ARBs, for pre-existing conditions, are at lower risk of 28-day all-cause mortality than those not treated with ACE inhibitors or ARBs (Wang et al., 2020; Zhang et al., 2020). Although ARBs and ACE inhibitors do not directly impact ACE2, they indirectly elevate ACE2 activity and the beneficial Ang-(1–7) production and counter the excessive production of the harmful Ang II (Hanff, Harhay, Brown, Cohen, & Mohareb, 2020). Therefore, it was proposed that maintaining the levels of ACE2 and its downstream effector Ang-(1–7) may limit cardiovascular damage secondary to COVID-19 (Wang, Edin, et al., 2020).

Interestingly, several reports showed that n-3 PUFAs can regulate the RAAS system by modulating both Ang II and ACE2 levels. For instance, emerging literature indicates n-3 PUFAs and their endogenously generated metabolites can directly reduce the expression and activity of ACE, thereby reducing angiotensin II formation and cardiovascular burden (Kumar & Das, 1997). Moreover, it has been demonstrated that supplementation of mice with an n-3 PUFA rich diet for three weeks resulted in attenuated Ang-II-induced blood pressure via up-regulation of ACE2 (Ulu et al., 2013). Alternatively, as previously discussed, incorporation of n-3 PUFAs into the cell membranes will alter key properties, which can consequently affect protein number and affinity of SARS-CoV-2 to ACE2 (Candelario & Chachisvilis, 2013; Das, 1999, 2020b; Glende et al., 2008). Together, these studies suggest

a novel role for n-3 PUFAs in regulating SARS-CoV-2 infection where the potential benefit as an adjuvant therapy involves increasing the production of Ang-(1-7) and reducing the levels of Ang II, thereby limiting COVID-19-triggered cardiovascular complications.

Importantly, evidence demonstrating upregulation and enhanced activity of ACE2 suggested it will facilitate the infectivity of SARS-CoV-2 (South, Diz, & Chappell, 2020). Accordingly, some researchers proposed that ACE inhibitors and ARBs should be discontinued in COVID-19 patients (Diaz, 2020; Esler & Esler, 2020). However, in addition to the direct effects on cardiac ACE2 other mechanisms such as triggering a cytokine storm will markedly contribute to SARS-CoV-2-induced injury (Chen, Li, Chen, Feng, & Xiong, 2020). A recent study conducted by Yang et al., demonstrated COVID-19 patients with hypertension using ACE inhibitors/ARBs had lower mortality rates than hypertensive COVID-19 patients that were not on ACE inhibitors/ARBs (Yang et al., 2020). Moreover, Mancía et al. examined 6272 patients and found no association between RAAS inhibitor use and susceptibility or development of COVID-19 (Mancía, Rea, Ludergrani, Apolone, & Corrao, 2020). In that sense, a published statement by American Heart Association (AHA), the American College of Cardiology (ACC) and the Heart Failure Society of America strongly recommended continuation of ACE inhibitor/ARBs (Zhang, Zhu, Cai, et al., 2020). Together, these data suggest therapies targeting ACE and Ang II do not appear to increase the likelihood of SARS-CoV-2 infection, but may have a role in abrogating the inflammatory response and vasoconstriction that contributes to the clinical deterioration in COVID-19 patients.

In summary, evidence has demonstrated infection with SARS-CoV-2 induces internalization and downregulation of ACE2, which may aggravate a patient's condition by limiting the degradation of Ang II. Elevated Ang II levels induce several detrimental effects on the cardiovascular system including elevated blood pressure, excessive recruitment and infiltration of inflammatory immune cells to the heart as well as increased secretion of pro-inflammatory cytokines. Reduced ACE2 levels are associated with decreased formation of Ang-(1-7) and thus loss of its vasodilatory, anti-inflammatory and CVD-protective effects. Therefore, intervention with treatments to correct an imbalance in the RAAS system, such as ACE inhibitors, ARBs and n-3 PUFAs, can possibly improve the outcomes.

8.5. N-3 PUFAs possess anti-oxidant properties

The pneumonia-induced hypoxemia caused by RNA virus infections reduces the energy production from cell metabolism, increases the anaerobic fermentation, intracellular acidosis and the generation of ROS (Li et al., 2020). The subsequent increased ROS production causes damage to different cellular components including the DNA, lipids and proteins. The increased ROS levels will deplete the antioxidant defense system resulting in severe oxidative stress and chronic activation of immune responses, aggravating tissue injury and damage (Khomich, Kochetkov, Bartosch, & Ivanov, 2018; Reshi, Su, & Hong, 2014).

Several studies reveal n-3 PUFAs possess anti-oxidant properties attributable to their ability to up-regulate anti-oxidant enzymes (e.g. superoxide dismutase), down-regulate pro-oxidant enzymes (e.g. nitric oxide synthase) and potential to interact directly with free radicals. Antioxidant effects of n-3 PUFAs have been demonstrated in different organs including lungs, kidneys and the cardiovascular system (Darwesh et al., 2020; Darwesh, Jamieson, et al., 2019; Darwesh, Keshavarz-Bahaghighat, et al., 2019; De Caterina, 2011; Mozaffarian & Wu, 2011). Anderson et al. reported patients were administered a moderately high dose of n-3 PUFAs (3.4g/day EPA and DHA ethyl-esters) for a period of 2-3 weeks before having elective cardiac surgery and then myocardial tissue was dissected from the right atrium during surgery. Intriguingly, myocardial tissues obtained from patients displayed improved antioxidant capacity attributed to increased expression and activity of key antioxidants such as glutathione peroxidase-1, glutathione peroxidase-4, NADPH-quinone oxido-reductase-1, thioredoxin reductase-2 and total

glutathione compared to the control patients. Moreover, the mitochondrial outer membrane-bound enzyme monoamine oxidase, a substantial generator of ROS, was also determined to have significantly lower activity in myocardial tissue obtained from n-3 PUFA-treated patients (Anderson et al., 2014). Interestingly, isolated mouse hearts perfused with DHA derived epoxy lipids had improved postischemic recovery which correlated with better activities of the antioxidants thioredoxin-1 and thioredoxin-2 (Darwesh, Jamieson, et al., 2019). Importantly, with COVID-19, especially in advanced stages and in ICU, severe inflammation, hypoxemia and mechanical ventilation with high oxygen concentrations will inevitably increase ROS generation locally and systemically notably within the lungs and the heart. Thus, it can be hypothesized that increased n-3 PUFAs and their corresponding metabolites would provide beneficial control of exaggerated inflammation and ROS production.

8.6. N-3 PUFAs have the potential to ameliorate coagulopathy

Laboratory examinations from COVID-19 patients indicate serious coagulopathy has occurred in some individuals. This is reflected by widespread microvascular thrombosis and consumption of coagulation factors as evidenced by markers such as thrombocytopenia, prolongation of the prothrombin, elevation of D-dimer, increased fibrin degradation product levels and decreased fibrinogen levels (Tang et al., 2020). In a study with 184 Dutch ICU COVID-19 patients, 38% were reported to have abnormal blood clotting and 33% with identified clots (Klok et al., 2020). Importantly, blood clots may cause lung emboli, cardiovascular complications or stroke. In addition, long-term bed rest has been linked to increased risk of venous thromboembolism in severe SARS-CoV-2 infected patients (Iba, et al., 2019; Zhang et al., 2020). Accordingly, the active application of anticoagulants (such as heparin) for patients with severe SARS-CoV-2 infection has been recommended and appears to be associated with better prognosis (Tang, Bai, et al., 2020). Tang et al. recently published a study indicating anticoagulant therapy, mainly with low molecular weight heparin, is associated with better prognosis in severe SARS-CoV-2 infected patients (Tang, Bai, et al., 2020).

N-3 PUFAs contain polar lipids that exhibit potent antithrombotic effects against platelet-activating factor and other prothrombotic pathways, including thrombin, collagen, and adenosine diphosphate (Lordan et al., 2020; Tsoupras et al., 2019; Tsoupras, O'Keefe, Lordan, Redfern, & Zabetakis, 2019). Increased levels of n-3 PUFAs may alter platelet phospholipid membrane composition and affect platelet function, which can be predicted to alter the progression and thrombotic complications of CVD. Adili et al. outlined that EPA and DHA act on the platelet membrane to reduce platelet aggregation and TX release via COX-1 and 12-LOX, which metabolize fatty acids into a group of beneficial oxylipins in platelets that contribute significantly to the regulation of platelet function in hemostasis and thrombosis (Adili, Hawley, & Holinstat, 2018). This is supported by Park and Harris who demonstrated healthy subjects supplemented with EPA for 4 weeks had reduced platelet activation, an early step in platelet aggregation (Park & Harris, 2002). While the evidence is limited, it appears EPA is more active than DHA in altering platelet function because it is a COX substrate. However, DHA appears to decrease TxA2 and PGH2 receptor affinity (Park & Harris, 2002). Although dietary supplementation of EPA and DHA has been shown to reduce platelet activation and aggregation in healthy subjects, a higher recommended dose of n-3 PUFAs may be needed in platelet hyperactivity prothrombotic conditions such as in CVD (Adili et al., 2018). These anticoagulant properties of n-3 PUFAs suggest potential effects on the platelet aggregation in severe cases of SARS-CoV-2 infected subjects. Our current level of knowledge only permits speculation on whether n-3 PUFAs can mitigate the coagulopathy associated with severe COVID-19.

8.7. Lipid-lowering properties of n-3 PUFAs in the context of COVID-19

Patients with comorbidities such as diabetes, dyslipidemia, aberrations in plasma cholesterol and triglycerides and coronary heart disease are more susceptible to severe COVID-19 outcomes such as cardiac complications, sepsis, ARDS and death (Chen et al., 2020; Petersen et al., 2020; Shi et al., 2020; Wang, Hu, et al., 2020; Zhou, Yu, et al., 2020). The acute inflammatory syndrome associated with COVID-19 has the capacity to destabilize plaques, which can lead to ischemic events (Madjid et al., 2007). Recent studies indicated serum triglyceride concentrations were significantly higher in individuals who died as a result of COVID-19 likely due to augmented inflammatory TNF- α levels causing reduced lipoprotein lipase activity (Chen, Wu, et al., 2020; Skevaki, Fragkou, Cheng, Xie, & Renz, 2020). Triglyceride-glucose index, a product of fasting triglyceride and fasting plasma glucose levels, is used as a surrogate marker for insulin resistance (Ren et al., 2020). COVID-19 patients with a higher triglyceride-glucose index have been shown to experience more severe COVID-19 infection and death. Furthermore, levels of high density lipoprotein cholesterol (HDL-c) are also reduced in COVID-19 patients with the magnitude of reduction correlating with disease severity (Hu, Chen, Wu, He, & Ye, 2020). Generally, HDL-c is considered to be anti-inflammatory and antithrombotic (Suzuki et al., 2010; van der Stoep, Korporaal, & Van Eck, 2014). So, the robust, maladaptive inflammatory and hypercoagulability responses observed in more severe COVID-19 cases could possibly be attributed – in part – to reduced levels of HDL-c and a dysregulated lipid profile. Given the potential for COVID-19 infection to alter the lipid profile acutely and the association of dyslipidemia with conditions such as diabetes, coronary artery disease, and obesity raises the question whether normalization of plasma lipid profiles in COVID-19 patients can offer clinical benefit.

Use of statins and other lipid-modulating therapies can reduce the risk of primary or secondary cardiovascular events in at-risk individuals, including those with diabetes, metabolic syndrome, and coronary artery disease – conditions that are risk factors for severe COVID-19 outcomes (Stone et al., 2013). A large retrospective study of over 13,000 COVID-19 patients has shown the in-hospital use of statin therapy, potent lipid-lowering agents with anti-inflammatory properties, was associated with a reduced rate of mortality compared to non-statin users (Zhang, Qin, Cheng, et al., 2020). This important study disrupts the previous dogma that statins may enhance the COVID-19 virus pathology via ACE2 expression and may in fact be overwhelmingly beneficial in the treatment of COVID-19. However, despite statin monotherapy, many patients with dyslipidemia still suffer from persistently elevated triglyceride levels which may continue to be a risk factor for coronary artery disease, cardiac events and more severe COVID-19 infection outcomes (Ballantyne et al., 2012; Davidson, et al., 2007). The triglyceride-lowering effect of n-3 PUFA supplementation has been demonstrated in a plethora of clinical trials (Abdelhamid et al., 2020; Ballantyne et al., 2012; Chan et al., 2003; Maki et al., 2013; Yanai et al., 2018; Zhou et al., 2019). Lower levels of triglycerides present a lower risk of developing a cytokine storm based on the score from the available secondary haemophagocytic lymphohistiocytosis score system (Mehta, et al., 2020). Additionally, n-3 PUFAs have been shown to significantly lower CRP in patients with hypertriglyceridemia (Ballantyne et al., 2012). Thus, the rationale for the use of n-3 PUFAs in COVID-19 patients not only focuses on the attenuation of the infection-induced respiratory disorders but also on an overall improvement of patients' wellbeing and prevention of potential complications due to comorbidities.

9. When and how to intervene with n-3 PUFAs in the context of COVID-19

An important aspect in considering n-3 PUFAs as adjunctive therapy in critically or severe ill patients is the time of intervention, duration of treatment, dose, composition of the preparation and route of administration. The type and intensity of supportive treatment required by a

patient is dependent upon the severity of disease and the possible need for hospitalization. Existing literature demonstrates it may take weeks or months for standard doses of n-3 PUFAs to exert a biological effect due to a gradual replacement of membrane AA. It has been hypothesized the acute supplementation with n-3 PUFAs may influence the inflammatory response in critically ill patients, particularly those with ALI (Martin & Stapleton, 2010). For example, a randomized clinical trial showed daily enteral feeding of critically ill ALI patients with elevated levels EPA, DHA and gamma-linolenic acid significantly reduced lung inflammation and improved oxygenation by 4 days. This was associated with a decreased duration of mechanical ventilation, ICU length of stay and mortality (Gadek et al., 1999; Singer et al., 2006). In a trial conducted by Pontes-Arruda et al. who studied patients with sepsis requiring mechanical ventilation, a diet enriched with EPA, gamma-linolenic acid and antioxidants delivered at a constant rate during a minimum of 4 days contributed to better ICU and hospital outcomes, oxygenation status, ventilator-free days and was associated with lower mortality at 28-day interval (Pontes-Arruda et al., 2006).

There are many studies suggesting the beneficial effects of parenteral fish oil emulsions in critically ill patients. For example, parenteral supplementation of severe ill patients with lipid emulsions containing fish oil was associated with reduced inflammation, improved gas exchange and shorter length of ICU and hospital stay (Zhao & Wang, 2018). In a study by Mayer et al., patients with sepsis were randomized in an open-label trial to receive an omega-3 FA rich lipid emulsion or a standard omega-6 rich lipid emulsion for 5 days. Within 2 days of fish oil infusion, free n-3 fatty acids increased and the n-3/n-6 ratio was reversed favoring EPA and DHA over AA, with rapid incorporation of n-3 fatty acids into mononuclear leukocyte membranes and reaching maximum effect in 3 days (Mayer et al., 2003). Furthermore, a parenteral lipid emulsion enriched in n-3 PUFA for 7 days was found to reduce acetic acid-induced colitis in rats (Campos et al., 2002). In a randomized controlled trial conducted by Wang et al., patients with severe acute pancreatitis were randomly assigned to receive parenteral nutrition for 5 days containing similar amounts of amino acids, glucose and fat but different lipid compositions: the control group received a soybean oil-based fat solution and the omega-3 group received fish oil. Interestingly, patients treated with the fish oil or n-3 PUFAs had a markedly lower inflammatory marker CRP and better oxygenation index after 5 days of parenteral nutrition (Wang, Li, Li, & Li, 2008).

Together, these studies demonstrated that acute enteral or parenteral administration of n-3 PUFAs in the setting of severe illness could significantly improve the clinical outcomes. Notably, it has been shown that fish oil emulsions containing substantial amounts of EPA and DHA have an excellent safety record in both critically ill adults and children (Calder, 2009, 2019; Nandivada, Fell, Gura, & Puder, 2016) making them a suitable candidate for use in severe stress conditions as in COVID-19 patients. However, with the research that has been completed to date, it is not possible to definitively determine the dose, route of administration and the best timing to intervene with n-3 PUFAs in the setting of COVID-19. More research is undoubtedly needed before definitive recommendations about the routine use of n-3 PUFAs in the context of COVID-19 can be made particularly that dosing data and pharmacokinetics studies of both enteral and parenteral n-3 PUFAs in critically ill patients are highly variable and incomplete.

10. Summary and conclusion

In summary, COVID-19 is rapidly spreading around the globe and our understanding of the virus is limited. To date, there is no effective, approved therapy or vaccination to treat the disease or protect against its complications. Although the lungs are considered the main target organ of SARS-CoV-2, the virus can affect many other organs, leading to multiple organ damage. Cardiovascular injury has been noted as a protruding clinical feature in COVID-19 patients. The dysregulation of RAAS can lead to a harmful inflammatory response and worsening of

cardiovascular consequences in patients with COVID-19. Therefore, intervention with drugs that counteract Ang II may have a potential role in preventing the deleterious cardiovascular outcomes. Although increased ACE2 levels may raise the concern of increased SARS-CoV-2 infectivity, we propose here that n-3 PUFAs may be beneficial rather than harmful for cardiovascular outcomes in COVID-19 patients by limiting Ang II-induced detrimental signaling and enhancing Ang (1-7) cardioprotective effects.

In this review we highlight the different mechanisms of cardiovascular complications secondary to COVID-19 and draw attention toward the potential roles n-3 PUFAs in mitigating these cardiovascular complications. Currently, there is no direct evidence of any beneficial or deleterious effect of n-3 PUFAs in COVID-19 patients. However, it is evident from the preceding discussion the dietary or non-dietary intake of n-3 PUFAs and/or their biologically active metabolites have many beneficial actions leading to prevention and management of cardiovascular complications. N-3 PUFAs and/or their biologically active metabolites have the potential to modulate many of the adverse effects of an exaggerated immune response, inactivate enveloped viruses, enhance macrophage phagocytic capacity, ameliorate coagulopathy, modify cell signaling and gene expression, shift the pattern of the lipid metabolites produced under stress conditions to a more anti-inflammatory metabolite profile and enhance the anti-oxidative capacity of the heart. Despite these promising effects of n-3 PUFAs, more experimental, randomized control trials and epidemiological research is warranted to test and translate these proposed effects in the setting of SARS-CoV-2 infection.

Authors contributions

A.D. and J.M.S. designed the outline of the review, A.D. screened the studies, extracted the data and wrote the manuscript. W.B. and D.S. provided significant contribution to the content of the review. J.M.S. reviewed and edited the manuscript.

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Declaration of Competing Interest

The authors declare that there are no conflicts of interest.

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