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## Statins and SARS-CoV-2 disease: Current concepts and possible benefits



Madhu Mary Minz, Manish Bansal\*, Ravi R. Kasliwal

Department of Cardiology, Medanta- the Medicity, Gurgaon, India

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### ABSTRACT

**Background and aims:** Inflammation-mediated tissue injury is the major mechanism involved in the pathogenesis of coronavirus disease 2019 (COVID-2019), caused by Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2). Statins have well-established anti-inflammatory, anti-thrombotic and immuno-modulatory effects. They may also influence viral entry into human cells.

**Methods:** A literature search was done using PubMed and Google search engines to prepare a narrative review on this topic.

**Results:** Statins interact with several different signaling pathways to exert their anti-inflammatory and vasculoprotective effects. They also variably affect cholesterol content of cell membranes and interfere with certain coronavirus enzymes involved in receptor-binding. Both these actions may influence SARS-CoV-2 entry into human cells. Statins also upregulate expression of angiotensin-converting enzyme 2 receptors on cell surfaces which may promote viral entry into the cells but at the same time, may minimize tissue injury through production of angiotensin [1-7]. The net impact of these different effects on COVID-19 pathogenesis is not clear. However, the retrospective clinical studies have shown that statin use is potentially associated with lower risk of developing severe illness and mortality and a faster time to recovery in patients with COVID-19.

**Conclusions:** Early observations suggest beneficial effect of statin use on the clinical outcomes in COVID-19. Prospective randomized studies as well as well-designed laboratory studies are required to confirm these observations and to elucidate the mechanisms of such benefits, if proven.

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The coronavirus disease 2019 (COVID-2019) has emerged as the greatest public health challenge of our lifetime, causing destruction of unprecedented magnitude. As on Oct 12, 2020, 235 countries/area/territories across the world have got infected with the virus, with 37.1 million confirmed cases and 1.07 million deaths [1]. The pandemic continues unabated, with several countries initially showing signs of recovery experiencing second peaks subsequently.

The rapid spread of COVID-19 at such a mass scale resulting in high global morbidity and mortality burden have led to frantic efforts to find effective treatment options for this illness, as well as to develop an effective vaccine. Since no specific treatment is available for COVID-19 at present, there has been an interest in repurposing of old drugs such as hydroxychloroquine and dexamethasone for combating this dreaded disease [2]. Statins are one such drug class which may have potential benefits in COVID -19 patients. Since

statins are inexpensive, easily available, and already in wide use for cardiovascular disease prevention, the initial favorable findings have spurred considerable interest in further exploring their role, efficacy and the underlying mechanisms of their benefits in COVID-19. This review summarizes the current understanding in this field.

### 1. Search methods

A literature search was done using PubMed and Google search engines for original and review articles, meta-analyses and expert commentaries published in relation to the role of statins in COVID-19. Search terms “COVID-19” and “coronavirus” were used in combination with “statins”. Relevant cross-references from these publications were also explored.

\* Corresponding author. Clinical and Preventive Cardiology, Medanta- The Medicity, Sector 38, Gurgaon, Haryana, 122001, India.  
E-mail address: [manishaiims@hotmail.com](mailto:manishaiims@hotmail.com) (M. Bansal).

## 2. Results

### 2.1. Rationale for statin use in COVID-19

Besides their lipid lowering effects, statins are known to have pleiotropic effects on inflammation and oxidative stress. They are known to reduce reactive oxygen species, augment antioxidant pathways and ameliorate nitric oxide bioavailability, thereby restoring vascular redox balance and improve endothelial function. Statins also modulate immune response working at different levels such as immune cell adhesion, migration, antigen presentation and cytokine production. These actions are mediated by statin-induced inhibition of production of isoprenoids which are basic units of small guanosine triphosphatases (such as Ras, Rho, Rac). Reduced isoprenoid production leads to downregulation of redox sensitive pro-inflammatory transcriptional factors such as nuclear factor kappa light chain enhancer of activated B cells (NF- $\kappa$ B) [3].

As an add-on therapy, statins have shown a beneficial role in various autoimmune inflammatory conditions such as systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis, graft versus host disease, etc. [3]. Additionally, statins have also been promising in several viral infections such as Avian influenza, H1N1 pandemic, and possibly also in Ebola outbreak in West Africa [4–8]. The Severe Acute Respiratory Syndrome-Coronavirus-1 (SARS-CoV-1), predecessor of SARS-CoV-2 causing the current COVID-19 pandemic, reacts with Toll-like receptors (TLR) on host cell membrane and increases myeloid differentiation factor 88 (MYD88) gene expression. MYD88 then activates NF- $\kappa$ B which triggers inflammatory cascade [6,9]. Inhibition of NF- $\kappa$ B has shown reduced lung infection and increased survival in murine models [10]. Experimental models have revealed that statins stabilize MYD88 levels and inhibit NF- $\kappa$ B through different pathways [11,12]. These evidences have provided the basis for exploring the role of statins in COVID -19.

### 2.2. Pathogenesis of COVID-19

SARS-CoV-2 binds to angiotensin-converting enzyme 2 (ACE2) present on type II pneumocytes in lungs, and on cellular surfaces in heart and vascular endothelium. The entry of virus is facilitated by interaction of receptor binding domain in its viral spike glycoprotein ectodomain with ACE2 receptors [13]. Inside the cells, the virus undergoes replication followed by exocytosis and release of mature virions.

The endocytic activity involved in the entry of the virus into the cells upregulates the activity of A Disintegrin And Metalloproteinases domain 17 (ADAM17), which cleaves ACE2 from the cell membrane. ACE2 is responsible for converting angiotensin II to angiotensin [1–7], which has several beneficial properties including vasodilatory, anti-inflammatory and antifibrotic effects [14,15]. Therefore, the reduced availability of ACE2 on cell surfaces results in a loss of ACE2-mediated protection against the deleterious effects of tissue renin-angiotensin-aldosterone system activation.

SARS-CoV-2 can also generate a multisystem inflammatory cascade due to cytokine storm by activating TLR3, TLR7, TLR8 and TLR9. There is triggering of downstream inflammatory cascade through MYD88-NF- $\kappa$ B pathway leading to increased production of pro-inflammatory agents like interleukin-1 (IL-1), IL-2, IL-3, IL-4, IL-6, which causes an increase in vascular permeability, alveolar epithelial damage, etc. resulting in acute respiratory distress syndrome [16].

COVID -19 infection also leads to coagulopathy and thromboembolic complications such as systemic venous thrombosis and pulmonary embolism [16].

### 2.3. Potential mechanisms of the effects of statins in COVID-19

Statins have several different effects which are relevant to COVID-19 (Fig. 1), These are summarized below.

#### 2.3.1. Anti-inflammatory effects

As anti-inflammatory agents, statins inhibit synthesis of isoprenoids which is important in generation of inflammation signaling molecules like Rho and Ras. Statins also bind to novel allosteric sites in the  $\beta$ 2-integrin and inhibit leucocyte adhesion molecule and T-cell activation [17].

Statins also down regulate expression of MYD88-NF- $\kappa$ B pathway and reduce expression of pro-inflammatory cytokines like IL-6, IL-8 and monocyte chemoattractant protein-1, thereby altering inflammatory pathway for host cell damage [11,12,17]. Statins also downregulate TLR-mediated inflammatory activation.

#### 2.3.2. Anti-thrombotic and vessel wall effects

Statins are well-known to increase production of nitric oxide, improve vascular endothelial function and possess antithrombotic properties through inhibition of platelet aggregation and minimizing production of procoagulant mediators such as plasminogen activator inhibitor-1 [18].

#### 2.3.3. Effects on virus entry into the cells

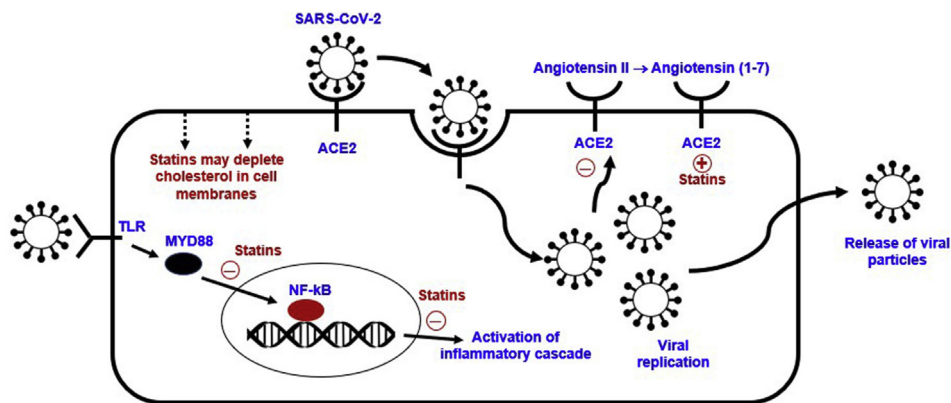
Several different theories have been proposed to describe the potential effects of statins on entry of SARS-CoV-2 into human cells. Both favorable and unfavorable effects have been suggested.

**2.3.3.1. Role of cell membrane cholesterol content.** The binding of SARS-CoV-2 receptor binding spikes to ACE2 receptors present on the cell surfaces is facilitated by the presence of lipid rafts on the cell membranes. It has been shown that depletion of cholesterol content of the cell membranes with agents such as cyclodextrin interferes with this process and hampers viral entry into the cells. Conversely, enrichment of cell membranes with cholesterol may promote viral entry [19–22].

The effect of statins on cell membrane cholesterol content is debated. Some investigators believe that statins, by reducing endogenous synthesis of cholesterol, deplete cell membranes of their cholesterol content [23]. On the contrary, the other investigators have suggested that reduced circulating cholesterol levels increase upregulation of low-density lipoprotein receptors on cell surfaces, thereby increasing cholesterol uptake from the circulation [24]. Statins also inhibit acylCoA:cholesterol acyltransferase (ACAT) present in endoplasmic reticulum, which is also responsible for removing cholesterol from the cell membranes. A recent study has shown that SARS-CoV-2 induces one of the interferon-stimulated genes cholesterol 25-hydroxylase (CH25H) in vitro and in COVID-19 patients. CH25H converts cholesterol to 25-hydrocholesterol (25HC) which activates ACAT, thereby preventing fusion of SARS-CoV-2 with cell membranes and viral entry into the cells. The effect of 25HC on preventing entry into the lung epithelial cells has been specifically demonstrated for USA-WA1/2020 isolate of SARS-CoV2 [25]. Inhibition of ACAT by statins may adversely impact this.

These opposing theories regarding the impact of statins on the cholesterol content of the cell membranes create uncertainty. Nevertheless, studies employing human respiratory epithelial cell cultures have demonstrated that statins such as Fluvastatin successfully inhibit SARS-CoV-2 entry into the cells [23].

**2.3.3.2. Effect on ACE2 expression.** Statins, just as ACE inhibitors and angiotensin-receptor blockers, are known to upregulate ACE2 expression on human cells [5,6]. It has been suggested that this



**Fig. 1.** Proposed molecular mechanisms involved in the effects of statins in coronavirus disease 2019. SARS-CoV-2, the causal agent of coronavirus disease 2019, enters the cell by binding to ACE2. Once in the cell, SARS-CoV-2 causes ACE2 down-regulation, thus reducing its protective effects mediated through conversion of angiotensin II to angiotensin [1–7]. Statins upregulate ACE2. Coronaviruses are also known to induce a pro-inflammatory host response via the activation of the TLR–MYD88–NF-κB pathway, which is inhibited by statins. Finally, statins may also reduce viral entry by depleting cholesterol content in cell membrane, but this effect remains controversial. ACE2-angiotensin-converting enzyme 2; MYD88-myeloid differentiation factor 88; NF-κB- nuclear factor kappa light chain enhancer of activated B cells; SARS-CoV-2- Severe Acute Respiratory Syndrome-Coronavirus-2; TLR- Toll-like receptor.

effect may increase susceptibility to SARS-CoV-2 infection.

Conversely, increased expression of ACE2 has been suggested to be a beneficial effect rather than a harmful one [5,14]. ACE2-mediated conversion of angiotensin II to angiotensin [1–7] has been shown to minimize lung injury in patients infected with coronaviruses [15].

**2.3.3.3. Other mechanisms.** A recent in silico docking study has suggested that statins inhibit SARS-CoV-2 Main protease (Mpro), a key coronavirus enzyme [26]. Disruption of this protease activity can interfere with viral infection by inhibition of viral glycoprotein processing. However, it is unclear whether this effect is also seen at the statin concentrations achieved at the doses used in the clinical practice.

**2.3.4. Cardiovascular benefits**

Epidemiological studies have shown that the patients with pre-existing cardiovascular disease are at a greater risk of contracting the infection as well as developing severe COVID-19 illness [27]. At the same time, the COVID-19 illness itself can lead to several cardiovascular complications. Statins have well-established efficacy in reducing the risk of cardiovascular events in a wide variety of patient populations [28,29]. Therefore, apart from any potential direct effect of statins on COVID-19, statins are as such helpful in reducing

the risk of cardiovascular complications in these patients and improving their clinical outcomes.

**2.4. Clinical outcomes with statins in COVID-19**

Several observational studies have evaluated the potential beneficial role of statins in COVID-19 [30–34] (Table 1). Zhang et al. performed a large retrospective cohort study of 13,981 COVID -19 patients in Hubei Province in China, among them 1219 received statins [31]. They observed a significantly lower crude 28-day mortality in statin group (mortality rate 5.5%) as compared to non-statin group (mortality rate 6.8%, P = 0.046). The mixed effect Cox model after propensity score matching found that the risk of 28-days all-cause mortality was 5.2% in the statin group and 9.4% in the non-statin group with adjusted hazard ratio of 0.58. The patients on statins were also found to have lower levels of c-reactive protein and IL-6 [31].

Daniels et al. recently published a retrospective single center study that looked at all patients hospitalized at their center between February 10, 2020 to 7 June 17, 2020 [30]. A total of 170 patients were found to be SARS-CoV-2 positive, of which 53% developed severe disease. It was observed that statin use prior to admission was associated with substantially lower risk of developing severe COVID disease (adjusted odds ratio 0.29, 95%

**Table 1**  
Salient studies evaluating the effect of statin use on clinical outcomes in COVID-19.

Study	Country	Study Design	Total no of patients	No of patients on statin	Key findings
Spiegeleer et al. June 2020 [32]	Belgium	Retrospective multicenter cohort (nursing home residents)	154	30	Significant association seen between use of statin and absence of symptoms during COVID-19 (odds ratio 2.91; confidence interval 1.27–6.71), which remained statistically significant after adjusting for covariates (odds ratio 2.65; confidence interval 1.13–6.68)
Rodriguez Nava et al. June 2020 [33]	USA	Retrospective cohort (intensive care unit patients)	87		In the multivariable Cox-proportional hazards regression model, statin (atorvastatin was used) non-users had a 73% chance of faster progression to death compared with statin users
Zhang et al. August 2020 [31]	China	Retrospective	13981	1219	Mortality rate 5.2% in the statin group and 9.4% in the non-statin group with adjusted hazard ratio of 0.58
Daniels et al. September 2020 [30]	USA	Retrospective cohort	170	27%	More than 50% reduction in severe COVID-19 disease and faster rate of recovery in the statin group

COVID-19- coronavirus disease 2019.

confidence interval 0.11 to 0.71,  $p < 0.01$ ). Statin use was also associated with a faster time to recovery among those without severe disease after controlling for comorbidities. The beneficial effect of statin use on reducing the risk of developing severe disease was also seen in COVID negative inpatients ( $n = 5281$ ), but this association was much weaker than that in COVID positive patients [30].

Another retrospective multi-centric cohort study on 154 COVID-19 positive vulnerable old population living in Belgian nursing homes showed a statistically significant association between statin intake and absence of symptoms during COVID-19 [32].

Statin use has also been shown to be associated with a lower risk of thromboembolic complications, including pulmonary embolism, in patients with COVID-19 [34].

Kow CS et al. published a meta-analysis of relevant studies evaluating statin effect on clinical outcomes in COVID-19 [35]. Four studies with a total of 8990 COVID-19 patients were included in this analysis, but two of these studies only inadequately described the relationship between statin use and clinical outcomes. Nevertheless, this pooled analysis revealed 30% lower hazard (pooled hazard ratio 0.7, 95% confidence interval 0.53–0.94) for fatal or severe disease with the use of statins compared to non-use of statins [35].

### 2.5. Implications for Indians

Dyslipidemia is widely prevalent among Indians with an estimated prevalence of 25–30% in urban populations and 10–15% in rural populations [36]. Indians and South Asians are also fivefold more prone for myocardial infarction and cardiovascular death [37] as compared to Caucasians and tend to develop cardiovascular disease at an early age (often before the age of 40 years) [38].

Despite these statistics, statin usage among Indians has been generally low. Choudhary et al. analyzed the prescription data for the period 2006–2009 and found that statins were being under prescribed in India with only 84.1 per 1000 patients with coronary heart disease using statins [39]. The overall usage of statins in the general population was also low, at 3.36 per 1000 people.

These findings assume greater significance in the context of COVID-19 pandemic. India has so far recorded the second largest number of documented COVID-19 cases in the world and 50000–80000 new cases are being reported every day [1]. If beneficial effects of statins in COVID-19 are proven in large, randomized studies, this would be yet another reason for rapidly upscaling usage of statins in India. Statins are easily available and very affordable in India and have good safety profile. Efforts to increase their usage in the population with documented cardiovascular disease alone could yield significant benefits, esp. because these are the patients who are at greater risk of developing severe COVID-19 disease and mortality [27].

### 3. Conclusions

COVID-19 is the largest pandemic of our lifetime. In the absence of a definite treatment for this illness at present, several innovative approaches are being evaluated. Statins have well-established anti-inflammatory, anti-thrombotic and immuno-modulatory effects. Initial retrospective clinical studies have shown that statin could potentially improve clinical outcomes in COVID-19 patients. If these benefits are proven in randomized studies, statins could become a useful therapeutic option for COVID-19, due to their low cost, easy availability, well-established safety and tolerability, and enormous clinical experience with their use for other indications.

### Declaration of competing interest

All the undersigned authors declare that we have no conflict of interest in relation to this manuscript.

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