Statins, COVID-19, and coronary artery disease: killing two birds with one stone

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Abbreviations: ACE2: angiotensin-converting enzyme 2; ARDS: Acute respiratory distress syndrome; COVID-19: Coronavirus disease 2019; CVD: Cardiovascular disease; LDL: low-density lipoprotein; MERS-CoV: Middle East respiratory syndrome coronavirus; MYD88: Myeloid differentiation primary response 88; NF-kB: nuclear factor kappa-light-chain-enhancer of activated B cells; SARS-CoV: Severe acute respiratory syndrome coronavirus; TLR: Toll-like receptor.

Although various pharmacologic agents are under active study [1], there are currently no effective and evidence-based antiviral drugs or drug combinations against severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection, namely coronavirus disease 2019 (COVID-19). Therefore, supportive therapy and active treatment of COVID-19 clinical manifestations by using feasible and currently available agents, especially Food and Drug Administration (FDA)-approved drugs, still remains an essential therapeutic approach [2-4].

To this regard, great interest has risen with respect to the potential beneficial effects against COVID-19 of drugs that are currently used for cardiovascular prevention [3,5]. Indeed, although the main clinical manifestations of COVID-19 involve the respiratory system, an increased risk of cardiovascular complications, including myocarditis, cardiac arrhythmias, and arterial and venous thrombosis, has been reported in COVID-19 patients [6-8]. In addition, underlying cardiovascular diseases (CVDs) and/or cardiovascular risk factors (*e.g.*, smoking, diabetes, obesity) have been associated with an increased risk of severe clinical complications and death in COVID-19 patients [6-12].

Whether statins may be re-purposed to treat COVID-19 patients is a matter of debate. There are several points that are worthy of being considered in support of possible beneficial effects of statins against COVID-19. First, statins are widespread, available, low-cost, and safe cholesterol-lowering drugs, that have been extensively demonstrated to reduce significantly CVD risk [13,14]. Each mmol/l reduction in LDL-cholesterol (LDL-C) reduces the risk of major cardiovascular events by about one quarter for each year statin therapy is continued [13,14]. Therefore, it is likely that statins may also mitigate CVD risk in COVID-19 patients. Second, due to their cholesterol-lowering activity and their pleiotropic effects, statins can inhibit inflammation, immune response, and oxidative stress [15-17], exert direct antiviral effects [18], improve endothelial function [19-21], and regulate hemostasis [22,23], potentially reducing the incidence of severe clinical manifestations and improving prognosis in COVID-19 patients. This latter point will be discussed in more depth in the following text.

Statins may conceivably protect against inflammation by controlling cytokine overexpression and modulating immune responses [15,16], thereby potentially preventing the development of acute distress respiratory syndrome (ARDS) and reducing the incidence of cardiovascular complications in COVID-19 patients. Indeed, statins have been shown to directly inhibit nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) (**Figure 1**), which is a crucial mediator of

inflammatory responses during infections, including those caused by coronaviruses [24]. In addition, they have been reported to negatively regulate the expression of toll-like receptor-4 (TLR4) and consequent activation of the TLR4-myeloid differentiation primary response (MYD)88-NF-kB signaling pathway, which plays a critical role in the recognition of pathogens and induction of the innate immune response against viral infections [25,26]. By counteracting cytokine storm statins may reduce the risk of myocardial injury and myocarditis in acute phases of COVID-19 [27]. In addition, statin-mediated anti-inflammatory effects may also promote stabilization of atherosclerotic plaques, thereby protecting from the occurrence of plaque rupture and cardiovascular events [8]. These effects provide an argument in support of statin continuation, even at high doses, for mitigating cardiovascular risk in the acute phases of COVID-19, especially in patients with manifest atherosclerotic CVD or CVD risk factors. Indeed, COVID-19-driven inflammation might promote atherosclerotic plaque instability [27]. In addition, although statin-mediated stabilization of atherosclerotic plaques is known to be time-dependent, there are reports showing that some modulation of inflammation and some reduction of plaque remodelling may be obtained also after a short period of treatment with high doses of statins [28,29]. However, it should be emphasized that they are currently lacking clinical studies showing a significant impact of statin therapy in reduction of incident cardiovascular events in COVID-19 patients.

Statins can exert some direct antiviral activity [18,30]. By inhibiting cholesterol synthesis, they can reduce the intracellular availability of a crucial compound for the viral cell cycle [31]. Indeed, the presence of cholesterol-rich subdomains on the plasma membrane of host cells, namely lipid rafts, is crucial for viral fusion and entry [18,30]. Furthermore, through cholesterol-dependent mechanisms, statins can inhibit the isoprenylation of different proteins (*e.g.*, RhoA, Rac, and Cdc42), which are critical downstream molecules regulating viral cell cycle [18,30]. To date, a number of observational studies have suggested that statin therapy can reduce the risk of various severe complications and mortality in patients admitted with Middle East respiratory syndrome coronavirus (MERS-CoV) infection and influenza [32-35]. Therefore, it is possible that the beneficial effects of statin therapy as an add-on treatment in viral infections could be extended to COVID-19. To this regard, it should be considered that a peculiar antiviral mechanism of action of statins against COVID-19 might consist of inhibition of SARS-CoV-2 entry into host cells due to the binding of its main protease [36]. Nonetheless, whether statin therapy may reduce the risk of SARS-CoV-2 infection still needs to be investigated.

Statins have well-known protective effects against endothelial dysfunction and injury [19-21]. Due to their ability to upregulate ACE2 signaling pathways *via* epigenetic histone modifications, statins might exert some beneficial effects in terms of endothelial protection in the supportive therapy of COVID-19 patients [37]. Indeed, high levels of ACE2 on pulmonary endothelium have been associated with reduced severity of ARDS [38]. In addition, by promoting endothelial repair statins might counteract SARS-CoV-2-induced endothelitis in lungs as a direct consequence of both infection of endothelial cells and the host inflammatory response [39,40], thereby potentially accelerating recovery from ARDS.

By inhibiting the activation of coagulation cascade and platelet function as well as increasing fibrinolytic activity, statins can exert antithrombotic effects [22] (**Figure 2**). Specifically, different statins have been shown to directly interfere with tissue factor expression, thrombin generation, fibrinogen cleavage, factor V and factor XIII activation, endothelial thrombomodulin expression, and platelet activation [22]. In addition, some inhibitory activity of statins on thrombus formation has been ascribed to their ability to modulate endothelial function and inflammatory response [22] (**Figure 2**). Arterial and venous thromboembolic events have been described as typical clinical features of severe COVID-19 [6-8]. Therefore, albeit being still not proved, it is plausible that statins might be useful to improve clinical outcomes of COVID-19 by reducing the incidence of COVID-19-related coagulopathy.

To date, most of available data from clinical studies support the protective effect of statins against SARS-CoV-2 infection. Indeed, a number of retrospective studies have shown lower inflammatory parameters, decreased incidence of severe clinical manifestations or reduced mortality rates in COVID-19 patients under statin treatment as compared to those not taking statins [41,42]. However, consistent evidence from prospective studies is not currently available. In addition, two recent meta-analyses of observational studies exploring the impact of statin therapy on COVID-19 outcomes have reported contrasting results [43,44]. Therefore, clinical trials investigating this issue are eagerly awaited.

Against the hypothesis of a clinical benefit of statin use in COVID-19 patients, some safety concerns need to be taken into account. The main doubt about the beneficial effects of statins as add-on therapy in COVID-19 may be raised when considering the possible detrimental impact of reduced low-density lipoprotein (LDL) cholesterol levels on COVID-19 prognosis, as suggested by some retrospective studies [45,46]. However, reverse causality (*i.e.*, viral infection as a cause

of LDL cholesterol reduction) instead of causality (*i.e.*, LDL cholesterol reduction as a factor promoting viral infection) might explain the association between LDL cholesterol and severe COVID-19 manifestations [47]. This could distract from refuting the potential benefits of statin treatment in this clinical setting.

Additional safety concerns may be raised considering the ability of statins to upregulate the expression of angiotensin-converting enzyme 2 (ACE2), which mediates SARS-CoV-2 entry into host cells [37,48]. However, such an effect may be clinically not significant if we assume that viral load is not necessarily related to the disease severity. Moreover, soluble ACE2 may bind to SARS-CoV-2, preventing it from fusion with the membrane of host cells and, therefore, inhibiting viral replication [48].

Another issue is represented by the risk of statin-related myotoxicity and hepatotoxity, which may be increased by drug-to-drug interactions between statins and antiviral, antiretroviral, antiparasitic, and antirheumatic drugs as well as antibiotics (mainly macrolides) that may be concomitantly administered to COVID-19 patients [49]. In some cases, either discontinuation of statin therapy or continuation with caution and at lower doses are possible options [49]. Nonetheless, when statin discontinuation is required, other lipid-lowering therapies could be considered, especially in patients at high CVD risk, which are more prone to undergo COVID-19 complications [49,50].

An additional reason for caution about statin therapy in COVID-19 patients may be the possible statin-mediated increase of lipoprotein(a), which is known to exert an anti-fibrinolytic activity by controlling the activity of plasminogen activators [51]. However, it should be emphasized that statin-mediated increasing effect on lipoprotein(a) is not consistent and in some cases may be not significant [52,53]. Therefore, it remains uncertain as to whether an increased thrombotic risk may be expected by statin impact on lipoprotein(a) levels in COVID-19 patients.

Further concerns are related to the observation that treatment with high-potency statins may be associated with an increased risk of incident type 2 diabetes, especially in obese patients [54]. Indeed, diabetes is a significant predictor of COVID-19 severe clinical manifestations. However, the risk of developing insulin resistance with initiation of statin therapy is relatively low according to available data [55]. Therefore, whether statin-induced diabetes may be a reason to discourage statin use in COVID-19 patients is questionable.

Finally, the benefit-risk balance of statin therapy should be carefully evaluated in older patients with COVID-19. Indeed, beyond being at higher risk of poor prognosis, these patients are also at higher risk of statin-related adverse effects [56].

Overall, available data and hypotheses based on biological plausibility do not support the notion that statin therapy may worsen the prognosis of patients with COVID-19. Conversely, they suggest that some clinical benefits in COVID-19 patients may derive from statin-mediated cholesterol-lowering and pleiotropic effects. To this regard, although no clinical studies are currently available clearly showing that statins can reduce the incidence of cardiovascular events in COVID-19 patients, evidence is emerging showing a possible benefit from statin therapy in reduction of COVID-19 severity and mortality. Therefore, the continuation of statin therapy in COVID-19 patients should be considered [49,57]. Further, despite a current lack of direct information in COVID-19 subjects, observational and interventional studies appear warranted to establish both the efficacy and safety of *de novo* initiation of statin therapy as add-on treatment for the management of COVID-19.

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Figure legends

Figure 1. Potential cellular pathways modulated by statins in SARS-CoV-2 infection. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) interacts strongly with the human angiotensin-converting enzyme 2 (ACE2), allowing the virus to enter host cells, including endothelial and epitelial cells. Statins can upregulate the expression of ACE2 on the surface of endothelial and epithelial cells. Recognition of SARS-CoV-2 by Toll-like receptors (TLRs) on the surface of leukocyes activates the MYD88–NF-κB pathway and the innate immune response of the host, with the release of proinflammatory mediators. Statins can inhibit the MYD88–NF-κB proinflammatory pathway and the production of inflammatory cytokines. Statins can exert anti-thrombotic effects by reducing the expression of tissue factor on activated endothelial cells and decreasing the cytosolic phospholipase A2 (cPLA2)-induced thromboxane A2 (TXA2) synthesis by platelets. Statins could reduce cholesterol content in the plasma membrane of SARS-CoV-2 host cells, thereby destabilizing viral replication phases. Through all these mechanisms, statins might prove beneficial effects in COVID-19 patients.

Figure 2. The possible statin-mediated modulation of SARS-CoV-2 infection pro-thrombotic profile. Endothelial activation and release of pro-inflammatory cytokines induced by SARS-CoV-2 (1) lead to increased expression of adhesion molecules (ICAM-1, P-selectins, von Willebrand factor, $\alpha_v\beta_3$) and further release of proinflammatory cytokines (2), promoting the recruitment of platelets and leukocytes (3). Activated endothelial cells also express tissue factor, which promotes the activation of factor VII, factor Xa, and the generation of thrombin (4). Thrombin cleaves fibrinogen into fibrin (5), which is crucial for thormbus formation (6). Pro-inflammatory mediators may also activate the coagulation cascade and influence platelet activation, promoting accelerated thrombus formation (7). Statins can inhibit the release of proinflammatory cytokines by endothelial cells, as well as the activation of coagulation cascade. Also, statins might inhibit SARS-CoV-2 entry into endothelial cells expressing ACE2 and subsequent endothelial activation.