



# Protective role of statins in COVID 19 patients: importance of pharmacokinetic characteristics rather than intensity of action

Rosario Rossi<sup>1</sup> · Marisa Talarico<sup>1</sup> · Francesca Coppi<sup>1</sup> · Giuseppe Boriani<sup>1</sup>

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Dear Editor,

Statins represent a family of drugs that are potentially able to defend COVID-19 patients against uncontrolled systemic inflammatory response produced by the virus Sars-Cov-2. Therefore, some physicians proposed and used anti-inflammatory agents in the treatment regimen of patients with COVID-19 [1]. Statins are well known for their anti-inflammatory effects [2], and some hospitals included them in the COVID-19 treatment protocol [3]. In addition, studies in vitro verified that “there is evidence suggesting that statins exert anti-viral activity and may block the infectivity of enveloped viruses” [4]. In other words, statins could be efficient SARS-CoV-2 inhibitors of the main protease, a key coronavirus enzyme, which is a potential drug target [4].

Considering the above premises, we hypothesized that patients taking statins were better protected against mortality risk than those who do not take statins. We verified this hypothesis in a population of 71 consecutive patients with a pre-existing chronic cardiovascular disease, who become ill from COVID-19 between February 29, 2020, and May 20, 2020. The follow-up ended on June 15, 2020. The only endpoint of the study was all-cause mortality.

Continuous variables were expressed as mean  $\pm$  one SD or median (range) values; and categorical data as percentages. All dichotomous variables were compared utilizing the  $\chi^2$  test; and continuous parameters using analysis of variance (ANOVA) or Mann–Whitney *U* test, as appropriate. Survival probabilities were estimated with the Kaplan–Meier method and survival curves plotted and compared between groups using the log-rank test.  $P < 0.05$  was considered statistically significant.

The baseline characteristics of the studied population were illustrated in Table 1. Groups were created according to the assumption, or not, of statins.

The mortality rate of patients taking statins resulted in 21.4% (9 of 42 patients died during the observation period in this group), while in the group of patients without statins it was 34.5% (10 of 29 patients);  $p < 0.05$ . The comparison of the survival curves showed a statistically not significant difference (Fig. 1a). In other words, there is a trend towards a reduction in mortality risk, but the effect of statins seems substantially not significant.

As a further analysis, to investigate whether the intensity of action of statins could influence the risk of mortality, we divided our 42 patients taking statins into two subgroups, based on the drug’s intensity of action, according to the ACC/AHA Classification [5]. The results were that 18 patients of 42 assumed a high-intensity statin (8 patients of these rosuvastatin 20 mg/die; 8 patients atorvastatin 40 mg/die; and 2 patients atorvastatin 80 mg/die), and 24 patients/42 a low- or moderate-intensity statin (6 patients rosuvastatin 10 mg/die; 2 patients pravastatin 40 mg/die; 2 patients atorvastatin 10 mg/die; 4 patients simvastatin 20 mg/die; and 14 patients atorvastatin 20 mg/die). In the subgroup of high-intensity statins, 4 patients of 18 (22.2%) died, with respect to 6 patients of 24 (25.0%) in the low-moderate-intensity group. The comparison between the survival curves, in contrast to patients who did not take statins, showed no significant differences (Fig. 1b).

To demonstrate whether the pharmacokinetic characteristics of statins were able to determine cardiovascular protection, we divided our 42 patients taking statins into two subgroups, based on the solubility of the used statin. The result was that 16 patients of 42 (38.1%) took a water-soluble (hydrophilic) statin (rosuvastatin in 14 patients and pravastatin in 2), while 26/42 (61.9%) a lipid-soluble (lipophilic) statin (atorvastatin in 22 patients, and simvastatin in 4). The comparison between the survival curves, in contrast to patients who did not take statins, indicated a significant

✉ Rosario Rossi  
rosario.rossi@unimore.it

<sup>1</sup> Cardiology Unit, Policlinico Di Modena Hospital, University of Modena and Reggio Emilia, Via del Pozzo 71, 41124 Modena, Italy

**Table 1** Baseline characteristics of the study population

Parameter	Statin YES	Statin NO	<i>p</i>
<i>n</i>	42 (59.1%)	29 (40.9%)	
Age, years, median (range)	71 (64–92)	73 (63–90)	0.5
Motivation of statin administration			
Post myocardial infarction	47.6% ( <i>n</i> = 20)		
Post stroke	23.8% ( <i>n</i> = 10)		
Prevention	28.5% ( <i>n</i> = 12)		
Risk factors for cardiovascular diseases			
Male gender	57.1% ( <i>n</i> = 24)	55.2% ( <i>n</i> = 16)	0.5
Hypertension	71.4% ( <i>n</i> = 30)	68.9% ( <i>n</i> = 20)	0.4
Type II Diabetes Mellitus	76.2% ( <i>n</i> = 32)	27.6% ( <i>n</i> = 8)	0.001
Hypercholesterolemia	95.2% ( <i>n</i> = 40)	13.8% ( <i>n</i> = 4)	0.0001
Obesity (BMI > 30 kg/m <sup>2</sup> )	40.5% ( <i>n</i> = 17)	37.9% ( <i>n</i> = 11)	0.3
Pre-existing chronic cardiovascular diseases			
Coronary artery disease	85.7% ( <i>n</i> = 36)	13.8% ( <i>n</i> = 4)	0.001
Cerebro-vascular disease	35.7% ( <i>n</i> = 15)	10.3% ( <i>n</i> = 3)	0.03
Aortic or Mitral valvulopathy	11.9% ( <i>n</i> = 5)	10.3% ( <i>n</i> = 3)	0.7
Chronic heart failure	52.4% ( <i>n</i> = 22)	51.7% ( <i>n</i> = 15)	0.8
History of pulmonary embolism	7.1% ( <i>n</i> = 3)	6.9% ( <i>n</i> = 2)	0.6
Chronic obstructive pulmonary disease	19.0% ( <i>n</i> = 8)	20.7% ( <i>n</i> = 6)	0.1
Chronic renal failure	16.7% ( <i>n</i> = 7)	17.2% ( <i>n</i> = 5)	0.3
Chronically taken drugs			
Aspirin	76.2% ( <i>n</i> = 32)	51.7% ( <i>n</i> = 15)	0.001
P2Y12 Inhibitors	14.3% ( <i>n</i> = 6)	13.8% ( <i>n</i> = 4)	0.2
Beta-blockers	71.4% ( <i>n</i> = 30)	72.4% ( <i>n</i> = 21)	0.3
DOAC	23.8% ( <i>n</i> = 10)	24.1% ( <i>n</i> = 7)	0.4
ACEIs	42.8% ( <i>n</i> = 18)	44.8% ( <i>n</i> = 13)	0.09
ARBs	30.9% ( <i>n</i> = 13)	31.0% ( <i>n</i> = 9)	0.8
Calcium-antagonists	14.3% ( <i>n</i> = 6)	13.8% ( <i>n</i> = 4)	0.2

ACEIs angiotensin converting-enzyme inhibitors; ARBs angiotensin II receptors blockers; BMI body mass index; DOAC direct oral anticoagulants

difference between groups. Particularly, the group of lipophilic statins demonstrated a significant reduction in mortality respect both patients who do not take statins, and patients who assumed hydrophilic statins (Fig. 1c). No differences were found regarding clinical characteristics and lipid profile between patients who assumed hydrophilic or lipophilic statins (Table 2).

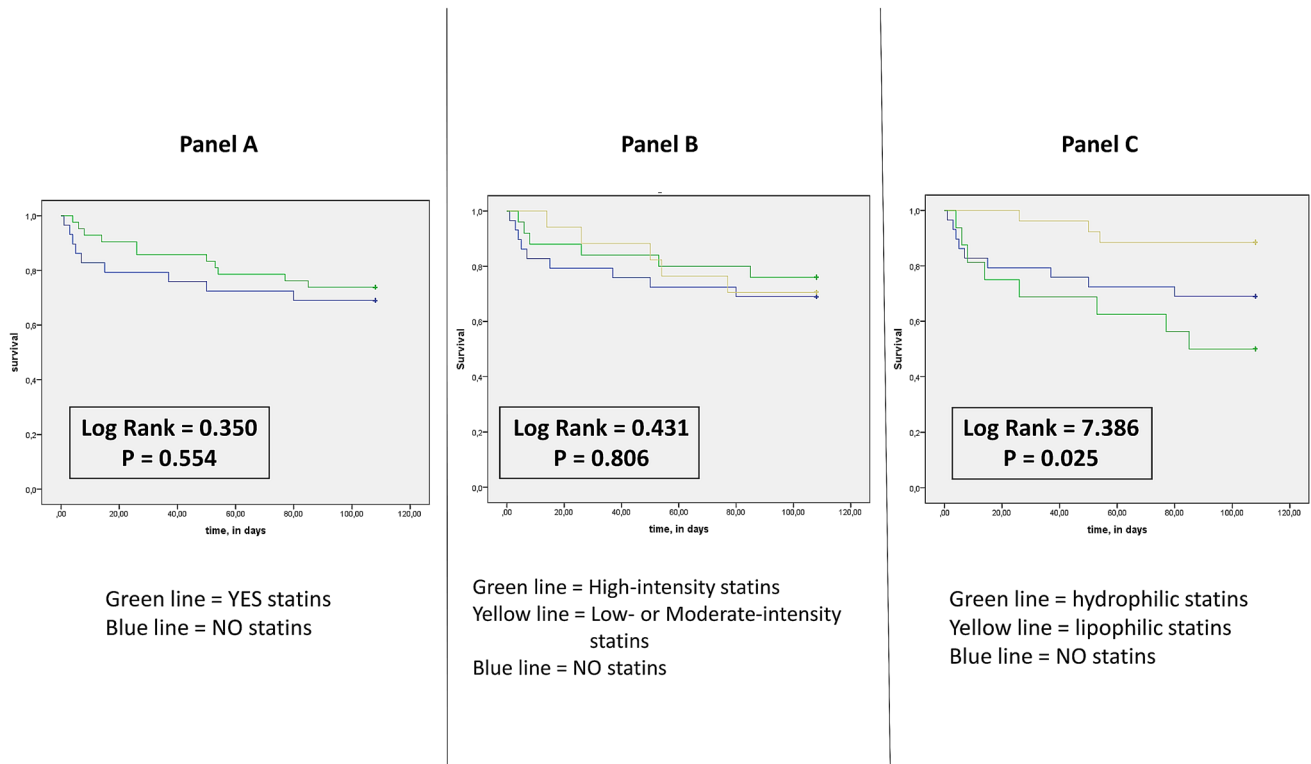
SARS-CoV-2 contaminates multiple cell types in different organs, binding glycoprotein angiotensin-converting enzyme 2 (ACE2), the critical receptor mediating the virus entry [6]. Many studies demonstrated that yet the lungs are massively deranged, COVID-19 infection can extend to many organs, including the blood vessels, heart, gut, and kidneys [6, 7]. Therefore, there are some abundantly infiltrated tissues, as they are particularly rich in ACE-2, which constitute the real “deposits of infection”, from where the virus spreads. These tissues are the brain, central nervous system [8] and the adipose tissue [9]. Moreover, adipose cell embolism amplifies both the inflammatory phenomena

and the pro-thrombotic status [9]. The latter is a well-known prognostic factor and chronic oral anti-coagulation showed a reduction in mortality in patients with chronic cardiac disease [10].

Given the availability, low cost, and safety of statins there was an intense debate concerning statins repurposing as part of COVID-19 treatment. In a recent study, no significant differences in statin chronic assumption were found in COVID-19 patients who developed a cardiac injury, even if this population showed an increased mortality risk in the brief period [11]. As a matter of facts, the promising result of chronic statins intake should be further investigated in randomized controlled trials [12] even if their use was recently related to a reduced mortality risk [13].

Moreover, the beneficial role of statins in this context can be explained either by their immunomodulatory action or by preventing cardiovascular damage [14].

Lipophilic statins have a large distribution volume, reaching all the body’s tissues, provide their protective



**Fig. 1** Event-free survival in patients affected by COVID 19 in connection with taking statins. Unadjusted cumulative event rates for the primary end-point (all-cause mortality) was estimated using the Kaplan–Meier method, and matched between the groups using the log-rank test. In the panel **a** we appreciate the comparison between patients who taking statins respect to do not take statins. The comparison between the survival curves showed no significant differences.

In the panel **b** the contrast concerns patients who take high-intensity versus low- or moderate-intensity statins. The comparison between the survival curves, in contrast to patients who did not take statins, showed no significant differences. In the panel **c** confrontation pertains patients who take lipophilic versus hydrophilic statins. The comparison between the survival curves, in contrast to patients who do not take statins, showed a significant differences

**Table 2** Comparisons between patients who take lipophilic and hydrophilic statins

	Number of patients = 42	High-intensity statins <i>n</i> = 22	Low/moderate-intensity statins <i>n</i> = 20	<i>p</i> value
<b>Clinical characteristics</b>				
Age, years, median (range)		70 (64–92)	72 (64–92)	0.7
Obesity (BMI > 30 kg/m <sup>2</sup> )		40.9% ( <i>n</i> = 9)	40.0% ( <i>n</i> = 8)	0.9
Male gender		59.0% ( <i>n</i> = 13)	55.0% ( <i>n</i> = 11)	0.3
<b>Pre-existing chronic cardiovascular diseases</b>				
Coronary artery disease		86.3% ( <i>n</i> = 19)	80.0% ( <i>n</i> = 16)	0.1
Cerebro-vascular disease		36.3% ( <i>n</i> = 8)	35.0% ( <i>n</i> = 7)	0.7
Aortic or mitral valvulopathy		13.6% ( <i>n</i> = 3)	10.0% ( <i>n</i> = 2)	0.5
Chronic heart failure		59.0% ( <i>n</i> = 13)	55.0% ( <i>n</i> = 10)	0.3
Hystory of pulmonary embolism		0.90% ( <i>n</i> = 2)	0.50% ( <i>n</i> = 1)	0.8
Chronic obstructive pulmonary disease		18.1% ( <i>n</i> = 4)	20.0% ( <i>n</i> = 4)	0.6
Chronic renal failure		18.1% ( <i>n</i> = 4)	15.0% ( <i>n</i> = 3)	0.5
<b>Lipid profile (mg/dl)</b>				
LDL		89 ± 13	91 ± 11	0.8
HDL		57 ± 11	52 ± 13	0.5
Triglycerides		112 ± 12	110 ± 15	0.8
Total Cholesterol		167 ± 16	172 ± 18	0.5

role against the virus. On the contrary, hydrophilic statins have some difficulties to permeate organs, including adipose tissue and tissues protected by functional barriers (i.e., blood–brain barrier). Therefore, even with the same lipid-lowering efficacy, hydrophilic statins have less anti-inflammatory properties.

The current study has several limitations. First of all, this is an observational study, so it can provide associations but not causality. An additional limitation is the small sample size. Even if the current study provided a novel point of view, for the limitation discussed above, our findings need to further validate on a larger population and randomized trials.

In conclusion, statins have been able to significantly reduce the risk of mortality of the COVID 19 patient, provided that they manage to reach the sites where the virus creates damages and where it accumulates, that is, provided that lipophilic statins are used.

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## Compliance with ethical standards

**Conflict of interest** The authors declare no conflict of interest.

**Ethical standards** This study was approved by the local Ethics Committee (Protocol Number AOU 0012597).

**Statements on human and animal rights** All procedures followed were in accordance with the Declaration of Helsinki.

**Informed consent** Informed consent was obtained from all individual participants included in the study.

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