ERJ open research
THE BEST IN OPEN ACCESS BASIC, TRANSLATIONAL & CLINICAL RESPIRATORY RESEARCH

Early View

Original article

Statin use is associated with reduced mortality after respiratory viral infection

Juan Antonio Franco-Peláez, Laura Esteban-Lucia, María de los Ángeles Zambrano Chacón, Ana María Pello-Lázaro, Ana María Venegas Rodriguez, Luis Nieto Roca, Camila Sofia García-Talavera, Andrea Kallmeyer Mayor, Felipe Villar Alvarez, Ricardo Fernandez Roblas, Oscar Gonzalez-Lorenzo, José Tuñón, Borja Ibañez, Alvaro Aceña

Please cite this article as: Franco-Peláez JA, Esteban-Lucia L, Zambrano Chacón Mía de los Ángeles, *et al*. Statin use is associated with reduced mortality after respiratory viral infection. *ERJ Open Res* 2020; in press (https://doi.org/10.1183/23120541.00365-2020).

TITLE PAGE

Statin use is associated with reduced mortality after respiratory viral infection

Juan Antonio Franco-Peláez MD, PhD[1]; Laura Esteban-Lucia MD[1]; María de los Ángeles Zambrano Chacón MD[2], Ana María Pello-Lázaro MD, PhD[1]; Ana María Venegas Rodriguez, MD[1]; Luis Nieto Roca, MD[1]; Camila Sofia García-Talavera, MD[1]; Andrea Kallmeyer Mayor MD[1], Felipe Villar Alvarez MD, PhD[2,4,5]; Ricardo Fernandez Roblas MD[3]; Oscar Gonzalez-Lorenzo, MD[1]; José Tuñón MD, PhD[1,4,6]; Borja Ibañez MD, PhD[1,6,7], Alvaro Aceña MD,PhD[1, 4]

Affiliations:

[1] Department of Cardiology, Instituto de Investigación Sanitaria-Fundación Jiménez Díaz, Madrid, Spain.

[2] Department of Pneumology, Instituto de Investigación Sanitaria -Fundación Jiménez Díaz, Madrid, Spain.

[3] Department of Microbiology, Instituto de Investigación Sanitaria -Fundación Jiménez Díaz, Madrid, Spain.

[4] Autonoma University, Madrid, Spain.

[5] CIBERES, Madrid, Spain

[6] CIBERCV, Madrid, Spain.

[7] Centro Nacional de Investigaciones Cardiovasculares (CNIC), Madrid, España.

***CORRESPONDING AUTHOR:**

Alvaro Aceña Navarro, PhD.

Department of Cardiology, Fundación Jiménez Díaz University Hospital

Avenida Reyes Católicos 2, 28040, Madrid, Spain.

AACena@fjd.es

Summary: Statin treatment is associated with reduced 1-year mortality after respiratory viral infections, even though the higher risk profile of patients on statins. Statins seem a good candidate to be tested during the current global pandemic.

ABSTRACT

Background: Several studies suggest that statins, besides reducing cardiovascular disease, have anti-inflammatory properties which might provide a benefit in downregulating the immune response after a respiratory viral infection (RVI) and, hence, decreasing subsequent complications. We aim to analyse the effect of statins on mortality after RVI.

Methods: Single-center, observational and retrospective study including all adult patients with a RVI confirmed by PCR tests from October 2nd, 2017 to May 20th, 2018. Patients were divided between statins and non-statins users and followed-up for 1 year, recording all causes of death. In order to analyze the effect of statin treatment on mortality after RVI we planned two different approaches, a multivariate Cox regression model with the overall population and a univariate Cox model with a propensity-score matched population.

Results: We included 448 patients, of which 154 (34.4%) were under statin treatment. They had worse clinical profile (older population with more comorbidities). During the 1-year follow-up, 67 patients died, 17 (11.0%) in the statin group, and 50 (17.1%) in the non-statin group. At Cox multivariate analysis, statins were associated with mortality benefit (HR=0.47, 95% CI (0.26- 0.83); p=0.01). In matched population (101 statins users and 101 non-statins users) statins also remained associated with mortality benefit (HR=0.32, 95% CI (0.14-0.72); p=0.006). Differences were mainly driven by non-cardiovascular mortality (HR 0.31, 95% CI (0.13-0.73); p=0.004).

Conclusions: Chronic statin treatment was associated with reduced 1-year mortality in patients with laboratory-confirmed RVI. Further studies are needed to determine the exact role of statin therapy after RVI.

INTRODUCTION

Acute Respiratory Infections are the leading cause of morbidity and one of the principal causes of mortality worldwide. Viruses are responsible for 53% of reported cases and when hospital admission is required, they become a serious health problem[1]. Recent studies have highlighted that, in association with respiratory damage, there is an increased risk of developing a cardiovascular event following the infectious process[2].

Within the first days after an influenza infection [2–4], respiratory syncytial virus and other respiratory viral infections (RVI)[3,5], patients have a 6-fold increased risk of acute myocardial infarction. Likewise, it occurs in case of bacterial infections such as pneumococcal pneumonia (reported a 7-8% higher risk of myocardial infarction[6,7]), haemophilus influenzae pneumonia[8], bacteremias[5], and urinary tract infections[9].

The pathophysiological mechanism proposed is wide, but predominantly RVI results in a powerful and sustained release of inflammatory mediators[2,10]. A considerable proportion of patients who have recovered from a RVI show higher values of pro-inflammatory molecules[11] such as protein-C reactive, Methyl-accepting chemotaxis proteins (MCP), or Interleukin-6, which suggests the presence of that sustained inflammation, associated with a significant increase in the risk of developing major adverse events, including death[12].

Currently there is no therapeutic option to reduce the post-RVI adverse clinical events[13]. Taking also into account that cholesterol allows invasion by pathogens by acting as a docking site for the internalization of virus[14], the effect of statin treatment has been

considered for this patients. This hypothesis was initially suggested by Fedson et al as a treatment to reduce mortality in the 2003 H5N1 pandemic[15].

Large clinical trials have shown evidence that statins reduce major adverse events by 35%. This benefit seems to be driven not only by cholesterol levels reduction, but also by the so-called "pleiotropic effects". The latter include a potential immunomodulatory and anti-inflammatory effect of statins[14,16]. That is why, according to the hypolipemic, immunomodulatory and anti-inflammatory effects of statins, this treatment could provide protection to patients who have suffered a RVI.

Few studies have investigated the treatment with statins after infection. A beneficial effect has been demonstrated by reducing levels of biomarkers related with increased cardiovascular risk such as IL-6[17], MCP-1[17] or C-reactive protein [18], and they seem to be useful in infections with significant immune system response[19], such as bacterial sepsis. However, regarding viral respiratory disorders, some studies have led to controversial conclusions, some of them showing mortality reduction in patients on statins after 30 days of follow-up[13], and others showing no effect within 90 days follow-up[20]. This controversy remains when considering other respiratory infections. Frost et al found a reduced risk of death from Chronic Obstructive Pulmonary Disease among statin users and a significantly reduced risk of death from influenza/pneumonia[19] while Majumdar reported no benefit in mortality reduction nor intensive care unit admission in patients with pneumonia[21].

Taking into account those controversies and the current situation with 2019 Coronavirus pandemia, where it has been shown that the pro-inflammatory effect plays a

key role in the evolution of the disease[22], we aim to assess in this study the prognostic effect of statin treatment in patients that have suffered a RVI.

METHODS

Patients and Study Design

We included all consecutive patients older than 18 years, who had been diagnosed with RVI after a confirmation with a polymerase chain reaction technique on nasopharyngeal swabs at the Microbiology Department of our institution, among the period between 2017-2018 Comprehensive Influenza Surveillance Period (established by the Carlos III National Institute Epidemiology Center; since October 2nd, 2017 to May 20th, 2018). Baseline characteristics and current prescribed drugs were recorded from electronic health records. Patients were divided into two groups, statin and non-statin users, and data from a 1 year follow-up after the date of the positive PCR test were taken from electronic health records, specifying vital status and, in case of death, its cause (cardiovascular or non-cardiovascular). The primary endpoint of our study was all-cause death and the secondary endpoints were cardiovascular and non-cardiovascular death. Cardiovascular death was defined as mortality related to myocardial infarction, heart failure or stroke.

Statistical Analysis

Quantitative data are presented as median and interquartile range. Comparisons between quantitative variables were performed with Student´s t-test of Mann-Whitney test when appropriate. Qualitative variables are shown as frequencies and percentages and were compared using chi-square of Fisher´s exact test when appropriate.

In order to analyze the effect of statin treatment on mortality after RVI we planned two different approaches, a multivariate proportional hazards Cox regression model with the overall population and a univariate Cox regression model with a propensity-

score matched population. To carry out the multivariate Cox model, we first performed a univariate analysis including all clinically relevant variables and those with a P level < 0.20 remained in the multivariate analysis, which were made with a backward stepwise method. We considered independent predictors those variables with a P level < 0.05 after this analysis. The propensity-score matched population was selected after performing a logistic binary logistic regression analysis, taking statin treatment as dependent variable and age, sex, hypertension, diabetes, smoking history, previous stroke, peripheral arterial disease and ischaemic heart disease as independent. With the estimated probability of statin treatment we matched both groups, in a 1:1 ratio, with the nearest neighbour method (caliper = 0.2 × SD[logitPs]). Finally, matched groups were compared with univariate Cox analysis and survival curves were drawn with Kaplan-Meier method.

All statistical analysis were performed with IBM SPSS Statistics for Windows, Version 20.0 (Armonk, NY: IBM Corp).

Ethics Statement

The research protocol complies with the Declaration of Helsinki and was approved by the ethics committee of our institution (EO012-20 FJD).

RESULTS

We included 448 patients who met the inclusion criteria; 154 of them (34.4%) were on statin treatment and 294 (65.6%) were not. Baseline characteristics are shown at **Table 1**. It should be noted that there were several differences between both groups: statin users were older, more frequently males have a higher prevalence of hypertension, diabetes, coronary artery disease, heart failure, peripheral artery disease or cerebrovascular disease and have lower glomerular filtration rate. However, patients the proportion of patients vaccinated from flu was higher among those on statins than among non-statin users.

Regarding the type of virus, influenza viruses (A or B) were responsible of 41.3% of RVI, far from rates of rhinovirus (19.6%), respiratory syncytial virus (14.3%) and metapneumovirus (12.7%). There were no significant differences between the study groups (**Table 2**). Biological samples were referred from hospitalization wards (55.1%), emergency department (43.1%) and primary care facilities (1.8%).

During the first-year follow-up period after RVI, 67 patients died (15.0%): 50 (17.1%) in the non-statin and 17 (11.0%) in the statin group. Non-cardiovascular death was attributed to 63 patients (16 statin and 47 non-statin users) and cardiovascular death to 3 patients (1 statin and 2 non-statin users).

At univariate Cox analysis, variables which met the criterion of $P < 0.20$ were age (0.029), gender (0.072), cancer (<0.001), influenza infection (0.168), hemoglobin (<0.001), platelet count (0.066), C-reactive protein peak (0.028) and angiotensin converting enzyme inhibitors or angiotensin receptor blockers prescription (0.132), in addition to statin intake

(0.040). Multivariate Cox regression showed that statin therapy was independent predictor of mortality (HR 0.47, 95% CI = (0.27-0.81), p = 0.005), along with age (HR 1.33 per 10 years, 95% CI = (1.11-1.58), p = 0.001), history of cancer (HR 3.23, 95% CI = (1.88-5.57), p < 0.001) and hemoglobin level (HR 0.81 per each g/dL, 95% CI = (0.72-0.92), p = 0.001) (**Figure 1**).

After propensity-score matching, 101 statin patients were matched with 101 control patients. Baseline characteristics can be seen at **Table 3**. Both groups had well balanced baseline characteristics except for heart failure prevalence (24% in statin and 9% in non-statin groups respectively, p=0.004). There were 30 deaths (2 cardiovascular and 28 non cardiovascular), 8 (7.9%) in the statin group and 22 (21.8%) in the non-statin group. Cox analysis showed that statin use was associated with less all-cause death during follow-up with a HR = 0.32 (95% CI (0.14-0.72); p=0.006). Differences in mortality were mainly driven by non-cardiovascular mortality (HR 0.31, 95% CI (0.13-0.73); p=0.004), whereas there were no differences in cardiovascular mortality (HR 0.44 [0.04-4.88]; p=0.49). **Figure 2** shows Kaplan-Meier survival curves of all-cause death**.** Kaplan-Meier survival curves of non-cardiovascular death are shown in **Figure 3** and cardiovascular death is represented in **Figure 4.**

DISCUSSION

The main finding of our study is that chronic statin treatment is associated with reduced 1-year mortality in patients with PCR-confirmed RVI, even though patients on statin had a significant higher risk profile (as they were older, more frequently males, with a higher prevalence of hypertension, diabetes, ischemic heart disease, heart failure, peripheral artery disease and cerebrovascular disease and with a lower glomerular filtration rate). In spite of our modest sample size (N=448), the high event rate observed in our study (67 deaths) reinforces the Cox regression findings, as the ratio of number of events: number of independent predictors is around 17 and above the level suggested by Peduzzi[23,24]. Furthermore, results were confirmed with the propensity-score matching approach, which it is other well-known way to avoid confounding factors in observational studies[25].

Statins are extensively recommended for treatment of hyperlipidaemia and cardiovascular diseases and for prevention of ischaemic heart disease and stroke. However, when analysing the causes of death among patients on statin treatment during recovery from RVI, we found that the reduction of mortality was clearly driven by non-cardiovascular causes, therefore suggesting a new pleiotropic effect far beyond the well-known cardiovascular protective properties of statins. Nevertheless, we cannot exclude a beneficial effect on cardiovascular mortality as the number of deaths in our study was scarce (only three patients) and then, not enough to show significant differences between groups, for what it would be advisable to perform larger studies in order to assess whether those differences exist or not.

Moreover, other therapeutic effects of statins are recently emerging. Some studies have shown that statin treatment is associated with lower cancer-related mortality

rates[26], e.g. lung cancer[27] and hepatocellular carcinoma[28]. Moreover, there is a negative association between statin therapy and the risk of hepatocellular carcinoma development in patients with viral B hepatitis[29], which, as well as our study results, suggests an immunomodulatory and anti-inflammatory effect of statins over the viral trigger.

A meta-analysis of five randomised clinical trials has shown that people vaccinated against influenza viruses have a 36% lower risk of cardiovascular events[30]. It happened the same in our population, where statin users, who were older and had a significantly higher prevalence of cardiovascular risk factors, had also higher proportion of previous influenza vaccination. However, interaction of statin treatment with age and flu vaccination was ruled out.

Concerning statin effect on viral respiratory infections, Valdemaar et al[13] showed a beneficial effect at 30 days follow-up while Atamna et al[20] showed no benefits at 90 days follow-up. In our study, we have observed that the beneficial did not appear in the first month as described by Valdemaar but instead, during the long-term follow-up (unlike Atamna results). This raises the hypothesis that statins might also have a mortality benefit if administered during the respiratory infection episode.

Most studies with statins in respiratory infections are referred to influenza viruses or bacterial pneumonia. However, our study includes different types of viruses, coronavirus amongst them, allowing us to assess the effect of statin treatment on infections caused by different viruses, without being limited to influenza infections. Therefore, given the current global Coronavirus pandemic of RVI, statins appear as good candidates to be tested in prospective randomized clinical trials recruiting patients discharged after viral infection.

Some limitations must be taken into account. First, this is an observational study and the information was obtained by reviewing electronic health records of patients. In addition, it is a single-centre study and the patients selected were those with RVI confirmed by laboratory tests, so the study might not be fully representative of the whole population. Besides, we recorded data of drug prescription, but we were not able to assure patient's treatment compliance, which can be another limitation. Finally, the number of cardiovascular deaths in our study was not enough to find significant differences between both groups. Studies with larger sample sizes would be needed to assess whether real differences exist.

CONCLUSION

Our study findings suggest that chronic statin treatment is associated with reduced 1-year mortality in patients with a laboratory-confirmed RVI. This mortality reduction was clearly driven by non-cardiovascular deaths (suggesting an important pleiotropic effect) and was maintained when comparing patients through a propensity-score matching. Thus, statins seem to be a good pharmacological treatment candidate to be tested in patients discharged after a RVI in a prospective randomized clinical trial.

ACKNOWLEDGMENTS

Author contributions

Alvaro Aceña, Juan Antonio Franco Peláez, Laura Esteban Lucia, María de los Ángeles Zambrano Chacón, Ana María Pello Lázaro, Ana María Venegas Rodriguez, Luis Nieto Roca, Camila Sofia García Talavera, Andrea Kallmeyer Mayor, Felipe Villar Alvarez, Ricardo Fernandez Roblas, Oscar Gonzalez Lorenzo, José Tuñón and Borja Ibañez contributed substantially to the study design, data analysis and interpretation, and the writing of the manuscript.

Financial/nonfinancial disclosures There was no financial support.

Role of the sponsors: There were no sponsors of the study.

BIBLIOGRAPHIC REFERENCES:

1. Visseaux B, Burdet C, Voiriot G, et al. Prevalence of respiratory viruses among adults, by season, age, respiratory tract region and type of medical unit in Paris, France, from 2011 to 2016. *PLoS One*. 2017;12(7):1-15. doi:10.1371/journal.pone.0180888

2. Musher DM, Abers MS, Corrales-Medina VF. Acute infection and myocardial infarction. *N Engl J Med*. 2019;380(2):171-176. doi:10.1056/NEJMra1808137

3. Kwong JC, Schwartz KL, Campitelli MA, et al. Acute myocardial infarction after laboratory-confirmed influenza infection. *N Engl J Med*. 2018;378(4):345-353. doi:10.1056/NEJMoa1702090

4. Warren-Gash C, Smeeth L, Hayward AC. Influenza as a trigger for acute myocardial infarction or death from cardiovascular disease: a systematic review. *Lancet Infect Dis*. 2009;9(10):601-610. doi:10.1016/S1473-3099(09)70233-6

5. Dalager-Pedersen M, Søgaard M, Schønheyder HC, Nielsen H, Thomsen RW. Risk for myocardial infarction and stroke after community-acquired bacteremia: A 20-year population-based cohort study. *Circulation*. 2014;129(13):1387-1396. doi:10.1161/CIRCULATIONAHA.113.006699

6. Musher DM, Alexandraki I, Graviss EA, et al. Bacteremic and nonbacteremic pneumococcal pneumonia: A prospective study. *Medicine (Baltimore)*. 2000;79(4):210-221. doi:10.1097/00005792-200007000-00002

7. Musher DM, Rueda AM, Kaka AS, Mapara SM. The Association between Pneumococcal Pneumonia and Acute Cardiac Events. *Clin Infect Dis*. 2007;45(2):158-

165. doi:10.1086/518849

8. Ramirez J, Aliberti S, Mirsaeidi M, et al. Acute Myocardial Infarction in Hospitalized Patients with Community-Acquired Pneumonia. *Clin Infect Dis*. 2008;47(2):182-187. doi:10.1086/589246

9. Smeeth L, Thomas SL, Hall AJ, Hubbard R, Farrington P, Vallance P. Risk of myocardial infarction and stroke after acute infection or vaccination. *N Engl J Med*. 2004;351(25):2611-2618. doi:10.1056/NEJMoa041747

10. Newton AH, Cardani A, Braciale TJ. The host immune response in respiratory virus infection: balancing virus clearance and immunopathology. *Semin Immunopathol*. 2016;38(4):471-482. doi:10.1007/s00281-016-0558-0

11. Corrales-Medina VF, Alvarez KN, Weissfeld LA, et al. Association between hospitalization for pneumonia and subsequent risk of cardiovascular disease. *JAMA - J Am Med Assoc*. 2015;313(3):264-274. doi:10.1001/jama.2014.18229

12. Ridker PM, MacFadyen JG, Glynn RJ, Bradwin G, Hasan AA, Rifai N. Comparison of interleukin-6, C-reactive protein, and low-density lipoprotein cholesterol as biomarkers of residual risk in contemporary practice: secondary analyses from the Cardiovascular Inflammation Reduction Trial. *Eur Heart J*. 2020;41(31):2952-2961. doi:10.1093/eurheartj/ehaa160

13. Vandermeer ML, Thomas AR, Kamimoto L, et al. Association between use of statins and mortality among patients hospitalized with laboratory-confirmed influenza virus infections: a multistate study. *J Infect Dis*. 2012;205(1):13-19.

doi:10.1093/infdis/jir695

14. Parihar SP, Guler R, Brombacher F. Statins: a viable candidate for host-directed therapy against infectious diseases. *Nat Rev Immunol*. 2019;19(2):104-117. doi:10.1038/s41577-018-0094-3

15. Fedson DS. Pandemic influenza: A potential role for statins in treatment and prophylaxis. *Clin Infect Dis*. 2006;43(2):199-205. doi:10.1086/505116

16. Blanco-Colio LM, Tuñón J, Martín-Ventura JL, Egido J. Anti-inflammatory and immunomodulatory effects of statins. *Kidney Int*. 2003;63(1):12-23. doi:10.1046/j.1523-1755.2003.00744.x

17. Oesterle A, Laufs U, Liao JK. Pleiotropic Effects of Statins on the Cardiovascular System. *Circ Res*. 2017;120(1):229-243. doi:10.1161/CIRCRESAHA.116.308537

18. Blake GJ, Ridker PM. Are statins anti-inflammatory? *Curr Control Trials Cardiovasc Med*. 2000;1(3):161-165. doi:10.1186/CVM-1-3-161

19. Frost FJ, Petersen H, Tollestrup K, Skipper B. Influenza and COPD mortality protection as pleiotropic, dose-dependent effects of statins. *Chest*. 2007;131(4):1006-1012. doi:10.1378/chest.06-1997

20. Atamna A, Babitch T, Bracha M, et al. Statins and outcomes of hospitalized patients with laboratory-confirmed 2017–2018 influenza. *Eur J Clin Microbiol Infect Dis*. 2019;38(12):2341-2348. doi:10.1007/s10096-019-03684-y

21. Majumdar SR, McAlister FA, Eurich DT, Padwal RS, Marrie TJ. Statins and outcomes in patients admitted to hospital with community acquired pneumonia: Population based

prospective cohort study. *Br Med J*. 2006;333(7576):999-1001. doi:10.1136/bmj.38992.565972.7C

22. Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report. *N Engl J Med*. July 2020. doi:10.1056/nejmoa2021436

23. Peduzzi P, Concato J, Feinstein AR, Holford TR. Importance of events per independent variable in proportional hazards regression analysis II. Accuracy and precision of regression estimates. *J Clin Epidemiol*. 1995;48(12):1503-1510. doi:10.1016/0895-4356(95)00048-8

24. Concato J, Peduzzi P, Holford TR, Feinstein AR. Importance of events per independent variable in proportional hazards analysis I. Background, goals, and general strategy. *J Clin Epidemiol*. 1995;48(12):1495-1501. doi:10.1016/0895-4356(95)00510-2

25. Austin PC. The use of propensity score methods with survival or time-to-event outcomes: Reporting measures of effect similar to those used in randomized experiments. *Stat Med*. 2014;33(7):1242-1258. doi:10.1002/sim.5984

26. Graaf MR, Beiderbeck AB, Egberts ACG, Richel DJ, Guchelaar HJ. The risk of cancer in users of statins. *J Clin Oncol*. 2004;22(12):2388-2394. doi:10.1200/JCO.2004.02.027

27. Khurana V, Bejjanki HR, Caldito G, Owens MW. Statins reduce the risk of lung cancer in humans: A large case-control study of US Veterans. *Chest*. 2007;131(5):1282-1288. doi:10.1378/chest.06-0931

28. Talesh GA, Trézéguet V, Merched A. Hepatocellular Carcinoma and Statins. *Biochemistry*. 2020:0-33. doi:10.1021/acs.biochem.0c00476

29. Tsan Y-T, Lee C-H, Ho W-C, Lin M-H, Wang J-D, Chen P-C. Statins and the Risk of Hepatocellular Carcinoma in Patients With Hepatitis C Virus Infection. *J Clin Oncol*. 2013;31(12):1514-1521. doi:10.1200/JCO.2012.44.6831

30. Udell JA, Zawi R, Bhatt DL, et al. Association between influenza vaccination and cardiovascular outcomes in high-risk patients: a meta-analysis. *JAMA*. 2013;310(16):1711-1720. doi:10.1001/jama.2013.279206

Table 1. Baseline characteristics of statin and non-statin users and overall cohort.

	Overall cohort (N=448)	Non-Statin users (N=294)	Statin Users (N=154)	p-Value
Age (years)	73.5 (60-84)	68 (54-83)	79 (71-85)	**<0.001**
Female sex (%)	234 (52.2)	167 (56.8)	67 (43.5)	**0.007**
Hypertension (%)	247 (55.1)	125 (42.5)	122 (79.2)	**<0.001**
Diabetes mellitus (%)	97 (21.7)	36 (12.2)	61 (39.6)	**<0.001**
Currentsmoker (%)	73 (16.3)	53 (18.0)	20 (13.0)	0.16
CAD (%)	46 (10.3)	5 (1.7)	41 (26.6)	**<0.001**
Heart failure (%)	53 (11.8)	19 (6.5)	34 (22.1)	**<0.001**
PAD (%)	35 (7.8)	7 (2.4)	28 (18.2)	**<0.001**
CVD (%)	24 (5.4)	7 (2.4)	17 (11.0)	**<0.001**
COPD (%)	81 (18.1)	54 (18.4)	27 (17.5)	0.83
Cancer (%)	122 (27.2)	83 (28.2)	39 (25.3)	0.51
Influenza vaccination (%)	185 (42.9)	96 (33.9)	89 (60.1)	**<0.001**
Haemoglobin (g/dl)	13.0 (11.8-14.0)	13.0 (11.8-14.1)	13.0 (11.7-14.0)	0.43

Platelets (x10^3cells/µl)	204 (152-259)	207 (155-267)	195 (150-234)	0.15
Leucocytes (x10^3cells/µl)	7.9 (5.5-10.6)	7.7 (5.0-10.2)	8.1 (6.0-11.6)	0.81
Neutrophils (x10^3cells/µl)	6.0 (3.7-8.9)	5.8 (3.3-8.6)	6.6 (4.5-9.3)	0.41
GFR (ml/min/1.73m^2)	80 (60-96)	86 (68-101)	72 (55-84)	**<0.001**
CRP peak (mg/dl)	5.8 (2.5-17.1)	5.8 (2.4-16.9)	6.0 (2.7-18.0)	0.76

Quantitative data are presented as median (interquartile range). P-Value denotes comparison between statin and non-statin users.

CAD: Coronary artery disease. COPD: Chronic obstructive pulmonary disease. CPR: C-reactive Protein. CVD: Cerebrovascular disease. GFR: Glomerular filtration rate. PAD: Peripheral artery disease.

Table 2. Type of virus detected in nasopharyngeal swabs and responsible for respiratory viral infection

Virus type	Overall cohort (N=448)	Non-Statin users (N=294)	Statin Users (N=154)
Influenza virus (%) * Influenza A (%) * Influenza B (%)	185 (41.5) * 115 (25.7) * 70 (15.6)	127 (43.2) * 76 (25.9) * 51 (17.3)	58 (37.7) * 39 (25.3) * 19 (12.3)
Rhinovirus (%)	88 (19.6)	62 (21.1)	26 (16.9)
Respiratory syncytial virus (%)	64 (14.3)	38 (12.9)	26 (16.9)
Metapneumovirus (%)	57 (12.7)	33 (11.2)	24 (15.6)
Coronavirus (%)	21 (4.7)	14 (4.8)	7 (4.5)
Human parainfluenza (%)	19 (4.2)	7 (2.4)	12 (7.8)
Adenovirus (%)	1 (0.2)	1 (0.3)	0 (0.0)
Multiple viruses (%)	13 (2.9)	12 (4.1)	1 (0.6)

Table 3. ***Baseline characteristics of the propensity-score matched population (*****statin and non-statin users*****)***

	Non-Statin users (N=101)	Statin Users (N=101)	p-Value
Age (years)	80 (69.5-88.0)	79 (70.5-84.0)	0.284
Female sex (%)	47 (46.5)	54 (53.5)	0.325
Hypertension (%)	81 (80.2)	76 (75.2)	0.398
Diabetes mellitus (%)	25 (24.8)	29 (28.7)	0.525
Current smoker (%)	13 (12.9)	12 (11.9)	0.831
CAD (%)	5 (5.0)	6 (5.9)	0.757
Heart failure (%)	9 (8.9)	24 (23.8)	**0.004**
PAD (%)	7 (6.9)	6 (5.9)	0.774
CVD (%)	7 (6.9)	8 (7.9)	0.788
COPD (%)	18 (17.8)	15 (14.9)	0.568
Cancer (%)	29 (28.7)	24 (23.8)	0.424
Influenza vaccination (%)	48 (48.5)	61 (63.5)	0.105
Haemoglobin (g/dl)	13.0 (11.9-13.9)	13.0 (12.2-14.0)	0.523

Platelets (x10^3cells/µl)	207 (140.0-266.0)	196 (154.5-250)	0.600
Leucocytes (x10^3cells/µl)	8.0 (5.3-11.0)	8.0 (6.1-11.9)	0.476
Neutrophils (x10^3cells/µl)	6.2 (3.6-9.2)	6.5 (4.6-9.9)	0.264
GFR (ml/min/1.73m^2)	77.9 (57.6-91.4)	77.1 (56.0-85.1)	0.208
CRP peak (mg/dl)	5.8 (2.6-17.6)	5.0 (2.7-20.0)	0.726

Quantitative data are presented as median (interquartile range). P-Value denotes comparison between statin and non-statin users.

CAD: Coronary artery disease. COPD: Chronic obstructive pulmonary disease. CPR: C-reactive Protein. CVD: Cerebrovascular disease. GFR: Glomerular filtration rate. PAD: Peripheral artery disease.

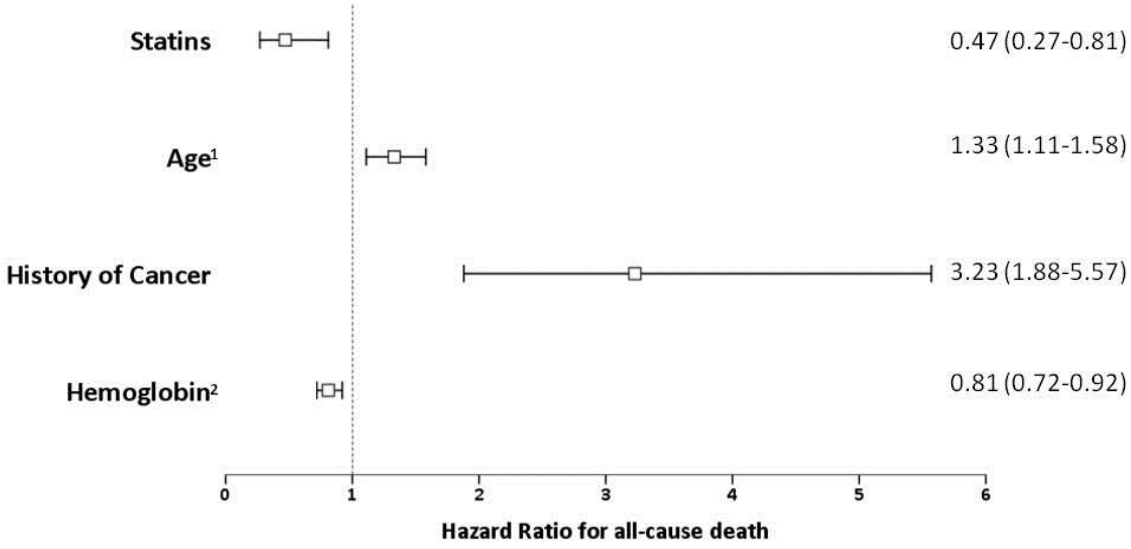
FIGURE LEGENDS

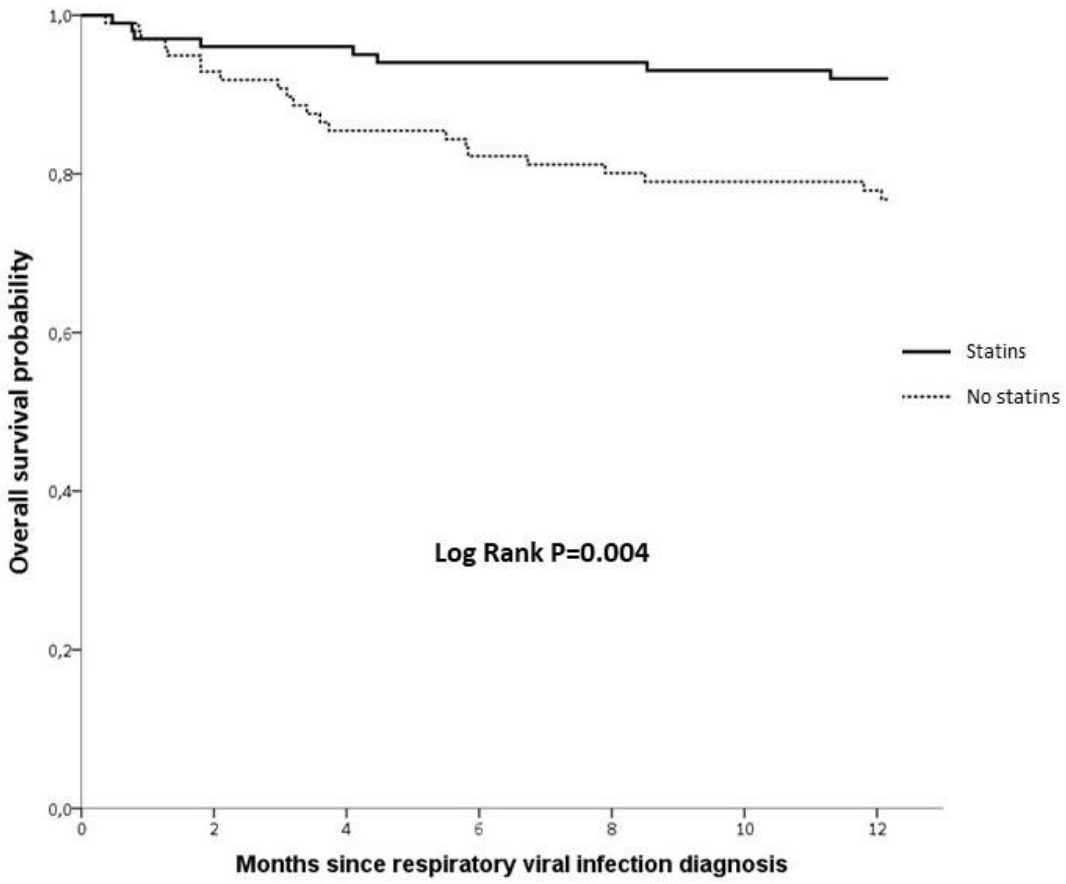
Figure 1 Independent predictors of all-cause death after multivariate proportional hazards Cox regression analysis in the overall population. [1]For every 10 years. [2]For every g/dL.

Figure 2. Kaplan-Meier survival curves showing the differences in all-cause death in matched population. Continuous line represents statin users. Dashed line represents non-statin users.

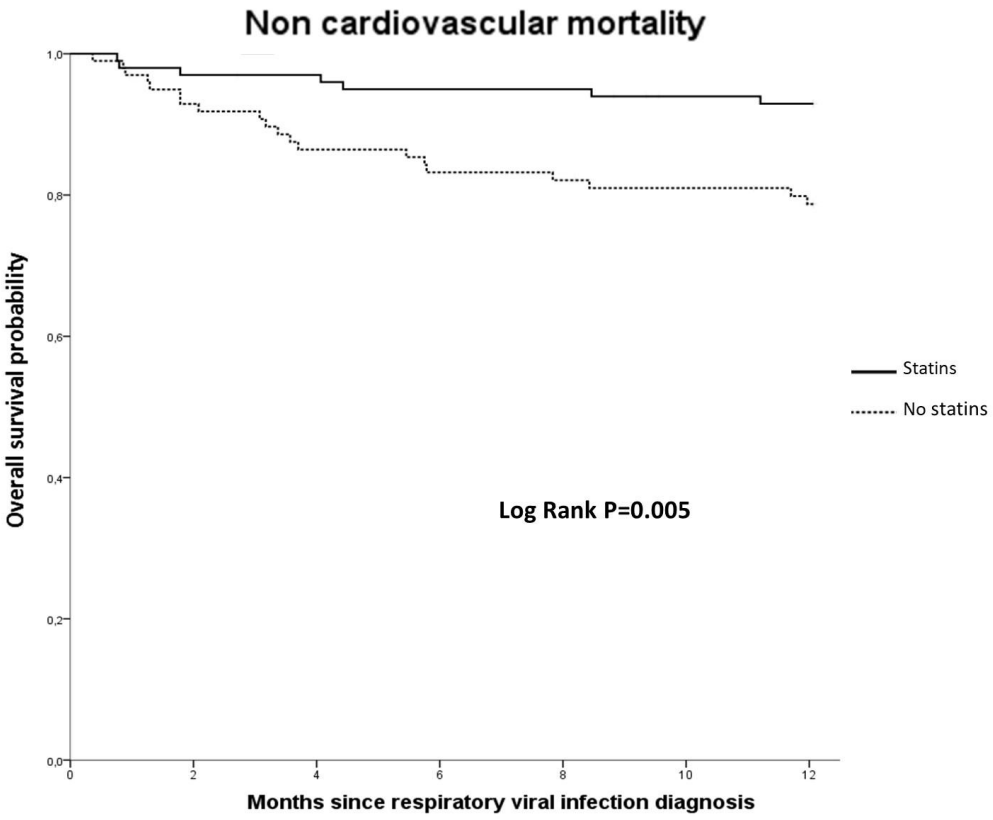
Figure 3. Kaplan-Meier survival curves showing the differences in non-cardiovascular death in matched population. Continuous line represents statin users. Dashed line represents non-statin users.

Figure 4. Kaplan-Meier survival curves showing the differences in cardiovascular death in matched population. Continuous line represents statin users. Dashed line represents non-statin users.

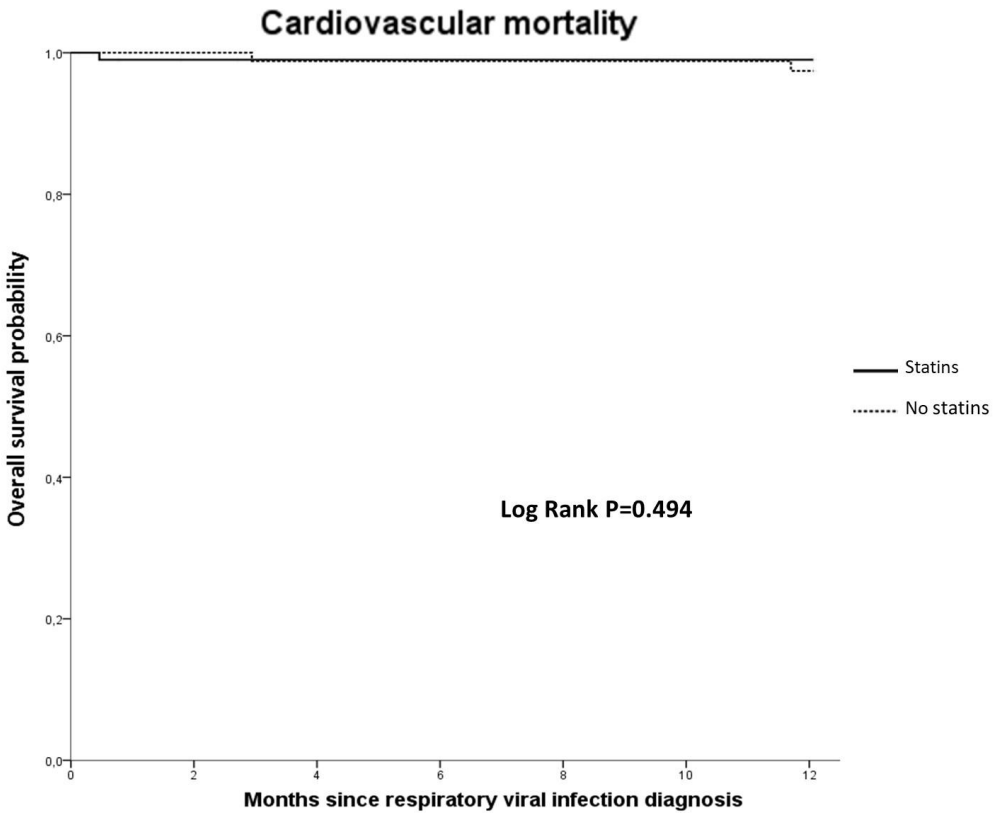

Statins
0.47 (0.27-0.81)
Age[1]
1.33 (1.11-1.58)
History of Cancer
3.23 (1.88-5.57)
Hemoglobin[2]
0.81 (0.72-0.92)
0
1
2
3
4
5
6
Hazard Ratio for all-cause death



No. At risk							
No statins	101	89	80	77	75	73	70
Statins	101	97	96	94	94	90	89



No. At risk							
No statins	101	89	80	77	75	73	68
Statins	101	97	96	94	94	90	89



No. At risk							
No statins	101	89	80	77	75	73	68
Statins	101	97	96	94	94	90	89