

1 **The effects of ARBs, ACEIs and statins on clinical outcomes of**
2 **COVID-19 infection among nursing home residents**

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34 **Abstract**

35 **Background.** COVID-19 infection has limited preventive or therapeutic drug options at this
36 stage. Some of common existing drugs like angiotensin-converting enzyme inhibitors (ACEi),
37 angiotensin II receptor blockers (ARB) and the HMG-CoA reductase inhibitors ('statins') have
38 been hypothesised to impact on disease severity. However, up till now, no studies investigating
39 this association were conducted in the most vulnerable and affected population groups, i.e. older
40 people residing in nursing homes. The purpose of this study has been to explore the association
41 of ACEi/ARB and/or statins with clinical manifestations in COVID-19 infected older people
42 residing in nursing homes.

43 **Methods and Findings.** We undertook a retrospective multi-centre cohort study in two Belgian
44 nursing homes that experienced similar COVID-19 outbreaks. COVID-19 diagnoses were
45 based on clinical suspicion and/or viral presence using PCR of nasopharyngeal samples. A total
46 of 154 COVID-19 positive subjects was identified. The outcomes were 1) serious COVID-19
47 defined as a long-stay hospital admission (length of stay ≥ 7 days) or death (at hospital or
48 nursing home) within 14 days of disease onset, and 2) asymptomatic, i.e. no disease symptoms
49 in the whole study-period while still being PCR diagnosed. Disease symptoms were defined as
50 any COVID-19-related clinical symptom (e.g. coughing, dyspnoea, sore throat) or sign (low
51 oxygen saturation and fever) for ≥ 2 days out of 3 consecutive days.

52 Logistic regression models with Firth corrections were applied on these 154 subjects to analyse
53 the association between ACEi/ARB and/or statin use with the outcomes. Age, sex, functional
54 status, diabetes and hypertension were used as covariates. Sensitivity analyses were conducted
55 to evaluate the robustness of our statistical significant findings.

56 We found a statistically significant association between statin intake and the absence of
57 symptoms during COVID-19 infection (unadjusted OR 2.91; CI 1.27-6.71; $p=0.011$), which

58 remained statistically significant after adjusting for age, sex, functional status, diabetes mellitus
59 and hypertension. The strength of this association was considerable and clinically important.
60 Although the effects of statin intake on serious clinical outcome (long-stay hospitalisation or
61 death) were in the same beneficial direction, these were not statistically significant (OR 0.75;
62 CI 0.25-1.85; $p=0.556$). There was also no statistically significant association between
63 ACEi/ARB and asymptomatic status (OR 1.52; CI 0.62-3.50; $p=0.339$) or serious clinical
64 outcome (OR 0.79; CI 0.26-1.95; $p=0.629$).

65 **Conclusions.** Our data indicate that statin intake in old, frail people could be associated with a
66 considerable beneficial effect on COVID-19 related clinical symptoms. The role of statins and
67 any interaction with renin-angiotensin system drugs need to be further explored in larger
68 observational studies as well as randomised clinical trials.

69

70 **Introduction**

71 Patients with serious and fatal COVID-19 infections are characterised by pneumonia-associated
72 acute respiratory distress syndrome (ARDS) and multi-organ failure. The underlying
73 mechanisms are linked to an imbalance between ACE and ACE2, as well as endothelial
74 dysfunction (1-3) (**Figure 1**). Animal experiments have indicated that ARBs, ACEis or statins
75 can prevent experimentally induced ARDS (4). These drugs are also likely to counteract the
76 effects of sepsis-associated coagulopathy, elevated pro-inflammatory cytokines (*e.g.* IL-6) and
77 sepsis-associated effects on pulmonary vascular permeability (5-12).

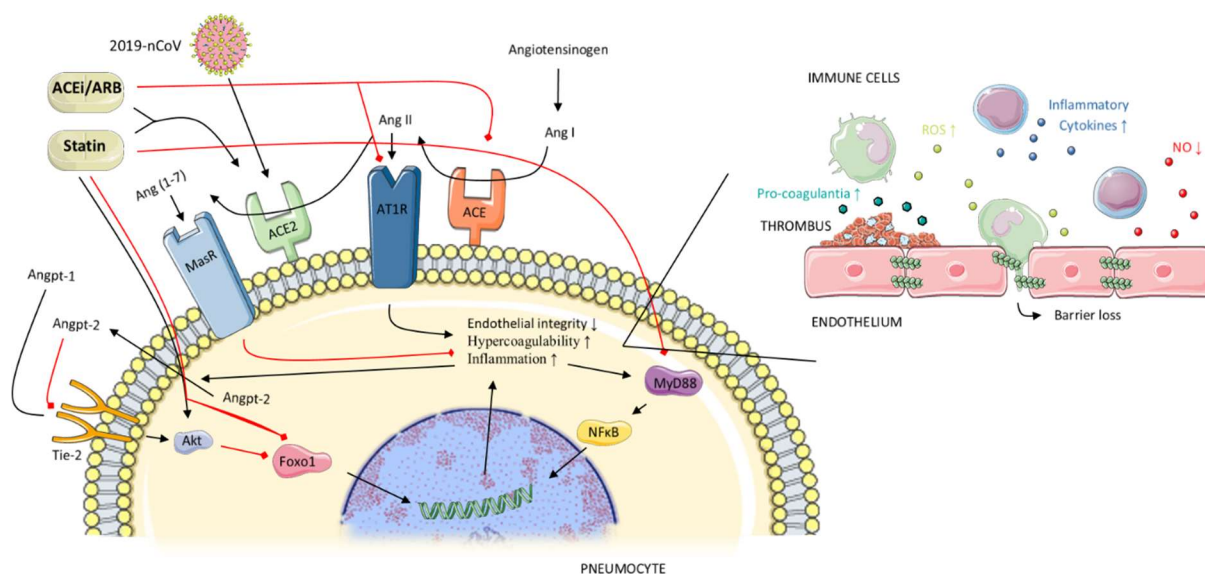
78 In a non-COVID-19 context, clinical investigators have observed that pneumonia patients who
79 had been taking statins, ARBs or ACEis had improved survival (13, 14). Moreover, recent
80 observational studies have reported similar findings for hospitalized COVID-19 patients (15-
81 19). Recently, randomized controlled clinical trials have begun to evaluate the clinical effects

82 of ARB, ACEi or statin treatment in hospitalized COVID-19 patients (e.g. NCT04348695,
 83 NCT04343001, NCT04351581). However, the estimated completion dates for these trials will
 84 be some time in 2021, and most will only consider ARB/ACEi monotherapy, *i.e.* not in
 85 combination with statins.

86 To our knowledge, no ARB/ACEi/statin studies have been or are being conducted among
 87 elderly nursing home residents, the most vulnerable individuals for COVID-19 morbidity and
 88 mortality. In Belgium, a country with a well-developed health care system, 3000 residents of
 89 nursing homes have died from COVID-19, with still around 100 residents a day currently dying
 90 (20). Estimates for the US suggest that almost 20% of all COVID-19 deaths have occurred in
 91 long-term care centers (21). Thus, every day without effective therapy comes at a high human
 92 cost.

93 We aimed to replicate the hospital findings to a frail, high-risk population living in nursing
 94 homes. While we wait for the results of prospective clinical trials, our findings allow us to make
 95 suggestions about the use of ACEis/ARBs and statins for these COVID-19 patients.

96



97

98 *Figure 1. Three mechanisms suggested for the effects of statins and ACEis/ARBs in preventing severe pulmonary disease in*
 99 *COVID-19. 1) Under normal conditions the Tie-2 receptor is continuously activated by Angiopoetin-1 (Angpt-1), which in turn*
 100 *activates Akt-kinase, leading to phosphorylation and hence inhibition of the transcription factor Foxo1. Unphosphorylated or*
 101 *active Foxo1 initiates the transcription of genes leading to increased inflammation, decreased endothelial barrier integrity*
 102 *and hypercoagulability. Angpt-2 is a partial antagonist of the Tie-2 receptor, stimulating inflammation, endothelial*

103 *dysfunction and hypercoagulability. COVID-19 infection and ARDS are associated with increased Angpt-2 levels in blood, while*
104 *statins simulate the Angpt-1 pathways. 2) The RAS system activates angiotensin-1 receptors (AT1R), stimulating inflammation,*
105 *hypercoagulability and endothelial permeability. The Ang II-ACE2-Ang(1-7)-Mas receptor pathway counteracts the effects of*
106 *this RAS system. COVID-19 enters the cell through ACE2 receptors, thereby decreasing these membrane-bound receptors, and*
107 *relatively stimulating the RAS system. ACEis/ARBs inhibit the RAS system, while concomitantly increasing ACE-2 expression,*
108 *which protects against ARDS. Statins also increase ACE-2 expression. 3) In ARDS there is an increase in the activation of the*
109 *MyD88-NFkB inflammatory pathway. Statins preserve MyD88 at normal levels and down regulate NFkB. Black lines =*
110 *stimulating effects; red lines = inhibiting effects.*

111

112 **Methods**

113 This retrospective study conformed with all legal guidelines and the protocol was approved by
114 the Ethical Committee of the Ghent University Hospital (reference BC-07671).

115 **Study design**

116 The retrospective study cohort was defined as all (anonymised) residents at two elderly care
117 homes with COVID-19 diagnosis based on clinical grounds and/or PCR lab testing from 1st of
118 March to 16th of April. Both elderly care homes experienced COVID-19 outbreaks during this
119 period. To determine the day of disease onset, structured and unstructured diagnostic records
120 were analysed for symptoms suggesting COVID-19 infection. The first day of suggestive
121 symptoms on two out of three consecutive days was considered as the day of disease onset. For
122 the PCR-diagnosed residents, the suggestive symptoms used for disease onset were cough,
123 shortness of breath (dyspnoea), sore throat, runny nose, general weakness, headache, confusion,
124 muscle pain, arthralgia, diarrhoea, abdominal pain, vomiting, fever ($T^{\circ} > 37.6^{\circ}\text{C}$), increased
125 oxygen need or low oxygen saturation ($\text{SpO}_2 \leq 92\%$). In cases where no symptoms were
126 mentioned (while still being PCR COVID-19-positive diagnosed), the date of nasopharyngeal
127 sampling was used as the day of disease onset. For the clinically diagnosed residents without a
128 confirmatory PCR lab test, the symptoms used for determining disease onset were defined more
129 strictly, i.e., respiratory complaints (cough, shortness of breath, sore throat, runny nose), fever
130 ($T^{\circ} > 37.6^{\circ}\text{C}$), increased oxygen-need or low oxygen saturation ($\text{SpO}_2 \leq 92\%$).

131 The primary outcomes were 1) serious COVID-19, i.e. long-stay hospital admission (length of
132 stay ≥ 7 days) or death (at nursing home or hospital) within 14 days of disease onset, and 2)
133 asymptomatic, i.e. no disease symptoms as defined above throughout the whole study-period
134 while still being PCR diagnosed.

135 All residents were stratified according to drug exposure to ACEi or ARB within 7 days before
136 the day of disease onset or during the disease (prior to an outcome being reached). Specifically,
137 we considered as treated all residents taking ≥ 2 days an ACEi (ramipril, lisinopril, enalapril,
138 captopril, quinapril, imidapril, fosinopril, trandolapril) or ARB (candesartan, irbesartan,
139 losartan, olmesartan, telmisartan, valsartan) up to 7 days before or 14 days after disease onset.
140 An identical protocol was used to stratify according to drug exposure to statins (atorvastatin,
141 fluvastatin, pravastatin, rosuvastatin, simvastatin).

142 We developed a mapping table based on clinical prescriptions to determine the diabetic and
143 hypertension status of all residents. It was designed by a specialist in elderly care and validated
144 by two independent physicians, one a general physician and the other a cardiologist.

145 The functional status of all residents was a dichotomous variable (high vs. low functioning).
146 This definition was based on the available Katz scale for residents before day of disease onset.
147 The Katz scale is a measure of independent activity of daily living.

148 **Data processing and quality control**

149 Anonymized data were imported in a relational database for processing, using Extract,
150 Transform, and Load (ETL) techniques. All received anonymized data were then evaluated on
151 basic data quality attributes such as completeness (i.e., the extent of missing data) and accuracy
152 (i.e., whether or not suspicious outliers were present in the individual attributes). Data were
153 enriched with ATC codes for the included drugs. Suggestive symptoms were searched for,
154 based on biometrical measurements as well as indications in text. For the later, basic Natural

155 Language Processing (NLP) techniques were used. For the residents still in the hospital on the
156 moment of data extraction, median imputation was used to estimate length of hospital duration.
157 Two independent physicians manually verified all recorded symptoms as well as all data for a
158 random subsample.

159 **Statistical Analysis**

160 We calculated the distributions for dependent and independent variables for the total cohort
161 using appropriate measures of central tendency and dispersion. For our main analysis, we
162 investigated the association between ACEi/ARB and/or statin treatment and 1) serious disease,
163 measured as long-stay hospital admission or death, or 2) asymptomatic disease using a series
164 of logistic regressions applying Firth's correction. This procedure has been used previously by
165 our group and shown to be robust for low prevalence events and low-dimensional settings (16,
166 22, 23). We first explored the independent association between ACEi/ARB and both outcomes,
167 as well as the association between statins and the same outcomes. Then we adjusted the models
168 stepwise for age, sex, functional status, hypertension, and diabetes mellitus. All statistical
169 analyses were performed using SAS 9.4 (SAS Institute, North Carolina, United States) and
170 RStudio 3.5.2 (R Foundation for Statistical Computing, Vienna, Austria).

171 **Sensitivity Analyses**

172 For the statistically significant associations, we also conducted sensitivity analyses to evaluate
173 our modelling assumptions and the extent to which the population selection influenced the main
174 results and conclusions. To control for the former (bias from modelling assumption) we
175 conducted exact logistic regressions with models adjusted variable by variable. To control for
176 the later (bias from population selection) we used the same modelling approach (logistic
177 regression with Firth's correction) to analyse only the PCR confirmed COVID-19+ residents.

178

179 Results

180 The study cohort included 154 COVID-19-diagnosed residents aged 86 ± 7 (mean \pm SD) years,
181 evenly distributed over the two nursing homes (76 and 78 residents, respectively). Baseline
182 characteristics are shown in **Table 1**. In our cohort (33% male), 20% were taking ACEis/ARBs
183 (16% ACEi and 4% ARB), and 20% were taking a statin. Eight residents (5%) were taking both
184 an ACEi/ARB and a statin. Important, none of the residents stopped ACEi/ARB or statin
185 treatment on the day of disease onset and all continued taking their drugs during the follow-up
186 period unless the clinical situation no longer allowed this. Also, none of the residents was taking
187 other renin-angiotensin system (RAS)-associated drugs such as renin-inhibitors or neprilysine-
188 inhibitors. Clinical symptoms detected by NLP in unstructured texts were all manually verified,
189 with 22% false positives, mostly due to mentioned symptoms with more complex negations in
190 the same sentence. Two physicians also independently evaluated manually all available data
191 from a minimum of five random residents each. This resulted in no changes in the result-matrix.

192 Of the 154 residents, 41 remained asymptomatic during the study period, i.e. 27% of the total
193 cohort and 47% of the PCR-tested COVID-19+ residents. These numbers are similar to those
194 from another study in a similar population (24). Thirty-seven residents (24%) experienced
195 serious COVID-19. Although this serious outcome number seems high compared to other
196 outpatient population studies, in view of the very vulnerable population this is not surprising
197 (25, 26). Among residents treated with ACEis or ARBs, 10/30 (33%) remained asymptomatic
198 vs. 31/124 (25%) of those without such treatment. Residents taking statins remained
199 asymptomatic in 45% of the cases (14/31) vs. 22% (27/123) of those not taking statins.

200 Evaluating COVID-19 severity, 20% (6/30) of the residents treated with ACEi/ARB died or
201 were admitted to hospital for long-stay vs. 25% (31/124) of those without such treatment.

202 Residents taking statins experienced serious COVID-19 in 19% of the cases (6/31) vs. 25%
203 (31/123) of those not taking statins. Interestingly, six of eight residents (75%) taking the

204 ACEi/ARB and statin combination remained asymptomatic throughout the study period. Only
205 one of them (13%) experienced serious COVID-19.

206 Although not reaching statistical significance, findings from unadjusted logistic regression
207 suggested a potential beneficial effect on COVID-19 symptoms among residents taking ACEis
208 or ARBs (OR 1.52; CI 0.62-3.50; $p=0.329$). Odds ratios adjusted for age, sex, functional status,
209 diabetes and hypertension were of similar magnitude (**Table 2**). The results for the statins were
210 most interesting, as we observed a clear and statistically significant association between statin
211 intake and asymptomatic status (unadjusted OR 2.91; CI 1.27-6.71; $p=0.011$). This association
212 was partially attenuated but remained statistically significant when adjusted for gender, age,
213 functional status, diabetes and hypertension (**Table 2**).

214 We also examined associations between ACEis/ARBs and statins, and serious COVID-19.
215 Although the available data failed to reach statistical significance, the directionality of the odds
216 ratios suggested a potential beneficial clinical effect of both ACEi/ARB and statins on serious
217 COVID-19 outcome. All odds ratios (unadjusted as well as adjusted for covariates), were
218 between 0.48 (CI 0.10-1.97; $p=0.316$) and 0.84 (CI 0.27-2.14; $p=0.736$) (**Table 3**).

219 We did not undertake regression analyses on the combined ACEi/ARB+statin group as there
220 were only eight residents in our cohort; nor did we undertake separate analyses for the ACEi or
221 ARB groups; only six residents were treated with an ARB.

222 Sensitivity analyses were conducted on the statistically significant association between statins
223 and symptoms. We found that estimates of the impact of statin treatment on asymptomatic
224 status were consistently of the same magnitude and statistically significant as the original
225 analyses.

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227
228

Table 1. Characteristics of the study cohort. All variables are shown as N (% of column), except age which is mean in years (SD). ACEi = Angiotensin converting enzyme inhibitor; ARB = Angiotensin receptor blocker.

Sample characteristics	Total (N = 154)	ACEi/ARB (N = 30)	No ACEi/ARB (N = 124)	Statin (N = 31)	No statin (N = 123)	Symptoms (N = 113)	No symptoms (N = 41)	Serious COVID (N = 37)	Non-serious COVID (N = 117)
Age	85.9 (7.2)	86.2 (6.6)	85.8 (7.4)	85.6 (5.3)	85.9 (7.6)	86.0 (7.4)	85.6 (6.6)	86.8 (6.8)	85.6 (7.3)
Male	51 (33.1%)	12 (40.0%)	39 (31.5%)	10 (32.3%)	41 (33.3%)	41 (36.3%)	10 (24.4%)	12 (32.4%)	39 (33.3%)
On ACEi/ARB	30 (19.5%)	30 (100%)	0 (0%)	8 (25.8%)	22 (17.9%)	20 (17.7%)	10 (24.4%)	6 (16.2%)	18 (20.5%)
On statin	31 (20.1%)	8 (26.7%)	23 (18.5%)	31 (100%)	0 (0%)	18 (15.9%)	14 (34.1%)	6 (16.2%)	25 (21.4%)
Low functioning	137 (89.0%)	23 (76.7%)	114 (91.9%)	26 (83.9%)	111 (90.2%)	106 (93.8%)	31 (75.6%)	35 (94.6%)	102 (87.2%)
Diabetes mellitus	28 (18.2%)	6 (20.0%)	22 (17.8%)	10 (32.3%)	18 (14.6%)	18 (15.9%)	10 (24.4%)	7 (18.9%)	21 (17.9%)
Hypertension	39 (25.3%)	28 (93.3%)	11 (8.87%)	8 (25.8%)	31 (25.2%)	29 (25.7%)	10 (24.4%)	10 (27.0%)	29 (24.8%)
Symptoms	113 (73.4%)	20 (66.7%)	93 (75.0%)	17 (54.8%)	96 (78.0%)	113 (100%)	0 (0%)	36 (97.3%)	77 (65.8%)
Serious COVID	37 (24.0%)	6 (20.0%)	31 (25.0%)	6 (19.4%)	31 (25.2%)	36 (31.9%)	1 (2.44%)	37 (100%)	0 (0%)

229

230 **Table 2. Summary of odds ratios for the asymptomatic COVID-19 infection using logistic**
 231 **regression with Firth's correction.**

Drug treatment	Adjustments	OR (95% CI) on drug vs. no drug	P-value
ACEi/ARB	-	1.52 (0.62-3.50)	0.339
	Age, sex	1.61 (0.65-3.80)	0.283
	Age, sex, functional status	1.35 (0.51-3.31)	0.521
	Age, sex, functional status, diabetes mellitus, hypertension	2.72 (0.59-25.1)	0.242
Statins	-	2.91 (1.27-6.71)	0.011
	Age, sex	2.88 (1.26-6.83)	0.013
	Age, sex, functional status	2.87 (1.23-7.07)	0.016
	Age, sex, functional status, diabetes mellitus, hypertension	2.65 (1.13-6.68)	0.028

232

233 **Table 3. Summary of odds ratios for the serious COVID-19 infection using logistic regression**
 234 **with Firth's correction.**

Drug treatment	Adjustments	OR (95% CI) on drug vs. not drug	P-value
ACEi/ARB	-	0.79 (0.26-1.95)	0.629
	Age, sex	0.78 (0.25-1.93)	0.610
	Age, sex, functional status	0.84 (0.27-2.14)	0.736
	Age, sex, functional status, diabetes mellitus, hypertension	0.48 (0.10-1.97)	0.316
Statins	-	0.75 (0.25-1.85)	0.556
	Age, sex	0.75 (0.25-1.86)	0.564
	Age, sex, functional status	0.77 (0.25-1.91)	0.597
	Age, sex, functional status, diabetes mellitus, hypertension	0.75 (0.24-1.87)	0.559

235

236 **Discussion**

237 There are currently no licensed antiviral treatments for COVID-19 approved. Also the
238 development of COVID-19 vaccines will take time. Moreover, there is no information on when
239 sufficient vaccine supplies will become widely available. Recently, the World Health
240 Organization (WHO) communicated a Solidarity “megatrial” evaluating four broad-spectrum
241 antiviral agents. Among them, the broad-spectrum experimental antiviral drug remdesivir was
242 shown to have low efficacy against Ebola and dropped from further study, although a recent
243 report of its compassionate use in serious COVID-19 was favourable (27). Lopinavir and
244 ritonavir (a protease inhibitor combination used to treat HIV patients) were ineffective in a
245 Chinese clinical trial (28). A lot of attention has gone to chloroquine and hydroxychloroquine.
246 Unfortunately prospects for their success against COVID-19 are not good (29). Convalescent
247 sera, obtained from recovered COVID-19 patients, might be an option to treat acute COVID-
248 19 infections (30), but its implementation will be cumbersome and unlikely to become widely
249 available. The first clinical trials of ACEi/ARB and statin treatments in hospital settings have
250 been initiated within the past month. While we await the results of these trials, which are
251 expected in 2021, this retrospective study should be regarded as both timely and
252 complementary, as it has focused on a frail, non-hospitalised population and demonstrated
253 clinical findings on the use of ACEi/ARB/statins using real world data.

254 Although statistically not significant, overall both ACEi/ARB and statins show clinical
255 beneficial odds ratios for the outcome serious COVID-19 in elderly people who live in nursing
256 homes. The results for statins and symptoms are most convincing, i.e. large effect sizes which
257 are statistically significant. Statins are most frequently used to prevent cardiovascular diseases.
258 The safety profile of statins is well known and excellent, even in the old population. Moreover,
259 these drugs are relatively inexpensive and widespread, some even as food supplements as red
260 yeast rice, making them easily available throughout the world. Although this observational

261 study does not have the power of a randomized controlled clinical trial, in the current absence
262 of other valuable therapies and considering the benefit-risk balance, an older person living in a
263 nursing home could consider taking a statin if at high COVID-19 infection risk. Currently,
264 therapeutic decisions for COVID-19 patients are driven by observational studies (31, 32). In
265 any case, based on our results, we recommend against stopping statins in patients who are
266 COVID-19-infected.

267 The combination of ACEi/ARB and statin treatment seemed to have additive beneficial effects
268 on symptoms and serious disease outcome: six of eight residents taking the combination
269 remained asymptomatic and only one of them developed serious COVID-19. Although this
270 result is promising, our sample size was too small to allow us to draw firm conclusions.

271 One strength of this study is the specific population, i.e., old people (mean age > 85years)
272 residing in nursing homes. Although they are considered highly vulnerable to COVID-19
273 clinical outcomes, no study has yet reported on the effects of ARB/ACEi and/or statin treatment
274 on COVID-19 in this population. Extracting reliable data from nursing homes with COVID-19
275 outbreaks is far more cumbersome than extracting data from hospitals. Another strength is that
276 drug treatment was based on real intake, in contrast to most hospital-based studies that use
277 prescriptions as proxies for drug treatment. Lastly, in contrast to most hospital studies,
278 asymptomatic COVID-19 patients were included in the study. People admitted to hospitals are
279 evidently always symptomatic.

280 One limitation of our study is its relatively small cohort size. Consequently, absence of
281 statistical significance should be interpreted with caution. However, the consistency in the
282 observed effect sizes, even without statistical significance due to small sample size, should be
283 considered in the overall evaluation. As number of cases increase, further analyses will be
284 undertaken to better understand our findings and confirm these associations. Also, another
285 limitation was the lack of other potential confounders, including chronic kidney injury and

286 BMI. Finally, our results apply to a very specific population (elderly people living in nursing
287 homes) and cannot be generalized to other groups such as young people or hospitalized people.

288

289 **Conclusions**

290 Our study, based on available data, indicates that in elderly nursing home residents, statin
291 treatment is associated with beneficial effects on COVID-19-related clinical symptoms.
292 Although not statistically significant, our findings also suggested that statin treatment in
293 combination with an ACEi or ARB was associated with less severe clinical outcomes. In the
294 light of these findings, a prudent recommendation is to continue or initiate statin treatment for
295 older people residing in nursing homes and at high risk for COVID-19 infection.

296

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301

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