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COVID-19 in-hospital mortality and use of renin-angiotensin system blockers in geriatrics patients.

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Brief summary: In very old subjects hospitalized for COVID-19 in geriatric settings, mortality was significantly lower in those treated with ARB or ACEI prior to the onset of infection.

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1 **COVID-19 in-hospital mortality and use of renin-angiotensin system blockers in geriatrics**
2 **patients.**

3 **ABSTRACT**

4 **Objective:** The role of treatment with renin-angiotensin-aldosterone system blockers at the onset of
5 COVID-19 infection is not known in geriatric population. The aim of this study was to assess the
6 relationship between angiotensin receptor blockers (ARB) and an ACE inhibitor (ACEI) use and in-
7 hospital mortality in geriatric patients hospitalized for COVID-19.

8 **Design:** This observational retrospective study was conducted in a French geriatric department.
9 Patients were included between March 17 and April 18, 2020.

10 **Setting and Participants:** All consecutive 201 patients hospitalized for COVID-19 (confirmed by RT-
11 PCR methods) were included. All non-deceased patients had 30 days of follow-up and no patient was
12 lost to follow-up.

13 **Methods:** Demographic, clinical, biological data and medications were collected. In-hospital mortality
14 of patients treated or not by ACEI/ARB was analyzed using multivariate Cox models.

15 **Results:** Mean age of the population was 86.3 (8.0) years old, 62.7% of patients were
16 institutionalized, 88.6% had dementia and 53.5% had severe disability (ADL score < 2). Sixty-three
17 patients were treated with ACEI/ARB and 138 were not. Mean follow-up was 23.4 (10.0) days, 66
18 (33.8%) patients died after an average of 10.0 days (6.0). Lower mortality rate was observed in
19 patients treated with ACEI/ARB compared with patients not treated with ARB nor ACEI (22.2% (14) vs.
20 37.7% (52), HR = 0.54 (95% CI = 0.30-0.97), p=0.03). In a multivariate Cox regression model including
21 age, sex, ADL score, Charlson index, renal function, dyspnea, CRP and white blood cells count, use of
22 ACEI/ARB was significantly associated with lower in-hospital mortality (HR = 0.52 (0.27–0.99),
23 p=0.048).

24 **Conclusion and Implications:** In very old subjects hospitalized in geriatric settings for COVID-19,
25 mortality was significantly lower in subjects treated with ARB or ACEI prior to the onset of infection.
26 The continuation of ACEI/ARB therapy should be encouraged during periods of coronavirus outbreak
27 in older subjects.

28

29

30 Introduction

31 Worldwide, as of June 15, 2020, according to John Hopkins University, more than 8 million people
32 have been affected by coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2, and more than
33 400 thousands died of COVID-19 since December 31, 2019.¹ In France according to *Santé Publique*
34 *France*, the French health agency, more than 141 thousand people have been contaminated and
35 more than 29 thousands died of COVID-19.²

36 COVID-19 predominantly affects elderly people. Subjects aged 75 years and older accounted
37 for 75% of all deaths related to COVID-19 in France² and mortality rate is 31.1% in Italy among
38 people > 80 years old.³ SARS-CoV-2 virus belongs to the family of orthocoronavirinae, and shares
39 some similarities with the MERS-CoV (75% identical genome sequence) and the SARS-CoV (85 % of
40 identical genome sequence respectively) that were responsible for severe pneumonia.⁴ Their S
41 protein (of their capsid) are 99% similar and they have the same binding site: the angiotensin 2
42 conversion enzyme.⁴ Angiotensin 2 converting enzyme has a role in the entry of SARS-CoV-2 into
43 target cells and animal experimental data indicate an increase in enzyme expression after
44 administration of renin–angiotensin–aldosterone system blockers (i.e., angiotensin-converting-
45 enzyme inhibitors (ACEI) and receptors blockers (ARB)).⁵ Thus the question has arisen as to whether
46 ACEI/ARB treatment could increase severity and mortality of COVID-19.⁶

47 In observational studies, subjects with cardiovascular diseases and hypertension are often
48 treated with ACEI or ARB, and have an increased risk of in-hospital mortality related to COVID-19.^{5, 7}
49 Meanwhile some studies have found no effect^{7, 8} or even a beneficial effect of ACEI/ARB on COVID-19
50 mortality.^{5, 9, -11} Older people are frequently treated with ACEI/ARB, however few data are available on
51 their use in geriatric population affected by COVID-19. The aim of this study was to assess the
52 relationship between ACEI/ARB and in-hospital mortality among geriatric patients hospitalized for
53 COVID-19.¹²

54

55 **Methods**

56 This retrospective study included all symptomatic patients admitted in Acute Geriatric Units
57 dedicated to treating COVID-19, between March 17 and April 18, 2020, in a geriatric department with
58 a positive reverse-transcription polymerase chain reaction (RT-PCR) for SARS-CoV-2 on nasal swabs.
59 Patients were followed-up until May 18, 2020. Before admittance in the Acute Geriatric Units,
60 patients with positive RT-PCR for SARS-CoV-2 were first examined in emergency room and had a
61 geriatric evaluation. Only patients who were assessed as not fit enough or had too severe
62 comorbidities for intensive care unit were admitted Acute Geriatric Units and included in the study.
63 As available, four different PCR tests were performed by the hospital's virology department (Abbott
64 real time SRAS CoV-2, Xpert Xpress SRAS CoV-2, Simplexa COVID 19 direct and Allplex 2019-nCoV
65 Assay).

66 The study was conducted in accordance with the ethical standards set forth in the Declaration of
67 Helsinki. The study protocol was approved by local ethics committee and the study complied with the
68 strengthening the reporting of observational studies in epidemiology statement guidelines¹³ All
69 patients' data were anonymized prior to analysis. No consent to participate was sought for the
70 participants in accordance with the French law because the study was observational in nature (as
71 part of usual care), and no nominative data were collected.¹⁴

72 **Data collection**

73 All data were collected as part of usual care. In-hospital mortality was assessed during a follow up of
74 30 days after RT-PCR confirmation. All patients included in the study were hospitalized at least 30
75 days in the geriatric department (acute unit and then rehabilitation unit if needed). Thus all non-
76 deceased patients had a full 30-day follow-up.

77 Ethnicity was not recorded but the sample was overwhelmingly white Caucasian (> 90%).
78 Demographic and clinical characteristics were recorded: sex, age, institutionalization, history of

79 cancer (localized or metastatic), heart failure, coronary heart disease, atrial fibrillation, hypertension
80 (defined as systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg or use of
81 antihypertensive medications or history of hypertension), diabetes mellitus (defined as self-report or
82 use of oral hypoglycemic medication or insulin or a history of diabetes), chronic respiratory disease
83 (chronic obstructive pulmonary disease or asthma), stroke or transient ischemic attacks, dementia
84 (based on the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition),¹⁵ chronic kidney
85 disease and major depression. Nutritional status was assessed by body mass index (BMI) and serum
86 albumin level and malnutrition was defined as BMI <21 kg/m² or Albumin < 35 g/l as defined in a Best
87 Practice Guideline by the French health authority.¹⁶ Comorbidity was evaluated with the Charlson
88 Comorbidity Index (CCI).¹⁷ Functional status was assessed with Activities of Daily Living (ADL).¹⁸ ADL
89 was regrouped in 3 classes, no disability to mild disability (ADL ≥ 4 to 6), moderate disability (ADI ≥ 2
90 to < 4) and severe disability (ADL 0 to < 2).

91 Symptoms that led to the COVID-19 diagnosis or occurred in the first 72 hours before or after
92 the RT-PCR confirmation, such as fever (defined as $T^{\circ} > 37.8^{\circ}\text{C}$), dyspnea, coughing, severe
93 hypotension (SBP < 95 mmHg), digestive disorders (diarrhea and nausea or vomiting) or falls were
94 also collected.

95 Ongoing treatments defined as treatment taken for at least 1 week before inclusion and
96 taken the day of the inclusion were recorded: ACEI, ARB, diuretics, beta-blockers, calcium channel
97 blockers, antiplatelet therapy, oral anticoagulants, benzodiazepines, neuroleptics, antidepressant
98 therapy and proton pump inhibitors.

99 Biological data were also collected at admission including hemoglobin level, white blood cell
100 count (WBC), lymphocyte and platelet count, C-reactive protein (CRP), serum creatinine, LDL and
101 albumin. Estimated glomerular filtration (eGFR) rate was calculated with CKD-EPI formula¹⁹ and
102 categorized in 3 classes, eGFR ≥ 50 ml/min, 50 ml/min $> eGFR \geq 30$ ml/min and eGFR < 30 ml/min.

103

104 **Statistical Analysis**

105 Baseline characteristics of the participants were analyzed in the whole sample and according to death
106 at 30 days using descriptive statistics: means and standard deviations for continuous variables, and
107 percentages and counts for categorical variables and compare with t-tests and χ^2 respectively.

108 Variables were also compared with univariate Cox model to take into account the different follow-up
109 durations.

110 Baseline characteristics of the participants were also analyzed according to the use of ACEI/ARB and
111 compare with t-tests for continuous variables and χ^2 for categorical variables.

112 A Kaplan Meier curve was drawn for the mortality according to ACEI/ARB use and compared with Log
113 Rank test.

114 A Cox regression model was built with 30-day in-hospital mortality as dependent variable and use of
115 ACEI/ARB as independent variable adjusted for age, sex and variables associated with 30-day in-
116 hospital mortality in univariate model (i.e., dyspnea, ADL, Charlson Comorbidity Index, eGFR, CRP,
117 WBC in addition with age and sex) and results were presented in a forest plot. CRP, WBC and Charlson
118 Comorbidity Index were standardized in order to obtain HR for an increase of 1 SD of each of those
119 variables. HR for age was calculated for an increase of 10 years.

120 Another multivariate regression Cox model was built with 30-day in-hospital mortality as dependent
121 variable and use of ARB and ACEI taken separately as independent variable and with the same
122 adjustment as the first Cox regression model.

123 LDH was not included in this model because it was missing in 50 subjects. Proportional hazard
124 assumption was checked graphically for all covariates and using Schoenfeld residuals.

125 All analyses were two-sided and a p-value < 0.05 was considered statistically significant. Data analysis
126 was performed using R software version 3.2.3, (R Core Team (2014). R: A language and environment
127 for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL [http://www.R-](http://www.R-project.org/)
128 [project.org/](http://www.R-project.org/)).

129 Results

130 Among 373 patients hospitalized in a geriatric department from March 17 to April 18, 2020, 201
131 patients had a positive SARS-CoV-2 RT-PCR and were included in this study.

132 Mean age of the sample was 86.3 (8.0) years old, 126 (62.7 %) patients lived in nursing homes, 178
133 (88.6%) had dementia and 107 (53.5%) had severe disability. The main symptoms at inclusion were
134 fever (82.1%), dyspnea (28.9%), coughing (32.0%), digestive symptoms (9.95%) and falls (12.4%)
135 (**Table 1**).

136 Sixty-six (33.8%) died after an average of 9.9 days in the hospital. All non-deceased patients
137 had a full follow-up of 30 days, thus no participant was lost to follow-up. No patients were managed
138 in intensive care units.

139 Dyspnea (39.4% in non survivors vs. 23.7% in survivors, $p=0.01$) and poor functional status (ADL score
140 < 2 , 67.7% vs. 46.7%, $p = 0.02$) were significantly associated with in hospital mortality (**table 1**). Mean
141 CRP (57.1 vs. 27.6 mg/L, $p < 0.0001$), creatinine (97.9 vs. 82.7 $\mu\text{mol/L}$, $p=0.007$), white blood cells
142 (8.59 vs. $6.03 \times 10^9/\text{L}$, $p<0.0001$) and LDH (359 vs. 241 UI/L, $p = 0.05$) were also significantly
143 associated with in hospital mortality (**table 1**).

144 Lower mortality rate was observed in patients treated with ARB or ACEI compared with
145 patients not treated with ARB nor ACEI (22.2% (14) vs. 37.7% (52), HR = 0.54 (95% CI = 0.30-0.97),
146 $p=0.03$) (**Figure 1**). Compared with patients not treated with ARB nor ACEI, patients treated with ARB
147 alone had a lower rate of death (HR = 0.36 (0.13-1.00), $p=0.05$) as well as those with ACEI alone (HR =
148 0.66 (0.34-1.31), $p=0.23$) (**Table 2**).

149 Among patients with hypertension, 46% (58/125) were treated with ACEI/ARB. Patients
150 receiving ACEI or ARB had more often hypertension and coronary artery disease and less often
151 dementia and lower level of hemoglobin. Overall they had a higher Charlson comorbidity index than

152 patients not treated with ACEI or ARB. They were more often treated with calcium channel blockers,
153 diuretics, and antiplatelet (**table 3**).

154 In a multivariate Cox regression model including age, sex, ADL, CCI, renal function, dyspnea,
155 CRP and WBC, use of ACEI or ARB was significantly associated with lower in-hospital mortality (HR =
156 0.52 (0.27–0.99), p=0.048) (**Figure 2**). Severe disability (ADL < 2), (HR = 2.54 (1.13-5.72)), high white
157 blood cells count (HR= 1.45 (1.16-1.81)) and high CRP (HR= 1.37 (1.11-1.69)) were significantly
158 associated with death (**Figure 2**).

159 In the multivariate Cox regression model analyzing ARB and ACEI separately, HR was 0.40
160 (0.14-1.15), p=0.09 for ARB and 0.60 (0.28-1.31), p=0.20 for ACEI (**Figure 2**).

161

162

163 Discussion

164 In this cohort of very old patients affected by COVID-19, a high rate of in-hospital mortality was
165 observed. The main factor associated with mortality was severe disability. In-hospital mortality
166 among patients treated with ACEI or ARB was significantly lower compared with patients without
167 ACEI or ARB therapy.

168 In our study, 33% of the patients died within 30 days of COVID-19 RP PCR confirmation. This
169 mortality is much higher than that of younger population and of other respiratory virus diseases like
170 influenza - and respiratory syncytial virus in elderly people.²⁰ Older age has already been found a
171 major risk factor for mortality from COVID-19 ranging from 14% to 30 % in patients aged > 80 years
172 old.^{3, 21, 22} As of May 28, 2020 among the 59,134 peoples aged > 80 years old affected by COVID- 19 in
173 Italy the mortality was 31.1%³. The relation of age and COVID-19 mortality is probably related to
174 immunosenescence that has been identified as a major risk factor for respiratory diseases and its
175 related mortality.²³

176 As already published, we also found that CRP and leukocytes increase were associated with
177 death.^{8, 24, 25} However in our geriatric population, the main factor associated with mortality was
178 severe disability and not factors usually associated with higher mortality in COVID-19 like,
179 cardiovascular diseases, diabetes mellitus, obesity and chronic obstructive pulmonary disease.²⁶⁻²⁸
180 Disability through ADL is an already known factor of all-cause mortality in the elderly.^{29, 30}
181 Interestingly, poor functional status was a most relevant factor associated with mortality than
182 respiratory symptoms like dyspnea that are major prognostic factors in younger population.³¹⁻³³
183 Conversely to other studies, age was not associated with in-hospital mortality in our study probably
184 because of the specificity of our population that was very old with a somewhat narrow age range.
185 Therefore our results suggest that in older geriatric patients affected by COVID-19, functional status is
186 the most important prognostic factor of mortality.

187 Studies on use of ACEI or ARB in COVID-19 patients have yielded conflicting results.
188 Hypertension had been associated with mortality in hospitalized COVID-19 patients, and
189 hypertensive patients are frequently treated with ACEI/ARB.²⁸ Because ARB or ACEI therapeutics
190 interact with ACE2 that is a required receptor for SARS-CoV-2 entry and propagation in host cells,
191 ARB or ACEI could promote SARS-CoV-2 susceptibility and COVID-19 severity through increase of
192 ACE2 expression.¹⁰ Some studies did not show any increased mortality associated with use of ACEI or
193 ARB in populations aged on average 45,³⁴ 55.5,⁸ 58³⁵ and 68⁷ years old. However few data were
194 available in very old geriatric patient at high risk of mortality from COVID-19 treated with ACEI/ARB.

195 In our study, mortality among patients treated with ACEI or ARB was significantly lower
196 compared with patients without ACEI or ARB therapy, after adjustment for confounding variables.
197 This result is consistent with a study from 9 hospitals in China including 1128 in-patients with
198 hypertension and COVID-19 that demonstrated lower risk of mortality among patients treated with
199 ACEI/ARB (HR = 0.42, 95% CI = 0.15-0.89, mean age 64 years old).¹⁰ Another collaborative study
200 analyzing data from 169 hospitals in Asia, Europe and North America showed that in-hospital
201 mortality was lower in ACEI-treated subjects (OR = 0.33, 95% CI = 0.20 to 0.54, mean age 49 years
202 old, 16.5% > 65 years old).⁵ Lastly, an analysis of the data from 7 Madrid's hospitals found a lower
203 risk of COVID-19 requiring hospitalization in diabetic patients treated with ACEI/ARB (OR = 0.53, 95%
204 CI = 0.34-0.80, mean age 69.1 years old).³⁶

205 It has been shown that SARS-CoV-2 cell entry leads to down-regulation of ACE2 contributing to an
206 increase in harmful Angiotensin II⁸ and a decrease in protective Angiotensin 1-7. This increase in
207 Angiotensin II might worsen lung injury from COVID-19 through excessive inflammatory response and
208 cytokine storm, stimulating vascular leakage and pulmonary fibrosis.¹⁰ Treatment with ARB may
209 protect against lung injury by Angiotensin I Type 1 receptor blockade and ACEI may protect by
210 reducing Angiotensin II levels due to inhibition of Angiotensin I to Angiotensin II conversion.

211 ACEI/ARB could also be beneficial to patients with COVID-19 because they modulate inflammation,
212 endothelial damage and fibrosis and may be involved in coagulation cascade.³⁷

213 In our geriatric population no patient were managed in intensive care unit because of high
214 level of comorbidity, dementia and low physiologic reserves that make prolonged intensive care
215 unreasonable. Indeed, among critically ill elderly geriatric patients, ICU admission do not reduce 6-
216 month mortality.³⁸ In this frail population at high risk of mortality, the need of effective treatment
217 before critical stage of COVID-19 is of paramount importance.

218 The high prevalence of dementia could be explained by the fact that only patients who were
219 assessed too debilitated or had too severe comorbidities for intensive care unit after a geriatric
220 evaluation were transferred in the Acute Geriatric Units and because 60% of our patients came from
221 nursing homes.

222 This study has several strengths. Very few data existed on geriatric population affected by
223 COVID-19, characterized by high risk of mortality and no access to intensive care unit.³⁸ Prevalence of
224 dementia was very high (89%) and few data exist on such population. There was no loss to follow-up
225 and all non-deceased patients were followed-up for 30 days enabling the estimate of the actual 30-
226 day mortality. Our results were adjusted on confounding factors including symptoms, comorbidity,
227 disability and biological factors and suggest that in this population the ACEI/ARB therapy could be
228 associated with better prognosis and ought to be confirm in other geriatric populations. Randomized
229 controlled trials are much needed to assess the benefit on mortality associated with ACEI/ARB
230 treatment in elderly patients with COVID-19.

231 This study has also some limitations, this cohort was monocentric and retrospective, so
232 causality between ACEI or ARB use and mortality cannot be ascertained. Moreover dosing, indication
233 and duration of ARB and ACEI prescriptions were not recorded as well as their continuations during
234 COVID-19 course. However, only 2 patients had a severe renal insufficiency and 2 had severe
235 hypotension (SBP < 95 mm Hg) at baseline in the ACEI/ARB group, conditions that would require

236 stopping ACEI/ARB. There was no sufficient power to analyze ARB and ACEI separately. Finally
237 duration of the infection before hospitalization was unknown. Statin use was not recorded even
238 though it has been recently shown to reduce mortality and severity in elderly patients with COVID-
239 19.^{12, 39} Some blood measurement like D-Dimer, Fibrinogen, BNP, Troponin and IL-6 were not
240 performed and others like LDH were only measured in portion of the sample, precluding their use in
241 multivariate models. The precise causes of death were not recorded and death within 30 days of
242 positive COVID-19 RP-PCR was assumed to be COVID-19 related. Lastly, diagnosis was only based on
243 RP-PCR and not on pulmonary CT-scan because it was difficult to move very frail patients with pulmonary
244 symptoms to another hospital to get the CT-scan. Therefore we might have missed some patients with
245 false negative COVID-19 RP-PCR.

246

247 **Conclusions and Implications**

248 In very old subjects hospitalized in geriatric settings for COVID-19, mortality was lower in subjects
249 treated with ARB or ACEI prior to the onset of infection. The continuation of ACEI/ARB therapy
250 should be encouraged during periods of coronavirus outbreak in older subjects.

251

252

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364 Table 1, General characteristics in the whole sample and according to 30-day in-hospital mortality

Characteristics, %(N)	Whole sample	Survivors	Non-survivors	p*
	N=201	N=135	N=66	
Age (years), M (SD)	86.3 (8.0)	86.2 (8.2)	86.4 (7.6)	0.87
Women	67.2 (135)	68.9 (93)	63.6 (42)	0.40
Nursing home	62.7 (126)	60.7 (82)	66.7 (44)	0.36
Activities of daily living score				0.02†
[0-2[53.5 (107)	46.7 (63)	67.7 (44)	
[2-4[25.5 (51)	28.1 (38)	20.0 (13)	
[4-6]	21.0 (42)	25.2 (34)	12.3 (8)	
BMI (kg/m ²), M (SD)	24.1 (6.0)	23.9 (5.8)	24.4 (6.4)	0.53
Comorbidity				
Charlson comorbidity index	3.17 (2.22)	3.03 (2.21)	3.46 (2.24)	0.17
Dementia	88.6 (178)	86.7 (117)	92.4 (61)	0.2
Cancer	18.0 (36)	15.7 (21)	22.7 (15)	0.18
Stroke or TIA	23.9 (48)	20.7 (28)	30.3 (20)	0.20
Chronic heart failure	34.8 (70)	34.1 (46)	36.4 (24)	0.67
Hypertension	62.2 (125)	63.0 (85)	60.6 (40)	0.73
Atrial fibrillation	34.3 (69)	34.1 (46)	34.8 (23)	0.77
Coronary artery disease	23.4 (47)	25.2 (34)	19.7 (13)	0.34
COPD	15.4 (31)	15.6 (21)	15.2 (10)	0.99
Diabetes mellitus	19.4 (39)	16.3 (22)	25.8 (17)	0.12
Depression	46.3 (93)	46.7 (63)	45.5 (30)	0.79
Anemia†	45.5 (90)	46.3 (62)	43.8 (28)	0.88
Malnutrition	74.4 (134)	73.6 (92)	76.4 (42)	0.66
Symptoms				
Fever (> 37.8°C)	82.1 (165)	80.0 (108)	86.4 (57)	0.26
Dyspnea	28.9 (58)	23.7 (32)	39.4 (26)	0.01
Coughing	32.0 (64)	34.1 (46)	27.7 (18)	0.32
SpO ₂ < 90%	4.19 (8)	3.03 (4)	6.78 (4)	0.22
Digestive symptoms	9.95 (20)	9.63 (13)	10.6 (7)	0.69
Fall	12.4 (25)	10.4 (14)	16.7 (11)	0.17
Severe hypotension (SBP < 95 mm Hg)	2.2 (4)	2.4 (3)	1.7 (1)	0.78
Biological characteristics, M (SD)				
Hemoglobin (g/dL)	12.4 (1.7)	12.4 (1.7)	12.5 (1.7)	0.86
WBC (× 10 ⁹ /L)	6.86 (3.83)	6.03 (2.49)	8.59 (5.32)	<.0001
Lymphocytes (× 10 ⁹ /L)	1.31 (0.81)	1.30 (0.75)	1.34 (0.93)	0.64
Platelets (× 10 ⁹ /L)	215 (89)	220 (84)	207 (98)	0.37
Creatinine (μmol/L)	87.5 (37.8)	82.7 (35.6)	97.9 (40.5)	0.007
eGFR (CPK EPI formula)				0.04
≥ 50 mL/min/1.73 m ²	71.1 (140)	75.4 (101)	61.9 (39)	
30-50 mL/min/1.73 m ²	21.8 (43)	20.1 (27)	25.4 (16)	
< 30 mL/min/1.73 m ²	7.11 (14)	4.48 (6)	12.7 (8)	
Albumin (g/L)	35.2 (10.1)	35.8 (11.8)	34.0 (4.0)	0.11
Albumin < 35 g/L	53.9 (89)	51.3 (59)	60.0 (30)	0.31
LDH	264(136)	241 (77)	359 (251)	0.05
CRP (mg/L)	37.0 (49.0)	27.6 (42.5)	57.1 (56.0)	<.0001

365 % (N), percentage (count); M (SD), mean (standard deviation), BMI, body mass index; TIA, transient
 366 ischemic attack; COPD, chronic obstructive pulmonary disease; SpO₂, peripheral oxygen saturation;
 367 WBC, white blood cells; eGFR, glomerular filtration rate estimated with CPK-EPI formula; CRP, C-
 368 reactive protein.

369 * p values from univariate Cox regression model; † Anemia according to World Health Organization
 370 definition: hemoglobin < 130 g/L in men and < 120 g/L in women.

371 Table 2, Medication in the whole sample and according to 30-day in-hospital mortality.

Medications, %(N)	Whole sample	Survivors	Non-survivors	p*
	N=201	N=135	N=66	
Renin-angiotensin system inhibitors				
ARB or ACEI	31.3 (63)	36.3 (49)	21.2 (14)	0.03
Renin-angiotensin system inhibitors†				
No ARB nor ACEI	68.7 (138)	63.7 (86)	78.8 (52)	Ref
ACEI	18.9 (38)	20.7 (28)	15.2 (10)	0.23
ARB	12.4 (25)	15.6 (21)	6.06 (4)	0.05
Calcium channel blockers	16.4 (33)	18.5 (25)	12.1 (8)	0.21
Diuretics	27.6 (55)	26.1 (35)	30.8 (20)	0.46
Beta-blockers	43.5 (87)	42.5 (57)	45.5 (30)	0.72
Anticoagulants	25.5 (51)	24.6 (33)	27.3 (18)	0.55
Anti-platelets	25.0 (50)	24.6 (33)	25.8 (17)	0.94
PPI	41.0 (82)	41.8 (56)	39.4 (26)	0.79
Antidepressants	54.0 (108)	56.7 (76)	48.5 (32)	0.22
Neuroleptics	23.5 (47)	21.6 (29)	27.3 (18)	0.49
Benzodiazepines	55.0 (110)	53.7 (72)	57.6 (38)	0.63

372 % (N), percentage (count); ARB, angiotensin II receptor blocker; ACEI, angiotensin-converting-enzyme

373 inhibitors; PPI, proton-pump inhibitor.

374 * p values from univariate Cox regression model;

375 † Overall difference between no ACEI nor ARB, ACEI, ARB in Cox regression model, p=0.06.

376

377 Table 3, Cohort characteristics according to ACEI/ARB use.

Variables, M (SD)	No ARB nor ACE inhibitors	ARB or ACE inhibitors	p*
	N=138	N=63	
Age (years)	86.0 (8.6)	86.9 (6.3)	0.46
Women, %(N)	65.2 (90)	71.4 (45)	0.48
Nursing home living, %(N)	67.4 (93)	52.4 (33)	0.06
Activities of daily living, %(N)			
[0-2[58.4 (80)	42.9 (27)	
[2-4[24.8 (34)	27.0 (17)	0.06
[4-6]	16.8 (23)	30.2 (19)	
BMI (kg/m ²)	23.9 (6.2)	24.5 (5.6)	0.47
Comorbidity, %(N)			
Charlson comorbidity index	2.98 (2.18)	3.59 (2.29)	0.07
Dementia	93.5 (129)	77.8 (49)	0.003
Cancer	17.5 (24)	19.0 (12)	0.95
Stroke or TIA	20.3 (28)	31.7 (20)	0.11
Chronic heart Failure	31.2 (43)	42.9 (27)	0.15
Hypertension	48.6 (67)	92.1 (58)	<.0001
Atrial fibrillation	34.1 (47)	34.9 (22)	0.99
Coronary artery disease	18.8 (26)	33.3 (21)	0.04
COPD	14.5 (20)	17.5 (11)	0.74
Diabetes mellitus	17.4 (24)	23.8 (15)	0.38
Depression	44.2 (61)	50.8 (32)	0.47
Anemia†	41.9 (57)	53.2 (33)	0.18
Malnutrition	76.2 (93)	70.7 (41)	0.54
Medication, %(N)			
Calcium blockers	12.3 (17)	28.6 (18)	0.009
Diuretics	22.6 (31)	38.7 (24)	0.03
Beta-blockers	39.9 (55)	51.6 (32)	0.16
DOACs	25.4 (35)	25.8 (16)	0.99
Anti-platelet	20.3 (28)	35.5 (22)	0.03
Antidepressant	52.2 (72)	58.1 (36)	0.54
Neuroleptics	24.6 (34)	21.0 (13)	0.70
Benzodiazepine	55.8 (77)	53.2 (33)	0.85
PPI	39.1 (54)	45.2 (28)	0.52
Symptoms, %(N)			
Fever (> 37.8°C)	83.3 (115)	79.4 (50)	0.63
Dyspnea	27.5 (38)	31.7 (20)	0.66
Coughing	31.4 (43)	33.3 (21)	0.91
SpO ₂ < 90%	4.62 (6)	3.28 (2)	0.97
Digestive symptoms	10.9 (15)	7.94 (5)	0.70
Falls	13.8 (19)	9.52 (6)	0.54
Severe hypotension (SBP < 95 mm Hg)	1.5 (2)	4.1 (2)	0.30‡
Biological characteristics			
Hemoglobin (g/dL)	12.6 (1.8)	12.1 (1.5)	0.05
WBC (× 10 ⁹ /L)	6.69 (3.40)	7.23 (4.65)	0.35
Lymphocytes (× 10 ⁹ /L)	1.25 (0.76)	1.44 (0.91)	0.13
Platelets (× 10 ⁹ /L)	212 (73)	222 (116)	0.50
Creatinine (μmol/L)	88.4 (39.4)	85.6 (34.4)	0.64
eGFR (CPK EPI formula)			
≥ 50 mL/min/1.73 m ²	72.0 (95)	64.0 (32)	
30-50 mL/min/1.73 m ²	19.0 (25)	32.0 (16)	0.12
< 30 mL/min/1.73 m ²	9.1 (12)	4.0 (2)	
Albumin (g/L)	34.4 (3.9)	37.0 (16.7)	0.11
Albumin < 35 mg/mL	53.8 (63)	54.2 (26)	0.99
LDH (UI/L)	247 (78)	292 (201)	0.11
CRP (mg/L)	36.6 (45.3)	37.9 (56.7)	0.86

378 % (N), percentage (count); M (SD), mean (standard deviation); ARB, angiotensin II receptor blocker;
379 ACEI, angiotensin-converting-enzyme inhibitors; BMI, body mass index; TIA, transient ischemic
380 attack; COPD, chronic obstructive pulmonary disease; PPI, proton-pump inhibitor; WBC, white blood
381 cells; eGFR, glomerular filtration rate estimated with CPK-EPI formula; CRP, C-reactive protein.

382 * p values from T-test or χ^2 ; † Anemia according to World Health Organization definition: hemoglobin
383 < 130 g/L in men and < 120 g/L in women; ‡ Fisher exact test.

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385 **Figure 1, 30-day in-hospital mortality according to ACEI or ARB use.**

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390 **Figure 2, Factors associated with 30-day in-hospital mortality in a multivariate Cox regression**
391 **model.**

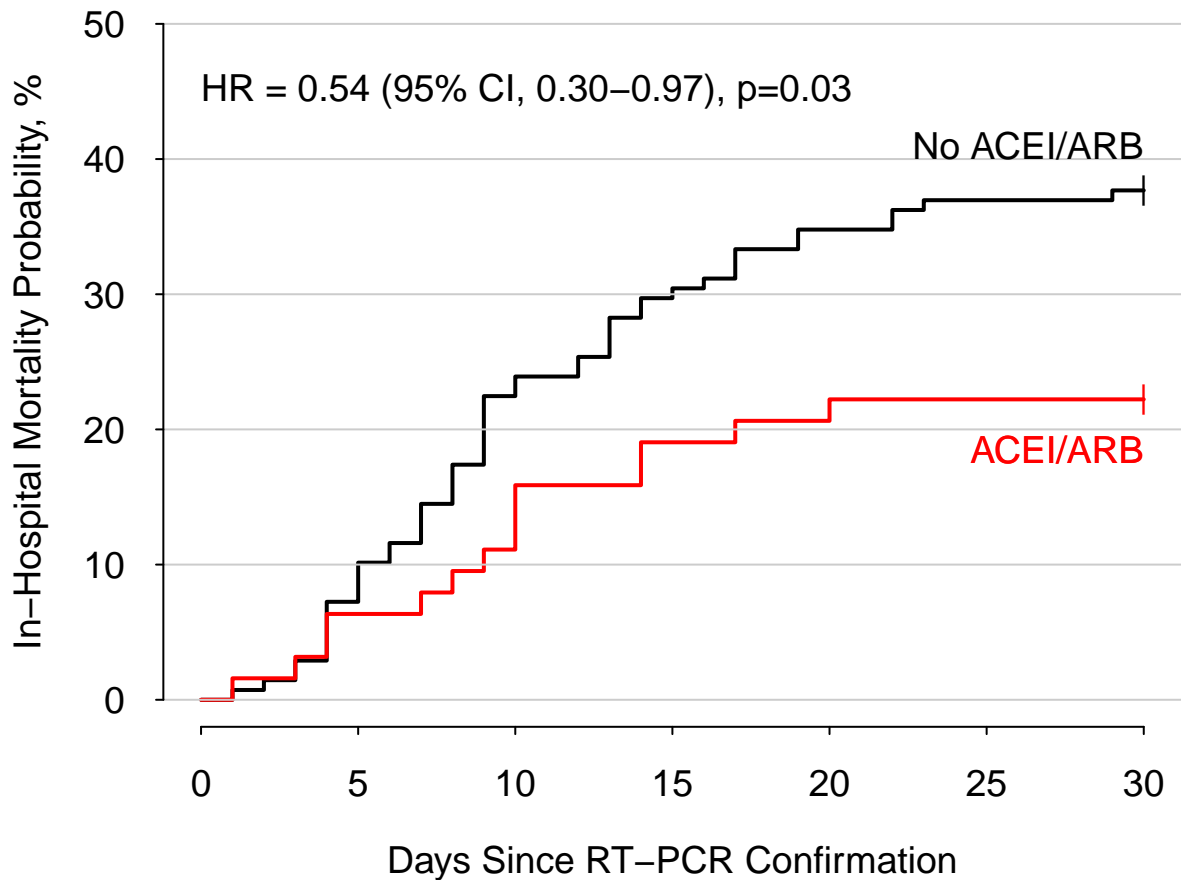
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394 SD, standard deviation; ADL, Activities of daily living; ; eGFR, glomerular filtration rate estimated with
395 CPK-EPI formula; CRP, C-reactive protein; WBC, white blood cells; ARB, angiotensin II receptor
396 blockers; ACEI, angiotensin-converting-enzyme inhibitors.

397 1 SD for age = 8.0 years, 1 SD for Charlson index = 2.2 points, 1 SD for CRP = 49 mg/mL, 1 SD for
398 WBC = 3.9×10^9 /L.

399 * p < 0.05; ** p < 0.01.



No. At Risk

No ACEI/ARB	138	128	107	97	90	87	86
ACEI/ARB	63	59	56	51	50	49	49

