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# Impact of Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers in Hypertensive Patients with COVID-19 (COVIDECA Study)



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**Effect of angiotensin-converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARB) among hypertensive patients with coronavirus disease 2019 (COVID-19) is debated. The aim of the COVIDECA study was to assess the outcome of ACEI and ARB among hypertensive patients presenting with COVID-19. We reviewed from the Assistance Publique-Hôpitaux de Paris healthcare record database all patients presenting with confirmed COVID-19 by RT-PCR. We compared hypertensive patients with ACEI or ARB and hypertensive patients without ACEI and ARB. Among 13,521 patients presenting with confirmed COVID-19 by RT-PCR, 2,981 hypertensive patients (mean age: 78.4 ± 13.6 years, 1,464 men) were included. Outcome of hypertensive patients was similar whatever the use or non-use of ACEI or ARB: admission in ICU (13.4% in patients with ACEI or ARB versus 14.8% in patients without ACEI/ARB,  $p = 0.35$ ), need of mechanical ventilation (5.5% in patients with ACEI or ARB vs 6.3% in patients without ACEI/ARB,  $p = 0.45$ ), in-hospital mortality (27.5% in patients with ACEI or ARB vs 26.7% in patients without ACEI/ARB,  $p = 0.70$ ). In conclusion, the use of ACEI and ARB remains safe and can be maintained in hypertensive patients presenting with COVID-19. © 2021 Elsevier Inc. All rights reserved. (Am J Cardiol 2021;147:58–60)**

Effect of angiotensin-converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARB) among hypertensive patients with coronavirus disease 2019 (COVID-19) is debated.<sup>1</sup> Hypertension is associated with a higher risk of severity and mortality in patients presenting with COVID-19.<sup>2</sup> Angiotensin converting enzyme inhibitor and ARB are widely used in hypertension and some concerns occurred concerning ACEI and ARB in COVID-19 patients. Indeed, some experimental studies found that ACEI and ARB exposures increased the expression of ACE2 receptor, which is the known cellular receptor and a

necessary entry point for acute respiratory syndrome coronavirus 2 (SARS-CoV-2),<sup>3</sup> but these findings were not confirmed in humans.<sup>4</sup> Furthermore, conflicting results in hypertensive patients with ACEI and ARB were published.<sup>5–16</sup> The aim of the COVIDECA study was to assess the outcome of ACEI and ARB among hypertensive patients presenting with COVID-19.

## Methods

We reviewed from the Assistance Publique-Hôpitaux de Paris (AP-HP) healthcare record database all patients presenting with confirmed COVID-19 by RT-PCR. AP-HP is the largest university hospital center (39 hospitals) in Europe and was completely involved in COVID-19 pandemic. Criteria for selection included age > 18 years, confirmed COVID-19 by RT-PCR and a previous history of hypertension. Patients were included between March 12 and June 1, 2020. We identified hypertensive patients with ACEI or ARB from hypertensive patients without ACEI and ARB. We assessed admission in intensive care unit (ICU), mechanical ventilation and death as in-hospital outcome of all hypertensive patients. The COVIDECA study (CSE-20-23) was approved by the EDS APHP Ethics Committee (Comité Scientifique et Éthique de l'Entrepôt de Données de Santé [<https://eds.aphp.fr>]).

## Results

We identified 13,521 patients presenting with confirmed COVID-19 by RT-PCR. Mean age of this population was 66.5 ± 19.2 years (men: 7,103, 52.5%). Among these

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See page 59 for disclosure information.

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Table 1  
Characteristics of the 2981 hypertensive patients presenting with COVID-19

Variable	All hypertensive patients (n = 2,981)	Hypertensive patients with ACEI or ARB (n = 946)	Hypertensive patients without ACEI/ARB (n = 2,035)	p Value
Mean age (years)	78.4 ± 13.6	78.7 ± 12.4	78.3 ± 14.1	0.32
Men	1464 (49.1%)	467 (49.4%)	997 (49%)	0.09
Body mass index	26.4 ± 6.6	26.6 ± 6.9	26.4 ± 6.4	0.75
COPD	161 (5.4%)	60 (6.3%)	101 (5%)	0.14
Obstructive sleep apnea	254 (8.5%)	93 (9.8%)	161 (7.9%)	0.19
Diabetes	1031 (34.6%)	415 (43.9%)	616 (30.3%)	<0.0001
Chronic kidney disease	414 (13.9%)	152 (16.1%)	262 (12.9%)	0.02
Coronary artery disease	599 (20.1%)	219 (23.2%)	380 (18.7%)	0.005
Heart failure	822 (27.6%)	258 (27.3%)	564 (27.7%)	0.04
Outcome				
Admission in ICU	428 (14.4%)	127 (13.4%)	301 (14.8%)	0.35
Mechanical ventilation	180 (6%)	52 (5.5%)	128 (6.3%)	0.45
Death	804 (27%)	260 (27.5%)	544 (26.7%)	0.70

ACEI = angiotensin-converting enzyme inhibitors; ARB = angiotensin II receptor blockers; COPD = chronic obstructive pulmonary disease; ICU = intensive care unit.

patients, 2,981 hypertensive patients (mean age: 78.4 ± 13.6 years, 1,464 [49.1%] men) were included in the study. Characteristics of the hypertensive population are presented in Table 1. Patients with ACEI or ARB had more likely diabetes ( $p < 0.0001$ ), chronic kidney disease ( $p = 0.02$ ), coronary artery disease ( $p = 0.005$ ) and heart failure ( $p = 0.04$ ).

Outcome of hypertensive patients was similar whatever the use or non-use of ACEI or ARB. Admission in ICU during hospitalization occurred in 14.4% of hypertensive patients: 13.4% in patients with ACEI or ARB versus 14.8% in patients without ACEI or ARB (RR = 1.10 [0.91 to 1.34],  $p = 0.35$ ). The need of mechanical ventilation was observed in 6% of hypertensive patients (5.5% in patients with ACEI or ARB vs 6.3% in patients without ACEI or ARB; RR = 1.14 [0.84 to 1.57],  $p = 0.45$ ). Among hypertensive patients admitted in ICU, 42% required a mechanical ventilation (40.9% in patients with ACEI or ARB versus 42.5% in patients without ACEI or ARB,  $p = 0.09$ ). The global in-hospital mortality was 27% (vs 13.9% in patients without hypertension): 27.5% in hypertensive patients with ACEI or ARB versus 26.7% in hypertensive patients without ACEI or ARB (RR = 0.97 [0.86 to 1.10],  $p = 0.70$ ). Multivariate analysis was adjusted for age, gender, body mass index, coronary artery disease, heart failure, chronic obstructive pulmonary disease, diabetes and chronic kidney disease: no significant difference concerning the use or non-use of ACEI or ARB was observed for admission in ICU (RR = 0.87 [0.69 to 1.1],  $p = 0.25$ ), need of mechanical ventilation (RR = 1.14 [0.83 to 1.58],  $p = 0.41$ ) and in-hospital mortality (RR = 0.93 [0.78 to 1.10],  $p = 0.39$ ). No significant difference was observed in univariate comparisons between hypertensive patients with ACEI ( $n = 488$ ) or with ARB ( $n = 397$ ) regarding admission in ICU (13.3% vs 13.8% respectively,  $p = 0.06$ ), mechanical ventilation (5.7% vs 4.8% respectively,  $p = 0.39$ ) and in-hospital mortality (26% vs 27.9% respectively,  $p = 0.52$ ).

## Discussion

With COVID-19 pandemic, initial warning concerning the use of ACEI and ARB has raised.<sup>5</sup> In case of severe

acute respiratory syndrome, ACE2 receptor expression is downregulated, leading to an excessive activation of renin-angiotensin-aldosterone system and an exacerbation of pneumonia progression. However, this potential negative effect may be counterbalanced by beneficial effect. Indeed, the administration of ACEI/ARB blocks ACE2 downregulation-induced hyperactivation of renin-angiotensin-aldosterone system, and thereby may prevent acute lung injury. First studies suggested an increased rate of mortality in patients with ACEI/ARB. Our data observed that ACEI and ARB use was not associated with an increased risk of ICU admission and in-hospital death. In-hospital mortality remains high (27%) in hypertensive patients presenting with COVID-19, but whatever the outcome assessed (mortality, admission in ICU and use of mechanical ventilation), the use of ACEI and ARB remains safe and can be maintained in hypertensive patients presenting with COVID-19.

## Credit Author Statement

**Hazrije Mustafic:** Conceptualization, Protocol Writing, Literature Search, Data Extraction and Analysis, Writing - Review & Editing; **Abdallah Fayssol:** Protocol Writing, Data Extraction and Analysis, Writing - Review & Editing; **Loïc Jossieran:** Methodology, Writing - Review & Editing; **Mounir Ouadahi:** Conceptualization, Literature Search, Writing - Review & Editing; **Lamiae Grimaldi-Bensouda:** Supervision, Writing - Review & Editing; **Olivier Dubourg:** Conceptualization, Study Design, Writing - Review & Editing; **Djillali Annane:** Conceptualization, Supervision, Writing - Review & Editing; **Nicolas Mansencal:** Conceptualization, Study Design, Data Extraction and Analysis, Writing - Original Draft, Writing - Review & Editing.

## Disclosures

The authors declare no conflict of interest.

## Declaration of Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

1. Watkins J. Preventing a covid-19 pandemic. *BMJ* 2020;368:m810.
2. Zheng Z, Peng F, Xu B, Zhao J, Liu H, Peng J, Li Q, Jiang C, Zhou Y, Liu S, Ye C, Zhang P, Xing Y, Guo H, Tang W. Risk factors of critical & mortal COVID-19 cases: a systematic literature review and meta-analysis. *J Infect* 2020;81:e16–e25.
3. Wu F, Zhao S, Yu B, Chen YM, Wang W, Song ZG, Hu Y, Tao ZW, Tian JH, Pei YY, Yuan ML, Zhang YL, Dai FH, Liu Y, Wang QM, Zheng JJ, Xu L, Holmes EC, Zhang YZ. A new coronavirus associated with human respiratory disease in China. *Nature* 2020;579:265–269.
4. Patel AB, Verma A. COVID-19 and angiotensin-converting enzyme inhibitors and angiotensin receptor blockers: what is the evidence? *JAMA* 2020;323:1769–1770.
5. Feng Y, Ling Y, Bai T, Xie Y, Huang J, Li J, Xiong W, Yang D, Chen R, Lu F, Lu Y, Liu X, Chen Y, Li X, Li Y, Summah HD, Lin H, Yan J, Zhou M, Lu H, Qu J. COVID-19 with different severities: a multi-center study of clinical features. *Am J Respir Crit Care Med* 2020;201:1380–1388.
6. Reynolds HR, Adhikari S, Pulgarin C, Troxel A B, Iturrate E, Johnson SB, Hausvater A, Newman JD, Berger JS, Bangalore S. Renin-angiotensin-aldosterone system inhibitors and risk of covid-19. *N Engl J Med* 2020;382:2441–2448.
7. Kuba K, Imai Y, Rao S, Gao H, Guo F, Guan B, Huan Y, Yang P, Zhang Y, Deng W, Bao L, Zhang B, Liu G, Wang Z, Chappell M, Liu Y, Zheng D, Leibbrandt A, Wada T, Slutsky AS, Liu D, Qin C, Jiang C, Penninger JM. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. *Nat Med* 2005;11:875–879.
8. Zhang X, Yu J, Pan LY, Jiang HY. ACEI/ARB use and risk of infection or severity or mortality of COVID-19: a systematic review and meta-analysis. *Pharmacol Res* 2020;158:104927.
9. Li J, Wang X, Chen J, Zhang H, Deng A. Association of renin-angiotensin system inhibitors with severity or risk of death in patients with hypertension hospitalized for coronavirus disease 2019 (COVID-19) infection in Wuhan, China. *JAMA Cardiol* 2020;5:825–830.
10. Mehta N, Kalra A, Nowacki AS, Anjewierden S, Han Z, Bhat P, Carmona-Rubio AE, Jacob M, Procop GW, Harrington S, Milinovich A, Svensson LG, Jehi L, Young JB, Chung MK. Association of use of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers with testing positive for coronavirus disease 2019 (COVID-19). *JAMA Cardiol* 2020;5:1020–1026.
11. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, and the Northwell COVID-19 Research Consortium. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City Area. *JAMA* 2020;323:2052–2059.
12. Conversano A, Melillo F, Napolano A, Fominskiy E, Spessot M, Ciceri F, Agricola E. RAAs inhibitors and outcome in patients with SARS-CoV-2 pneumonia. A case series study. *Hypertension* 2020;76:e10–e12.
13. Tedeschi S, Giannella M, Bartoletti M, Trapani F, Tadolini M, Borghi C, Viale P. Clinical impact of renin-angiotensin system inhibitors on in-hospital mortality of patients with hypertension hospitalized for COVID-19. *Clin Infect Dis* 2020;71:899–901.
14. de Abajo FJ, Rodríguez-Martín S, Lerma V, Mejía-Abril G, Aguilar M, García-Luque A, Laredo L, Laosa O, Centeno-Soto GA, Ángeles Gálvez M, Puerro M, González-Rojano E, Pedraza L, de Pablo I, Abad-Santos F, Rodríguez-Mañas L, Gil M, Tobías A, Rodríguez-Miguel A, Rodríguez-Puyol D. MED-ACE2-COVID19 study group. Use of renin-angiotensin-aldosterone system inhibitors and risk of COVID-19 requiring admission to hospital: a case-population study. *Lancet* 2020;395:1705–1714.
15. Fosbøl EL, Butt JH, Østergaard L, Andersson C, Selmer C, Kragholm K, Schou M, Phelps M, Gislason GH, Gerds TA, Torp-Pedersen C, Køber L. Association of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use with COVID-19 diagnosis and mortality. *JAMA* 2020;324:168–177.
16. Gao C, Cai Y, Zhang K, Zhou L, Zhang Y, Zhang X, Li Q, Li W, Yang S, Zhao X, Zhao Y, Wang H, Liu Y, Yin Z, Zhang R, Wang R, Yang M, Hui C, Wijns W, McEvoy JW, Soliman O, Onuma Y, Serruys PW, Tao L, Li F. Association of hypertension and antihypertensive treatment with COVID-19 mortality: a retrospective observational study. *Eur Heart J* 2020;41:2058–2066.