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Do ACE inhibitors and angiotensin receptor antagonists increase the risk of severe COVID-19?

DEBATT

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Hypertension and diabetes mellitus are risk factors for a severe course of COVID-19.

Questions have been raised as to whether this association is related to the use of ACE inhibitors and angiotensin II receptor blockers.

People with hypertension and diabetes mellitus are more prone to a severe course of illness should they contract COVID-19 (1). Clinical data and understanding of the cellular mechanisms of COVID-19 have raised the question of whether this correlation is related to the use of angiotensin-converting enzyme inhibitors (ACE inhibitors) and angiotensin II receptor blockers (AII receptor blockers, also known as ARBs), since these drugs may in principle affect the pathophysiology of COVID-19 (2, 3).

ACE inhibitors and AII receptor blockers are used by around 14 % of the population of the Nordic countries, mainly for hypertension and heart failure as well as for migraine prophylaxis (4). The SARS-CoV-2 virus enters its target cell by binding to the angiotensin-converting enzyme 2 (ACE2) receptor on the cell surface (5), and increased expression of ACE2 can facilitate infection with SARS-CoV (6). As ACE inhibitors and AII receptor blockers increase the expression of ACE2 (7), some have advised caution in the use of these drugs (8). However, the European Society of Cardiology (ESC) and several other international professional associations have recommended that they not be discontinued (9), as discontinuation has been shown to increase the risk of complications and mortality (10). Recent studies published in The New England Journal of Medicine support the latter recommendations.

New studies on COVID-19 and the use of antihypertensive drugs

In a new population-based case-control study from Lombardy in Italy, 6 272 patients with COVID-19 were compared with 30 759 control subjects (11). The average age was 68 years, and 37 % were women. Although a higher proportion of individuals in the COVID-19 group were receiving antihypertensive treatment (including ACE inhibitors and AII receptor blockers) than in the control group, there was no association between use of these drugs and COVID-19. Subgroup analyses also revealed no association between severe or fatal cases of COVID-19 and the use of ACE inhibitors or AII receptor blockers (11).

There are no grounds for changing prescribing practices or the use of ACE inhibitors and angiotensin II receptor blockers during the coronavirus pandemic

A study with clinical data from a total of 8 910 patients with COVID-19 from 169 hospitals in Asia, Europe and North America found that 515 (5.8 %) of the patients died while in hospital (12). Factors associated with mortality were age over 65, coronary artery disease, heart failure, arrhythmias, COPD and smoking. Neither the use of ACE inhibitors nor of AII receptor blockers was associated with mortality.

An observational study that included the review of medical records of 12 594 patients tested for COVID-19 in New York also showed no association between the results of the tests and the use of antihypertensive drugs (13).

These three studies provide important information on COVID-19 and the use of antihypertensive drugs, and indicate that the increased vulnerability of people with hypertension and diabetes mellitus is due to factors other than the use of specific types of antihypertensives. There is thus no definitive evidence to date that the use of ACE inhibitors or AII receptor blockers entails an increased risk of a severe course of COVID-19. The results of these studies support the advice issued by the ESC. There are no grounds for changing prescribing practices or the use of ACE inhibitors or AII receptor blockers during the coronavirus pandemic.

REFERENCES:

1. Ruan Q, Yang K, Wang W et al. Clinical predictors of mortality due to COVID-19 based on an analysis

of data of 150 patients from Wuhan, China. Intensive Care Med 2020; 46: 846–8. [PubMed][CrossRef]

2. Patel AB, Verma A. COVID-19 and angiotensin-converting enzyme inhibitors and angiotensin receptor blockers: What is the evidence? JAMA 2020; 323: 1769–70. [PubMed][CrossRef]

3. Vaduganathan M, Vardeny O, Michel T et al. Renin-angiotensin-aldosterone system inhibitors in patients with Covid-19. N Engl J Med 2020; 382: 1653–9. [PubMed][CrossRef]

4. Folkehelseinstituttet. Statistikk fra Reseptregisteret. http://www.reseptregisteret.no/prevalens.aspx Accessed 13.5.2020.

5. Hoffmann M, Kleine-Weber H, Schroeder S et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 2020; 181: 271–280.e8. [PubMed][CrossRef]

6. Regla-Nava JA, Jimenez-Guardeño JM, Nieto-Torres JL et al. The replication of a mouse adapted SARS-CoV in a mouse cell line stably expressing the murine SARS-CoV receptor mACE2 efficiently induces the expression of proinflammatory cytokines. J Virol Methods 2013; 193: 639–46. [PubMed][CrossRef]

7. Soler MJ, Barrios C, Oliva R et al. Pharmacologic modulation of ACE2 expression. Curr Hypertens Rep 2008; 10: 410–4. [PubMed][CrossRef]

8. Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? Lancet Respir Med 2020; 8: e21. [PubMed][CrossRef]

9. ESC. Position statement of the ESC Council on Hypertension on ACE-inhibitors and angiotensin receptor blockers.
https://www.escardio.org/Councils/Council-on-Hypertension-(CHT)/News/position-statement-of-the-esc-council-on-hypertension-onace-inhibitors-and-ang Accessed 13.5.2020.

10. Hirakawa Y, Arima H, Webster R et al. Risks associated with permanent discontinuation of blood pressure-lowering medications in patients with type 2 diabetes. J Hypertens 2016; 34: 781–7. [PubMed][CrossRef]

11. Mancia G, Rea F, Ludergnani M et al. Renin-angiotensin-aldosterone system blockers and the risk of Covid-19. N Engl J Med 2020; 382. doi: 10.1056/NEJMoa200923. [PubMed][CrossRef]

12. Mehra MR, Desai SS, Kuy S et al. Cardiovascular Disease, Drug Therapy, and Mortality in Covid-19. N Engl J Med 2020; 382: NEJMoa2007621. [PubMed][CrossRef]

13. Reynolds HR, Adhikari S, Pulgarin C et al. Renin-angiotensin-aldosterone system blockers and the risk of Covid-19. N Engl J Med 2020; 382: NEJMoa2008975. [PubMed][CrossRef]

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