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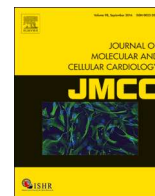
Letter to the editor

## An epidemiological study exploring a possible impact of treatment with ACE inhibitors or angiotensin receptor blockers on ACE2 plasma concentrations

The current SARS-CoV-2 pandemic has high fatality rates and imposes increasingly severe social and economic impacts worldwide. Covid-19 patients with cardiovascular disease are at increased risk of death. They are very often treated with drugs targeting the renin-angiotensin-aldosterone system, where angiotensin converting enzyme (ACE) is of particularly importance. Angiotensin converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARBs) are standard therapies for high blood pressure and heart failure (HF) and currently prescribed to more than 25 Mio people in Germany alone (approx. 30% of the general population).

In addition to the classical ACEI target ACE, a second isoform, ACE2, exists that generates the vasoprotective angiotensin 1–7 from angiotensin II and is insensitive to ACEI [1]. ACE2 has been identified as the receptor for SARS corona virus [2] and is also considered the main receptor for SARS-CoV-2 [3]. ACE2 expression is particularly high in lung epithelial cells, but also present in cardiac myocytes and endothelial cells [1,4,5]. Levels of ACE2 in human plasma are very low/ undetectable in healthy humans, but upregulated in patients with heart failure [1,6].

ACEI can upregulate ACE2 expression because they reduce levels of angiotensin II, which itself downregulates ACE2 [7]. Similar actions have been shown for ARBs [7], but their action differs from that of ACEI in as much as they specifically block the AT1 receptor and indirectly increase angiotensin II levels. The increase in angiotensin II could have additional effects by stimulating a second receptor, AT2, insensitive to ARB. The AT2 receptor has been suggested to participate in beneficial effects of ARB and this may also involve ACE2 [8]. However, the role of the AT2/ACE2/angiotensin 1–7 axis is not fully resolved, particularly not if the net effect on ACE2 differs from that of ACEI in humans, where evidence for superior therapeutic efficacy of ARB vs. ACEI is lacking.

Upregulation of ACE2 by ACEI and ARB has led to the hypothesis that these antihypertensive drugs might increase the susceptibility to Covid-19 infection and the progression of the disease. Whether patients who are treated with an ACEI or ARB should be advised to switch to other therapeutic options is unclear and further evidence is required. The question is complex because the prevailing evidence suggests a beneficial role of high ACE2 and angiotensin 1–7 levels on cardiovascular and pulmonary diseases, arguing for this pathway to participate in the overall benefit of therapy with ACEI. It is also possible that the cardiovascular and pulmonary benefit of ACEI or ARBs in humans already infected with Covid-19 outweighs the possible negative impact of increased spreading.

To answer one of the basic underlying questions, we decided to investigate (i) the impact of ACEI and ARBs in individuals with and without HF on the circulatory ACE2 concentration (as surrogate for the expression by cardiac and pulmonary cells), and (ii) the potential relation between ACE2 concentration, clinical status and cardiovascular and pulmonary outcome or complications measured by hospitalizations and cardiac mortality.

We hypothesize that (i) treatment with ACEI and ARB is associated with changes in ACE2 concentration in plasma (as surrogate of expression in the lung) and (ii) ACE2 concentrations are associated with pulmonary and cardiovascular outcome.

We will make use of large-scale data from a cohort study with biosamples including measurements of ACE2 concentration in plasma, genetic SNP array data in the *ACE2* region, gene expression data from whole blood (RNASeq), proteomic data on the inflammasome, and clinical and outcome data from > 3200 deeply phenotyped individuals with and without ACE-I or ARB medication. We will continue to monitor the cohort over the SARS-CoV-2 pandemic in the next months and assess infection rates, severity of infections and outcome in relation to medication, prior molecular and clinical data, and ACE2 concentrations.

Results from the first phase are expected in June 2020. While they will not answer the question whether ACEI therapy increases the risk of Covid-19 infection, they will show whether ACEI and ARB differ in their effect on ACE2 levels in patients with and without HF. Such information may be helpful in guiding decision making about switching ACE-I to ARB for the prevention of Covid-19 infections. Data from the second surveillance phase will be evaluated in the further course of the pandemic to get insights into potential causal relations between drug intake and Covid-19 infections and to define actions to contain or prevent the infection.

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