In a letter to Hypertension, Esler and Esler\(^1\) suggested angiotensin II receptor blockers (ARB) to be potential contributors to severe and fatal Coronavirus disease 2019 (COVID-19). Others have similarly implicated ACE (angiotensin-converting enzyme) inhibitors.\(^2,3\) The underlying hypothesis is that these drugs facilitate massive infection by upregulating the ACE2 enzyme, which in its membrane-bound form is used by severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) to enter pulmonary cells. Hypertension, coronary artery disease, and diabetes mellitus are associated with severe course in COVID-19.\(^4\) Because ACE inhibitors/ARBs are often used to treat these conditions, the increased risk may be partly due to adverse drug effects.

Data will soon be out on the chronic use of ACE inhibitors/ARBs in COVID-19 patients. To put these into perspective, it is important to know how frequently the drugs are used in similar patients and to what degree use is associated with higher mortality. We, therefore, examined the chronic use of ACE inhibitors/ARBs and associated mortality in a historic cohort of septic patients admitted to the Intensive Care Unit.

Data were collected between January 2008 and December 2015 on a nationwide Swedish cohort of 2700 patients, aged 18 years and over, with community-acquired severe sepsis and septic shock admitted to the Intensive Care Unit within 24 hours of arrival to any of 32 emergency departments throughout the country. Further details on inclusion criteria, definitions, etc are described elsewhere.\(^5\) The database includes information concerning dispensed drugs to individual patients from the Swedish Prescribed Drug Register during 5 years preceding admittance. Dispensed drug during the past 365 days was considered an indicator of chronic use. We describe fraction of patients on ACE inhibitors, ARBs, and ACE inhibitors or ARBs in different strata, including sex, focus of infection, age category, and year of admittance. \(\chi^2\) and Wilcoxon rank-sum tests were used to assess the distribution of age and 30-day mortality between ACE inhibitors and ARB users/nonusers in the various strata.

Results are summarized in the Table. ACE inhibitors/ARB use was common among patients admitted to the Intensive Care Unit because of sepsis. The drugs were used to a slightly higher extent in men than in women, and use increased with age. There was a temporal trend towards increased use. This is confirmed using recent official statistics from the Swedish Prescribed Drug Register, which shows that the number of patients aged 20–85+ years using ACE inhibitors/ARB drugs nationwide increased linearly from 144 to 183 out of 1000 people between 2010 and 2019, https://sdb.socialstyrelsen.se/if_lak/resultat.aspx. Chronic use among the general population in 2020 is around 10% higher than in 2015, which likely also applies to septic Intensive Care Unit patients.

Use indicates higher age and comorbidity, and the fraction of patients that died was higher, but not markedly so, among users compared to nonusers. Surprisingly, there was no difference in death rates between users/nonusers in the subgroup with respiratory infection.

ACE inhibitors/ARB use and associated mortality among critically ill COVID-19 patients can be compared with this data. A high incidence of chronic use should be expected, but a major disparity in death rates between users and nonusers may indicate important underlying differences in pathophysiology, including, possibly, adverse effects of ACE inhibitors/ARBs.

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Disclosures

None.
## Table
### Chronic Use of ACE Inhibitors and Angiotensin Receptor Blockers in Critical Care Patients Admitted Because of Community-Acquired Sepsis

| Community-Acquired Sepsis Requiring ICU Care | ACE Inhibitors (n=688)* | ARB (n=464)* | ACE Inhibitors/ARB (n=1098)* | Not on ACE Inhibitors/ARB (n=1622) | ACE Inhibitors/ARB (n=1098) | P Value |
|---------------------------------------------|-------------------------|--------------|-----------------------------|-----------------------------------|-----------------------------|---------|
| All patients (N=2720)                       | 72 (65–79)              | 71 (64–78)   | 72 (65–79)                  | 65 (51–74)                       | 72 (65–79)                  | <0.0001 |
| Age, y, median, IQR                        | 72 (65–79)              | 71 (64–78)   | 72 (65–79)                  | 65 (51–74)                       | 72 (65–79)                  | <0.0001 |
| Chronic user, %                             | 25.3                    | 17.1         | 40.4                        | 21.9                             | 27.0                        | 0.03    |
| 30-day mortality, %                         | 25.3                    | 17.1         | 40.4                        | 21.9                             | 27.0                        | 0.03    |
| All patients (n=1510)                       | 25.3                    | 17.1         | 40.4                        | 21.9                             | 27.0                        | 0.03    |
| Focus of infection                          |                         |              |                             |                                  |                             |         |
| RTI (n=919)                                 | 23.5                    | 16.5         | 37.9                        | 23.6                             | 24.1                        | 0.9     |
| UTI (n=558)                                 | 24.9                    | 17.4         | 41.2                        | 14.6                             | 17.0                        | 0.5     |
| Abd infection (N=298)                       | 28.5                    | 14.0         | 40.6                        | 27.1                             | 40.5                        | 0.02    |
| Other site (n=586)                          | 26.1                    | 17.7         | 41.0                        | 17.1                             | 23.8                        | 0.05    |
| Unknown site (n=359)                        | 26.5                    | 19.2         | 44.3                        | 33.0                             | 42.1                        | 0.08    |
| Age category, y                             |                         |              |                             |                                  |                             |         |
| <50 (n=433)                                 | 7.4                     | 5.1          | 10.9                        | 7.8                              | 17.0                        | 0.03    |
| 50–59 (n=357)                               | 19.9                    | 14.3         | 32.8                        | 20.4                             | 15.4                        | 0.3     |
| 60–69 (n=674)                               | 26.6                    | 19.9         | 43.6                        | 21.1                             | 18.4                        | 0.4     |
| 70–79 (n=777)                               | 31.2                    | 20.5         | 50.2                        | 25.6                             | 29.2                        | 0.3     |
| 80+ (N=479)                                 | 34.2                    | 20.5         | 52.3                        | 42.8                             | 40.8                        | 0.7     |
| Year of admittance                          |                         |              |                             |                                  |                             |         |
| 2008–2010 (n=501)                           | 24.0                    | 14.2         | 37.3                        | 22.9                             | 25.1                        | 0.6     |
| 2011 (n=434)                                | 27.4                    | 16.4         | 40.6                        | 16.3                             | 29.6                        | 0.001   |
| 2012 (n=481)                                | 24.5                    | 15.2         | 37.6                        | 21.3                             | 26.5                        | 0.2     |
| 2013 (n=521)                                | 25.7                    | 16.7         | 40.1                        | 23.7                             | 26.8                        | 0.4     |
| 2014 (n=479)                                | 26.5                    | 17.5         | 42.8                        | 24.5                             | 25.4                        | 0.8     |
| 2015 (n=304)                                | 23.0                    | 25.7         | 46.5                        | 22.6                             | 29.3                        | 0.2     |

Abd indicates abdominal; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ICU, Intensive Care Unit; IQR, interquartile range; RTI, respiratory tract infection; and UTI, urinary tract infection.

*In 54 patients, both ACE inhibitors and ARB were prescribed during the year preceding admittance. The category ACE inhibitors/ARB counts these only once.

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