Annals of Internal Medicine REVIEW

Risks and Impact of Angiotensin-Converting Enzyme Inhibitors or Angiotensin-Receptor Blockers on SARS-CoV-2 Infection in Adults

A Living Systematic Review

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Background: The role of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin-receptor blockers (ARBs) in COVID-19 disease susceptibility, severity, and treatment is unclear.

Purpose: To evaluate, on an ongoing basis, whether use of ACEIs or ARBs either increases risk for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection or is associated with worse COVID-19 disease outcomes, and to assess the efficacy of these medications for COVID-19 treatment.

Data Sources: MEDLINE (Ovid) and Cochrane Database of Systematic Reviews from 2003 to 4 May 2020, with planned ongoing surveillance for 1 year; the World Health Organization database of COVID-19 publications and medRxiv.org through 17 April 2020; and ClinicalTrials.gov to 24 April 2020, with planned ongoing surveillance.

Study Selection: Observational studies and trials in adults that examined associations and effects of ACEIs or ARBs on risk for SARS-CoV-2 infection and COVID-19 disease severity and mortality.

Data Extraction: Single-reviewer abstraction confirmed by another reviewer, independent evaluation by 2 reviewers of study quality, and collective assessment of certainty of evidence.

Data Synthesis: Two retrospective cohort studies found that ACEI and ARB use was not associated with a higher likelihood of receiving a positive SARS-CoV-2 test result, and 1 case–control study found no association with COVID-19 illness in a large community (moderate-certainty evidence). Fourteen observational studies, involving a total of 23 565 adults with COVID-19, showed consistent evidence that neither medication was associated with more severe COVID-19 illness (high-certainty evidence). Four registered randomized trials plan to evaluate ACEIs and ARBs for treatment of COVID-19.

Limitation: Half the studies were small and did not adjust for important confounding variables.

Conclusion: High-certainty evidence suggests that ACEI or ARB use is not associated with more severe COVID-19 disease, and moderate-certainty evidence suggests no association between use of these medications and positive SARS-CoV-2 test results among symptomatic patients. Whether these medications increase the risk for mild or asymptomatic disease or are beneficial in COVID-19 treatment remains uncertain.

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Concerns exist that angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin-receptor blockers (ARBs) increase susceptibility to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2, the viral agent that causes the disease COVID-19) and the likelihood of severe COVID-19 illness (1). Early reports from Wuhan, China, showed that hypertension and diabetes were common among patients with COVID-19 and were associated with worse outcomes (2). Although these early studies did not specify whether patients were using ACEIs or ARBs before becoming infected, these medications are widely used to treat hypertension and diabetes (3, 4).

The proposed mechanism by which ACEIs and ARBs may play a role in COVID-19 is through upregulation of angiotensin-converting enzyme 2 (ACE2), which is presumed to act as a functional receptor for SARS-CoV-2 to gain entry to host cells (5) (**Figure 1**). Angiotensin-converting enzyme 2 exists primarily as a membrane-bound monocarboxypeptidase with robust expression in such tissues as lung, vasculature, intestine, and kidney (5). A soluble or circulating form of ACE2 (sACE2) has cardiovascular effects in the renin–angiotensin system (6–8). Related to viral pathogenesis, sACE2 was shown to block SARS viral entry into cells (9) and is now being considered as a potential therapy (10).

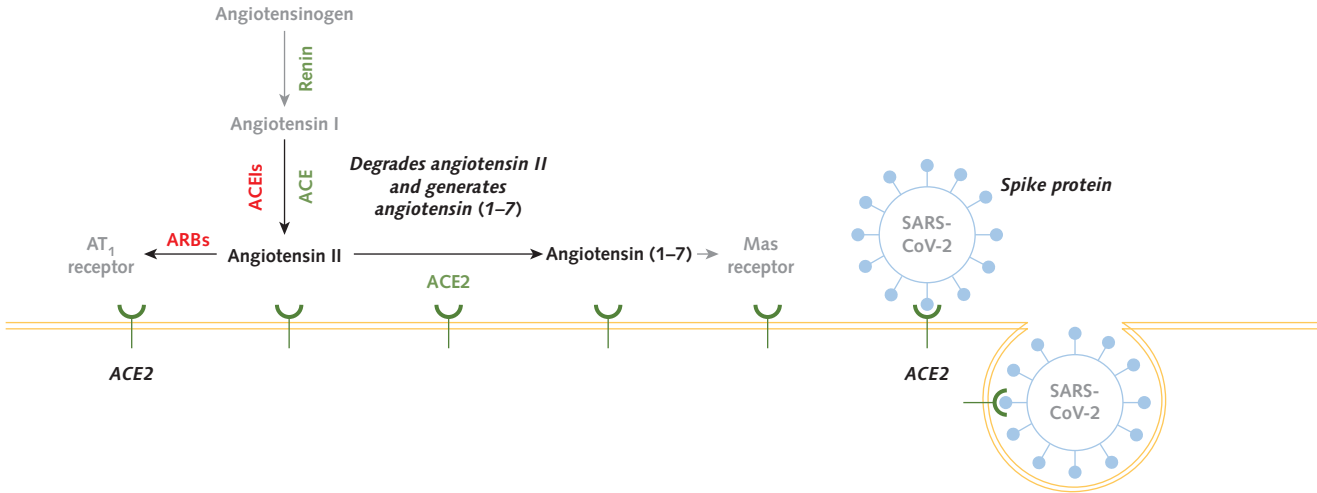
Angiotensin-converting enzyme 2 is distinct and not directly related to the clinical use of ACEIs or ARBs, or to their mechanisms of action. Angiotensin-converting enzyme inhibitors target angiotensin-converting enzyme 1 (ACE) to inhibit conversion of angiotensin I to angiotensin II, thereby reducing levels of angiotensin II available to bind and activate the type 1 angiotensin receptor (AT_1), which mediates most of the vasopressor effects of angiotensin II (11). Angiotensin-receptor blockers work by binding to AT_1 receptors and directly blocking the actions of angiotensin II. In contrast to ACE, which acts to generate angiotensin II, ACE2 degrades angiotensin II into angiotensin (1-7) and is thus a negative regulator of the renin–angiotensin system (**Figure 1**) (12).

See also:

Editorial comment

Web-Only
Supplement

Figure 1. ACE2, the RAS, and SARS-CoV-2 infection.



As part of the RAS, ACE2 (green) regulates the levels of angiotensin II. As the functional receptor for SARS-CoV-2, ACE2 may facilitate viral entry into cells. This figure illustrates the role of ACE2 in the RAS and how pharmacologic RAS blockade with ACEIs or ARBs (red) could theoretically increase the amount of ACE2 available for viral binding. ACE2 = angiotensin-converting enzyme 2; ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker; AT_1 = type 1 angiotensin receptor; RAS = renin–angiotensin system; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Although postulated as a mechanism for increased susceptibility to SARS-CoV-2 (13), upregulation of ACE2 due to ACEIs or ARBs has not been consistently demonstrated in human and animal studies (14). In addition to ACEI and ARB exposure, several other mechanisms of ACE2 upregulation are being explored, including exposure to nonsteroidal anti-inflammatory agents (2) and thiazide diuretics (15), tobacco use (16), diabetes (17), and cytokines produced by the body in response to viral infections (18). Finally, polymorphisms in the *Ace2* gene in humans previously were associated with hypertension and diabetes, suggesting that there is some genetic determination of ACE2 levels and function (19).

Paradoxically, mechanisms by which ACEIs and ARBs may be protective in SARS-CoV-2 infection are also being proposed (12, 20). Animal studies have found that direct angiotensin II suppression with ACEIs and AT_1 receptor antagonism with ARBs may promote and stabilize cell membrane complexes between ACE2 and AT_1 receptors (21). In theory, these complexes may reduce the ability of the virus to enter host cells (14). Suppression of angiotensin II may also prevent virus-mediated acute lung injury (22) and other organ dysfunction, which is another proposed mechanism by which use of ACEIs and ARBs may be beneficial in COVID-19.

Uncertainty regarding the role of ACEIs and ARBs in the COVID-19 disease course has generated several questions for clinicians. The aims of this living systematic review are to synthesize evidence related to the following questions: Does use of ACEIs or ARBs among adults before infection with SARS-CoV-2 increase the risk for COVID-19? Is the use of these medications before infection associated with more severe COVID-19 disease and worse outcomes? What are the benefits and harms of initiating these drugs as treatment for patients with COVID-19?

METHODS

This is a living systematic review with ongoing literature surveillance and critical appraisal. It was originally conducted in response to a request from the World Health Organization. We registered the review with PROSPERO (registration number pending) and followed standard methods and reporting guidelines for systematic reviews (23, 24). Key questions were developed by World Health Organization staff and revised with input from authors (D.K., V.J.K., and K.M.). Methods of the review included searches and review of data related to SARS-CoV-2 and 2 other coronaviruses associated with earlier pneumonia outbreaks: SARS-CoV-1, causing severe acute respiratory syndrome (SARS), and MERS-CoV, causing Middle East respiratory syndrome (MERS). This report and the ongoing surveillance focus on questions and data related to SARS-CoV-2 and disease from SARS-CoV-2 (COVID-19).

Data Sources and Searches

We searched, without language restrictions, the following databases: MEDLINE (Ovid) and the Cochrane Database of Systematic Reviews from 1 January 2003 to 4 May 2020, the World Health Organization database of COVID-19 publications (25) and medRxiv.org from inception to 17 April 2020, and ClinicalTrials.gov to 24 April 2020. (See the **Supplement**, available at Annals.org, for search strategy and terms.) We also identified additional citations through hand-searching of reference lists.

Study Selection

Selection criteria were as follows: observational studies of adults in any setting examining associations between use of ACEIs or ARBs and risks for acquiring SARS-CoV-2 and COVID-19, SARS, or MERS; observational studies of adults with COVID-19, SARS, or MERS, in any setting, examining associations between ACEI or ARB use and risks for a broad range of clinical outcomes, including death, severity of illness (mechanical ventilation, intensive care unit [ICU] admission, length of stay, need for noninvasive ventilation, hospitalization, organ dysfunction), cardiovascular events, and radiologic findings; and trials in adults with COVID-19, in any setting, comparing laboratory or clinical outcomes between patients treated with either ACEIs or ARBs and those receiving "usual care," placebo, or other treatments. We did not limit selection criteria by language. We excluded case reports and case series with fewer than 10 patients. One author (V.J.K. or D.K.) examined titles and abstracts for potential relevance, and 2 authors (D.K. and K.M.) independently reviewed full-text articles for inclusion.

Data Extraction and Quality Assessment

One author (M.K. or E.L.) abstracted details of study setting, population, exposures, and outcomes of interest, and a second author (K.M. or D.K.) checked entries for accuracy. Two authors (V.J.K, K.M., or D.K.) independently assessed the quality of observational studies by using the Newcastle–Ottawa Quality Assessment Scale (26).

Data Synthesis and Analysis

We synthesized evidence qualitatively. We collectively rated the certainty of the body of evidence by using criteria that assessed study limitations, directness of the population studied and the outcomes measured, consistency of results across studies, and precision of effect estimates (27).

Literature Surveillance

We plan weekly literature surveillance of MEDLINE and the Cochrane Database of Systematic Reviews for studies about SARS-CoV-2 and COVID-19 through March 2021 by using the search strategy presented in the Supplement. We will use the selection, data abstraction, and quality assessment methods described earlier. If we identify clinical trials, we will use the Cochrane Risk of Bias Tool for quality assessment (28). New evidence that does not substantively change our review conclusions will be summarized briefly on a monthly basis; a major update will be performed when new evidence changes the nature or strength of the conclusions.

Role of the Funding Source

Authors did not receive funding for this study outside of salary support.

RESULTS

The PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) (23) flowchart (Figure 2)

Figure 2. Evidence search and selection based on the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) approach (as of 4 May 2020).

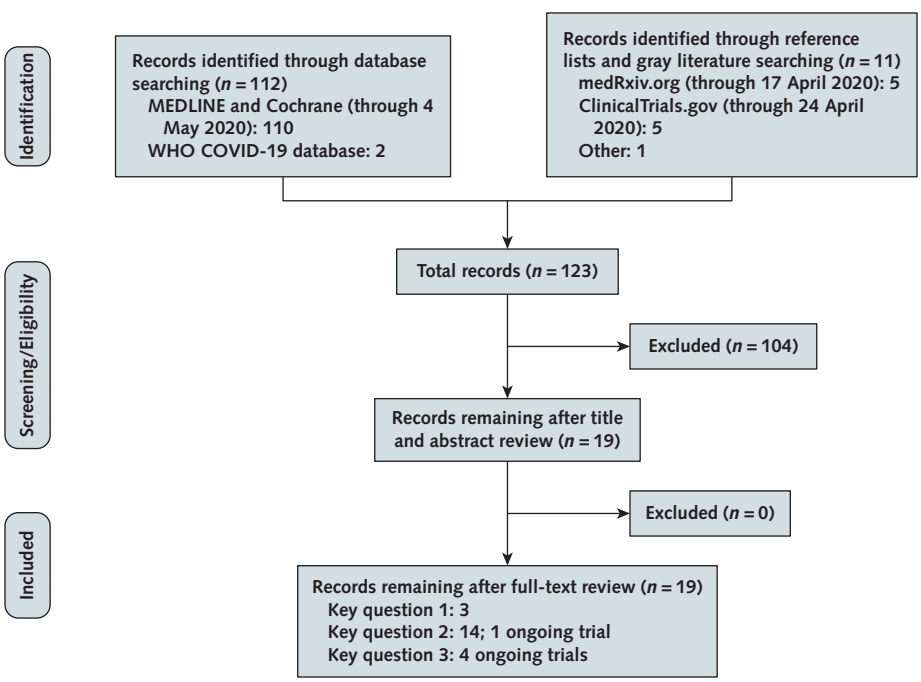


Table 1. Use of ACEIs or ARBs and Odds of Receiving a Positive COVID-19 Test Result

Study (Reference)*	Period; Population; Setting	Patient Characteristics	Patients With Positive COVID-19 Test Result/Patients Tested, *n/N (%)*	Patients With Positive COVID-19 Test Result Receiving ACEI or ARB, *n/N (%)*; Not Receiving ACEI or ARB, *n/N (%)*	aOR for Positive COVID-19 Test Result With ACEI or ARB Use (95% CI)
Mancia et al (33)	2/21/20–3/11/20; patients with COVID-19 aged >40 y; Lombardy, Italy	*n* = 6272 Mean age: 68 y Male: 63% HTN (receiving medication): 58% CVD: 30% CKD: 3%	NA	Case patients receiving ACEI: 1502/6272 (23.9) Case patients receiving ARB: 1394/6272 (22.2)	ACEI: 0.96 (0.87 to 1.07) ARB: 0.95 (0.86 to 1.05)†
Rentsch et al (36)	2/8/20–3/30/20; adults born 1945–1965 with SARS-CoV-2 test; U.S. Veterans Health Administration	*n* = 3789 Mean age: 66 y Male: 90% HTN: 65% Diabetes: 38% Vascular disease: 29% CKD: 15%	585/3789 (15.4)	255/585 (43.6); 330/585 (56.4)	0.98 (0.78 to 1.23)‡
Reynolds et al (37)	3/1/20–4/15/20; all patients with SARS-CoV-2 test result in 1 health system; United States	*n* = 12 594 Median age: 49 y Male: 42% HTN: 35% Diabetes: 18% History of MI: 4% CKD: 10%	5894/12 594 (46.8)	1110/1909 (58.1); 1101/1909 (57.7)	Median difference in proportion with positive SARS-CoV-2 test result between treated and untreated patients: −0.5 (−2.6 to 3.6)§

ACEI = angiotensin-converting enzyme inhibitor; aOR = adjusted odds ratio; ARB = angiotensin-receptor blocker; CKD = chronic kidney disease; CVD = cardiovascular disease; HTN = hypertension; MI = myocardial infarction; NA = not applicable; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
* All studies from 2020.
† Adjusted for comorbid conditions and other medication classes.
‡ Adjusted for demographics, comorbid conditions, medications, health behaviors, and vital signs.
§ Propensity-matched analysis; propensity model included age, sex, race, body mass index, smoking history, comorbid conditions, and other classes of medications.

summarizes the results of the search and study selection processes. As of 4 May 2020, we included 14 observational studies (29–42).

Key Question 1: Does the Use of ACEIs and ARBs Before Infection With SARS-CoV-2 Increase the Risk for COVID-19?

Three studies (33, 36, 37), which included a total of 8766 patients with COVID-19 and presented analyses adjusted for important confounding factors, had consistent results and provide moderate-certainty evidence that ACEIs or ARBs are not associated with a higher likelihood of positive SARS-CoV-2 test results among symptomatic patients (Table 1). Two U.S. studies examined patients tested for SARS-CoV-2. A Veterans Health Administration study found that prior ACEI or ARB use was not associated with an increased likelihood of a positive SARS-CoV-2 test result (adjusted odds ratio [aOR], 0.98 [95% CI, 0.78 to 1.23]) (36). A study from the New York University Langone Health System found that the proportion of patients with positive SARS-CoV-2 test results was similar between patients treated and those not treated with ACEIs or ARBs (adjusted median difference, −0.5 [CI, −2.6 to 3.6]) (37).

A community-based case–control study from the Lombardy region of Italy included all patients older than 40 years with diagnosed COVID-19 (33). The study found that patients with COVID-19 were not more likely to have been receiving ACEIs (aOR, 0.96 [CI, 0.87 to 1.07]) or ARBs (aOR, 0.95 [CI, 0.86 to 1.05]).

These results may not apply to patients with mild or no symptoms, because most of the patients included in these studies were probably symptomatic and had undergone testing before widespread testing of asymptomatic or mildly symptomatic patients was available.

Key Question 2: Is Use of ACEIs and ARBs Associated With More Severe COVID-19 Illness?

We found 13 retrospective cohort studies (29–32, 34, 36–42) and 1 case–control study (33) that examined whether a history of ACEI or ARB use was associated with severity of illness in patients with COVID-19. Overall, these studies included a total of 23 565 patients with COVID-19, had consistent results, and provided high-certainty evidence that a history of ACEI or ARB use is not associated with increased severity of COVID-19 illness. Eight studies were conducted in China (32–37, 39–41), 2 in Italy (33, 38), 1 in the United Kingdom (29), 2 in the United States (36, 37), and 1 in several countries (34) (Table 2). Nine studies included only hospitalized patients; the outcome of interest for most of these studies was death or severe or critical illness, defined as hypoxemic respiratory distress with or without the need for intensive care. One multicenter study from northern Italy included patients with symptomatic COVID-19 and examined hospitalization as an outcome (38). One U.S. study (36), conducted in the Veterans Health Administration, examined hospitalization and ICU admission as outcomes in all birth cohort veterans (ages 54 to 75 years) tested for COVID-19. The

Table 2. Use of ACEIs or ARBs and Odds of Severe COVID-19 Illness

Study (Reference)*	Period; Population; Setting	Patient Characteristics	Disease Severity Definition	Patients Receiving ACEI or ARB With Severe Illness, *n/n (%)*; With Nonsevere Illness, *n/n (%)*	Unadjusted OR for Severe Illness With ACEI or ARB (95% CI)	aOR for Severe Illness With ACEI or ARB (95% CI)	Other Outcomes
Bean et al (29)	3/1/20–3/22/20; adults with COVID-19 admitted to 2 hospitals; United Kingdom	*n* = 205 Mean age: 63 y Male: 52% HTN: 51% Diabetes: 30% Heart disease: 15%	Mortality and transfer to critical care within 7 d of symptom onset	ACEI only: 9/53 (17); 37/152 (24)	0.64 (0.28–1.43)†	0.29 (0.10–0.75)‡	–
Feng et al (30)	1/1/20–2/15/20; adults with COVID-19 admitted to 3 hospitals; China	*n* = 476 Median age: 53 y Male: 57% HTN: 24% Diabetes: 10% Heart disease: 8%	Per National Health Commission of China§	2/124 (2); 29/352 (9)	0.18 (0.04–0.78)	NR	–
Li et al (31)	1/15/20–3/15/20; adults with COVID-19 and HTN admitted to 1 hospital; China	*n* = 362 Mean age: 66 y Male: 52% HTN: 100% Diabetes: 35% Heart disease: 17%	Per National Health Commission of China§	57/173 (32.9); 58/189 (30.7)	1.11 (0.71–1.73)	NR (in subgroups of patients with comorbid conditions, there was no significant difference in proportion of patients receiving ACEIs or ARBs (*P* = 0.30–0.99)	Unadjusted OR for death, 0.76 (0.43–1.33)
Liu et al (32)	Time varied by site (range, 12/27/19–2/29/20); adults with COVID-19 aged >65 y with preexisting HTN admitted to 3 hospitals; China	*n* = 46 Age, sex, and comorbid conditions NR	Per National Health Commission of China§	4/28 (14.3); 8/18 (44.4)	0.21 (0.05–0.85)	NR	–
Mancia et al (33)	Patients with COVID-19 aged >40 y; Lombardy, Italy	*n* = 6272 Mean age: 68 y Male: 63% HTN (receiving medication): 58% CVD: 30% CKD: 3%	Assisted ventilation or death	–	–	ACEI: 0.91 (0.69–1.21) ARB: 0.83 (0.63–1.10)‖	–
Mehra et al (34)	12/20/19–3/15/20; patients with COVID-19 admitted to 169 hospitals in Asia, Europe, and North America with discharge status available in registry	*n* = 8910 Mean age: 49 y HTN: 26% Coronary artery disease: 11% Diabetes: 14%	Death	ACEI: 16/515 (3.1); 754/8395 (9.0) ARB: 38/515 (7.4); 518/8395 (6.2)	ACEI: 0.33 (0.19–0.54) ARB: 1.21 (0.86–1.71)	ACEI: 0.33 (0.20–0.54) ARB: 1.23 (0.87–1.74)¶	–
Meng et al (35)	1/11/20–2/23/20; adults with COVID-19 and preexisting HTN receiving medication and admitted to 1 hospital; China	*n* = 42 Median age: 65 y Male: 57% HTN: 100%	Per National Health Commission of China§	4/17 (23.5); 12/25 (48)	0.33 (0.09–1.31)	NR	–
Rentsch et al (36)	2/8/20–3/30/20; adults born 1945–1965 with positive COVID-19 test result; U.S. Veterans Health Administration	*n* = 585 Median age: 66 y Male: 95% HTN: 72% Diabetes: 44% Vascular disease: 28%	Hospitalization or ICU admission	Hospitalization: 147/297 (49.5) ICU admission: 69/122 (56.6) Not hospitalized: 108/288 (37.5)	Hospitalization: 1.63 (1.17–2.27) ICU admission: 1.94 (1.30–2.90)	Hospitalization: 1.24 (0.79–1.95)** ICU admission: 1.69 (1.01–2.84)	aOR for positive COVID-19 test result, 0.98 (0.78–1.23)
Reynolds et al (37)	3/1/20–4/15/20; patients with HTN and positive COVID-19 test result in 1 health system; United States	*n* = 2573 (Demographics reported for patients with HTN tested for COVID-19) Median age: 64 y Male: 51% HTN: 100% Diabetes: 40% History of MI: 11% CKD: 25%	ICU admission, use of noninvasive or mechanical ventilation, or death	–	–	Median difference in proportion with severe illness between treated and untreated patients: −0.5%††	–
Rossi et al (38)	2/27/20–4/2/20; patients with COVID-19; Reggio Emilia, Italy	*n* = 2653 Mean age: 63 y Male: 50% HTN: 18% Diabetes: 12% Heart failure: 6%	Hospitalization	501/1075 (46.6)‡‡; 317/1578 (20.1)	3.47 (2.92–4.13)	HR for hospitalization with ACEI§§: 1.13 (1.1–1.5) HR with ACEI‖‖: 1.12 (0.82–1.54)¶¶	HR for death with ACEI‖‖, 0.8 (0.50–1.3)

Continued on following page

Table 2–Continued

Study (Reference)*	Period; Population; Setting	Patient Characteristics	Disease Severity Definition	Patients Receiving ACEI or ARB With Severe Illness, *n/n (%)*; With Nonsevere Illness, *n/n (%)*	Unadjusted OR for Severe Illness With ACEI or ARB (95% CI)	aOR for Severe Illness With ACEI or ARB (95% CI)	Other Outcomes
Yang et al (39)	1/5/20–2/22/20; adults with preexisting HTN at 1 hospital; Hubei, China	*n* = 126 Median age: 66 y Male: 49% HTN: 100% Diabetes: 30% Heart disease: 18%	Per National Health Commission of China§; mortality	15/50 (30.0); 28/76 (36.8)	0.74 (0.34–1.58)	NR	Unadjusted OR for death, 0.32 (0.07–1.51)
Peng et al (40)	1/20/20–2/15/20; adults with COVID-19 and preexisting CVD at 1 hospital; China	*n* = 112 Patients with preexisting CVD Mean age: 62 y Male: 47% HTN: 82% Diabetes: 21%	Per National Health Commission of China§; mortality	3/16 (18.6); 19/96 (19.8)	0.94 (0.24–3.61)	NR	–
Zeng et al (41)	1/5/20–3/8/20; adults with COVID-19 admitted to 1 hospital; China	*n* = 75 Patients with COVID pneumonia and HTN Mean age: 67 y Male: 55% HTN: 100% Diabetes: 31%	Pneumonia severity	15/30 (50); 13/45 (29)	2.46 (0.94–6.45)	NR	Unadjusted OR for death, 0.65 (0.12–3.58)
Zhang et al (42)	12/31/19–2/20/20; adults aged 18–74 y with COVID-19 admitted to 9 hospitals; China	*n* = 1128 Mean age: 64 y Male: 53% HTN: 100%	Death, septic shock, ARDS	NR	HR for septic shock, 0.38 (0.17–0.87) HR for ARDS, 0.70 (0.47–1.02)	HR for septic shock, 0.36 (0.16–0.84) HR for ARDS, 0.69 (0.47–1.02)***	Adjusted HR for death, 0.42 (0.19–0.92)***

ACEI = angiotensin-converting enzyme inhibitor; aOR = adjusted odds ratio; ARB = angiotensin-receptor blocker; ARDS = acute respiratory distress syndrome; CKD = chronic kidney disease; CVD = cardiovascular disease; HR = hazard ratio; HTN = hypertension; ICU = intensive care unit; MI = myocardial infarction; NR = not reported; OR = odds ratio.
* All studies from 2020.
† Study reports 0.42 (0.14–1.00) applying the Firth correction.
‡ ACEI exposure only; adjusted for age, sex, HTN, diabetes, ischemic heart disease, and heart failure.
§ National Health Commission of China severity definition: mild—mild symptoms but no imaging evidence of pneumonia; moderate—fever and other respiratory tract symptoms with imaging findings of pneumonia; severe—respiratory distress, tachypnea (≥30 breaths per minute), O_2 saturation ≤93%, PaO_2/FIO_2 ≤300 mm Hg; critical—need for mechanical ventilation, shock, organ failure requiring intensive care.
‖ Adjusted for comorbid conditions and other medication classes.
¶ Adjusted for age, race, comorbid conditions, country, and medication classes.
** Adjusted for age, race, comorbid conditions, and Veterans Aging Cohort Study index (a measure of physiologic injury).
†† (−4.3% to 3.2%) (propensity-matched analysis; propensity model included age, sex, race, body mass index, smoking history, comorbid conditions, and other classes of medications).
‡‡ Assuming no one was using both ACEIs and ARBs.
§§ Adjusted for age, sex, and Charlson comorbidity score.
‖‖ Adjusted for age, sex, and Charlson comorbidity score, and restricted to patients with CVD.
¶¶ Results for ARBs were similar.
*** Adjusted for age, sex, comorbid conditions, and in-hospital medications.

other U.S. study included patients with COVID-19 in the New York University health system and examined ICU admission, assisted ventilation, and death as outcomes (37).

Seven studies, each including more than 200 patients with COVID-19, found that a history of ACEI or ARB use was not associated with more severe illness in analyses adjusted for important confounders, such as age and comorbid cardiovascular conditions (29, 33, 34, 36–38, 42). In an Italian study, the unadjusted odds of severe illness were higher among patients with a history of ACEI or ARB use, but the differences were no longer evident in adjusted analyses restricted to those with cardiovascular disease (adjusted hazard ratio, 1.12 [CI, 0.82 to 1.54]) (38). Likewise, in the Veterans Health Administration study, the unadjusted odds of hospitalization or ICU admission were higher among patients with ACEI or ARB exposure (36). When analyses were adjusted for age, race, comorbid conditions, and a composite of physiologic injury, this difference was no longer statistically significant for hospitalization risk (aOR, 1.24 [CI, 0.79 to 1.95]), and the observed increase in ICU admission risk was reduced after adjustment for confounders, although it remained statistically significant (aOR, 1.69 [CI, 1.01 to 2.84]). Three studies found that a history of ACEI or ARB use was actually associated with lower odds of severe illness or death (29, 34, 42).

The 7 other studies either included small samples of patients with COVID-19 or had few patients with a history of ACEI or ARB use, or they did not adjust for important confounding factors (30, 32, 35, 39–41). Unadjusted analyses of the data presented in these studies consistently showed that the odds of severe illness were not higher among patients with a history of ACEI or ARB use. These smaller studies commonly did not include detailed information on how baseline use of ACEIs and ARBs was verified. Most studies did not specify the exact duration of follow-up for outcomes, although this probably would not have altered the results substantially because the outcomes of interest were typically short-term, hospital-based outcomes.

Of note, a trial in Ireland is enrolling patients with COVID-19 who are receiving ACEIs or ARBs for hyper-

tension and is randomly assigning them to continue this treatment or switch to an alternate antihypertensive therapy (43). The primary outcomes of this study are the number of patients with COVID-19 who die, require intubation in the ICU, or require hospitalization for noninvasive ventilation, and the time from randomization to the first occurrence of any of these outcomes (43). The study criteria exclude patients who have an indication for ACEI or ARB therapy other than essential hypertension, such as heart failure or diabetes.

Key Question 3: What Are the Benefits and Harms of Initiating ACEI or ARB Treatment for Patients With COVID-19?

Although we found no completed studies addressing this key question, we discovered 4 potentially pertinent trials that are registered in the ClinicalTrials.gov database of the U.S. National Institutes of Health:

Efficacy of Captopril Nebulization in COVID-19 Patients Suffering of SARS-CoV-2 Pneumonia. A Randomized Phase II Study (NCT04355429 [France; not yet recruiting]) (44)

Randomized Trial of ACEIs in Treatment of COVID-19 (NCT04345406 [Egypt; not yet recruiting]) (45)

Randomized Controlled Trial of Losartan for Patients With COVID-19 Not Requiring Hospitalization (NCT04311177 [University of Minnesota; patient enrollment started, completion expected April 2021]) (46)

Randomized Controlled Trial of Losartan for Patients With COVID-19 Requiring Hospitalization (NCT04312009 [University of Minnesota; patient enrollment started, completion expected April 2021]) (47)

DISCUSSION

We conducted a systematic review examining the relationship between ACEI or ARB use and COVID-19 illness. We found moderate-certainty evidence from 3 studies (33, 36, 37) that ACEI or ARB use was not associated with an increased likelihood of a positive SARS-CoV-2 test result among symptomatic patients, but we found no studies that examined whether ACEI or ARB use is associated with a higher likelihood of acquiring mild or asymptomatic SARS-CoV-2 infection. We found no studies examining the efficacy of ACEIs or ARBs in reducing the risk for complications in COVID-19 illness, although trials examining this question are under way (43–47). Fourteen studies across several countries provided high-certainty evidence consistently showing that ACEIs and ARBs do not increase the risk for more severe illness in patients with COVID-19.

As expected and appropriate, the body of evidence examining the question of potential harm related to ACEI or ARB use in patients with COVID-19 consists only of observational studies. Our confidence in these findings is strengthened by several factors. The lack of association between ACEI or ARB use and illness severity is consistent across all studies, across several continents. These studies included more than 23 000 patients with COVID-19, and all studies included consecutive series of patients, which makes it unlikely that large cohorts of patients with COVID-19 exist that are substantially different from those represented in these 14 studies. Although initial studies addressing this question were smaller and had methodologic limitations, the rapidly expanding evidence base now includes large, methodologically sound observational studies.

These larger studies have accounted for confounding factors, which is important because the factors that might compel ACEI or ARB use, such as comorbid cardiovascular conditions or diabetes, might also contribute to more severe COVID-19 illness. We would expect this type of "confounding by indication" to contribute to spuriously elevated odds of severe illness. Unmeasured, or residual, confounding is a concern in interpreting any body of observational evidence. In this case, residual confounding factors would tend to inflate the association between ACEI or ARB treatment and COVID-19 outcomes—that studies still did not show an association of ACEIs or ARBs with severe COVID-19 illness strengthens our confidence in the findings.

Likewise, the factors contributing to our confidence in the lack of association between ACEI or ARB use and the likelihood of positive SARS-CoV-2 test results include the consistency of findings, as well as the size and quality of these 3 studies (33, 36, 37). However, our confidence in these findings is not as strong as for the question about severity of illness, because far fewer studies exist and we cannot draw conclusions about the association between ACEI or ARB use and the risk for mild COVID-19 illness or asymptomatic SARS-CoV-2 infection.

In 5 studies (29, 30, 32, 34, 42), ACEI or ARB use was associated with a lower risk for severe illness. Although these results are intriguing, they do not provide enough evidence to draw conclusions about the potential efficacy of these medications in treating COVID-19. However, several trials are under way that are designed to examine this question.

The concern about ACEI or ARB use in patients with COVID-19 stemmed largely from arguments of biologic plausibility, particularly the observation that ACEIs and ARBs have the potential to upregulate ACE2 receptors (which seem to be the cellular entry point for SARS-CoV-2) (5). However, even this observation has not been consistent across animal and human models, and biologic plausibility arguments suggest that ARBs may be helpful in treating COVID-19 (14, 20).

On the basis of the findings from this rapidly expanding literature, no indication exists to prophylactically stop ACEI or ARB treatment because of concerns about COVID-19. Indeed, withdrawal of long-term ACEIs or ARBs may be harmful, especially in patients with heart failure because observational studies and trials have suggested that discontinuation of ACEI or ARB therapy is associated with worse outcomes (48–50). The potential harms of not initiating ACEI or ARB therapy in patients with a compelling indication also may be important to consider.

Limitations of our review methods include searching the ClinicalTrials.gov and medRxiv.org databases

by using keywords and the possibility that we missed relevant studies. However, we anticipate that many studies currently available in preprint form will eventually be published and that we will identify them through ongoing electronic literature surveillance.

In conclusion, high-certainty evidence exists that patients receiving long-term ACEI or ARB therapy are not at increased risk for poor outcomes from COVID-19 illness. Moderate-certainty evidence also exists that ACEI or ARB use is not associated with a greater likelihood of positive SARS-CoV-2 test results among symptomatic patients. Whether these medications are beneficial in COVID-19 treatment remains uncertain.

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