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Systematic Review/Meta-analysis

Angiotensin Receptor Blockers and Angiotensin-Converting Enzyme Inhibitors in COVID-19: Meta-analysis/Meta-regression Adjusted for Confounding Factors

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ABSTRACT

Background: Angiotensin receptor blockers (ARBs) and/or angiotensin-converting enzyme (ACE) inhibitors could alter mortality from coronavirus disease 2019 (COVID-19), but existing meta-analyses that combined crude and adjusted results may be confounded by the fact that comorbidities are more common in ARB/ACE inhibitor users.

Methods: We searched PubMed/MEDLINE/Embase for cohort studies and meta-analyses reporting mortality by preexisting ARB/ACE inhibitor treatment in hospitalized COVID-19 patients. Random

RÉSUMÉ

Introduction : Les antagonistes des récepteurs de l'angiotensine (ARA) et/ou les inhibiteurs de l'enzyme de conversion de l'angiotensine (IECA) feraient varier la mortalité liée à la COVID-19, mais il est possible que les méta-analyses actuelles qui combinaient les résultats bruts et ajustés soient invalidées du fait que les comorbidités sont plus fréquentes chez les utilisateurs d'ARA/IECA.

Méthodes : Nous avons effectué des recherches dans les bases de données PubMed/MEDLINE/Embase pour trouver des études de cohorte et des méta-analyses qui portent sur la mortalité associée à un

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which has resulted in unprecedented global morbidity and mortality. The World Health Organization and other groups are performing numerous randomized controlled trials of vaccines and novel therapeutic agents to target SARS-CoV-2. However, the critical illness and many complications associated with COVID-19 are caused in part by the binding and inhibition of angiotensin-converting enzyme (ACE2) by SARS-CoV-2[1,2] and the consequent dysregulated host response.

SARS-CoV-2, H1N1, and H5N1[3] downregulate ACE2. SARS-CoV-2 is then endocytosed, and surface ACE2 is downregulated,[1] thereby increasing angiotensin II (ATII, a potent vasoconstrictor) in COVID-19 because ACE2 catalyzes conversion of angiotensin II to angiotensin 1-7.[4] Downregulation of ACE2 occurs in H1N1, H5N1, H7N9, and SARS[5-8] infection, leading to worsened lung injury in influenza models[5-7] and increased viral load, disease progression, and mortality.[9] Accordingly, angiotensin receptor blockers (ARBs) and ACE inhibitors are candidate therapies for COVID-19 because they block excessive angiotensin II.

There is clinical uncertainty regarding the safety and effectiveness of ARBs/ACE inhibitors for COVID-19 because of conflicting cohort studies and even conflicting meta-analyses. There is an inherent potential bias in cohort studies of use of

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Ethics Statement: No formal ethics approval was required to conduct meta-analysis of published studies.

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See page 973 for disclosure information.

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effects meta-regression was used to compute pooled odds ratios for mortality adjusted for imbalance in age, sex, and prevalence of cardiovascular disease, hypertension, diabetes mellitus, and chronic kidney disease between users and nonusers of ARBs/ACE inhibitors at the study level during data synthesis.

Results: In 30 included studies of 17,281 patients, 22%, 68%, 25%, and 11% had cardiovascular disease, hypertension, diabetes mellitus, and chronic kidney disease. ARB/ACE inhibitor use was associated with significantly lower mortality after controlling for potential confounding factors (odds ratio 0.77 [95% confidence interval: 0.62, 0.96]). In contrast, meta-analysis of ARB/ACE inhibitor use was not significantly associated with mortality when all studies were combined with no adjustment made for confounders (0.87 [95% confidence interval: 0.71, 1.08]).

Conclusions: ARB/ACE inhibitor use was associated with decreased mortality in cohorts of COVID-19 patients after adjusting for age, sex, cardiovascular disease, hypertension, diabetes, and chronic kidney disease. Unadjusted meta-analyses may not be appropriate for determining whether ARBs/ACE inhibitors are associated with mortality from COVID-19 because of indication bias.

traitement préexistant par ARA/IECA chez les patients hospitalisés atteints de la COVID-19. Nous avons utilisé la métarégression à effets aléatoires pour calculer les rapports de cotes regroupés de mortalité ajustés en fonction du déséquilibre de l'âge, du sexe, et de la prévalence des maladies cardiovasculaires, de l'hypertension, du diabète sucré et de l'insuffisance rénale chronique entre les utilisateurs et les non-utilisateurs d'ARA/IECA dans le cadre de l'étude durant la synthèse des données.

Résultats : Dans les 30 études portant sur 17 281 patients, 22 %, 68 %, 25 % et 11 % avaient respectivement une maladie cardiovasculaire, de l'hypertension, le diabète sucré et de l'insuffisance rénale chronique. L'utilisation des ARA/IECA a été associée à une mortalité significativement plus faible après avoir tenu compte des facteurs confusionnels potentiels (rapport de cotes 0,77 [intervalle de confiance à 95 % : 0,62, 0,96]). En revanche, la méta-analyse sur l'utilisation des ARA/IECA n'a pas été associée de façon significative à la mortalité lorsque toutes les études ont été combinées sans ajustement sur les facteurs confusionnels (0,87 [intervalle de confiance à 95 % : 0,71, 1,08]).

Conclusions : L'utilisation des ARA/IECA a été associée à la diminution de la mortalité au sein des cohortes de patients atteints de la COVID-19 après l'ajustement en fonction de l'âge, du sexe, des maladies cardiovasculaires, de l'hypertension, du diabète et de l'insuffisance rénale chronique. Les méta-analyses non ajustées peuvent ne pas permettre de déterminer si les ARA/IECA sont associés à la mortalité liée à la COVID-19 en raison du biais d'indication.

ARBs or ACE inhibitors for COVID-19 because patients who are on ARBs or ACE inhibitors have underlying comorbidities, including chronic cardiovascular disease, hypertension, diabetes mellitus, and chronic kidney disease, that increase the risk of complications and/or death from COVID-19. Accordingly, one *must* adjust for indication bias in patients who are or are not on ARBs or ACE inhibitors.

Some prior meta-analyses and studies found that use of ARBs and/or ACE inhibitors was not associated with altered mortality risk,[10-16] whereas one meta-analysis found that ACE inhibitors but not ARBs were associated with decreased COVID-19 mortality or critical illness,[17] and others found that the use of ARBs or ACE inhibitors was associated with decreased mortality overall,[18,19] in patients with cardiovascular disease,[20] or in patients with hypertension.[21-25] The reason for these conflicting results could be due partly to methodological differences. Several meta-analyses[10,11,18,19,25] restricted their main or sensitivity analysis to studies that reported adjusted results and thus limited the number of studies that could be included. In contrast, other meta-analyses[12-17,21-24] have combined only crude results together or improperly combined unadjusted and adjusted results together—and thus may suffer from indication bias—and/or combined incompatible adjusted effect measures together (odds ratio [OR] and hazard ratio) to obtain the pooled estimates, which might yield biased results.

Meta-regression traditionally is used to examine the relationship between effect estimates of the included studies (eg, OR) and study-level covariates (eg, proportion of patients with hypertension in each study). Several prior meta-regression analyses[17,23,26,27] have examined the effects of average age, sex distribution, or overall comorbidity prevalence of the included studies on patient outcome for ARB/ACE inhibitor users vs nonusers. A less well known use of meta-regression is to obtain pooled effect estimates adjusted for study-level covariates.[28] In the current context, meta-regression provides a methodologically attractive approach to explicitly adjust the crude results for confounding, including indication bias, during data synthesis and further combine them with existing adjusted results to form a pooled adjusted estimate. To the best of our knowledge, no meta-analysis of the association of use of ARBs and/or ACE inhibitors with mortality from COVID-19 has explicitly adjusted the crude results for imbalance in comorbidities between ARB/ACE inhibitor users and nonusers and properly combined them with existing adjusted results through meta-regression.

We hypothesized that use of ARBs and/or ACE inhibitors is associated with decreased mortality from COVID-19 in analyses adjusted for underlying comorbidities.

Methods

This meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) statements[29] (Supplemental Table S1).

Data sources and searches

We conducted a literature search of PubMed/MEDLINE on August 19, 2020 for cohort and case-control studies that reported the frequencies of ARB or ACE inhibitor treatment and mortality in hospitalized patients infected with COVID-19 (Supplemental Appendix S1). More specifically, the studies evaluated the associations between prior use (ie, prehospitalization chronic use) of ARBs and/or ACE inhibitors in hospitalized patients infected with COVID-19. A further search of PubMed and Embase was performed on November 17, 2020 to

identify meta-analyses for use of ARBs/ACE inhibitors and mortality in COVID-19 (Supplemental Appendices S1 and S2). Two authors (A.C. and T.L.) screened titles and abstracts to identify relevant studies.

Study selection

Studies were included if they provided data for at least 10 hospitalized COVID-19 patients. For the purpose of performing meta-regression, studies also need to report either (i) the frequency of ARB/ACE inhibitor use by patients, the number of deaths by ARB/ACE inhibitor usage, and the following patient characteristics by ARB/ACE inhibitor usage: age, sex, and prevalence of the comorbidities of interest (chronic cardiovascular disease, hypertension, diabetes mellitus, and chronic kidney disease); or (ii) the adjusted OR of mortality for ARB/ACE inhibitor usage. We included full-text peer-reviewed articles, peer-reviewed articles published ahead of print, and letters and commentaries. Other studies meeting the inclusion criteria were identified from the references in review articles and other meta-analyses. Only articles in English were included in the final analysis. We excluded non-peer-reviewed articles, article abstracts, incomplete articles, research posters, conference abstracts, books, theses, and retracted articles.

Data extraction and quality assessment

Information on age, sex, comorbidities, ARB/ACE inhibitor usage, mortality, and adjusted OR of mortality for ARB/ACE inhibitor usage was extracted independently by 2 of the authors (AC and TL). The Newcastle-Ottawa Scale[30] was used to assess the quality of the included studies. Studies with scores of ≥ 7 were regarded as high quality, 4-6 as fair quality, and < 4 as low quality.

Statistical analyses

The pooled OR of mortality for ARB/ACE inhibitor use was computed within each study type (studies reporting only crude results vs studies with results adjusted for confounders) using random effects meta-analysis based on the DerSimonian-Laird model. Publication bias was examined through visual inspection of the funnel plot for asymmetry. Statistical heterogeneity was assessed by τ^2, I^2, and Cochran's Q test.

Random effects meta-regression was further used to compute the pooled OR by combining the results from all studies (both crude-results and confounder-adjusted studies). For studies with only crude results reported, meta-regression adjusted for the difference in average age, sex distribution, and the prevalence of comorbidities as defined by the individual studies (specifically, cardiovascular disease, hypertension, diabetes mellitus, and chronic kidney disease) between users and non-users of ARBs/ACE inhibitors. These 4 comorbidities were chosen because they are the most common reasons for prescribing ARBs and/or ACE inhibitors, and they are the comorbidities most commonly associated with COVID-19 and to death due to COVID-19. For confounder-adjusted studies, meta-regression did not apply any further adjustment to the reported OR.

Meta-regression examined the relationship between the degree of imbalance in mean age, gender distribution, and comorbidity prevalence of ARB/ACE inhibitor users vs nonusers and the OR for mortality of ARB/ACE inhibitor users vs nonusers. It also provided the pooled effect size adjusted for age, sex, and comorbidity. The outcome variable was the log of the OR for mortality. Studies that reported only crude results used the unadjusted OR as the outcome variable, whereas confounder-adjusted studies used the adjusted OR. The regression model included the mean age ratio, the ratio of the percentage of males, and the comorbidity prevalence ratio between the 2 groups as adjustment variables. For studies that reported adjusted results, the reported results were interpreted as if the 2 groups had been adjusted to be balanced in terms of the confounders. Even though some of the included studies did not adjust for all the variables we considered, we believe that the authors of these studies would have examined the potential confounders and adjusted for those that were imbalanced between groups to obtain the adjusted results. Thus, for the adjustment variables we considered herein, we assumed that they have a value of 1 for these studies. This assumption is essentially the same implicit assumption made when adjusted ORs are combined to form a pooled estimate in a traditional meta-analysis.

Given the number of studies available, we were able to adjust for only a limited number of confounders simultaneously before running the risk of overfitting the data.[31,32] The general recommendation is that 10 to 20 studies be included for each adjustment variable[31]; the inclusion of 6 adjustment variables in our current analysis would require 60 to 120 studies, which exceeds this the number of studies available. Thus, as a sensitivity analysis, we conducted an additional analysis that we adjusted for only age and sex, and then 4 other separate analyses in which we adjusted for age, sex, and each of the 4 comorbidities. We further conducted a sensitivity analysis to examine the robustness of the meta-regression approach. For confounder-adjusted studies that provided patient characteristics (age, sex, and comorbidities) by ARB/ACE inhibitor usage, we used their crude data (mortality and patient characteristics) instead of the reported adjusted OR for the meta-regression analysis.

The adjusted pooled OR represented the OR for mortality if the 2 groups were to have the same mean age, sex distribution, and comorbidity prevalence and was obtained from the estimated meta-regression model by setting the mean age ratio, the male ratio, and the comorbidity prevalence ratio to 1.

Random effects meta-analysis and meta-regression were performed using the meta package in R 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria). A P value of < 0.05 was considered statistically significant.

Results

Literature review

After screening titles and abstracts, 76 full-text articles and 28 meta-analyses (with literature searches covering up to October 12, 2020 [date refers to literature search performed

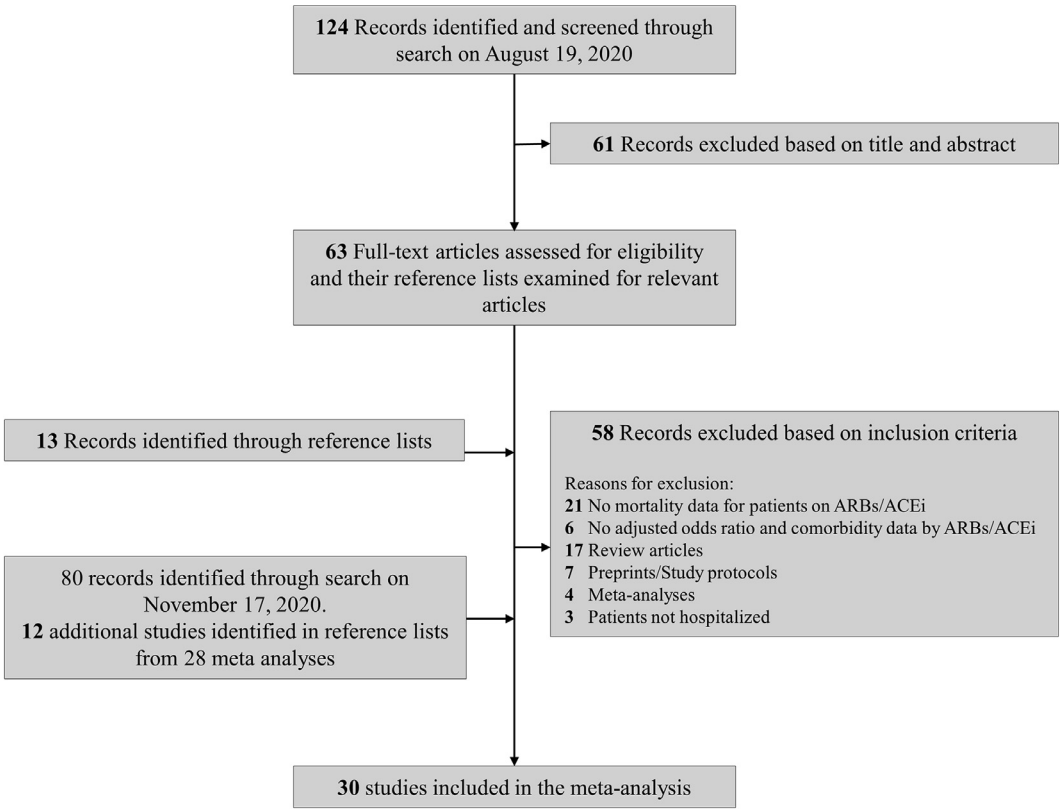

Figure 1. Flowchart of studies of angiotensin receptor blockers/angiotensin-converting enzyme (ARBs/ACE) inhibitors in COVID-19 included in final analyses.

by the authors in the 28 meta-analyses]) were reviewed (Fig. 1). We included 30 studies, with a total of 17,281 patients hospitalized with COVID-19. Thirteen studies reported only crude results for mortality, whereas 17 reported adjusted OR for mortality. Among the 13 crude-results studies, 1 reported an adjusted hazard ratio of mortality, 1 reported an OR of mortality within preexisting ARB/ACE inhibitor users for continuation vs discontinuation of treatment during hospitalization, and 3 reported adjusted ORs of the composite outcome of death or severe disease (Supplemental Table S2).

Comorbidities and ARB/ACE inhibitor treatment in COVID-19 patients

The baseline characteristics of patients in the included studies are shown in Table 1. Among hospitalized COVID-19 patients, 22% (n = 3161 of 14,682), 68% (n = 9919 of 14,682), 25% (n = 3621 of 14,370), and 11% (n = 1079 of 9952) had cardiovascular disease, hypertension, diabetes mellitus, and chronic kidney disease, respectively. Mortality of patients taking either ARBs or ACE inhibitors was 19% (n = 847 of 4477), whereas this endpoint was reached in 15% (n = 1609 of 10,990) among those not taking ARBs/ACE inhibitors (Table 2). In 3 studies, information on continuing ARBs or ACE inhibitors was collected. Two showed that continuing ARBs or ACE inhibitors was significantly associated with decreased mortality,[33,34] and one reported an OR that was substantially less than 1 but did not reach statistical significance.[35]

Analyses by study type

Among studies that reported only crude results (ie, with no adjustment for differences between groups in important prognostic factors) for mortality, the use of ARBs/ACE inhibitors was not significantly associated with mortality (OR 1.05 [95% confidence interval {CI}: 0.69, 1.61]; $P = 0.82$). The pooled OR among confounder-adjusted studies was also not significant (0.80 [95% CI: 0.63, 1.00; $P = 0.055$]). When combining all studies together without adjustment of confounders for the crude-results studies, the pooled OR was not significant (0.87 [95% CI: 0.71, 1.08; $P = 0.21$]; Fig. 2). Considerable statistical heterogeneity among studies was observed within both types of studies (τ^2: 0.278 & 0.113; I^2: 66.3% & 57.9%, $P < 0.001$ for both). No asymmetry in the funnel plot was observed within each study type (Supplemental Figure S1).

Adjusted analyses by meta-regression

After adjusting for age, sex, cardiovascular disease, hypertension, diabetes, and chronic kidney disease, the use of ARBs/ACE inhibitors was associated with significantly lower mortality when all studies were combined (OR: 0.77 [95% CI: 0.62, 0.96]; $P = 0.022$; Fig. 2). This conclusion was unchanged in the sensitivity analyses, which adjusted for only a subset of confounders to avoid the possibility of overfitting the data. The adjusted OR of mortality from one study[34] was reported separately for continuation of ARBs/ACE inhibitors vs no therapy and for discontinuation of ARBs/ACE

Table 1. Characteristics of studies included in meta-analysis

Study	City/State/ Country	Number of patients				
		Total	Cardiovascular disease	Hypertension	Diabetes mellitus	Chronic kidney disease
With only crude results						
Bean[57]	London, United Kingdom	1200	267	645	418	206
Bravi[58]	Pescara, Italy	646	192	336	129	63
Chaudhri[35]	New York, USA	300	96	133	74	34
Hu[36]	Zhejiang, China	149	7	149	30	6
Huang[59]	Wuhan, China	50	1	50	4	—
Li[60]	Wuhan, China	362	62	362	127	35
Meng[61]	Shenzhen, China	42	8	42	6	0
Oussalah[62]	Nancy, France	147	38/133	66/133	38/133	8/133
Sardu[63]	Naples, Italy	62	21	62	16	6
Şenkal[64]	Turkey	156	55	156	64	15
Tan[65]	Wuhan, China	100	18	100	28	8
Yang[66]	Wuhan, China	251	45	126	55	4
Zhang[67]	Hubei, China	1128	131	1128	240	35
With adjusted results						
Chen[20]	Wuhan, China	312	80	293	—	—
Cannata[34]	Lombardy, Italy	397	—	—	—	—
Covino[69]	Rome, Italy	166	70	166	22	—
Di Castelnuovo[68]	Italy	4069	667	2057	793	—
Felice[70]	Treviso, Italy	133	24	133	34	—
Iaccarino[42]	Italy	1591	404	873	269	87
Imam[41]	Michigan, USA	1305	283	734	393	228
Jung[71]	38 countries	324	108	211	95	49
Jung[72]	Seoul, Korea	1954	—	—	—	—
Lam[33]	New York City, USA	614	230	614	250	95
López-Otero[73]	Spain	234	—	—	—	—
Matsuzawa[74]	Kanagawa, Japan	39	1	39	14	3
Negreira-Caamaño[75]	Spain	545	139	545	165	98
Selçuk[76]	Turkey	113	37	113	48	13
Shah[77]	Georgia, USA	531	116	425	228	77
Xu[78]	Wuhan, China	101	13	101	19	2
Yuan[79]	Shanghai, China	260	48	260	62	7

Cardiovascular disease includes coronary artery disease, congestive heart failure or heart failure, cardiopathy, ischemic heart disease, coronary heart disease, and cardiovascular disease. Dash (—) indicates no information was reported by the study.

inhibitors vs no therapy. The former was much lower compared to other included studies, and exclusion of this study from the analysis did not alter our conclusion (Fig. 2).

Nine confounder-adjusted studies also provided the distribution for age, sex, and comorbidities by ARB/ACE inhibitor usage (Table 2). Our conclusion was unchanged in the sensitivity analyses, which replaced the reported adjusted OR with crude data from these studies (Fig. 2; pooled OR was not adjusted for chronic kidney disease as it was not reported in 2 of these studies).

All studies with adjusted results were deemed to be of good quality based on the Newcastle-Ottawa Scale (Supplemental Table S3). The quality of studies with only crude results was lower, as the crude mortality data reported could have been influenced by indication bias. Accordingly, we attempted to minimize this impact analytically through meta-regression. The exception was the Hu et al. study,[36] for which the poor quality was mainly due to insufficient description of how the data were extracted. Exclusion of this study did not alter our conclusion (Fig. 2).

Discussion

The use of ARBs and the use of ACE inhibitors were associated with significantly decreased mortality in observational studies of hospitalized patients with COVID-19 after adjusting for age, sex, cardiovascular disease, hypertension, diabetes, and chronic kidney disease. In contrast, we found that the use of ARBs and the use of ACE inhibitors were not associated with significantly decreased mortality in unadjusted analyses, possibly because patients on ARBs and patients on ACE inhibitors had more comorbidities, an imbalance that may have contaminated the crude association between ARB/ACE inhibitor use and mortality.

However, for both the analysis restricted to confounder-adjusted studies and the unadjusted analysis by meta-regression, the point estimate of the pooled OR and most of the 95% confidence interval were less than 1, suggesting that the effect may be important. There was substantial overlap in the confidence intervals for the pooled OR from the adjusted and unadjusted meta-regression, partly because the same set of data from the adjusted studies was used in both analyses. The degree of indication bias in the unadjusted meta-regression analysis clearly would depend on the number of included studies that have only crude results and the severity of indication bias in these studies. In particular, for studies that have restricted the analysis population to patients with a specific comorbidity (eg, hypertension), the degree of such bias might be lower, as the reported crude results have implicitly accounted for that particular comorbidity.

To our knowledge, no meta-analysis of ARBs and ACE inhibitors in COVID-19 has properly combined unadjusted

Table 2. Patient characteristics and outcome by ARB/ACE inhibitor usage

Study	Number of deaths/total			Patient characteristics—ARB or ACEi / no ARB or ACEi					
	ARB or ACEi	No ARB or ACEi	Adjusted OR for death (95% CI)	Age, y (mean)*	Male (%)	Cardiovascular disease (%)	Hypertension (%)	Diabetes mellitus (%)	CKD (%)
With only crude results									
Bean[57]	106/399	182/801	—	73/65	58/57	37/15	85/38	54/25	27/12
Bravi[58]	87/267	67/379	—	77/64	58/51	45/19	100/18	30/13	14/7
Chaudhri[35]	14/80	25/220	—	69/56	60/59	60/22	100/24	46/17	19/9
Hu[36]	1/65	0/84	—	56/58	62/57	3/6	100/100	25/17	6/2
Huang[59]	0/20	3/30	—	53/68	50/57	0/3	100/100	0/13	—
Li[60]	21/115	56/247	—	65/67	59/49	23/14	100/100	37/34	11/9
Meng[61]	0/17	1/25	—	62/62	47/60	12/24	100/100	12/16	0/0
Oussalah[62]	10/43	9/104	—	70/63	65/61	49/19	86/32	58/14	9/4
Sardu[63]	7/45	2/17	—	57/59	64/71	33/35	100/100	24/29	9/12
Şenkal[64]	7/104	5/52	—	63/65	51/58	34/38	100/100	42/38	10/10
Tan[65]	0/31	11/69	—	67/68	45/54	16/19	100/100	26/29	13/6
Yang[66]	2/43	19/208	—	65/67	49/20	16/18	100/40	30/20	0/2
Zhang[67]	7/188	92/940	—	64/64	53/54	15/11	100/100	23/21	4/3
With adjusted results									
Chen[20]	7/81	66/231	0.136 (0.035, 0.532)	—	—	—	—	—	—
Cannata[34,†]	7/56	39/224	0.05 (0.01, 0.54)	—	—	—	—	—	—
Cannata[34,†]	32/117	39/224	1.11 (0.38, 3.45)	—	—	—	—	—	—
Covino[69]	38/111	13/55	0.78 (0.29, 2.09)	72/77	70/56	43/40	100/100	16/7	—
Di Castelnuovo[68,‡]	116/549	423/2807	0.89 (0.67, 1.19)	—	62/61	31/11	92/31	28/16	—
Di Castelnuovo[68,‡]	112/542	423/2807	0.93 (0.69, 1.24)	—	64/61	24/11	94/31	26/16	—
Felice[70]	15/82	18/51	0.56 (0.17, 0.83)	71/76	72/53	10/31	100/100	24/27	—
Iaccarino[42,§]	63/348	125/1243	1.45 (0.99, 1.98)	—	—	—	—	—	—
Imam[41]	−/565	−/740	1.20 (0.86, 1.68)	—	—	—	—	—	—
Jung[71,§]	19/62	128/262	0.32 (0.15, 0.67)	—	—	—	—	—	—
Jung[72]	33/377	51/1577	0.88 (0.53, 1.44)	—	—	—	—	—	—
Lam[33]	58/335	62/279	0.811 (0.529, 1.243)	68/73	56/53	36/39	100/100	45/35	9/23
López-Otero[73]	8/78	16/156	1.04 (0.16, 6.57)	—	—	—	—	—	—
Matsuzawa[74]	2/21	3/18	0.36 (0.03, 3.53)	71/72	62/78	0/6	100/100	52/17	10/6
Negreira-Caamaño[75]	119/392	63/153	0.550 (0.304, 0.930)	76/78	53/50	25/27	100/100	32/26	17/22
Selçuk[76]	31/74	4/39	3.66 (1.11, 18.18)	67/58	49/59	42/15	100/100	42/44	14/8
Shah[77]	38/207	48/324	0.82 (0.45, 1.50)	64/58	42/40	24/21	97/69	56/35	16/13
Xu[78]	11/40	21/61	0.78 (0.32, 1.93)	67/65	48/56	13/13	100/100	20/18	0/3
Yuan[79]	6/130	22/130	0.50 (0.07, 3.58)	67/66	45/45	18/18	100/100	26/22	4/2

Cardiovascular disease includes coronary artery disease, congestive heart failure or heart failure, cardiopathy, ischemic heart disease, coronary heart disease, cardiovascular disease. Dash (—) indicates no information was reported by the study.

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CI, confidence interval; CKD, chronic kidney disease; OR, odds ratio.

*Median age is shown if mean age was not reported.

†Numbers are for ARBs/ACEis continued vs no therapy in the first row for Cannata, and for ARBs/ACEis discontinued vs no therapy in the second row.

‡Numbers are for ACEis vs no therapy in the first row for Di Castelnuovo, and for ARBs vs no therapy in the second row.

§Numbers are for ACEis vs no ACEis.

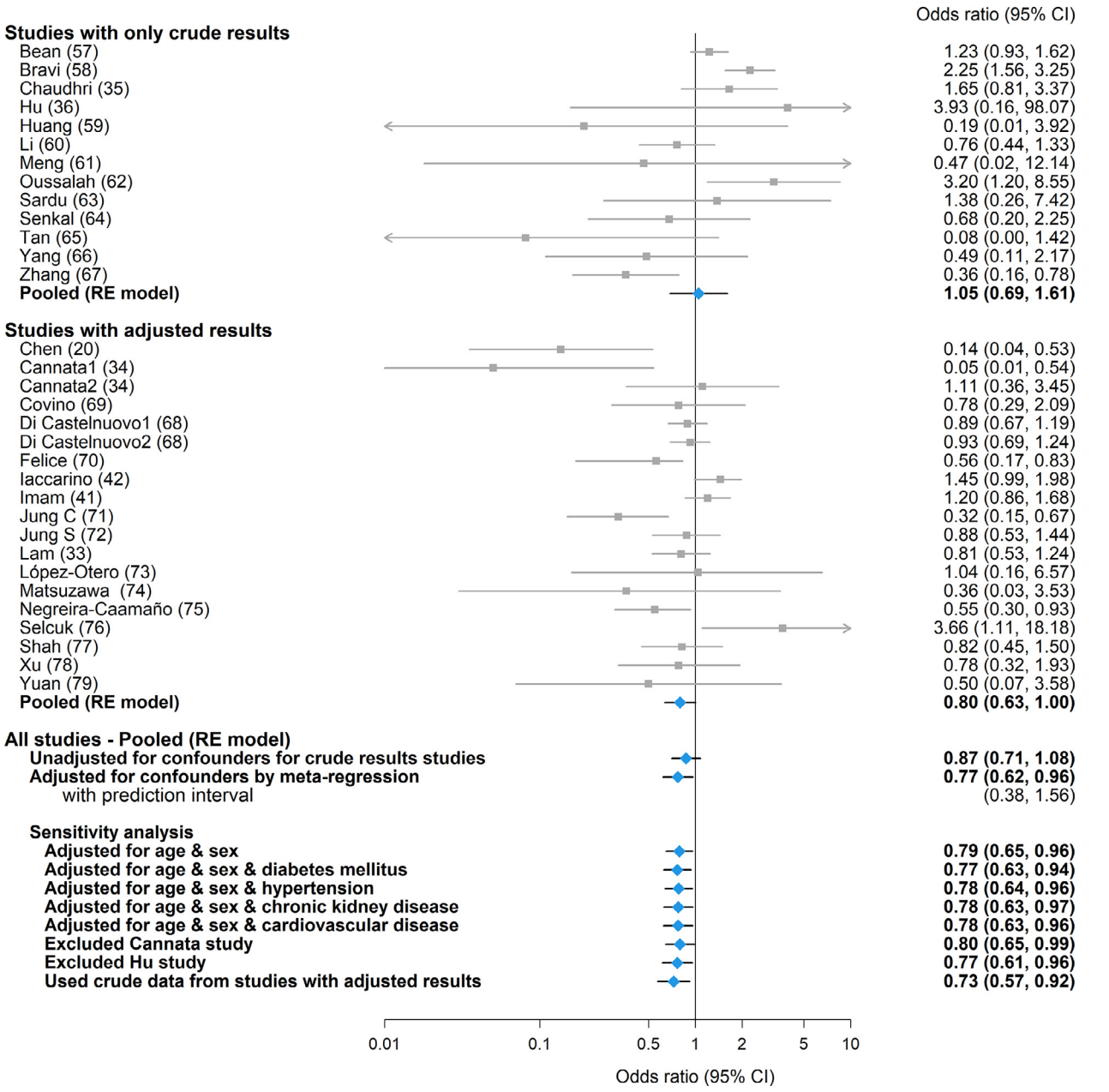

Figure 2. Forest plot of odds ratio of mortality for angiotensin receptor blockers/angiotensin-converting enzyme inhibitors in coronavirus disease 2019. CI, confidence interval; RE, random effects.

and adjusted results by explicitly accounting for confounders during data synthesis, and so our findings must be interpreted as being hypothesis-generating. Among the included studies, 17 reported an adjusted OR of mortality, and by applying the meta-regression approach, we were able to increase the total number of studies to be included by also using data from studies that reported only crude results, to form an overall adjusted OR. Using this approach increased the statistical power of our analysis.

We emphasize that the results of observational studies of the use of ARBs and ACE inhibitors in COVID-19 are commonly confounded by indication bias. Prior research suggests that comorbidities, including chronic cardiovascular disease, hypertension, diabetes mellitus, and chronic kidney disease, have a high prevalence, occurring in 30%-50% of COVID-19 patients,[37-39] and these comorbidities themselves increase the risk of complications and/or death in COVID-19.[40-44] Patients with these comorbidities are often treated with ARBs or ACE inhibitors.

Canadian hypertension guidelines recommend ARBs if ACE inhibitors are not tolerated,[45] and ARBs and ACE inhibitors are very commonly prescribed (to 59% of hypertension patients,[46] 35% of hypertensive patients with chronic kidney disease,[47] and 32% of diabetes patients[48]). ARBs/ACE inhibitors are recommended first-line therapy in Canadian heart failure guidelines.[49] They were used in 50%-70% of heart failure patients in Alberta, Canada[50] and 52%-87% of heart failure patients in other countries.[51-53]

For all these reasons, one must adjust for indication bias in patients who are or are not on ARBs or ACE inhibitors when assessing the effect of these drugs on outcomes of COVID-19.

However, our findings are limited because a cohort association study is generally limited in addressing causation. There may be variables that we did not adjust for that confound the analyses and the results, so it is not possible to address causal relationship. For example, ARBs and ACE inhibitors may be tolerated in only patients who have less-severe disease (ie, the underlying comorbidities) and thus lower mortality of COVID-19, such that the underlying severity of disease and not the use of ARBs or ACE inhibitors *caused* the decreased mortality.

However, we suggest that only randomized controlled trials of ARBs and ACE inhibitors in COVID-19 can directly address causation—that is, whether ARBs and/or ACE inhibitors alter the mortality of COVID-19. There are several such randomized controlled trials that are currently ongoing, and one conference presentation[54] of a randomized controlled trial (n = 659) from Brazil of stopping vs continuing ARBs and ACE inhibitors reports that ARBs and/or ACE inhibitors did not alter mortality of COVID-19 (2.7% vs 2.8%, respectively).

Among the 3 studies included in our analysis that reported comparison of continuation vs discontinuation of ARBs or ACE inhibitors, mortality was found to be lower for those who continued use of ARBs or ACE inhibitors. However, we suggest that cohort studies that address the therapeutic benefits of continuation of use of ARBs or ACE inhibitors are confounded by the fact that the decision to discontinue could be driven partly by disease progression or side effects of the treatment. Although the current recommendation by scientific societies is to not discontinue treatment, we agree that further studies are needed, such as the registered trials that randomize patients already on ARBs or ACE inhibitors to continue vs discontinue the ARB or ACE inhibitor use.

As for H1N1 and H5N1, ACE2 is the receptor for COVID-19[2] and SARS-CoV-2 downregulates ACE2.[1] Downregulation of ACE2 by SARS-Cov-2 dysregulates the renin-angiotensin system, leading to increased plasma levels of angiotensin II in COVID-19. Plasma angiotensin II levels are increased in COVID-19 patients compared to healthy controls[4] and are higher in critically ill than non–critically ill COVID-19 patients.[55] Losartan (an ARB) decreases viral replication and lung injury in murine influenza pneumonia.[56] Consequently, ARBs and ACE inhibitors are suitable drugs to evaluate in COVID-19 because they inhibit excess angiotensin II through 2 different mechanisms by blocking the angiotensin II type 1 receptor or inhibiting production of angiotensin II, respectively, and thus they may have different effects on outcomes of COVID-19.

We did not examine the effects of ARBs and ACE inhibitors separately in our current analysis as most included studies evaluated the 2 effects together. Based on a different set of 3 studies, one previous meta-analysis[16] did not find the effect of ARBs on mortality to be different from that of ACE inhibitors, whereas another[27] found that use of ARBs but not ACE inhibitors reduced mortality compared to nonuse. A recent meta-analysis that included both patients admitted vs not admitted to the hospital[24] has synthesized these 2 effects separately using crude mortality data from 9 studies restricted to hypertensive patients and found no significant association between ARBs or ACE inhibitors and mortality.

There are other limitations of our study. First, as we do not have patient-level data, we could adjust only for potential confounders at the study level. Second, to avoid overfitting the data, we included only major confounding variables in the analysis. Also, for studies reporting adjusted results, not all have adjusted for the confounder variables we considered herein (ie, age, sex, and comorbidities). It is possible that the selection of adjustment variables was pre-specified based on prior knowledge rather than chosen based on observed imbalance. Thus, residual confounding may explain the association. It is also possible that our findings are subject to publication bias, although this bias should be limited given the urgency of COVID-19 research. Another limitation is that we have restricted our literature search to English-language articles and thus, findings could suffer from language bias. Finally, some of the included studies have censored the patients who were still hospitalized at the time of data extraction and reported them as survivors, which might not accurately reflect the final outcome of these patients.

Conclusion

In conclusion, meta-regression analyses found that the use of ARBs/ACE inhibitors was associated with significantly decreased mortality of COVID-19 after adjusting for age, sex, cardiovascular disease, hypertension, diabetes, and chronic kidney disease. Unadjusted meta-analyses may not be appropriate for determining whether ARBs or ACE inhibitors are associated with mortality of COVID-19 because of the potential for indication bias. In contrast, combining unadjusted and adjusted results with careful consideration of indication bias through meta-regression is methodologically sound and increases the statistical power of the analysis. Although association cannot prove causality, our findings support the need for randomized controlled trials evaluating ARBs and ACE inhibitors as therapeutic interventions to reduce mortality in hospitalized patients with COVID-19.

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Dr Russell reports patents owned by the University of British Columbia (UBC) that are related to the use of PCSK9 inhibitor(s) in sepsis and to the use of vasopressin in septic shock. Dr Russell is an inventor on these patents. Dr Russell

was a founder, director, and shareholder in Cyon Therapeutics Inc. and is a shareholder in Molecular You Corp. Dr Russell reports receiving consulting fees in the last 3 years from: (i) Asahi Kesai Pharmaceuticals of America (AKPA; was developing recombinant thrombomodulin in sepsis); (ii) SIB Therapeutics LLC (developing a sepsis drug); and (iii) Ferring Pharmaceuticals (manufactures vasopressin and is developing selepressin). Dr Russell is no longer actively consulting for the following: (iv) La Jolla Pharmaceuticals (developing angiotensin II; Dr Russell chaired the data and safety monitoring board of a trial of angiotensin II from 2015 to 2017); and (v) PAR Pharma (sells prepared bags of vasopressin). Dr Russell reports having received an investigator-initiated grant from Grifols (entitled "Is HBP a mechanism of albumin's efficacy in human septic shock?") that was provided to and administered by UBC. Dr Cheng reports grants from McGill Interdisciplinary Initiative in Infection and Immunity, and grants from the Canadian Institutes of Health Research, during the conduct of the study; personal fees from GEn1E Lifesciences (as a member of the Scientific Advisory Board), and personal fees from nplex biosciences (as a member of the scientific advisory board), outside the submitted work. Dr Todd Lee receives research salary support from the Fonds de recherche du Québec—Santé. Dr Murthy receives research salary support from Innovative Medicines Canada. Dr Rewa has received consulting fees from Baxter Healthcare Inc. Dr Walley reports a patent owned by UBC that is related to the use of PCSK9 inhibitor(s) in sepsis. Dr Walley is an inventor on this patent. Dr Walley was a founder, director, and shareholder in Cyon Therapeutics Inc.

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Supplementary Material

To access the supplementary material accompanying this article, visit *CJC Open* at https://www.cjcopen.ca/ and at https://doi.org/10.1016/j.cjco.2021.03.001.