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META-ANALYSIS

Cardiovascular drugs and COVID-19 clinical outcomes: A living systematic review and meta-analysis

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Aims: The aim of this study was to continually evaluate the association between cardiovascular drug exposure and COVID-19 clinical outcomes (susceptibility to infection, disease severity, hospitalization, hospitalization length, and all-cause mortality) in patients at risk of/with confirmed COVID-19.

Methods: Eligible publications were identified from more than 500 databases on 1 November 2020. One reviewer extracted data with 20% of the records independently extracted/evaluated by a second reviewer.

Results: Of 52 735 screened records, 429 and 390 studies were included in the qualitative and quantitative syntheses, respectively. The most-reported drugs were angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin receptor blockers (ARBs) with ACEI/ARB exposure having borderline association with confirmed COVID-19 infection (OR 1.14, 95% CI 1.00–1.31). Among COVID-19 patients, unadjusted estimates showed that ACEI/ARB exposure was associated with hospitalization (OR 1.76, 95% CI 1.34–2.32), disease severity (OR 1.40, 95% CI 1.26–1.55) and all-cause mortality (OR 1.22, 95% CI 1.12–1.33) but not hospitalization length (mean difference −0.27, 95% CI −1.36–0.82 days). After adjustment, ACEI/ARB exposure was not associated with confirmed COVID-19 infection (OR 0.92, 95% CI 0.71–1.19), hospitalization (OR 0.93, 95% CI 0.70–1.24), disease severity (OR 1.05, 95% CI 0.81–1.38) or all-cause mortality (OR 0.84, 95% CI 0.70–1.00). Similarly, subgroup analyses involving only hypertensive patients revealed that ACEI/ARB exposure was not associated with confirmed COVID-19 infection (OR 0.93, 95% CI 0.79–1.09), hospitalization (OR 0.84, 95% CI 0.58–1.22), hospitalization length (mean difference −0.14, 95% CI −1.65–1.36 days), disease severity (OR 0.92, 95% CI 0.76–1.11) while it decreased the odds of dying (OR 0.76, 95% CI 0.65–0.88). A similar trend was observed for other cardiovascular drugs. However, the validity of these findings is limited by a high level of heterogeneity and serious risk of bias.

Conclusion: Cardiovascular drugs are not associated with poor COVID-19 outcomes in adjusted analyses. Patients should continue taking these drugs as prescribed.

KEYWORDS
cardiovascular drugs, COVID-19, living systematic review, meta-analysis

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19) was first reported on 8 December 2019 in Wuhan, Hubei province, China.[1] It is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which infects cells through the human angiotensin-converting enzyme 2 (ACE2) receptor.[2] It was designated a pandemic by the World Health Organization on 11 March 2020[3] and has since affected 192 countries/regions, more than 112 million patients and led to close to 2.5 million deaths (as of 24 February 2021[4]). To put it into context, cardiovascular diseases such as ischaemic heart disease, stroke and heart failure remain the leading causes of global deaths, being responsible for an estimated 17.8 million deaths in 2017.[5] The interaction between COVID-19 and cardiovascular disease appears complex and bi-directional with cardiovascular disease increasing susceptibility to SARS-CoV-2 infection or COVID-19 severity and at the same time COVID-19 causing injury to the cardiovascular system in some patients.[6,7] Consequently, the relationship between COVID-19 and cardiovascular drugs is of interest because: (a) patients with increased susceptibility to SARS-CoV-2 infection may be taking these drugs, (b) they may alleviate cardiovascular injury caused by COVID-19, and (c) cardiovascular drugs such as angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) may play a direct role in COVID-19 pathology.[2]

Recent systematic reviews, including a living systematic review,[8] have characterized the relationship between COVID-19 outcomes and cardiovascular drugs. These reviews have, however, focused on ACEIs and ARBs. However, being a novel disease, a lot is still unknown about COVID-19, which makes a broader systematic review (in terms of the drugs studied) necessary. Moreover, there are emerging reports that other drug classes such as anticoagulants, calcium channel blockers and statins could be beneficial.[9–11] Additionally, many cardiovascular disease patients are on combination therapies and a broader review may facilitate understanding of the interplay between the different classes of cardiovascular drugs. Lastly, evidence in this field is rapidly evolving which means that recently published reviews soon become outdated. To provide more comprehensive and up-to-date evidence, we have conducted a systematic review and meta-analysis to evaluate all the current evidence on the association between cardiovascular drug exposure and COVID-19 clinical outcomes in patients at risk of/with confirmed COVID-19. Due to the rapidly evolving nature of this field, we will periodically update this baseline review for up to 2 years to reflect emerging evidence.

2 | METHODS

A predefined protocol (PROSPERO: CRD42020191283[12]), based on the principles of the Cochrane Handbook for Systematic Reviews of Interventions[13] with living systematic review considerations[14] was followed. This report adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA, Table S1).

2.1 | Identification of studies

A final search of the University of Liverpool's DISCOVER platform (which links, through EBSCOhost, to sources from more than 500 databases including MEDLINE, Table S2), several preprint servers, COVID-19 specific databases (such as the COVID-19 Clinical Trials registry and the World Health Organization database of COVID-19 publications), and other registries/results databases (such as ClinicalTrials.gov and the International Clinical Trials Registry Platform) was undertaken on 1 November 2020 using medical subject headings and text words related to "cardiovascular drugs" and "COVID-19" as previously detailed.[12,15] A separate MEDLINE search[15] was conducted to ensure that the DISCOVER search was retrieving all eligible records. Because we separately searched for grey literature, the DISCOVER search was limited to studies published in academic journals. EndNote (version X9, Clarivate, Philadelphia, PA, USA) was used to upload DISCOVER search results and de-duplicate studies by information regarding author, year of publication, title, and reference type. Lastly, lists of references from the identified studies and previous systematic reviews were hand-searched to identify additional eligible articles.

2.2 | Selection criteria

This review included observational (e.g. retrospective or prospective cohort and case–control studies) and interventional (e.g. randomized controlled trials) studies that: (a) reported cardiovascular drug exposure (cardiovascular drug classes/sub-classes [Table S3] were those derived from Chapter 2 ["Cardiovascular system"] of the British National Formulary[16]), and (b) investigated the association between cardiovascular drug exposure and COVID-19 clinical outcomes (outlined below). Case series were included if they reported at least five patients. Unless translated text could be obtained, non-English studies were excluded. We did not exclude any studies based on publication status.

2.3 | Outcomes

COVID-19 clinical outcomes included susceptibility to infection (for those at risk of COVID-19), and disease severity,[15] hospitalization, hospitalization length and all-cause mortality (for those with COVID-19).

2.4 | Study selection and data extraction

One reviewer (I.G.A.) screened titles and abstracts of all retrieved bibliographic records according to eligibility. In addition to conducting an independent MEDLINE search, a second reviewer (S.P.) independently screened 20% of the records to check for consistency. Full texts of potentially eligible studies were retrieved, a data extraction form

developed and piloted in a subset of ten randomly selected papers and used to extract relevant information (related to study design, patient characteristics, cardiovascular drugs, COVID-19 outcomes and study quality). Data from all eligible studies were extracted and summarized by one reviewer (I.G.A.). As a quality control measure, a second reviewer (S.P. or R.M.T.) independently extracted and evaluated 20% of the records, between them, to ascertain consistency. Any disagreements were resolved by consensus.

2.5 | Assessment of study quality

To assess the quality of each included study, the modified Oxford Centre for Evidence-based Medicine for ratings of individual studies was used as detailed in the protocol[12] and Table S4. Again, I.G.A. evaluated all records with S.P. and R.M.T. independently evaluating 20% of the records between them, and disagreements being resolved by consensus.

2.6 | Data synthesis

Where two or more studies reporting on the same exposure–outcome combination were reported, effect estimates were pooled by way of random-effects meta-analyses (inverse-variance method for effect size, DerSimonian-Laird estimator for variance) using R version 3.6.1 (R meta package[17]). Odds/hazards/risk ratios and mean differences (with 95% confidence intervals) were generated for dichotomous and continuous outcomes, respectively. Both unadjusted (or in the case of binary outcomes, count data, which is preferred to unadjusted odds ratios as it provides more reliable estimates[18]) and adjusted estimates were extracted and pooled separately. Where there was more than one adjusted estimate, the estimate adjusting for the most covariates was preferred. Since different studies adjust for different covariates, we did not limit our inclusion criteria to a given set of covariates. Where median values and ranges/interquartile ranges were provided (for example for length of hospitalization), they were used to estimate the mean values and standard deviations.[19] Where necessary, means and standard deviations were combined using formulae available in the Cochrane Handbook.[13]

Where two or more studies used the same dataset for a given exposure–outcome combination (identified with reference to authors and their affiliations, recruitment sites, recruitment periods and patient eligibility criteria), then peer-reviewed publications and those reporting a larger number of patients were preferred. In instances where it was not obvious if the included patients were the same but there was a possibility of overlap (e.g. studies recruiting from similar sites with overlapping recruitment periods but different authors), only one of these studies (the one with the largest sample size) was included in the primary meta-analyses. Because of the uncertainty with identifying studies with overlapping data, pooled estimates in which all studies, regardless of any overlapping, were included are also reported. Forest plots were prepared for each exposure–outcome combination. Studies that could not be pooled due to being the only ones reporting on an exposure–outcome combination were also included as part of qualitative synthesis.

2.7 | Heterogeneity measures

The magnitude of inconsistency in the study results was assessed by visually examining forest plots and considering the I^2 statistic. Arbitrarily-defined categories of heterogeneity were: I^2 < 30%, low; I^2 = 30–70%, moderate; and I^2 > 70%, high.

2.8 | Publication bias

Where enough (≥10) studies were available for a given exposure–outcome combination, publication bias was assessed using the linear regression test of funnel plot asymmetry (Egger's test, implemented using the metabias function in the R meta package[17]). A *P*-value of <.1 was considered to suggest the presence of publication bias. When asymmetry was suggested by a visual assessment, we performed exploratory analyses to investigate and adjust for it (trim and fill analysis) using the trimfill function (R metafor package[20]).

2.9 | Subgroup analyses

Based on our preliminary meta-regression results,[15] we conducted sub-group analyses only based on treatment of hypertension.

2.10 | Confidence in cumulative evidence

The strength of the body of evidence and the quality and strength of recommendations was assessed according to the GRADE (Grading of Recommendations, Assessment, Development and Evaluations) criteria.[21]

2.11 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20.[22]

3 | RESULTS

3.1 | Study selection and characteristics

Of the 52 735 titles screened, 429 and 390 studies were included in the qualitative and quantitative syntheses respectively (Figure 1).

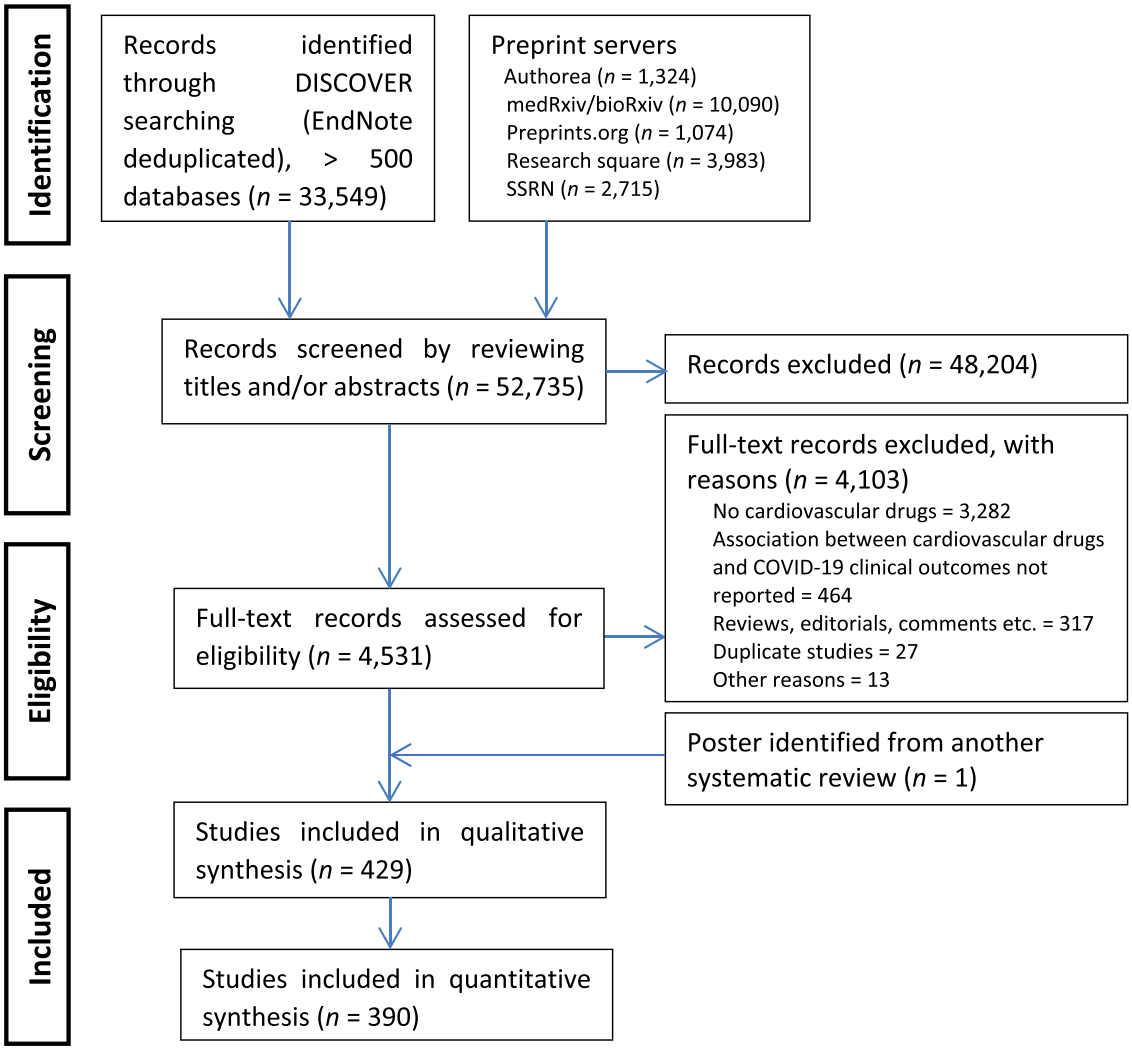


FIGURE 1 PRISMA flow chart of included studies. Abbreviations: SSRN, Social Science Research Network

The characteristics of the included studies are shown in Table S5 while Spreadsheet S1 contains quantitative data for all included papers. Of the 429 studies, more than a third ($n = 156$, 36%) were preprints. Almost all studies ($n = 427$, >99%) were observational with only two (<1%) studies[23,24] being interventional in nature (open-label randomized control trials, RCTs). Moreover, the two RCTs both conducted retrospective/non-pre-specified interim analyses of their currently recruited trial participants. Based on the modified Oxford Centre for Evidence-based Medicine for ratings of individual studies, all pooled estimates received quality ratings of either 3 or 4 for including mostly observational studies (case–controls, respective cohorts, case series and/or cross-sectional studies).

The most commonly reported drug exposure was with angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin receptor blockers (ARBs) (ACEI/ARBs), which therefore became the main focus. This report is additionally restricted to the major cardiovascular drug classes (ARBs, ACEIs, anticoagulants, antiplatelets, beta blockers, calcium channel blockers, diuretics and lipid-modifying drugs) and for exposure–outcome combinations that were reported by at least 10 studies.

3.2 | Meta-analysis

Table 1, Figures 2–3 and Figures S1–36 summarize the pooled estimates for the associations between all reported cardiovascular drug exposures and the various COVID-19 clinical outcomes. The text below is focused on the most reported drug (ACEI/ARB) exposure.

3.2.1 | Susceptibility to infection (patients at risk of COVID-19)

Fifty-nine studies reported count data and/or crude odds ratios (OR) for the association between ACEI/ARB exposure and susceptibility to infection (Figure S1). Eleven studies were removed to minimize

TABLE 1 Summary results for associations between cardiovascular drug exposure and COVID-19 outcomes[b]

Outcome (population)	Exposure	All studies[b]	Primary meta-analysis: Included studies	Primary meta-analysis: Sample size	Primary meta-analysis: Unadjusted estimates estimate (95%), I^2, Egger's P[c]	Hypertensive patients estimate (95%), I^2	Adjusted estimates (95% CI)	Reference figures/ tables
Susceptibility (patients at risk of COVID-19)	ACEI/ARB	59	48	10 522 649	OR 1.14 (1.00; 1.31), $I^2 = 97\%$, 0.18	OR ($n = 9$): 0.93 (0.79; 1.09), $I^2 = 82\%$	OR ($n = 16$): 0.92 (0.71; 1.19), $I^2 = 85\%$ HR ($n = 6$): 0.88 (0.75; 1.04), $I^2 = 76\%$ RR ($n = 7$): 0.99 (0.86; 1.14), $I^2 = 76\%$	Figures 2–3, Figure S1
	ACEI	39	31	9 779 752	OR 1.11 (0.96; 1.30), $I^2 = 96\%$, <0.10	OR ($n = 9$): 0.89 (0.77; 1.03), $I^2 = 73\%$	OR ($n = 14$): 0.95 (0.79; 1.14), $I^2 = 43\%$ HR ($n = 6$): 0.81 (0.72; 0.90), $I^2 = 59\%$ RR ($n = 5$): 0.93 (0.76; 1.14), $I^2 = 58\%$	Figure S2
	ARB	38	30	9 767 469	OR 1.16 (0.99; 1.36), $I^2 = 96\%$, 0.49	OR ($n = 9$): 1.10 (0.96; 1.26), $I^2 = 69\%$	OR ($n = 13$): 0.97 (0.76; 1.25), $I^2 = 88\%$ HR ($n = 5$): 0.95 (0.70; 1.29), $I^2 = 96\%$ RR ($n = 4$): 1.09 (0.79; 1.50), $I^2 = 85\%$	Figure S3
	Anticoagulant	24	24	9 421 814	OR 1.27 (0.87; 1.85), $I^2 = 99\%$, 0.29	Not analysed[d]	OR ($n = 3$): 1.00 (0.59; 1.71), $I^2 = 91\%$ HR ($n = 2$): 1.30 (1.18; 1.42), $I^2 = 0\%$ RR ($n = 2$): 1.51 (1.30; 1.75), $I^2 = 0\%$	Figure S4
	Antiplatelet	18	18	8 952 450	OR 1.13 (0.78; 1.64), $I^2 = 99\%$, 0.13	Not analysed[d]	OR ($n = 3$): 0.78 (0.31; 1.95), $I^2 = 87\%$ HR ($n = 2$): 1.32 (1.16; 1.50), $I^2 = 0\%$ RR ($n = 2$): 1.44 (1.22; 1.70), $I^2 = 0\%$	Figure S5
	Beta blocker	23	19	9 219 560	OR 1.06 (0.82; 1.38), $I^2 = 99\%$, 0.10	OR ($n = 4$): 0.88 (0.75; 1.03), $I^2 = 55\%$	OR ($n = 7$): 0.96 (0.88; 1.04), $I^2 = 26\%$ HR ($n = 2$): 0.98 (0.94; 1.03), $I^2 = 0\%$ RR ($n = 4$): 1.15 (0.92; 1.44), $I^2 = 83\%$	Figure S6
	CCB	22	18	9 582 060	OR 1.13 (0.88; 1.45), $I^2 = 99\%$, 0.25	OR ($n = 5$): 1.03 (0.96; 1.11), $I^2 = 0\%$	OR ($n = 7$): 1.02 (0.86; 1.20), $I^2 = 73\%$ HR ($n = 2$): 1.04 (0.77; 1.41), $I^2 = 72\%$ RR ($n = 5$): 1.04 (0.93; 1.16), $I^2 = 0\%$	Figure S7
	Diuretic	21	19	13 390 831	OR 1.24 (1.06; 1.44), $I^2 = 97\%$, 0.25	OR ($n = 4$): 1.33 (0.90; 1.95), $I^2 = 92\%$	OR ($n = 7$): 0.86 (0.62; 1.19), $I^2 = 82\%$ HR ($n = 2$): 0.90 (0.53; 1.53), $I^2 = 91\%$ RR ($n = 3$): 1.51 (0.82; 2.78), $I^2 = 99\%$	Figure S8
	LMD	22	21	9 549 627	OR 1.04 (0.79; 1.37), $I^2 = 99\%$, <0.10	OR ($n = 2$): 1.20 (0.26; 5.61), $I^2 = 93\%$	OR ($n = 6$): 0.85 (0.49; 1.48), $I^2 = 86\%$ HR ($n = 2$): 0.90 (0.86; 0.94), $I^2 = 0\%$ RR ($n = 3$): 1.16 (0.95; 1.42), $I^2 = 63\%$	Figure S9
Hospitalization (COVID-19 patients)	ACEI/ARB	31	27	63 132	OR 1.76 (1.34; 2.32), $I^2 = 95\%$, 0.26	OR ($n = 4$): 0.84 (0.58; 1.22), $I^2 = 66\%$	OR ($n = 11$): 0.93 (0.70; 1.24), $I^2 = 62\%$ HR ($n = 4$): 1.08 (0.90; 1.28), $I^2 = 63\%$	Figures 2–3, Figure S10
	ACEI	20	18	45 677	OR 1.64 (1.22; 2.22), $I^2 = 92\%$, 0.98	OR ($n = 4$): 0.73 (0.46; 1.15), $I^2 = 29\%$	OR ($n = 9$): 0.83 (0.60; 1.16), $I^2 = 58\%$ HR ($n = 3$): 1.02 (0.77; 1.35), $I^2 = 82\%$	Figure S11
	ARB	19	17	45 620	OR 1.45 (1.09; 1.93), $I^2 = 90\%$, 0.87	OR ($n = 4$): 0.86 (0.64; 1.15), $I^2 = 29\%$	OR ($n = 8$): 1.04 (0.73; 1.47), $I^2 = 61\%$ HR ($n = 3$): 1.06 (0.89; 1.27), $I^2 = 20\%$	Figure S12
	Anticoagulant	12	12	24 770	OR 3.32 (2.20; 5.01), $I^2 = 92\%$, 0.79	Not analysed[d]	NA	Figure S13
	Beta blocker	10	9	22 223	OR 2.64 (1.68; 4.14), $I^2 = 92\%$, NA	NA	OR ($n = 3$): 0.87 (0.38; 2.03), $I^2 = 79\%$	Figure S14

TABLE 1 (Continued)

Outcome (population)	Exposure	All studies[b]	Primary meta-analysis: Included studies	Primary meta-analysis: Sample size	Primary meta-analysis: Unadjusted estimates estimate (95%), I^2, Egger's P[c]	Hypertensive patients estimate (95%), I^2	Adjusted estimates (95% CI)	Reference figures/ tables
	CCB	10	9	43 515	OR 1.85 (1.16; 2.95), $I^2 = 96\%$, NA	OR ($n = 2$): 1.49 (0.75; 2.94), $I^2 = 0\%$	OR ($n = 5$): 1.03 (0.84; 1.27), $I^2 = 0\%$	Figure S15
	LMD	10	9	18 826	OR 3.44 (2.33; 5.10), $I^2 = 91\%$, NA	NA	OR ($n = 2$): 1.00 (0.31; 3.21), $I^2 = 86\%$	Figure S16
Hospitalization length (COVID-19 patients)	ACEI/ARB	27	9	1697	MD -0.27 (−1.36; 0.82) days, $I^2 = 24\%$, NA	MD ($n = 6$): −0.14 (−1.65; 1.36) days, $I^2 = 0\%$	NA	Figures 2–3, Figure S17
	Anticoagulants	10	10	2358	MD 3.39 (0.29; 6.48) days, $I^2 = 80\%$, NA (2 studies with zero weight)	Not analysed[d]	NA	Figure S18
Severity (COVID-19 patients)	ACEI/ARB	165	132	182 841	OR 1.40 (1.26; 1.55), $I^2 = 87\%$, 0.74	OR ($n = 38$): 0.92 (0.76; 1.11), $I^2 = 72\%$	OR ($n = 54$): 1.05 (0.81; 1.38), $I^2 = 85\%$ HR ($n = 14$): 0.84 (0.65; 1.10), $I^2 = 75\%$ RR ($n = 8$): 1.53 (0.54; 4.31), $I^2 = 97\%$	Figures 2–3, Figure S19
	ACEI	83	78	153 113	OR 1.45 (1.27; 1.66), $I^2 = 85\%$, 0.28	OR ($n = 20$): 0.93 (0.77; 1.14), $I^2 = 33\%$	OR ($n = 18$): 0.90 (0.67; 1.19), $I^2 = 61\%$ HR ($n = 5$): 1.07 (0.94; 1.23), $I^2 = 47\%$ RR ($n = 4$): 0.87 (0.68; 1.11), $I^2 = 8\%$	Figure S20
	ARB	79	75	145 684	OR 1.36 (1.20; 1.53), $I^2 = 83\%$, 0.97	OR ($n = 21$): 0.85 (0.70; 1.03), $I^2 = 55\%$	OR ($n = 24$): 1.13 (0.82; 1.55), $I^2 = 62\%$ HR ($n = 6$): 0.75 (0.39; 1.44), $I^2 = 77\%$ RR ($n = 5$): 0.99 (0.82; 1.19), $I^2 = 45\%$	Figure S21
	Anticoagulant	40	40	66 404	OR 1.59 (1.25; 2.02), $I^2 = 88\%$, 0.21	Not analysed[d]	OR ($n = 6$): 0.84 (0.59; 1.18), $I^2 = 69\%$ HR ($n = 3$): 0.88 (0.69; 1.12), $I^2 = 0\%$ RR ($n = 2$): 1.29 (0.74; 2.25), $I^2 = 0\%$	Figure S22
	Antiplatelet	33	31	50 384	OR 1.29 (1.04; 1.61), $I^2 = 85\%$, 0.29	Not analysed[d]	OR ($n = 6$): 0.69 (0.45; 1.06), $I^2 = 37\%$ HR ($n = 3$): 0.91 (0.58; 1.43), $I^2 = 77\%$ RR ($n = 2$): 0.62 (0.36; 1.05), $I^2 = 0\%$	Figure S23
	Beta blocker	36	32	66 586	OR 1.61 (1.28; 2.03), $I^2 = 91\%$, 0.57	OR ($n = 10$): 1.02 (0.87; 1.20), $I^2 = 0\%$	OR ($n = 9$): 1.23 (0.82; 1.85), $I^2 = 57\%$ HR ($n = 3$): 0.97 (0.72; 1.28), $I^2 = 15\%$ RR ($n = 2$): 1.02 (0.84; 1.24), $I^2 = 0\%$	Figure S24
	CCB	38	36	123 756	OR 1.58 (1.27; 1.97), $I^2 = 90\%$, 0.86	OR ($n = 14$): 1.13 (0.98; 1.31), $I^2 = 0\%$	OR ($n = 8$): 0.93 (0.56; 1.54), $I^2 = 33\%$ HR ($n = 2$): 1.15 (0.83; 1.58), $I^2 = 77\%$ RR ($n = 3$): 1.14 (0.89; 1.46), $I^2 = 30\%$	Figure S25
	Diuretic	32	29	60 368	OR 1.60 (1.14; 2.24), $I^2 = 94\%$, 0.50	OR ($n = 8$): 0.94 (0.76; 1.15), $I^2 = 0\%$	OR ($n = 7$): 0.80 (0.43; 1.47), $I^2 = 17\%$ HR ($n = 2$): 0.95 (0.75; 1.21), $I^2 = 0\%$ RR ($n = 2$): 0.85 (0.69; 1.06), $I^2 = 0\%$	Figure S26
	LMD	42	40	63 456	OR 1.42 (1.18; 1.69), $I^2 = 88\%$, 0.76	OR ($n = 2$): 0.77 (0.11; 5.54), $I^2 = 68\%$	OR ($n = 10$): 0.83 (0.56; 1.23), $I^2 = 71\%$ HR ($n = 4$): 0.95 (0.70; 1.27), $I^2 = 78\%$	Figure S27

(Continues)

TABLE 1 (Continued)

Outcome (population)	Exposure	All studies[b]	Primary meta-analysis: Included studies	Primary meta-analysis: Sample size	Primary meta-analysis: Unadjusted estimates estimate (95%), I^2, Egger's P[c]	Hypertensive patients estimate (95%), I^2	Adjusted estimates (95% CI)	Reference figures/ tables
All-cause mortality (COVID-19 patients)	ACEI/ARB	163	131	188 944	OR 1.22 (1.12; 1.33), I^2 = 83%, <0.10	OR (n = 39): 0.76 (0.65; 0.88), I^2 = 62%	OR (n = 48): 0.84 (0.70; 1.00), I^2 = 66% HR (n = 27): 0.76 (0.61; 0.95), I^2 = 78% RR (n = 10): 0.71 (0.46; 1.09), I^2 = 68%	Figures 2–3, Figure S28
	ACEI	67	63	143 470	OR 1.26 (1.11; 1.43), I^2 = 81%, <0.10	OR (n = 18): 0.92 (0.81; 1.06), I^2 = 23%	OR (n = 17): 0.88 (0.66; 1.17), I^2 = 72% HR (n = 13): 0.92 (0.73; 1.16), I^2 = 39% RR (n = 4): 1.08 (0.47; 2.52), I^2 = 50%	Figure S29
	ARB	66	63	146 614	OR 1.17 (1.05; 1.30), I^2 = 75%, <0.10	OR (n = 18): 0.84 (0.68; 1.03), I^2 = 67%	OR (n = 16): 0.98 (0.73; 1.30), I^2 = 56% HR (n = 13): 0.67 (0.46; 0.98), I^2 = 81% RR (n = 3): 1.41 (0.74; 2.69), I^2 = 0%	Figure S30
	Anticoagulant	82	71	110 049	OR 1.28 (1.05; 1.57), I^2 = 93%, <0.10	Not analysed[d]	OR (n = 16): 0.93 (0.61; 1.41), I^2 = 84% HR (n = 8): 0.54 (0.37; 0.77), I^2 = 85% RR (n = 4): 1.28 (1.05; 1.56), I^2 = 0%	Figure S31
	Antiplatelet	50	47	87 328	OR 1.68 (1.38; 2.03), I^2 = 88%, <0.10	Not analysed[d]	OR (n = 5): 0.79 (0.48; 1.28), I^2 = 23% HR (n = 5): 0.74 (0.48; 1.15), I^2 = 62% RR (n = 3): 0.89 (0.51; 1.53), I^2 = 39%	Figure S32
	Beta blocker	41	38	63 757	OR 1.87 (1.51; 2.31), I^2 = 87%, <0.10	OR (n = 8): 1.17 (0.88; 1.56), I^2 = 33%	OR (n = 8): 1.15 (0.94; 1.41), I^2 = 54% HR (n = 3): 1.13 (1.06; 1.21), I^2 = 0% RR (n = 2): 0.83 (0.47; 1.48), I^2 = 0%	Figure S33
	CCB	38	32	103 729	OR 1.58 (1.33; 1.88), I^2 = 80%, <0.10	OR (n = 11): 0.91 (0.75; 1.10), I^2 = 2%	OR (n = 7): 1.01 (0.80; 1.27), I^2 = 20% HR (n = 5): 0.77 (0.35; 1.67), I^2 = 71% RR (n = 2): 1.45 (0.83; 2.53), I^2 = 0%	Figure S34
	Diuretic	30	28	85 555	OR 2.46 (1.78; 3.40), I^2 = 94%, <0.10	OR (n = 5): 1.01 (0.59; 1.74), I^2 = 64%	OR (n = 8): 1.44 (1.19; 1.75), I^2 = 1% HR (n = 6): 0.93 (0.39; 2.21), I^2 = 65%	Figure S35
	LMD	51	48	111 346	OR 1.39 (1.16; 1.67), I^2 = 92%, <0.10	OR (n = 3): 1.01 (0.45; 2.25), I^2 = 66%	OR (n = 11): 0.88 (0.68; 1.13), I^2 = 72% HR (n = 7): 0.76 (0.59; 0.98), I^2 = 77% RR (n = 2): 0.85 (0.35; 2.05), I^2 = 89%	Figure S36

[a]Based on the modified Oxford Centre for Evidence-based Medicine for ratings of individual studies, all pooled estimates received quality ratings of either 3 or 4 for including mostly observational studies. In terms of GRADE rating, all estimates were downgraded to moderate certainty due to a serious risk of bias for all. Estimates with heterogeneity (I^2 > 70) were further downgraded to low certainty.

[b]With reference to studies reporting unadjusted estimates.

[c]A P-value <0.1 was suggestive of publication bias. However, trim and fill random effects analysis revealed that missing trials neither changed the direction of the pooled effect estimates nor affected their statistical significance.

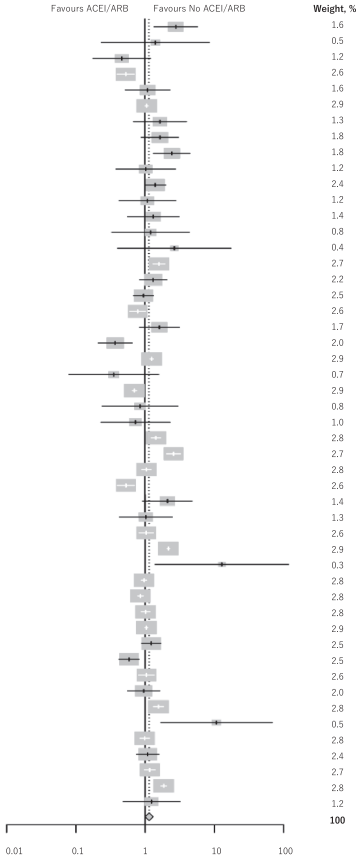
[d]Anticoagulants and antiplatelets not primarily used to treat hypertension.

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; I^2, I-squared (a heterogeneity measure); HR, hazard ratio; LMD, lipid-modifying drug; MD, mean difference; NA, not applicable; OR, odds ratio; RR, risk ratio.

(A) Infectivity (patients at risk of COVID-19)

First Author (Country)	ACEI/ARB (Events/Total)	No ACEI/ARB (Events/Total)	Odds ratio (95% CI)
Trubiano, J (Australia)	9/98	99/2837	2.80 (1.37–5.71)
Vangoitsenhoven, M (Belgium)	2/747	3/1589	1.42 (0.24–8.51)
Jantzen, R (Canada)	5/145	36/504	0.46 (0.18–1.21)
Yan, H (China)	55/8095	523/41150	0.53 (0.40–0.70)
Zhou, H (China)	17/54	26/88	1.10 (0.53–2.28)
Reilev, M (Denmark)	1589/57223	9533/364596	1.06 (1.01–1.12)
Bar, S (France)	13/34	18/66	1.65 (0.69–3.97)
Blanc, F (France)	38/66	51/113	1.65 (0.89–3.05)
Dauchet, L (France)	62/79	125/209	2.45 (1.34–4.48)
Desbois, A-C (France)	6/45	20/154	1.03 (0.39–2.75)
Georges, J-L (France)	148/215	286/469	1.41 (1.00–1.99)
Khider, L (France)	21/30	45/66	1.09 (0.43–2.78)
Kibler, M (France)	12/335	10/367	1.33 (0.57–3.11)
Lairez, O (France)	11/16	20/31	1.21 (0.33–4.39)
Wernhart, S (Germany)	2/17	3/63	2.67 (0.41–17.42)
Chodick, G (Israel)	132/991	1185/13529	1.60 (1.32–1.94)
Fasano, A (Italy)	28/326	77/1160	1.32 (0.84–2.07)
Gnavi, R (Italy, circulatory/diabetes)	93/568	78/458	0.95 (0.69–1.33)
Gnavi, R (Italy, hypertension cohort)	215/1369	101/527	0.79 (0.61–1.02)
Langer, T (Italy)	40/57	84/142	1.62 (0.84–3.14)
Maddaloni, E (Italy)	33/137	46/100	0.37 (0.21–0.65)
Mancia, G (Italy)	2896/15375	3376/21656	1.26 (1.19–1.33)
Miyake, S (Japan)	2/222	14/561	0.36 (0.08–1.58)
Jeon, H-L (South Korea)	992/42990	6085/187575	0.70 (0.66–0.75)
Amat-Santos, IJ (Spain)	5/50	6/52	0.85 (0.24–2.99)
Arenas, MD (Spain)	8/16	26/45	0.73 (0.23–2.30)
Lopez-Otero, D (Spain)	210/72527	755/375452	1.44 (1.24–1.68)
Martín-Sánchez, FJ (Spain)	387/513	803/1480	2.59 (2.07–3.24)
Morales, DR (Spain)	627/45239	250/19007	1.05 (0.91–1.22)
Vila-Corcoles, A (Spain)	110/23873	95/11063	0.53 (0.41–0.70)
Alkurt, G (Turkey)	8/35	111/897	2.10 (0.93–4.73)
Abu-Jamous, B (UK)	11/21	259/500	1.02 (0.43–2.45)
Haroon, S (UK)	148/31194	126/27500	1.04 (0.82–1.31)
Hippisley-Cox, J (UK)	4281/954458	15205/7321491	2.17 (2.09–2.24)
Kempegowda, P (UK)	6/7	14/44	12.86 (1.41–117.2)
McGurnaghan, SJ (UK)	1158/172266	1025/147086	0.96 (0.89–1.05)
McKeigue, P (UK)	745/12585	1633/23806	0.85 (0.78–0.93)
Raisi-Estabragh, Z (UK)	314/1535	1125/5564	1.01 (0.88–1.17)
Rezel-Potts, E (UK)	2712/13596	14154/73407	1.04 (1.00–1.09)
Ullah, AZMD (UK)	54/3412	158/12174	1.22 (0.90–1.67)
Caraballo, C (USA)	64/366	142/534	0.59 (0.42–0.81)
Chang, TS (USA)	65/1828	778/22805	1.04 (0.81–1.35)
Colon, C (USA)	56/85	144/215	0.95 (0.56–1.62)
Dublin, S (USA)	204/56105	622/265939	1.56 (1.33–1.82)
Gubatan, J (USA)	3/23	2/145	10.73 (1.69–68.17)
Mehta, N (USA)	212/2285	1523/16187	0.98 (0.85–1.15)
Morales, DR (USA,)	59/10286	58/11008	1.09 (0.76–1.57)
Rentsch, CT (USA)	255/1532	330/2257	1.17 (0.98–1.39)
Reynolds, HR (USA)	1374/2319	4520/10275	1.85 (1.69–2.03)
Shah, SJ (USA)	6/49	27/267	1.24 (0.48–3.18)
Random-effects model	**19503/1535439**	**65735/8987210**	**1.14 (1.00–1.31)**

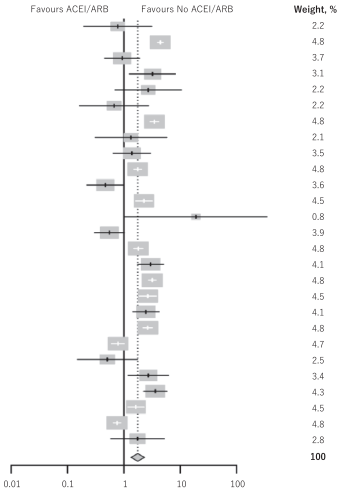
(Q = 1770.63; df = 49; P = 0; I^2 = 97.2%)



(B) Hospitalization (COVID-19 patients)

First Author (Country)	ACEI/ARB (Events/Total)	No ACEI/ARB (Events/Total)	Odds ratio (95% CI)
Mazzoleni, L (Belgium)	7/12	18/28	0.78 (0.19–3.10)
Reilev, M (Denmark)	727/1589	1527/9533	4.42 (3.95–4.95)
Caillard, S (France)	97/112	146/167	0.93 (0.46–1.89)
Dauchet, L (France)	56/62	93/125	3.21 (1.26–8.16)
Alberici, F (Italy)	11/14	46/80	2.71 (0.70–10.47)
Felice, C (Italy)	75/82	48/51	0.67 (0.17–2.72)
Giorgi Rossi, P (Italy)	501/818	574/1835	3.47 (2.92–4.12)
Becchetti, C (Multiple)	10/13	30/42	1.33 (0.31–5.70)
Garassino, M (Multiple)	44/55	104/140	1.38 (0.65–2.97)
Jung, S (South Korea)	377/762	1577/4417	1.76 (1.51–2.06)
Golpe, R (Spain)	48/121	21/36	0.47 (0.22–1.00)
Lopez-Otero, D (Spain)	78/210	156/755	2.27 (1.63–3.16)
Ochoa-Callejero, L (Spain)	9/9	24/48	19.00 (1.05–344.77)
Kolin, DA (UK)	58/74	516/595	0.56 (0.30–1.01)
McGurnaghan, SJ (UK)	858/1158	629/1025	1.80 (1.50–2.16)
Chang, TS (USA)	27/65	150/778	2.97 (1.76–5.03)
Dashti, H (USA)	586/1104	795/3036	3.19 (2.76–3.68)
Dublin, S (USA)	85/204	132/622	2.65 (1.89–3.72)
Ebinger, JE (USA)	48/72	166/370	2.46 (1.45–4.18)
Jehi, Lb (USA)	244/653	714/3883	2.65 (2.22–3.16)
Khera, R (USA)	170/1453	117/810	0.78 (0.61–1.01)
Lubetzky, M (USA)	12/19	27/35	0.51 (0.15–1.72)
Nakamichi, K (USA)	12/37	23/153	2.71 (1.20–6.15)
Nguyen, AB (USA)	99/127	194/392	3.61 (2.27–5.74)
Rentsch, CT (USA)	147/255	150/330	1.63 (1.17–2.27)
Schneeweiss, MC (USA)	447/16055	317/8653	0.75 (0.65–0.87)
Wang, B (USA)	18/26	18/32	1.75 (0.59–5.19)
Random-effects model	**4851/25161**	**8312/37971**	**1.76 (1.34–2.32)**

(Q = 553.71; df = 26; P < 0.0001; I^2 = 95.3%)



(C) Hospitalization length, days (COVID-19 patients)

First Author (Country)	ACEI/ARB Total	ACEI/ARB Mean (SD)	No ACEI/ARB Total	No ACEI/ARB Mean (SD)	MD (95% CI)
Chen, Y (China)	32	23.67 (14.36)	39	24.00 (13.85)	-0.33 (-6.94; 6.27)
Cui, H (China)	14	19.20 (6.10)	13	16.90 (7.90)	2.30 (-3.05; 7.65)
Hu, J (China)	64	20.42 (9.67)	84	20.50 (9.43)	-0.08 (-3.19; 3.03)
Wang, Wenjun (China)	22	27.41 (6.43)	45	30.07 (8.92)	-2.66 (-6.40; 1.08)
Xie, Y (China)	8	24.80 (6.60)	69	25.50 (8.40)	-0.70 (-5.68; 4.28)
Xu, J (China)	29	12.33 (4.68)	40	11.17 (5.78)	1.17 (-1.30; 3.64)
Yang, G (China)	27	25.60 (9.50)	116	28.52 (8.77)	-2.92 (-6.85; 1.00)
García-Menaya, JM (Spain)	37	15.66 (12.63)	76	11.36 (8.17)	4.30 (-0.16; 8.76)
Richardson, S (USA)	283	4.21 (3.04)	699	4.90 (3.34)	-0.69 (-1.12; -0.25)
Random-effects model	**516**		**1181**		**-0.27 (-1.36; 0.82)**

(Q = 10.50; df = 8; P = 0.2318; I^2 = 23.8%)

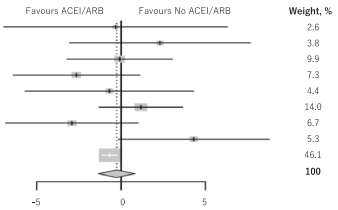


FIGURE 2 Forest plots for associations between COVID-19 outcomes and being on an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB)

(D) Severity (COVID-19 patients)

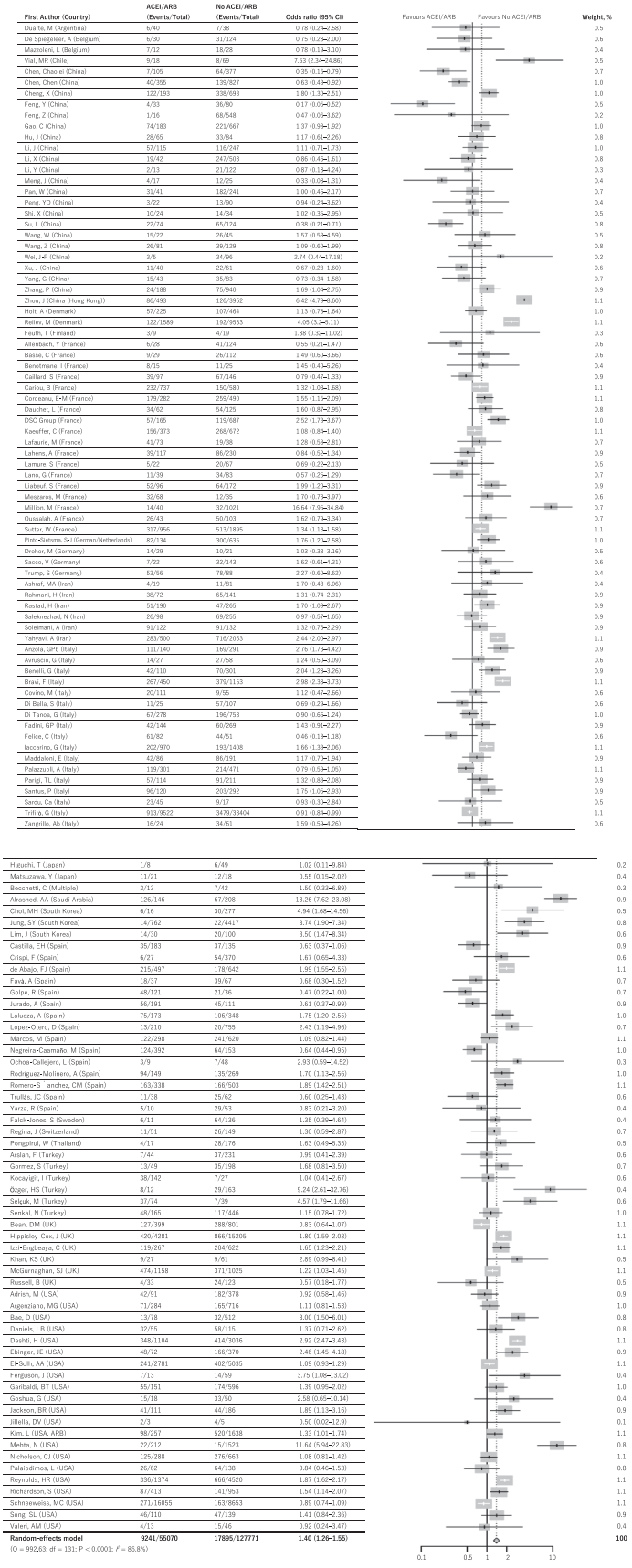


FIGURE 2 (Continued)

(E) Mortality (COVID-19 patients)

First Author (Country)	ACEI/ARB (Events/Total)	No ACEI/ARB (Events/Total)	Odds ratio (95% CI)	Weight, %
Duarte, M (Argentina)	2/40	2/38	0.95 (0.13–7.09)	0.2
Catteau, L (Belgium)	540/2174	1388/6733	1.27 (1.14–1.43)	1.4
Mazzoleni, L (Belgium)	2/12	9/28	0.42 (0.08–2.34)	0.2
Chen, Chaolei (China)	5/105	53/377	0.31 (0.12–0.79)	0.5
Chen, Chen (China)	12/355	95/827	0.27 (0.15–0.50)	0.8
Gao, C (China)	4/183	30/667	0.47 (0.17–1.36)	0.5
Guo, T (China)	7/19	36/168	2.14 (0.79–6.83)	0.5
Hu, J (China)	1/65	0/84	3.93 (0.16–98.07)	0.1
Li, J (China)	21/115	56/247	0.76 (0.44–1.33)	0.9
Pan, W (China)	4/41	63/241	0.31 (0.10–0.89)	0.5
Peng, YD (China)	4/22	13/90	1.32 (0.38–4.51)	0.4
Shi, X (China)	0/24	1/34	0.46 (0.02–11.67)	0.1
Su, L (China)	6/74	16/124	0.60 (0.22–1.60)	0.5
Wang, Z (China)	7/81	5/129	2.35 (0.72–7.66)	0.4
Xu, J (China)	11/40	21/61	0.72 (0.30–1.73)	0.6
Yang, G (China)	2/43	11/83	0.32 (0.07–1.51)	0.3
Zhou, F (China)	70/906	272/1812	0.47 (0.36–0.62)	1.2
Reiley, M (Denmark)	198/1589	379/9533	3.44 (2.87–4.12)	1.3
Caillard, S (France)	17/97	26/146	0.98 (0.50–1.92)	0.8
Cariou, B (France)	92/737	48/580	1.58 (1.09–2.28)	1.1
Cordeanu, E-M (France)	82/282	91/490	1.80 (1.28–2.53)	1.2
Lafaurie, M (France)	9/73	7/38	0.62 (0.21–1.83)	0.4
Laheris, A (France)	20/117	27/230	1.55 (0.83–2.90)	0.8
Lamure, S (France)	10/22	20/67	1.96 (0.73–5.26)	0.5
Liabeuf, S (France)	17/96	30/172	1.02 (0.53–1.96)	0.8
Meszaros, M (France)	15/68	3/35	3.02 (0.81–11.24)	0.3
Oussalah, A (France)	10/43	9/104	3.20 (1.20–8.55)	0.5
Tanaka, S (France)	7/16	9/32	1.99 (0.57–6.96)	0.4
Vrillon, A (France)	6/19	16/57	1.18 (0.38–3.65)	0.4
Daher, A (Germany)	8/34	5/23	1.11 (0.31–3.94)	0.4
Roth, D (Germany)	8/60	8/63	1.06 (0.37–3.02)	0.5
Alamdari, NM (Iran)	13/134	50/325	0.59 (0.31–1.13)	0.8
Ashraf, MA (Iran)	2/19	10/81	0.84 (0.17–4.17)	0.2
Mirsoleymani, S (Iran)	4/23	15/82	0.94 (0.29–3.17)	0.4
Rastad, H (Iran)	38/190	41/265	1.37 (0.84–2.22)	1.0
Soleimani, A (Iran)	33/122	35/132	1.03 (0.59–1.79)	0.9
Yahyavi, A (Iran)	113/500	365/2053	1.35 (1.06–1.71)	1.3
Anzola, GP (Italy)	29/139	22/82	0.72 (0.38–1.36)	0.8
Benelli, G (Italy)	25/110	47/301	1.59 (0.92–2.74)	0.9
Braude, P (Italy/UK)	106/392	257/979	1.04 (0.80–1.36)	1.2
Cannata, F (Italy)	39/173	39/224	1.38 (0.84–2.27)	1.0
Conversano, A (Italy)	21/69	21/122	2.10 (1.05–4.22)	0.7
Covino, M (Italy)	38/111	13/55	1.68 (0.81–3.51)	0.7
Desai, A (Italy)	40/154	80/421	1.50 (0.97–2.31)	1.0
Di Castelnuovo, A (Italy)	269/1262	423/2807	1.53 (1.29–1.81)	1.3
Di Gennaro, F (Italy)	1/7	0/7	3.46 (0.12–100.51)	0.1
Di Tanna, G (Italy)	61/278	156/753	1.08 (0.77–1.50)	1.2
Felice, C (Italy)	15/82	18/51	0.41 (0.18–0.92)	0.6
Giacomelli, A (Italy)	23/62	25/171	3.44 (1.77–6.71)	0.8
Giorgi Rossi, P (Italy)	108/818	109/1835	2.41 (1.82–3.19)	1.2
Iaccarino, G (Italy)	106/655	82/936	2.01 (1.48–2.73)	1.2
Inciardi, RM (Italy)	9/30	17/69	1.31 (0.51–3.40)	0.5
Palazzuoli, A (Italy)	47/304	71/477	1.05 (0.70–1.56)	1.1
Polverino, F (Italy)	302/951	487/1917	1.37 (1.15–1.62)	1.3
Rossi, R (Italy)	27/63	4/7	0.56 (0.12–2.73)	0.3
Russo, Vb (Italy)	50/170	57/244	1.37 (0.88–2.13)	1.0
Santus, P (Italy)	35/120	69/292	1.33 (0.83–2.14)	1.0
Sardu, Ca (Italy)	7/45	2/17	1.38 (0.26–7.42)	0.2
Trecarichi, E (Italy)	3/16	11/32	0.44 (0.10–1.88)	0.3
Trifirò, G (Italy)	3146/9522	8059/33404	1.55 (1.48–1.63)	1.4
Violi, F (Italy)	19/111	45/208	0.75 (0.41–1.36)	0.9
Zangrillo, Aa (Italy)	5/18	12/55	1.38 (0.41–4.64)	0.4
Matsuzawa, Y (Japan)	2/21	3/18	0.53 (0.09–3.56)	0.2
Ayed, M (Kuwait)	5/10	40/93	1.33 (0.36–4.89)	0.3
Becchetti, C (Multiple)	3/13	3/42	3.90 (0.68–22.32)	0.2
Cravedi, P (Multiple)	13/44	33/100	0.85 (0.39–1.84)	0.7
Garassino, M (Multiple)	17/53	47/135	0.88 (0.45–1.74)	0.8
GeMRC (Multiple)	405/1330	1191/4381	1.17 (1.03–1.34)	1.4
Jung, C (Multiple)	62/157	85/167	0.63 (0.41–0.98)	1.0
Gameiro, J (Portugal)	15/81	20/111	1.03 (0.49–2.17)	0.7
Alrashed, AA (Saudi Arabia)	3/146	2/208	2.16 (0.36–13.1)	0.2
An, C (South Korea)	67/970	161/9267	4.20 (3.13–5.63)	1.2
Hwang, JM (South Korea)	5/13	21/90	2.05 (0.61–6.95)	0.4
Lim, J (South Korea)	14/30	22/100	3.10 (1.31–7.33)	0.6
Amat-Santos, IJ (Spain)	2/5	2/6	1.33 (0.11–15.7)	0.1
Aparisi, A (Spain)	84/266	65/388	2.29 (1.58–3.32)	1.1
Castilla, EH (Spain)	23/183	20/135	0.83 (0.43–1.58)	0.8
Fava, A (Spain)	10/37	18/67	1.01 (0.41–2.49)	0.6
Graziani, D (Spain)	47/550	27/243	0.75 (0.45–1.23)	1.0
Lopez-Otero, D (Spain)	11/210	27/755	1.49 (0.73–3.06)	0.7
López-Zúñiga, MA (Spain)	16/131	31/187	0.70 (0.37–1.34)	0.8
Lorente-Ros, A (Spain)	60/225	80/482	1.83 (1.25–2.67)	1.1
Mostaza, JM (Spain)	65/212	80/192	0.62 (0.41–0.93)	1.1
Muñoz, PJA (Spain)	82/333	89/560	1.73 (1.23–2.42)	1.2
Negreira-Caamaño, M (Spain)	119/392	63/153	0.62 (0.42–0.92)	1.1
Pérez-Sáez, MJ (Spain)	10/26	16/54	1.48 (0.56–3.97)	0.5
Pobladó-Plou, B (Spain)	159/631	612/3781	1.74 (1.43–2.13)	1.3
Rodilla, E (Spain)	1179/4238	1451/7988	1.74 (1.59–1.90)	1.4
Rodriguez-Molinero, A (Spain)	37/149	42/269	1.79 (1.09–2.93)	1.0
Romero-Cristóbal, M (Spain)	38/77	46/137	1.93 (1.09–3.41)	0.9
Ruiz-Antorán, B (Spain)	66/198	54/308	2.35 (1.55–3.57)	1.1
Yarza, R (Spain)	1/10	15/53	0.28 (0.03–2.42)	0.1
Falck-Jones, S (Sweden)	1/11	11/136	1.14 (0.13–9.72)	0.1
Tehrani, S (Sweden)	28/89	42/166	1.36 (0.77–2.39)	0.9
Kocayigit, I (Turkey)	26/142	4/27	1.29 (0.41–4.05)	0.4
Selçuk, M (Turkey)	31/74	4/39	6.31 (2.03–19.58)	0.4
Senkal, N (Turkey)	7/104	5/52	0.68 (0.20–2.25)	0.4
Abu-Jamous, B (UK)	6/19	130/226	0.34 (0.13–0.93)	0.5
Baker, KF (UK)	17/70	63/216	0.78 (0.42–1.45)	0.8
Bean, DM (UK)	106/399	182/801	1.23 (0.93–1.62)	1.2
Chinnadurai, R (UK)	17/54	69/161	0.61 (0.32–1.18)	0.8
Desborough, MJR (UK)	8/20	12/46	1.89 (0.62–5.73)	0.4
Goodall, JW (UK)	104/255	250/726	1.31 (0.98–1.76)	1.2
Khan, KS (UK)	5/27	14/61	0.76 (0.24–2.39)	0.4
Philipose, Z (UK)	55/128	144/338	1.02 (0.67–1.53)	1.1
Razzi-Potts, E (UK)	254/2712	667/14154	2.09 (1.80–2.43)	1.4
Ullah, AZMD (UK)	19/54	35/158	1.91 (0.97–3.74)	0.8
Adrish, M (USA)	32/91	138/378	0.94 (0.58–1.52)	1.0
Bae, D (USA)	1/78	5/512	1.32 (0.15–11.42)	0.1
Bhatti, S (USA)	18/43	27/103	2.03 (0.96–4.28)	0.7
Caraballo, C (USA)	7/58	27/148	0.62 (0.25–1.50)	0.6
Dashti, H (USA)	118/1104	69/3036	5.15 (3.79–6.99)	1.2
Garibaldi, BT (USA)	11/151	102/596	0.38 (0.20–0.73)	0.8
Gayam, V (USA)	12/32	120/375	1.28 (0.60–2.69)	0.7
Gupta, S (USA)	311/766	473/1449	1.41 (1.18–1.69)	1.3
Imam, Z (USA)	105/565	95/740	1.55 (1.15–2.10)	1.2
Ip, A (USA)	137/460	262/669	0.66 (0.51–0.85)	1.3
Jackson, BR (USA)	25/111	26/186	1.79 (0.97–3.29)	0.8
Khera, R (USA)	664/4587	466/3346	1.05 (0.92–1.19)	1.4
Kim, L (USA, ARB)	52/257	266/1638	1.31 (0.94–1.82)	1.2
Lam, K (USA)	58/335	62/279	0.73 (0.49–1.09)	1.1
Mehta, N (USA)	8/211	34/1494	1.69 (0.77–3.71)	0.7
Nguyen, AB (USA)	11/99	19/194	1.15 (0.52–2.53)	0.7
Nicholson, CJ (USA)	67/314	144/726	1.10 (0.79–1.52)	1.2
Palaiodimos, L (USA)	13/62	35/138	0.78 (0.38–1.61)	0.7
Raad, M (USA)	62/361	118/659	0.95 (0.68–1.33)	1.2
Richardson, S (USA)	130/413	254/953	1.26 (0.98–1.63)	1.3
Sweed, O (USA)	76/361	653/1905	0.51 (0.39–0.67)	1.2
Song, SL (USA)	26/110	16/139	2.38 (1.20–4.71)	0.8
Valeri, AM (USA)	3/13	15/46	0.62 (0.15–2.59)	0.3
Wang, B (USA)	9/26	5/32	2.86 (0.82–9.98)	0.4
Random-effects model	**11191/49709**	**22820/139235**	**1.22 (1.12–1.33)**	**100**

(Q = 780.99; df = 130; P < 0.0001; I^2 = 83.4%)

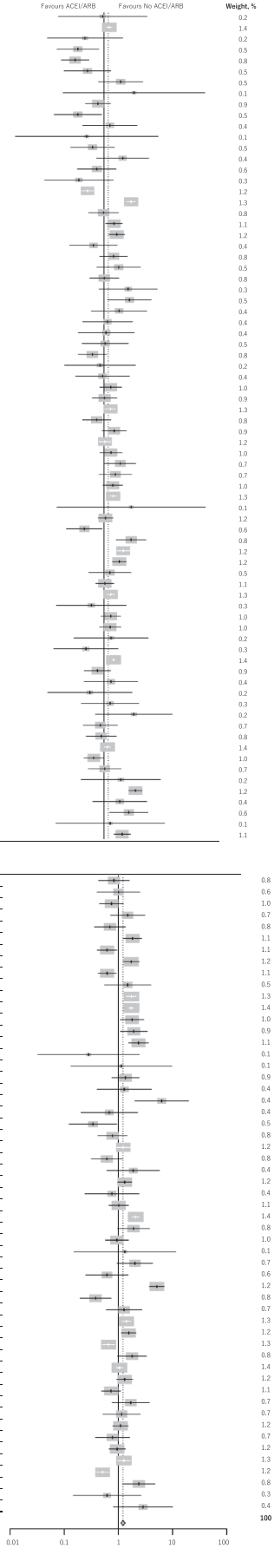


FIGURE 2 (Continued)

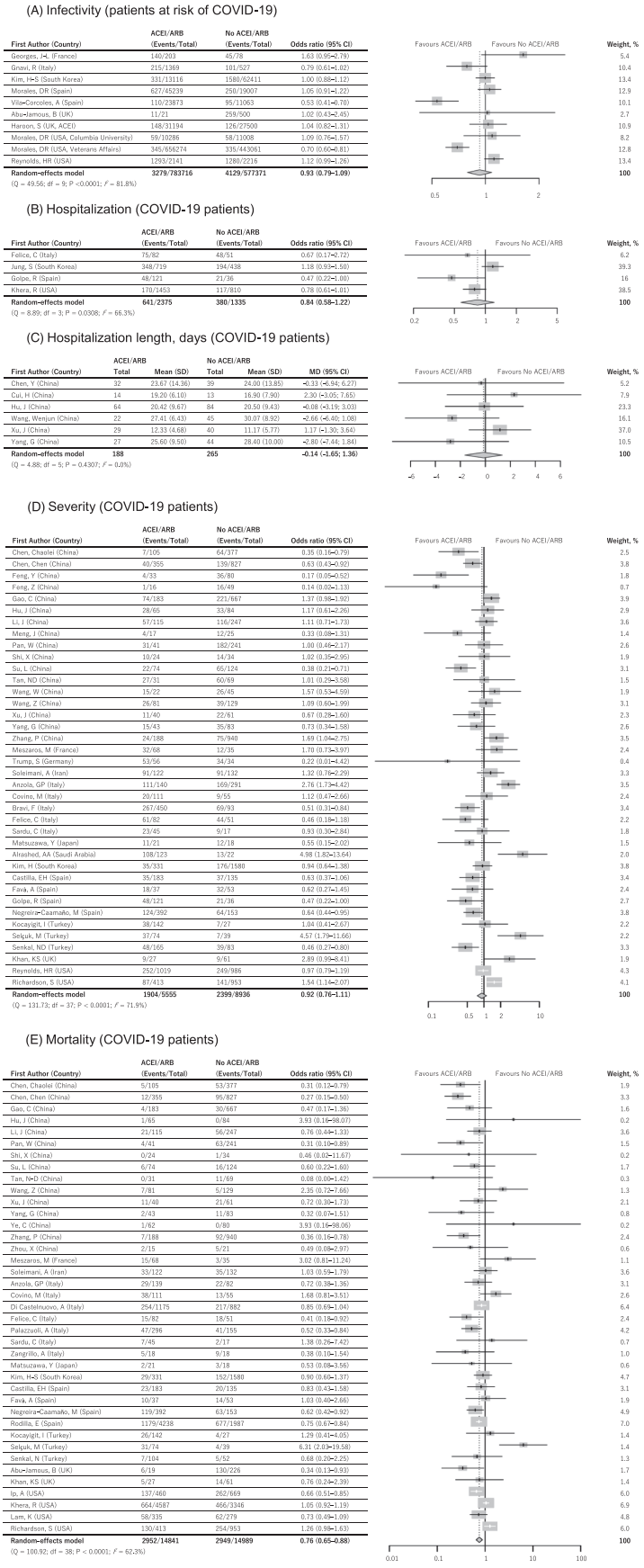


FIGURE 3 Forest plots for associations between COVID-19 outcomes and being on an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB)—only hypertensive patients included

the inclusion of studies with overlapping data. The primary meta-analysis (48 studies, 10 522 649 participants) revealed that ACEIs/ARBs had borderline association with confirmed COVID-19 infection (pooled unadjusted OR 1.14, 95% CI 1.00–1.31, $I^2 = 97\%$, Figure 2). The linear regression test of funnel plot asymmetry (Egger's test, $P = .18$) was not significant (funnel plot in Figure S1). The pooled estimate was no longer statistically significant when analysis was restricted to only hypertensive patients ($n = 9$ studies, OR 0.93, 95% CI 0.79–1.09, $I^2 = 82\%$, Figure 3). Sixteen studies reported adjusted or propensity score-weighted odds ratios (pooled adjusted OR 0.92, 95% CI 0.71–1.19, $I^2 = 85\%$), six studies reported adjusted hazards ratios (pooled adjusted HR 0.88, 95% CI 0.75–1.04, $I^2 = 76\%$) while adjusted risk ratios were obtained from seven studies (pooled adjusted RR 0.99, 95% CI 0.86–1.14, $I^2 = 76\%$) (Figure S1). Except for diuretics (unadjusted estimates), none of the other cardiovascular drug exposures (including ACEIs and ARBs assessed separately) were associated with susceptibility to infection as detailed in Table 1.

3.2.2 | Hospitalization (COVID-19 patients)

Thirty-one studies explored the association between being hospitalized and being on ACEIs/ARBs (Figure S10). When four studies were excluded to reduce potentially overlapping data, ACEIs/ARBs were associated with higher odds of hospitalization (pooled unadjusted OR 1.76, 95% CI 1.34–2.32, $I^2 = 95\%$, Figure 2) in a total of 63 132 patients. Egger's test was not significant (P-value $= .26$). Four studies included only hypertensive patients and for these, the pooled estimate lost statistical significance (0.84, 95% CI 0.58–1.22, $I^2 = 66\%$, Figure 3). The pooled adjusted odds ratio (11 studies) was not statistically significant at 0.93 (95% CI 0.70–1.24, $I^2 = 62\%$), a result which was similar to the pooled adjusted hazards ratio (1.08, 95% CI 0.90–1.28, $I^2 = 63\%$, four studies). Other cardiovascular drugs were also associated with higher odds of hospitalization in unadjusted, but not adjusted, estimates (Table 1).

3.2.3 | Hospitalization length (COVID-19 patients)

Twenty-seven studies reported length of hospitalization (Figure S17). Eighteen studies were excluded from the primary analysis because some had potentially overlapping data while others included patients who were deceased/still admitted. For the nine included studies (1697 patients), ACEIs/ARBs were not significantly associated with longer hospitalization length (mean difference −0.27, 95% CI −1.36; 0.82 days, $I^2 = 24\%$, Figure 2). When six studies that included only hypertensive patients were pooled, the result was similar (mean difference −0.14, 95% CI −1.65; 1.36 days, $I^2 = 0\%$, Figure 3). This outcome was also assessed for anticoagulant drug exposure, with unadjusted estimates being statistically non-significant (Table 1).

3.2.4 | Severity (COVID-19 patients)

One hundred and sixty-five studies reported the association between ACEIs/ARBs and severity outcomes (Figure S19). Thirty-three studies were excluded due to having potentially overlapping data which resulted in a primary meta-analysis of 132 studies (182 841 patients) in which ACEIs/ARBs were associated with higher odds of severe disease (pooled OR 1.40, 95% CI 1.26–1.55, $I^2 = 87\%$, Figure 2). Publication bias assessment revealed funnel plot symmetry (Egger's test $P = .69$, Figure S19). Sub-group analysis based on use in hypertension (38 studies) produced pooled estimates that were no longer statistically significant (OR 0.92, 95% CI 0.76–1.11, $I^2 = 72\%$, Figure 3). Adjusted odds ratios were obtained from 54 studies (pooled adjusted OR 1.05, 95% CI 0.81–1.38, $I^2 = 85\%$), hazard ratios were obtained from 14 studies (pooled adjusted HR 0.84, 95% CI 0.65–1.10, $I^2 = 75\%$) while risk ratios were obtained from eight studies (pooled adjusted RR 1.53, 95% CI 0.54–4.31, $I^2 = 97\%$) (Figure S19). Other cardiovascular drugs were associated with higher odds of severe disease in the unadjusted estimates, with statistical significance being lost when subgroup analyses or adjusted estimates were considered (Table 1).

3.2.5 | All-cause mortality (COVID-19 patients)

One hundred and sixty-three studies reported the association between ACEI/ARB exposure and all-cause mortality (Figure S28). Because some studies had potentially overlapping datasets, only 131 (188 941 patients) were included in the primary meta-analysis with ACEIs/ARBs being associated with higher odds of all-cause mortality (pooled OR 1.22, 95% CI 1.12–1.33, $I^2 = 83\%$, Figure 2). Egger's test was statistically significant ($P < .10$, funnel plot in Figure S28). The trim and fill random effects analysis method, however, showed that missing trials neither changed the direction of the pooled effect estimate nor affected its statistical significance (Figure S28). When analysis was restricted to only hypertensive patients (39 studies), ACEI/ARB exposure became protective (pooled OR 0.76, 95% CI 0.65–0.88, $I^2 = 62\%$, Figure 3). The pooled adjusted odds ratio (48 studies) was 0.84 (95% CI 0.70–1.00, $I^2 = 66\%$), pooled adjusted hazards ratio (27 studies) was 0.76 (95% CI 0.61–0.95, $I^2 = 78\%$) while the pooled adjusted risk ratio (10 studies) was 0.71 (95% CI 0.46–1.09, $I^2 = 68\%$). Other cardiovascular drugs were associated with higher odds of all-cause mortality in the unadjusted estimates but this was lost when only hypertensive patients were considered (Table 1). Except for diuretics, statistical significance was lost for other cardiovascular drugs when adjusted ORs were pooled. When adjusted hazards ratios were considered, only beta-blockers remained associated with higher odds of all-cause mortality. On the other hand, ACEIs, antiplatelets, calcium channel blockers and diuretics were not associated with all-cause mortality while ARBs, anticoagulants and lipid-modifying drugs decreased the odds of dying. Lastly, statistical significance was lost for other drug classes except for anticoagulants when adjusted risk ratios were pooled (Table 1).

4 | DISCUSSION

We have conducted a systematic review and meta-analysis to evaluate the current evidence on the influence of cardiovascular drugs on five COVID-19 clinical outcomes. The most reported drug classes were angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) with ACEI/ARB exposure having borderline association with confirmed COVID-19 infection, which is similar to a previous estimate by Xu et al. (1.13, 95% CI 1.05–1.22, $n = 23$ studies).[25] Among COVID-19 patients, ACEI/ARB exposure was associated with hospitalization, disease severity, and all-cause mortality but not hospitalization length. Xu et al.[25] reported similar results for hospitalization length (mean difference −0.04 days, 95% CI −0.19–0.11, $n = 11$ studies) and disease severity (OR 1.28, 95% CI 1.06–1.54, $n = 58$ studies) but not mortality (OR 1.06, 95% CI 0.85–1.31). Our study, which included 131 studies for the mortality outcome, is, however, more comprehensive than Xu et al.'s which included only 44 studies for the same outcome. With a higher rate of hospitalization and more severe disease, one would expect longer hospital stay, which makes our results seem counterintuitive. However, the hospitalization length outcome excluded patients who died or those who were still hospitalized at the time of analysis, which may have contributed to the observed discrepancy. A reason such patients were excluded in the primary analysis is that shorter hospitalization length is a desirable outcome if a patient is discharged but a shorter hospitalization length that results in death is not. Nevertheless, an analysis that included studies with patients who were deceased/still admitted produced a similar result (mean difference −0.31 days, 95% CI −0.56 to 1.17, $n = 27$ studies). It is also important to note that these results are from pooling unadjusted estimates, which did not account for confounding factors such as cardiovascular comorbidities. For instance, because hypertension might necessitate ACEI/ARB use, and hypertension contributes to poor COVID-19 clinical outcomes, estimates that do not adjust for hypertension might be spuriously elevated as seen above (an example of "confounding by indication"). Indeed, when subgroup analyses that included only hypertensive patients were conducted, ACEI/ARB exposure was no longer associated with susceptibility to infection, hospitalization or disease severity while it decreased the odds of dying. Lastly, co-interventions such as steroids and remdesivir that could influence these results have not been accounted for since studies rarely reported these co-interventions and stratified them by cardiovascular drug exposure in our preliminary results.[15]

We also reported pooled adjusted estimates in which ACEI/ARB exposure was not associated with confirmed COVID-19 infection, hospitalization and disease severity. Xu et al.[25] explored two of these outcomes (susceptibility to COVID-19 and disease severity) and reported similar results. For all-cause mortality, ACEI/ARB exposure was protective based on the adjusted hazards ratios but not with odds or risk ratios (Xu et al.[25] reported lack of association based on the adjusted odds and hazard ratios but their estimates were again based on fewer studies). It is important to note that although pooling adjusted estimates can protect against the effect of confounders present in unadjusted estimates, these pooled adjusted estimates should still be cautiously interpreted since many studies did not include adjustment for important confounders, and odds/hazard/risk ratios that adjust for different sets of covariates may not be comparable.[18] Further, adjusted odds/hazards ratios are expected to be further from zero (the "non-collapsibility" of effect estimates).[26]

Regarding other cardiovascular drug classes, this is the first review to be broad in this context (most previous reviews have focused solely on ACEIs/ARBs) with most other drugs not being associated with poor COVID-19 clinical outcomes in the pooled adjusted estimates. One key result is that anticoagulants and lipid-modifying drugs appear to protect against all-cause mortality based on the adjusted hazards ratios, similar to previous reports.[27,28] However, the number of included studies (eight and seven respectively) was small and the adjusted odds/risk ratios were not statistically significant. The potential mechanisms in which cardiovascular drugs can influence COVID-19 outcomes have been discussed previously.[6,7,9–11]

4.1 | Limitations of this review

For most of the meta-analyses, heterogeneity in effect estimates was high, which is similar to previous observations.[25,29,30] Consequently, following GRADE rating,[21] all estimates with high heterogeneity ($I^2 > 70$) were downgraded by one level (high to moderate certainty rating). Additionally, almost all estimates received quality ratings of either 3 or 4 for including mostly observational studies, which we previously ranked to be at a serious risk of bias.[15] Again following GRADE[21] recommendations, the evidence certainty rating was downgraded by one level for estimates with a serious risk of bias (from high to moderate or from moderate to low). Based on this level of rating, we need to be cautious of over-interpreting both these positive and negative findings. Despite our comprehensive search strategy and to facilitate timely publication, we did not contact study authors to include potentially eligible studies. We also included several preprint publications that have not been certified by peer review. This we felt necessary since many COVID-19 studies are being first published as preprints. We tried to exclude potentially overlapping data; however, we may have missed some overlapping data or inadvertently excluded non-overlapping data. We also relied on single-reviewer extraction for 80% of the studies, which could introduce bias from simple errors. The overall low contributions/assigned weights of the individual studies make the reported estimates robust to these errors. Additionally, consistency was observed in the 20% of records that were independently extracted by a second reviewer, with the first reviewer not missing out on key studies or crucial information (specifically the quantitative data used in the meta-analyses and the information important to assessing the overall rating of individual studies). Lastly, we could not explore the interplay of the various cardiovascular drugs because of the insufficient quality of included studies. Once more high-quality studies become available (in particular randomized controlled studies, RCTs), we will compare how the different drug classes perform in combination and against each other. Indeed, in our

next update, to be conducted within 6 months of the publication of this review, we will focus on RCTs. The COVID-19 situation is extremely dynamic, and it is not possible to tell when we will be transitioning out of the living systematic review mode. Nevertheless, updating for up to 2 years is currently planned.

4.2 | Conclusions

Low- to moderate-certainty evidence suggests that cardiovascular drugs are not associated with poor COVID-19 clinical outcomes in high-risk patients such as those with hypertension. For ACEIs/ARBs, this is consistent with a recent RCT.[31] High-quality evidence in the form of more RCTs is urgently required and will be the focus of our next systematic review update. As we await further evidence, patients on cardiovascular drugs should continue taking their medications as is recommended worldwide for ACEIs/ARBs.

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CONTRIBUTORS

Concept and design: all authors. Acquisition, analysis or interpretation of data: all authors. Drafting of the manuscript: I.G.A. Critical revision of the manuscript for important intellectual content: S.P., R.M.T., R.K-D., A.J. and M.P. Statistical analysis: I.G.A.

DATA AVAILABILITY STATEMENT

All relevant material is provided in the supplementary material.

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REFERENCES

1. Hui DS, Azhar EI, Madani TA, et al. The continuing 2019-nCoV epidemic threat of novel coronaviruses to global health—The latest 2019 novel coronavirus outbreak in Wuhan, China. *Int J Infect Dis*. 2020;91:264-266.
2. 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(2):271-280.
3. World Health Organisation. WHO Director-General's opening remarks at the media briefing on COVID-19—11 March 2020. World Health Organisation. https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19—11-march-2020. Published 11 March 2020. Accessed 6 June 2020.
4. Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time. *Lancet Infect Dis*. 2020;20(5):533-534.
5. GBD 2017 Causes of Death Collaborators. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet*. 2018;392(10159):1736-1788.
6. Clerkin KJ, Fried JA, Raikhelkar J, et al. COVID-19 and cardiovascular disease. *Circulation*. 2020;141(20):1648-1655.
7. Pranata R, Huang I, Lim MA, Wahjoepramono PEJ, July J. Impact of cerebrovascular and cardiovascular diseases on mortality and severity of COVID-19—systematic review, meta-analysis, and meta-regression. *J Stroke Cerebrovasc Dis*. 2020;29:104949.
8. Mackey K, King VJ, Gurley S, et al. Risks and impact of angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers on SARS-CoV-2 infection in adults: a living systematic review. *Ann Intern Med*. 2020;173(3):195-203.
9. Muthuswamy B. COVID-19: Is it time to revisit the research on calcium channel drug targets? *EMJ Diabet*. 2020:1-3. https://doi.org/10.33590/emjdiabet/200608
10. Rodrigues-Diez RR, Tejera-Muñoz A, Marquez-Exposito L, et al. Statins: could an old friend help in the fight against COVID-19? *Br J Pharmacol*. 2020;177(21):4873-4886.
11. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. *J Thromb Haemost*. 2020;18(5):1094-1099.
12. Asiimwe IG, Pushpakom S, Turner RM, Kolamunnage-Dona R, Jorgensen A, Pirmohamed M. Cardiovascular drugs and COVID-19: a living systematic review and meta-analysis. PROSPERO 2020.
13. Higgins JPT, Green SE. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. https://handbook-5-1.cochrane.org/. Updated March 2011. Accessed 1 Juner 2021.
14. Elliott JH, Synnot A, Turner T, et al. Living systematic review: 1. Introduction—the why, what, when, and how. *J Clin Epidemiol*. 2017;91:23-30.
15. Asiimwe IG, Pushpakom S, Turner RM, Kolamunnage-Dona R, Jorgensen A, Pirmohamed M. Cardiovascular drugs and COVID-19 clinical outcomes: a living systematic review and meta-analysis. *medRxiv preprint*. 2020. https://doi.org/10.1101/2020.10.07.20208918
16. Joint Formulary Committee. *British National Formulary 78 September 2019 – March 2020*. London: BMJ Group and Pharmaceutical Press; 2019.
17. Schwarzer G. meta: an R package for meta-analysis. *R News*. 2007;7(3):40-45.
18. Chang BH, Hoaglin DC. Meta-analysis of odds ratios: current good practices. *Med Care*. 2017;55(4):328-335.
19. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol*. 2014;14(1):135.
20. Viechtbauer W. Conducting meta-analyses in R with the metafor package. *J Stat Softw*. 2010;36(3):1-48.
21. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336(7650):924-926.

22. Alexander SPH, Fabbro D, Kelly E, et al. The Concise Guide to PHARMACOLOGY 2019/20: Enzymes. *Br J Pharmacol*. 2019;176 (Suppl 1):S297-S396.
23. Amat-Santos IJ, Santos-Martinez S, López-Otero D, et al. Ramipril in high risk patients with COVID-19. *J Am Coll Cardiol*. 2020;76(3): 268-276.
24. Duarte M, Pelorosso F, Nicolosi L, et al. Telmisartan for treatment of Covid-19 patients: an open randomized clinical trial. Preliminary report. *medRxiv preprint*. 2020.
25. Xu J, Teng Y, Shang L, et al. The effect of prior ACEI/ARB treatment on COVID-19 susceptibility and outcome: a systematic review and meta-analysis. *Clin Infect Dis*. 2021;72(11):e901-e913.
26. Greenland S, Robins JM, Pearl J. Confounding and collapsibility in causal inference. *Stat Sci*. 1999;14:29-46.
27. Kow CS, Hasan SS. Meta-analysis of effectiveness of statins in patients with severe COVID-19. *Am J Cardiol*. 2020;134:153-155.
28. Kamel AM, Sobhy M, Magdy N, Sabry N, Farid S. Anticoagulation outcomes in hospitalized Covid-19 patients: a systematic review and meta-analysis of case-control and cohort studies. *Rev Med Virol*. 2021;31(3):e2180.
29. Zhang X, Yu J, Pan LY, Jiang HY. ACEI/ARB use and risk of infection or severity or mortality of COVID-19: a systematic review and meta-analysis. *Pharmacol Res*. 2020;158:104927.
30. Diaz-Arocutipa C, Saucedo-Chinchay J, Hernandez AV. Association between ACEIs or ARBs use and clinical outcomes in COVID-19 patients: a systematic review and meta-analysis. *medRxiv*. 2020.
31. Cohen JB, Hanff TC, William P, et al. Continuation versus discontinuation of renin-angiotensin system inhibitors in patients admitted to hospital with COVID-19: a prospective, randomised, open-label trial. *Lancet Respir Med*. 2021;9(3):275-284.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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