

Angiotensin Converting Enzyme Inhibitors and Angiotensin Receptor Blockers and The Risk of SARS-CoV-2 Infection: A Systematic Review and Meta-analysis

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Abstract

Importance:

SARS-CoV-2 virus gains access and infects target cells via angiotensin converting enzyme 2 (ACE2) receptor. Because angiotensin converting enzyme inhibitors (ACEIs)/angiotensin receptor blockers (ARBs) could increase the expression of ACE2, there are growing concerns that their use could increase the risk of SARS-CoV-2 infection. Cardiac societies have called for epidemiological research about this emerging controversy.

Objective:

We sought to systematically review the literature and perform a meta-analysis about prior use of ACEI/ARBs and risk of SARS-CoV-2 infection.

Data source:

We searched multiple data sources including PubMed , ClinicalTrial.org , and medrxiv.org from November 2019 through May 16, 2020.

Study selection:

Any study that reported on the adjusted association of prior use of ACEIs / ARBs and risk of acquiring SARS-CoV-2 infection was eligible. Two authors independently reviewed eligible studies and extracted data into a prespecified data collection form.

Data synthesis:

An inverse variance meta-analytic approach was used to pool adjusted odds ratios using a random effect model meta-analysis. I^2 test was used to assess in-between studies heterogeneity. The Newcastle–Ottawa quality assessment scale (NOS) was used to assess the quality of included studies.

Main outcome and Measures:

The association between the prior use of ACEIs or ARBs and risk of SARS-CoV-2 infection was assessed using pooled OR and 95% confidence interval.

Results:

Six case control studies that enrolled a total of 5657 patients (2536 patients in ACEIs arm and 3121 patients in ARBs arm) and 721,859 controls were included in our meta-analysis. Two of the included studies were from the USA, one from Italy, one from China, one from Spain, and one from South Korea. All included studies scored high based on NOS scale. Prior use of ACEIs was not significantly associated with an increased risk of SARS-CoV-2 infection, OR 0.93, CI (0.85,1.02), $I^2=20\%$. Similarly, prior use of

ARBs was not significantly associated with an increased risk of SARS-CoV-2 infection, OR 0.86, CI (0.67,1.10), $I^2=93\%$. Sensitivity analysis was performed by removing a study that could have been affected by residual confounding; OR for ARB 1.04, CI (0.96,1.12), $I^2=32\%$.

Conclusion:

Findings from this systematic review and meta-analysis suggest that prior use of ACEIs or ARBs is not associated with a higher risk of COVID-19. Our results are in support of the recent recommendations of cardiac societies and provide a reassurance to the public not to discontinue prescribed ACEIs/ARBs due to fear of COVID-19.

Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is the causative pathogen for COVID-19 pandemic. SARS-CoV-2 belongs to *Betacoronavirus genus* and SARS related coronavirus species¹. The virus is highly contagious, has infected millions of people globally, and is causing devastating outcome with hundreds of thousands of fatalities worldwide.

SARS-CoV-2 gains access and infect the target cells via angiotensin converting enzyme 2 (ACE2) receptor², a membrane-bound protein found on the surface of type 2 pneumocytes, epithelial cells, and enterocytes. Once viral replication starts, damage to host cells is caused by both direct viral cytopathic effect and host immune response resulting in cytokine storm. Treatment with angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptors blockers (ARB) has been shown to increase ACE2 expression by up to 2 to 5 fold⁴⁻⁶. Moreover, the 3D structure studies of SARS-CoV-2 demonstrated that it has a better binding stability than SARS-CoV-1 virus with 10-15 times higher estimated binding affinity to ACE2^{7,8}.

These findings coupled with several observations of the high prevalence and mortality among SARS-CoV-2 infected patients with underlying cardiovascular disease (CVD) have led to a speculation that ACEIs/ARBs may predispose to higher risk of being infected with SARS-CoV-2 and more severe COVID-19 disease given the widespread use of these medications among patients with underlying CVD^{9,10}.

Despite these theoretical concerns, several major cardiac societies have cautioned patients and physicians not to discontinue these drugs in patients already taking these medications,^{11,12} although no epidemiological data were available at that time to support their recommendations. Subsequently, emerging epidemiological studies have not identified a significant association between prior use of ACEIs/ARBs and development of COVID-19. However, studies might have been underpowered to detect such an association. Therefore, we systematically reviewed the literature and performed a meta-analysis of the association between prior use of ACEIs and ARBs and development of COVID-19.

Methods

We searched multiple electronic databases including Pubmed, ClinicalTrial.org, and medrxiv.org using the following terms (“coronavirus” OR “covid-19” OR “SARS” AND “Angiotensin” OR “Angiotensins”) from November 2019 through May 15, 2020. Any clinical study in humans that reported an association between prior use of ACEI and/or ARB and the risk of SARS-CoV-2 infection were eligible for inclusion if it reported an adjusted effect estimate.

We followed Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA)¹³ and Meta-Analysis of Observational Studies in Epidemiology guidelines for reporting systematic review and meta-analysis of observational studies guidelines¹⁴. Two authors independently (AB, HT) extracted the data into a prespecified data collection form. We collected data about study's population and characteristics, exposure to ACEIs and or ARBs, and outcome (development of COVID-19)

The eligible studies were assessed according to the Newcastle–Ottawa quality assessment scale (NOS)¹⁵. NOS scale rates case-controls studies based on 3 parameters: selection of cases and controls, comparability between the cases and controls, and exposure assessment. It assigns a maximum of 4 stars for selection, 2 stars for comparability, and 3 stars for exposure assessment.

Studies with less than 5 stars were considered low quality, 5–7 stars moderate quality, and more than 7 stars high quality. Two reviewers (AN and HT) assessed the quality of the included studies.

Adjusted odds ratios (OR) with corresponding 95% confidence interval from included studies were pooled into a random effects model inverse variance meta-analytic approach. The outcome of interest was the association between prior use of ACEIs and ARBs and risk of infection with SARS-CoV-2. We reported pooled adjusted effect estimates separately for ACEIs and ARBs.

Heterogeneity among the included studies was assessed using χ^2 and I^2 tests. The I^2 statistic describes the proportion of variation in treatment estimate that is not related to sampling error¹⁶. A value of zero indicates no heterogeneity, 25%–49% low, 50%–74% moderate, and 75% a high degree of heterogeneity. No formal assessment of publication bias was performed because of the low number of studies as per Cochrane guidelines.

Two-sided P value of < 0.05 was considered statistically significant for all included analyses. The statistical software Review Manager, version 5.3.5 (The Nordic Cochrane Center, The Cochrane Collaboration, 2018, Copenhagen, Denmark) was used for all analyses.

Results

Six case control studies^{17–23} that enrolled a total of 5657 patients (2536 patients in ACEIs arm and 3121 patients in ARBs arm) and 721,859 controls were included in our meta-analysis. Figure 1 shows the result of our search strategy. Table 1 illustrates the general characteristics of the included studies. Two of the included studies were from the USA, one from Italy, one from China, one from Spain, and one from South Korea. All studies have reported an adjusted OR for ACEIs and ARBs separately. Table 2 shows the

analytical approaches used in each study and its methodological quality. All included studies scored high based on NOS scale.

Prior use of ACEIs was not significantly associated with an increased risk of acquiring SARS-CoV-2 infection, OR 0.93, CI (0.85,1.02) with no significant degree of between studies heterogeneity, $I^2= 20\%$ (Figure 2). Similarly, Prior use of ARBs was not significantly associated with an increased risk of acquiring SARS-CoV-2 infection, OR 0.86, CI (0.67,1.10) with high degree of between studies heterogeneity $I^2=93\%$ (Figure 3). Sensitivity analysis was performed by excluding the study by Yan et al. in an attempt to explain the high degree of heterogeneity. The OR for ARB use in the study by Yan et al. was only adjusted for age, sex and BMI and therefore, could have been affected by residual confounding. Pooling studies without the study by Yan et al. showed that ARBs use was not significantly associated with an increased risk of acquiring SARS-CoV-2 infection, OR 1.04, CI (0.96,1.12) with mild degree of between studies heterogeneity $I^2=32\%$.

Discussion

Findings from our systematic review and meta-analysis suggest that prior use of ACEIs or ARBs is not associated with a higher risk of COVID-19. Our pooled effect estimates are precise with narrow confidence intervals which argues against the possibility of underpowered findings. Our results are in support of the recent recommendations of cardiac societies not to discontinue ACEI or ARB in patients who have indications for their use because of COVID-19 concerns^{11,12}.

The hypothesis that the use of ACEIs or ARBs is associated with a higher risk of COVID-19 emerged based on two facts from multiple previous studies. First, the observations that ACEIs or ARBs upregulate the expression of ACE2. Second, the high prevalence of comorbidities such as hypertension, diabetes, and ischemic heart disease among COVID-19 patients where these drugs are commonly used. However, this hypothesis is an oversimplification of a very complex interaction of multiple signaling pathways involved in SARS-CoV-2 infection and COVID-19 disease.

Several possible explanations can be offered for the possible lack of association between ACE2 expression and the risk of COVID-19. Increased ACE2 protein expression does not necessarily mean increased number of ACE2 molecules on the cell membrane since the ACE2 cell membrane density is determined not only by the gene expression and protein production but also by the rate of ACE2 shedding from the cell membrane. It is well established that ACE2 is cleaved at the cell membrane by the metalloprotease ADAM17 generating soluble ACE2 that is released into the circulation. ADAM17 expression and activity can alter ACE2 shedding and consequently may affect cell membrane ACE2 density²⁴.

Another possible explanation would be that even if ACEIs or ARBs increase the risk of SARS-CoV-2 infection, it is conceivable that many of these cases are mild or asymptomatic and therefore not tested and go undiagnosed. This is due to the fact that ACEIs and ARBs seem to exert protective effect against

severe COVID-19 through modulation of inflammatory and immune responses. ACEIs and ARBs have been shown to influence several signaling pathways involved in inflammation and the regulation of immune responses, which include nuclear factor Kappa-B, mitogen activated protein kinases and Rho/ROCK pathway. These effects result in reduction in inflammatory cytokines, TNF-alpha, IL-1beta and IL-6, inhibition of dendritic cell maturation and Th1 and Th17 cell polarization responses , and suppression of Rho/ROCK pathway²⁵⁻²⁷. Additionally, in one study, losartan inhibited dendritic cell maturation and Th1 and Th17 cell polarization responses²⁶. These inflammatory and immune modulating effects of ACEIs and ARBs may have clinical relevance in the context of COVID-19 disease.

Moreover, ACE2 is a well-known cardioprotective protein as it mediates vasodilatory, anti-fibrotic, immune modulating, anti-inflammatory, and anti-proliferative effects. These effects are realized through conversion of angiotensin-II to angiotensin-(1-7) peptide and angiotensin I to angiotensin-(1-9) peptide which leads to reduction in angiotensin II levels. In addition, angiotensin-(1-7) peptide activates Mas receptor through which it exerts its cardiovascular protective effects²⁸. Interestingly, Angiotensin II is pro-inflammatory and has been shown to play a significant role in the pathogenesis of acute lung injury/adult respiratory distress syndrome (ARDS) in several animal models including SARS-CoV-1. Conversely administration of ARBs and ACE2 were protective in animal model studies ²⁹. It was intriguing that it has been reported recently that COVID-19 patients exhibit high levels of angiotensin II and was associated with higher viral load and lung injury³⁰. Hence, up-regulation of ACE2 expression by ACEIs and ARBs may have lung protective effects against SARS-CoV-2 triggered acute lung injury. In a recent systematic review and meta-analysis, we observed that use of ACEIs/ARBs is associated with a decreased risk of death or critical outcome among SARS-CoV-2 infected patients³¹.

We observed a high degree of heterogeneity for the pooled effect estimate of the ARB use and COVID-19 due to the study by Yan et al. The study by Yan et al. from China reported lower effect estimates as compared to the other identified studies and this could be related to residual confounding or an underlying biological explanation. The OR for ARB use in the study by Yan et al. was only adjusted for age, sex and BMI and therefore, could have been affected by residual confounding. On the other hand, it has been shown in a, Chinese population that rs12692386 G promotor polymorphism was associated with higher ADMA17 expression³².Moreover, several ACE2 polymorphisms have been reported in different populations including the Chinese. These polymorphisms have been shown to be associated with HTN, DM and CVD as well as with ACE2 activity, and serum ACE2 and angiotensin-(1-7) peptide levels³³.It remains to be determined whether increased circulating ACE2 levels are due to increased shedding or due to both increased shedding and expression. Notwithstanding, these differences in regulatory processes of ACE2 may modify membrane ACE2 density and theoretically, could influence susceptibility to SARS-CoV-2 infection. Lastly, SARS-CoV-2 needs not only ACE2 but it is also dependent on the serine protease TMPRSS2 and it has been demonstrated that inhibition of TMRSS2 blocks SARS-CoV-2 cell entry ³⁴. Thus, factors regulating TMRSS2 expression or its enzymatic activity would modulate SARS-CoV-2 infectivity. For example, TMPRSS2 expression is regulated by androgens and has been reported in a recent study that men treated with antiandrogenic therapy were less susceptible to CoV-2 infection³⁵.

Accordingly, population differences in testosterone levels, androgen receptor function and its downstream signaling pathway could affect TMPRSS2 levels and hence susceptibility to SARS-CoV-2 infection.

Our systematic review has several strengths. First, the hypothesis that treatment with ACEI or ARB increases ACE2 expression by several folds and therefore increases the risk of COVID-19 can only be feasibly tested using an observational study design similar to studies included in our meta-analysis. It is not conceivable to randomize patients for years of ACEI or ARB use vs. control groups to see if they are at a higher risk for COVID-19. Second, we included all published studies including pre-prints. Third, we pooled only adjusted effect estimates to decrease the chance of confounding effect. Fourth, the pooled effect estimates were very precise. Nevertheless, inferences from our meta-analysis could be weakened by limitations inherent to the meta-analysis and the individual studies. Given the observational design of included studies and retrospective data collection, the possibility that the observed association between ACEI/ARB use and COVID -19 was affected by bias or confounding should be considered. For example, comorbidities and severity of illness are known confounders that are associated with ACEI/ARB intake and mortality and the healthy user effect could theoretically explain a potential role for ACEI/ARB in infection outcome. However, the opposite could also be the case where the sicker patients have more exposure to ACEI/ARB because patients with hypertension and cardiovascular risk factors have higher risk for COVID. Although we have pooled effect estimates from regression models that adjusted for possible confounders including age, comorbidities and medications—although the models were not uniform—residual confounding cannot be fully excluded. Finally, the presence of publication bias is very unlikely during this pandemic, where to date (May 15,2020) 3477 articles about COVID-19 were published on pre-print servers (2790 medRxiv, 687 bioRxiv).

Despite the recommendations of major cardiac societies advising patients and physicians not to discontinue ACEI or ARB because of fear of COVID-19, recent data from at least one large cohort of 5700 patients with COVID-19 admitted to 12 hospitals in New York between March 1, 2020, and April 4, 2020, have shown otherwise. In this cohort, of the patients who were taking an ACEI or ARB prior to hospitalization, only (48.1%) continued taking an ACEI while in the hospital and (50.1%) continued taking an ARB while in the hospital³⁶.

Conclusions

Findings from this systematic review and meta-analysis suggest that prior use of ACEIs or ARBs is not associated with a higher risk of COVID-19. Our results are in support of the recent recommendations of cardiac societies and provide a reassurance to the public not to discontinue prescribed ACEIs/ARBs due to fear of COVID-19.

Declarations

There is no conflict of interest to declare.

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Tables

Table 1: General characteristics of included studies

ication	Country	Study type	Age	Males (%)	Total cases N	ACEI N (%)	ARB N (%)	Control N	COVID test positivity Adjusted OR (95%CI)
l 2020	USA	Retrospective cohort study	64 years (mean)	58	1735	116(7)	98(6)	18472	ACEI 0.89 (0.72-1.10) ARB 1.09 (0.87-1.37)
tal	USA	Retrospective cohort study	64 years (median)	50.8	5894	627(60.1)	664(58.4)	12594	ACEI 0.92 (0.79, 1.08) ARB 1.00 (0.86, 1.15)
al 2020	Italy	Population based case control study	68 years (mean)	63.3	6272	1502(23.9)	1394(22.2)	30759	ACEI 0.96 (0.87-1.07) ARB 0.95 (0.86-1.05)
020	China	Population based case control study	48.75 (mean)	51.10	610	5(0.82)	53(8.69)	48667	ACEI 0.65(0.26-1.57) ARB 0.24(0.17-0.34)

Abbreviation: ACEI, angiotensin converting enzyme inhibitor, ARB, angiotensin receptor blocker

Table 2: Analytic approaches and result of quality assessment of included studies

Study	Exposure	Cases Selection	Control Selection	Analytical method to calculate adjusted OR	Factors adjusted for	Quality assessment
Mehta et al 2020	ACEI, ARB	Patients who tested positive for COVID-19 by PCR from March 8 to April 12, 2020 within Cleveland Clinic health system	Patients who tested negative for COVID-19 based in the same health system	Propensity score model	Age, Sex, Co-morbid conditions	High Quality
Reynolds et al 2020	ACEI, ARB	Patients who tested positive for COVID-19 by PCR in the New York University (NYU) Langone Health electronic health record from March 1 to April 15, 2020	Patients who tested negative for COVID-19 based in the same health system	Propensity score model	Age; Sex; Race; Ethnic group, Coexisting conditions, and medications	High Quality
Mancia et al 2020	ACEI, ARB	Patients above age of 40 who tested positive for COVID-19 in the Lombardy region in Italy from February 11 to March 11, 2020	Up to five controls were randomly selected from the target population of Lombardy to be matched for sex, age at index date, and municipality of residence.	Conditional logistic-regression models	Drugs and coexisting conditions	High Quality
Yan et al 2020	ACEI, ARB	Patients who tested positive for COVID-19 by PCR in 14 hospitals in Zhejiang province, China from January 10 to February 28, 2020	All adults from the population of Gulin town, a suburban area of Ningbo City, Zhejiang province, China who had electronic medical record	Logistic regression	Age, Sex, BMI	High Quality

Abbreviation: ACEI, angiotensin converting enzyme inhibitor, ARB, angiotensin receptor blocker

Figures

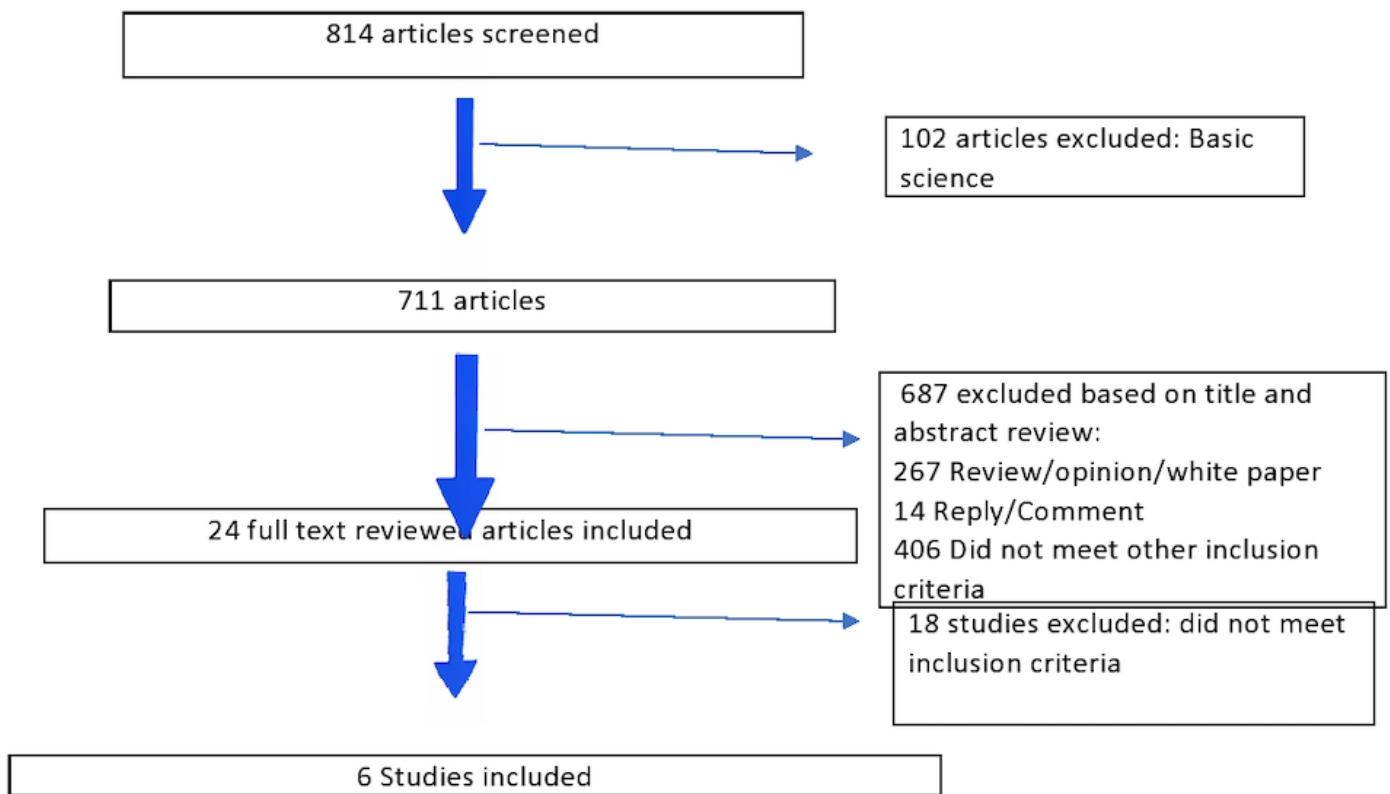


Figure 1

Flow diagram of included studies

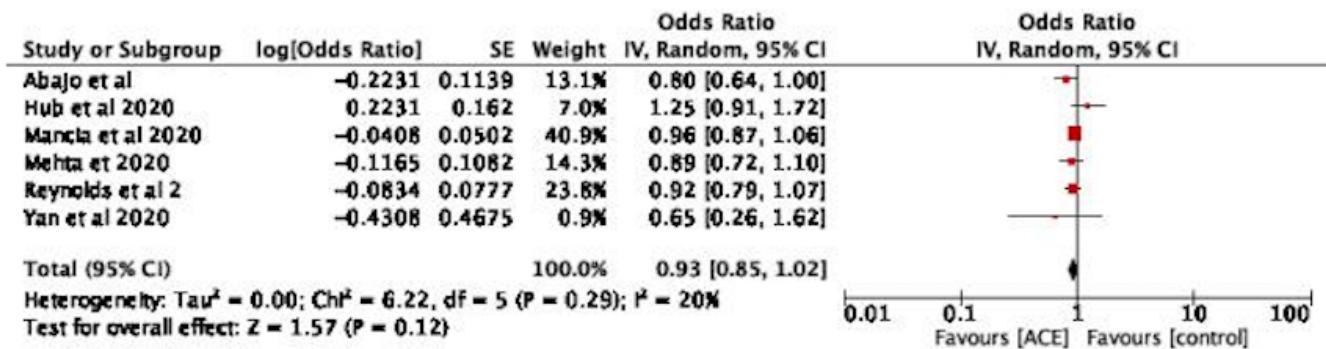


Figure 2

Random effect model meta-analysis of the adjusted pooled effect estimate of the association between ACEIs user and risk of COVID-19

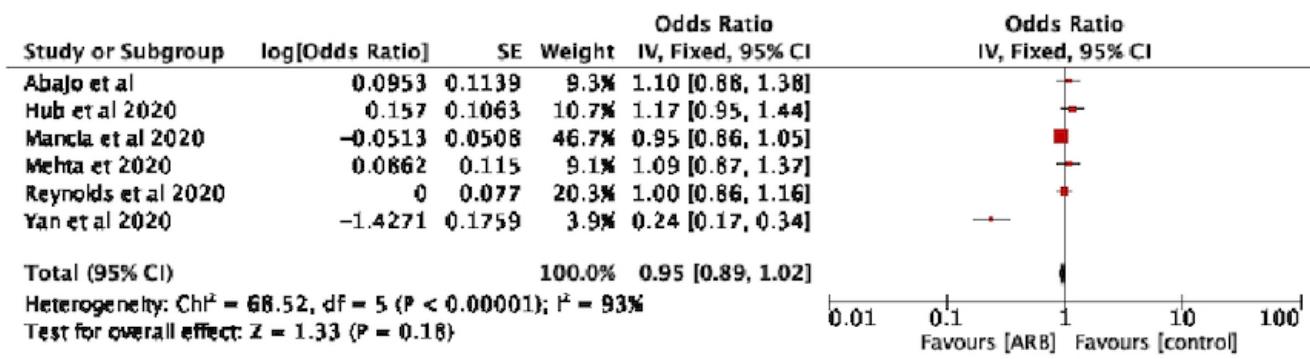


Figure 3

Random effect model meta-analysis of the adjusted pooled effect estimate of the association between ARBs user and risk of COVID-19