NICE National Institute for Health and Care Excellence

Evidence review

Angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) in people with or at risk of COVID-19

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This evidence review sets out the best available evidence on angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) in people with or at risk of COVID-19. It should be read in conjunction with the evidence summary, which gives the key messages.

Evidence review commissioned by NHS England

Disclaimer

The content of this evidence review was up-to-date on 1 April 2020. See summaries of product characteristics (SPCs), British national formulary (BNF) or the MHRA or NICE websites for up-to-date information. For details on the date the searches for evidence were conducted see the search strategy.

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Contents

Background

As of 26 March 2020, the COVID-19 interactive web-based dashboard developed at Johns Hopkins University (Dong et al. 2020) had recorded that over 510,000 people globally have COVID-19. This disease is caused by a novel coronavirus (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]), which emerged in Wuhan, China in December 2019. Other diseases caused by coronaviruses include severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS) and the common cold.

COVID-19 manifests as a respiratory illness of widely varying clinical severity. The most common symptoms are fever and cough (Huang et al. 2020). At its most severe, it results in severe pneumonia needing mechanical ventilation, and can result in death. People with COVID-19 are offered best supportive care, with no established effective medication.

Intervention

ACEIs are a class of medicines used to manage hypertension and heart failure as well as other conditions such as diabetes and kidney disease. ACEIs block the conversion of angiotensin I to angiotensin II. Angiotensin II causes vasoconstriction and fluid retention, resulting in hypertension. By reducing blood pressure and fluid retention, ACEIs help to prevent heart failure. ACEIs include perindopril, ramipril, captopril, enalapril, and lisinopril.

ARBs work by blocking the actions of angiotensin II. They can be used to manage hypertension as an alternative if ACEIs are not tolerated. ARBs are also used to treat other health conditions, including heart failure, chronic kidney disease, and kidney failure in patients with diabetes. ARBs include candesartan, losartan and valsartan

Clinical problem

COVID-19 is a rapidly evolving global pandemic, with countries facing different stages of the spread of disease. Therefore, there is limited published information about the disease course, vulnerable populations and mortality rate. The best available data are currently from China, particularly Wuhan, where the virus first emerged. Data from this region suggest that people aged over 70 and those with comorbidities are most at risk of critical care admission and death. Children and

young people appear to be less affected by the virus, with low numbers of deaths and critical care admissions.

ACE2 is a receptor that is abundant in the epithelial cells of the lung and is integral in the renin-angiotensin pathway. Both ACEIs and ARBs act on the renin-angiotensin pathway and are thought to upregulate ACE2 expression. ACE2 has 2 possible roles in COVID-19:

1. Coronaviruses, including those responsible for MERS, SARS, and COVID-19, bind to ACE2 to gain access to the epithelial cells. Therefore, upregulation of ACE2 could in theory increase a person's risk of developing COVID-19 or developing more severe COVID-19.

2. Upregulation of ACE2 has been shown to be protective in acute respiratory disease and downregulation of ACE2 has been indicated in lung injury.

Both hypotheses above originated from in-vitro and animal studies (Hamming et al 2007, Kuba et al 2005).

ACEIs and ARBs are commonly used to manage hypertension, diabetes, coronary heart disease, and kidney disease. People with these conditions have been identified as high-risk groups for developing COVID-19 (Huang et al 2020). There is also evidence that people with comorbidities have worse outcomes (Zhou et al 2020, Yang et al 2020, Li et al 2020). Correspondence in the Lancet Respiratory Medicine hypothesises that treatment with ACE2-stimulating drugs increases the risk of developing severe and fatal COVID-19 (Fang et al 2020). The authors also explain that the most frequent comorbidities associated with developing more severe COVID-19 (hypertension, type 2 diabetes, and coronary heart disease) are all frequently treated with ACEIs or ARBs. Letters by Esler et al 2020, Diaz 2020 and Roncati et al 2020 express similar views.

A reduction in ACE2 has also been shown to be a factor in more severe disease or acute lung injury in the SARS coronavirus (SARS-CoV) (Kuba et al 2005) and, in contrast to the correspondence above, Gurwitz 2020 and Mei et al 2020 advocate the use of ACEIs and ARBs in the potential management of COVID-19 because of their possible role in preventing lung injury.

A public health report from the Italian Health Service described the characteristics of 3,200 COVID-19 patients dying in Italy up to 20 March 2020. Among people who tested positive for COVID-19 and subsequently died, 36% were taking an ACEI and 16% an ARB before hospitalisation. The authors noted that these figures could be an underestimation because data on medicines use were not always recorded. No comparison was given for rates of prescribing in people who did not die or in the general population.

Objective

The purpose of this review is to assess the best available evidence to determine:

1. If there is any increased risk of developing COVID-19 due to ACEIs or ARBs.
2. If ACEIs or ARBs can lead to an increased risk of developing more severe COVID-19.

Methodology

A description of the relevant Population, Intervention, Comparison and Outcomes (PICO) for this review was provided by NHS England for the topic (see the literature search terms section for more information). The research questions for this evidence review are:

1. In people taking ACEIs or ARBs is there evidence of being at greater risk of developing COVID-19 (or similar coronavirus infection)?
2. Are there any subgroups of people taking ACEIs or ARBs who may be at greater risk of developing COVID-19 (or similar coronavirus infection)?
3. In people with confirmed or suspected COVID-19 (or similar coronavirus infection), is there evidence that taking ACEIs or ARBs is associated with:
    a. More severe COVID-19-related illness/symptoms?
    b. Worsening of the underlying condition (hypertension, heart failure, diabetes mellitus, kidney disease)?
4. Are there any subgroups of people taking ACEIs or ARBs who may be at greater risk of developing:

a. More severe COVID-19?

b. Worsening of the underlying condition (hypertension, heart failure, diabetes mellitus, kidney disease)?

The searches for evidence on ACEIs and ARBs and risk of COVID-19 were undertaken by NICE Guidance Information Services. Results from the literature searches were screened using their titles and abstracts for relevance against the criteria from the PICO. Full text references of potentially relevant evidence were obtained and reviewed to determine whether they met the PICO inclusion criteria for this evidence review. More information can be found in the sections on search strategy and evidence selection.

The NICE evidence summary: process guide (2017) sets out the how the summaries are developed and approved for publication.

Summary of included studies

Two studies identified from the search are included in this evidence summary. One is a retrospective analysis of 112 patients with COVID-19 and pre-existing cardiovascular disease (CVD) who were admitted to a hospital in Wuhan from 20 January 2020 to 15 February 2020 (Peng et al 2020).The other is a retrospective analysis of 3,154 suspected and screened cases of MERS-CoV and 348 confirmed cases from September 2013 to December 2018 (Alburikan et al 2020).

No other evidence was identified that met the PICO criteria.

A summary of the included studies is shown in table 1.

Table 1 Summary of included studies

Study	Population	Intervention	Primary outcome
Peng et al. 2020 retrospective cohort study	112 adults (53% female, median age 62) with confirmed COVID-19 and pre-existing CVD. There were 16 (14.3%) people in the critical group	Not relevant to this study type	Percentage of people taking an ACEI or ARB in the critical group compared with the non-critical group

	and 96 (86.7%) in the non-critical group.		
Alburikan et al. 2020 retrospective cohort study	3,154 (51% male, mean age 40) with suspected MERS-CoV infection. 348 (62% male, mean age 52) with confirmed MERS-CoV (a subgroup of those with suspected MERS-CoV infection).	Not relevant to this study type	Percentage of people taking an ACEI or ARB in the screened group compared with the confirmed group
Abbreviations: COVID-19, coronavirus disease 2019; MERS-CoV, Middle East respiratory syndrome-Coronavirus; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker			

Details of the excluded studies are listed in the section on evidence selection.

Results

Research Q1. In people taking ACEIs or ARBs is there evidence of being at greater risk of developing COVID-19 (or similar coronavirus infection)?

The study by Alburikan et al. found that ACEI or ARB prescribing was not associated with an increase or decrease in the likelihood of contracting MERS-CoV. Baseline characteristics, including medication history, were obtained for 3,154 suspected MERS-CoV cases and compared with 348 confirmed cases. ACEIs or ARBs were prescribed in 16% of suspected cases and 15% of confirmed cases, p=0.40.

Confirmed MERS-CoV infection was independently associated with age (adjusted odds ratio [aOR] 1.06, 95% confidence interval [CI] 1.02 to 1.1, p=0.004), male gender (aOR 1.62, 95% CI 1.37 to 1.77, p< 0.001) and comorbid diabetes (aOR 1.68, 95% CI 1.35 to 1.85, p=0.002).

Research Q3 In people with confirmed or suspected COVID-19 (or similar coronavirus infection), is there evidence that taking ACEIs or ARBs is associated with:

a) More severe COVID-19?

The paper by Peng et al. found no statistically significant difference in the proportion of patients using an ACEI or ARB between people who had critical (defined as requiring mechanical ventilation for respiratory failure or shock, combined with other organ failure that required intensive care unit monitoring and treatment) and non-

critical COVID-19 (3/16 [18.8%] compared with 19/96 [19.8%] respectively, p=1.00). There was also no statistically significant difference in the proportion of ACEI or ARB use between people who were cured (18/95 [19.0%]) and people who died (4/17 [23.5%]) p=0.74.

Comorbid heart failure was significantly higher in the critical group (9/16 [56.3%] compared with the non-critical group 31/96 [32.3%], p=0.06). Median BMI (kg/m2) was significantly higher in the critical group (25.5, inter-quartile range [IQR] 23.0 to 27.5) compared with the non-critical group (22.0, IQR 20.0 to 24.0), p=0.003. Age and comorbid diabetes were not significantly different between the groups and comorbid hypertension was significantly lower in the critical group (10/16 [62.5] compared with 82/96 [85.4%] in the non-critical group, p=0.04).

No evidence was found that addresses research questions 2 or 3b.

Discussion and limitations of the evidence

The studies included in this evidence review are observational studies, which can be subject to bias and confounding and have many limitations affecting their application to clinical practice. Retrospective observational studies are subject to data being recorded accurately, completely and consistently. Observational studies cannot reliably answer the research questions: the results can only be considered hypothesis-generating and cannot support any definitive conclusions.

The study by Alburikan et al. was a large study that addressed the question of whether people taking an ACEI or ARB are more likely to contract a coronavirus. However, the study was carried out in people with suspected and confirmed MERS-CoV and, although the mechanism for cell entry is the same as SARS-CoV-2 (the virus that causes COVID-19), the results may not be generalisable to people at risk of developing COVID-19.

The study by Peng et al. was small and limited to people with cardiovascular disease only. It addressed the question of whether ACEIs and ARBs increased the risk of severe outcomes but did not address the question of whether people taking an ACEI or ARB are more likely to develop COVID-19.It was translated into English using a web-based translator so could include errors.

Because SARS-CoV-2 is a novel virus and new data are emerging every day, the search was expanded to include indirect evidence to inform the background. In addition to the 2 studies presented in the evidence review, this evidence summary also reviews hypotheses presented in letters published on the biological plausibility of the role of ACEIs and ARBs in COVID-19.

The conclusions of these letters were primarily based on data from in-vitro and animal models. Furthermore, the correspondence is conflicting, presenting arguments for both stopping and using ACEIs and ARBs in COVID-19. Some letters also referenced epidemiological data in which the conditions commonly treated with ACEIs and ARBs, for example hypertension, diabetes and coronary heart disease, were shown to be associated with an increased risk of COVID-19 and more severe COVID-19. Such extrapolation is subject to bias and there are many known confounders associated with both ACEI or ARB prescribing and developing COVID-19 or more severe COVID-19 (such as age, diabetes, hypertension, obesity and smoking).

Conclusion

Whilst no increase in risk of developing COVID-19 or more severe disease was found in the 2 observational studies included, the studies were of poor quality and subject to bias and confounding. Therefore, conclusions cannot be drawn on whether ACEIs or ARBs increase the risk of developing COVID-19 or developing more severe COVID-19.

Despite the biological plausibility for both an increased risk of developing COVID-19 and a decreased risk of more severe COVID-19, there was no clear justification of either of these assertions in the indirect evidence above. However, the risks of stopping treatment with ACEIs and ARBs are well understood and include worsening of symptoms and conditions for which they are being used (such as heart failure and hypertension).

References

Alburikan K, and Abuelizz H (2020) Identifying factors and target preventative therapies for Middle East Respiratory Syndrome susciptable patients Saudi Pharm J 28(2): 161-164

Diaz J (2020) Hypothesis: angiotensin-converting enzyme inhibitors and angiotensin receptor blockers may increase the risk of severe COVID-19. J Travel Med doi: 10.1093/jtm/taaa041

Esler M, and Esler D (2020) Can angiotensin receptor-blocking drugs perhaps be harmful in the COVID-19 pandemic? Journal of Hypertension doi: 10.1097/HJH.0000000000002450

Fang L, Karakiulakis G, and Roth M (2020) Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? Lancet Respir Med https://doi.org/10.1016/S2213-2600(20)30116-8

Gurwitz, David (2020) Angiotensin receptor blockers as tentative SARS-CoV-2 therapeutics. Drug development research DOI: 10.1002/ddr.21656

Hamming I, Cooper M, Haagmans B (2007) The emerging role of ACE2 in physiology and disease The Journal of Pathology 212:1

Huang C, Wang Y, Li X et al. (2020) Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 395(10223):497–506

Kuba K, Imai Y, Rao S et al. (2005) A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. Nat Med 11(8):875-9

Li B, Yang J, Zhao F et al. (2020) Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China. Clin Res Cardiol (2020). https://doi.org/10.1007/s00392-020-01626-9

Mei S, Jianmin Y, Yuping S et al. (2020) RAS inhibitors are one of the possible options for treating new coronavirus pneumonia

Peng, Y D, Meng, K, Guan, H Q et al. (2020) Clinical characteristics and outcomes of 112 cardiovascular disease patients infected by 2019-nCoV. Chinese Journal of Cardiovascular Diseases 48(0): e004

Roncati, L, Gallo G, Manenti A et al. (2020) Renin-angiotensin system: the unexpected flaw inside the human immune system revealed by SARS-CoV-2. Medical Hypotheses: 109686

Yang, Jing, Zheng, Ya, Gou, Xi et al. (2020) Prevalence of comorbidities in the novel Wuhan coronavirus (COVID-19) infection: a systematic review and meta-analysis. IJID

Zhang, Jin-Jin, Dong, Xiang, Cao, Yi-Yuan et al. (2020) Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. Allergy

Zhou, Fei, Yu, Ting, Du, Ronghui et al. (2020) Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet

Appendices

Appendix A: Literature search terms

Search strategy	
P – Patients / Population Which patients or populations of patients are we interested in? How can they be best described? Are there subgroups that need to be considered?	1. Relating to research questions 1 and 2: People taking angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs) without Covid-19 or similar coronaviruses 2. Relating to research questions 3 and 4: People taking ACEIs or ARBs with suspected or confirmed Covid-19 or a similar coronavirus. Subgroups: • Over 70 years • Immunocompromised • Underlying conditions (hypertension, diabetes mellitus, heart failure and kidney disease) Infective agent (particularly Covid-19 (SARS-CoV-2) and others such as severe acute respiratory syndrome (SARS-CoV-1) and Middle East respiratory syndrome (MERS)).
I – Intervention Which intervention, treatment or approach should be used?	1. ACEIs (including – captopril, enalapril maleate, fosinopril sodium, imidapril hydrochloride, lisinopril, moexipril hydrochloride, perindopril arginine, perindopril erbumine, quinapril, ramipril and trandolapril). 2. ARBs (including – azilsartan medoxomil, candesartan cilexetil, eprosartan, irbesartan, losartan, olmesartan medoxomil, telmisartan and valsartan).
C – Comparison What is/are the main alternative/s to compare with the intervention being considered?	No comparator
O – Outcomes What is really important for the patient? Which outcomes should be considered? Examples include intermediate or short-term outcomes; mortality; morbidity and quality of life; treatment complications; adverse effects; rates of relapse; late morbidity and re-admission	*Critical to decision-making:* • Mortality • Requirement for critical care admission • Requirement for mechanical/non-invasive ventilation • Incidence of Covid-19 (or similar coronaviruses) *Important to decision-making:*

	• Requirement for admission to hospital • Length of stay in critical care • Length of stay in hospital • Duration of Covid-19-related illness/symptoms1 or symptoms related to worsening of the underlying condition • Severity of Covid-19-related illness/symptoms2 or symptoms related to worsening of the underlying condition • Complications of disease
Assumptions / limits applied to search	
Systematic reviews, randomised controlled trials, controlled clinical trials, observational studies including case series. If no higher-level quality evidence is found, case reports can be considered. All ages, 2000-2020	

[1] Covid-19 symptoms and signs include fever, non-productive cough, dyspnoea, myalgia, fatigue, normal or decreased leukocyte counts and radiographic evidence of pneumonia. Severe cases can cause organ dysfunction including shock, acute respiratory distress syndrome (ARDS), acute cardiac injury and acute kidney injury (AKI) leading to death.

Appendix B: Search strategy

Cochrane Central Register of Controlled Trials (CENTRAL)

Cochrane Central Register of Controlled Trials Issue 3 of 12, March 2020

#1 MeSH descriptor: [Coronavirus] explode all trees 11

#2 MeSH descriptor: [Coronavirus Infections] explode all trees 12

#3 ((corona* or corono*) near/1 (virus* or viral* or virinae*)):ti,ab,kw 8

#4 (coronavirus* or coronovirus* or coronavirinae* or Coronavirus* or Coronovirus* or Wuhan* or Hubei* or Huanan or "2019-nCoV" or 2019nCoV or nCoV2019 or "nCoV-2019" or "COVID-19" or COVID19 or "CORVID-19" or CORVID19 or "WN-CoV" or WNCoV or "HCoV-19" or HCoV19 or CoV or "2019 novel*" or Ncov or "n-cov" or "SARS-CoV-2" or "SARSCoV-2" or "SARSCoV2" or "SARS-CoV2" or SARSCov19 or "SARS-Cov19" or "SARSCov-19" or "SARS-Cov-19" or Ncovor or Ncorona* or Ncorono* or NcovWuhan* or NcovHubei* or NcovChina* or NcovChinese*):ti,ab,kw 410

#5 (((respiratory* near/2 (symptom* or disease* or illness* or condition*)) or "seafood market*" or "food market*") near/10 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)):ti,ab,kw 30

#6 ((outbreak* or wildlife* or pandemic* or epidemic*) near/1 (China* or Chinese* or Huanan*)):ti,ab,kw 1

#7 MeSH descriptor: [Middle East Respiratory Syndrome Coronavirus] explode all trees 1

#8 ("middle east respiratory syndrome*" or "middle eastern respiratory syndrome*" or MERSCoV or "MERS-CoV" or MERS):ti,ab,kw 35

#9 ("severe acute respiratory syndrome*" or SARS):ti,ab,kw 150

#10 ("SARS-CoV-1" or "SARSCoV-1" or "SARSCoV1" or "SARS-CoV1" or SARSCoV or SARS-CoV):ti,ab,kw 8

#11 {or #1-#10} 590

#12 MeSH descriptor: [Angiotensin-Converting Enzyme Inhibitors] explode all trees 3965

#13 (("Angiotensin* convert*" or Angiotensinconvert*) near/2 enzyme* inhibitor*):ti,ab 3354

#14 ((ACE or dipeptidyl* or carboxypeptidase* or peptidyl* or peptidyldipeptide* or kininase*) near/3 inhibit*):ti,ab 5127

#15 (ACE2 near/1 stimulat*):ti,ab 0

#16 ACEI*:ti,ab 2550

#17 (captopril* or Noyada* or enalapril* or fosinopril* or imidapril* or Tanatril* or lisinopril* or Zestril* or moexipril* or perindopril* or Coversyl* or quinapril* or Accupro* or ramipril* or Tritace* or trandolapril*):ti,ab 8616

#18 MeSH descriptor: [Angiotensin Receptor Antagonists] explode all trees 2110

#19 (Angiotensin* adj4 (antagonist* or blocker* or blocking*)).ti,ab. 3871

#20 ARB:ti,ab 1781

#21 (Azilsartan* or Edarbi* or Candesartan* or Amias* or Eprosartan* or Teveten* or Irbesartan* or Losartan* or Cozaar* or Olmesartan* or Sevikar* or telmisartan* or Micardis* or Tolura* or valsartan* or Exforge* or Amlodipine* or sacubitril* or Entresto*):ti,ab 9662

#22 {or #12-#21} 25396

#23 #11 and #22 5

#24 MeSH descriptor: [Hypertension] explode all trees 17585

#25 hypertens*:ti,ab 52862

#26 (elevat* near/2 blood near/1 pressur*):ti,ab 1286
#27 (high* near/1 blood near/1 pressur*):ti,ab 2728
#28 (increase* near/2 blood pressur*):ti,ab 3160
#29 ((systolic* or diastolic* or arterial*) near/2 pressur*):ti,ab 38814
#30 MeSH descriptor: [Diabetes Mellitus] explode all trees 30189
#31 (diabete* or diabetic*):ti,ab 83277
#32 MeSH descriptor: [Heart Failure] explode all trees 9088
#33 MeSH descriptor: [Cardiomyopathy, Dilated] this term only 532
#34 MeSH descriptor: [Shock, Cardiogenic] this term only 244
#35 MeSH descriptor: [Ventricular Dysfunction] explode all trees 2178
#36 MeSH descriptor: [Cardiac Output, Low] this term only 372
#37 ((heart* or cardiac* or myocardial*) near/2 (failure* or decompensat*)):ti,ab 25365
#38 ((dilated* or congestive*) near/2 cardiomyopath*):ti,ab 961
#39 "cardiogenic shock*":ti,ab 976
#40 ((ventricular* or ventricle*) near/2 (failure* or insufficien* or dysfunction*)):ti,ab 3171
#41 lvsd:ti,ab 82
#42 {or #24-#41} 176916
#43 #11 and #42 52
#44 #23 or #43 54
#45 #23 or #43 with Cochrane Library publication date Between Jan 2000 and Apr 2020, in Cochrane Reviews, Cochrane Protocols 2
#46 #23 or #43 with Publication Year from 2000 to 2020, in Trials 50

Cochrane Database of Systematic Reviews (CDSR)

Before doing new searches check the Cochrane special collections for curated resources:

Coronavirus (COVID-19): infection control and prevention measures
Assembles Cochrane Reviews identified as most directly relevant to the prevention of infection. – no additional reviews
https://www.cochranelibrary.com/collections/doi/SC000040/full

Coronavirus (COVID-19): evidence relevant to critical care
Assembles Cochrane Reviews identified as most directly relevant to the management of people hospitalized with severe acute respiratory infections. – no additional reviews
https://www.cochranelibrary.com/collections/doi/SC000039/full

Cochrane Database of Systematic Reviews Issue 3 of 12, March 2020
#1 MeSH descriptor: [Coronavirus] explode all trees 11
#2 MeSH descriptor: [Coronavirus Infections] explode all trees 12
#3 ((corona* or corono*) near/1 (virus* or viral* or virinae*)):ti,ab,kw 8
#4 (coronavirus* or coronovirus* or coronavirinae* or Coronavirus* or Coronovirus* or Wuhan* or Hubei* or Huanan or "2019-nCoV" or 2019nCoV or nCoV2019 or "nCoV-2019" or "COVID-19" or COVID19 or "CORVID-19" or CORVID19 or "WN-CoV" or WNCoV or "HCoV-19" or HCoV19 or CoV or "2019 novel*" or Ncov or "n-cov" or "SARS-CoV-2" or "SARSCoV-2" or "SARSCoV2" or "SARS-CoV2" or SARSCov19 or "SARS-Cov19" or "SARSCov-19" or "SARS-Cov-19" or Ncovor or Ncorona* or Ncorono* or NcovWuhan* or NcovHubei* or NcovChina* or NcovChinese*):ti,ab,kw 410
#5 (((respiratory* near/2 (symptom* or disease* or illness* or condition*)) or "seafood market*" or "food market*") near/10 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)):ti,ab,kw 30
#6 ((outbreak* or wildlife* or pandemic* or epidemic*) near/1 (China* or Chinese* or

Huanan*)):ti,ab,kw 1
#7 MeSH descriptor: [Middle East Respiratory Syndrome Coronavirus] explode all trees 1
#8 ("middle east respiratory syndrome*" or "middle eastern respiratory syndrome*" or MERSCoV or "MERS-CoV" or MERS):ti,ab,kw 35
#9 ("severe acute respiratory syndrome*" or SARS):ti,ab,kw 150
#10 ("SARS-CoV-1" or "SARSCoV-1" or "SARSCoV1" or "SARS-CoV1" or SARSCoV or SARS-CoV):ti,ab,kw 8
#11 {or #1-#10} 590
#12 MeSH descriptor: [Angiotensin-Converting Enzyme Inhibitors] explode all trees 3965
#13 (("Angiotensin* convert*" or Angiotensinconvert*) near/2 enzyme* inhibitor*):ti,ab 3354
#14 ((ACE or dipeptidyl* or carboxypeptidase* or peptidyl* or peptidyldipeptide* or kininase*) near/3 inhibit*):ti,ab 5127
#15 (ACE2 near/1 stimulat*):ti,ab 0
#16 ACEI*:ti,ab 2550
#17 (captopril* or Noyada* or enalapril* or fosinopril* or imidapril* or Tanatril* or lisinopril* or Zestril* or moexipril* or perindopril* or Coversyl* or quinapril* or Accupro* or ramipril* or Tritace* or trandolapril*):ti,ab 8616
#18 MeSH descriptor: [Angiotensin Receptor Antagonists] explode all trees 2110
#19 (Angiotensin* adj4 (antagonist* or blocker* or blocking*)).ti,ab. 3871
#20 ARB:ti,ab 1781
#21 (Azilsartan* or Edarbi* or Candesartan* or Amias* or Eprosartan* or Teveten* or Irbesartan* or Losartan* or Cozaar* or Olmesartan* or Sevikar* or telmisartan* or Micardis* or Tolura* or valsartan* or Exforge* or Amlodipine* or sacubitril* or Entresto*):ti,ab 9662
#22 {or #12-#21} 25396
#23 #11 and #22 5
#24 MeSH descriptor: [Hypertension] explode all trees 17585
#25 hypertens*:ti,ab 52862
#26 (elevat* near/2 blood near/1 pressur*):ti,ab 1286
#27 (high* near/1 blood near/1 pressur*):ti,ab 2728
#28 (increase* near/2 blood pressur*):ti,ab 3160
#29 ((systolic* or diastolic* or arterial*) near/2 pressur*):ti,ab 38814
#30 MeSH descriptor: [Diabetes Mellitus] explode all trees 30189
#31 (diabete* or diabetic*):ti,ab 83277
#32 MeSH descriptor: [Heart Failure] explode all trees 9088
#33 MeSH descriptor: [Cardiomyopathy, Dilated] this term only 532
#34 MeSH descriptor: [Shock, Cardiogenic] this term only 244
#35 MeSH descriptor: [Ventricular Dysfunction] explode all trees 2178
#36 MeSH descriptor: [Cardiac Output, Low] this term only 372
#37 ((heart* or cardiac* or myocardial*) near/2 (failure* or decompensat*)):ti,ab 25365
#38 ((dilated* or congestive*) near/2 cardiomyopath*):ti,ab 961
#39 "cardiogenic shock*":ti,ab 976
#40 ((ventricular* or ventricle*) near/2 (failure* or insufficien* or dysfunction*)):ti,ab 3171
#41 lvsd:ti,ab 82
#42 {or #24-#41} 176916
#43 #11 and #42 52
#44 #23 or #43 54
#45 #23 or #43 with Cochrane Library publication date Between Jan 2000 and Apr 2020, in Cochrane Reviews, Cochrane Protocols 2

Embase

Database(s): Embase 1974 to 2020 March 20
Search Strategy:

#	Searches	Results
1	exp Coronavirinae/	11005
2	exp Coronavirus infection/	11127
3	((corona* or corono*) adj1 (virus* or viral* or virinae*)).ti,ab,kw.	515
4	(coronavirus* or coronovirus* or coronavirinae* or Coronavirus* or Coronovirus* or Wuhan* or Hubei* or Huanan or "2019-nCoV" or 2019nCoV or nCoV2019 or "nCoV-2019" or "COVID-19" or COVID19 or "CORVID-19" or CORVID19 or "WN-CoV" or WNCoV or "HCoV-19" or HCoV19 or CoV or "2019 novel*" or Ncov or "n-cov" or "SARS-CoV-2" or "SARSCoV-2" or "SARSCoV2" or "SARS-CoV2" or SARSCov19 or "SARS-Cov19" or "SARSCov-19" or "SARS-Cov-19" or Ncovor or Ncorona* or Ncorono* or NcovWuhan* or NcovHubei* or NcovChina* or NcovChinese*).ti,ab,kw.	20582
5	(((respiratory* adj2 (symptom* or disease* or illness* or condition*)) or "seafood market*" or "food market*") adj10 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)).ti,ab,kw.	548
6	((outbreak* or wildlife* or pandemic* or epidemic*) adj1 (China* or Chinese* or Huanan*)).ti,ab,kw.	74
7	Middle East respiratory syndrome/	802
8	("middle east respiratory syndrome*" or "middle eastern respiratory syndrome*" or MERSCoV or "MERS-CoV" or MERS).ti,ab,kw.	4922
9	("severe acute respiratory syndrome*" or SARS).ti,ab,kw.	10686
10	("SARS-CoV-1" or "SARSCoV-1" or "SARSCoV1" or "SARS-CoV1" or SARSCoV or SARS-CoV).ti,ab,kw.	2733
11	or/1-10	36448
12	limit 11 to medline	8585
13	11 not 12	27863
14	exp dipeptidyl carboxypeptidase inhibitor/	171871
15	(("Angiotensin* convert*" or Angiotensinconvert*) adj2 enzyme* inhibit*).ti,ab.	26016
16	((ACE or dipeptidyl* or carboxypeptidase* or peptidyl* or peptidyldipeptide* or kininase*) adj3 inhibit*).ti,ab.	36362
17	(ACE2 adj1 stimulat*).ti,ab.	14
18	ACEI*.ti,ab.	9125
19	(captopril* or Noyada* or enalapril* or fosinopril* or imidapril* or Tanatril* or lisinopril* or Zestril* or moexipril* or perindopril* or Coversyl* or quinapril* or Accupro* or ramipril* or Tritace* or trandolapril*).ti,ab.	34413
20	exp angiotensin receptor antagonist/	89843
21	(Angiotensin* adj4 (antagonist* or blocker* or blocking*)).ti,ab.	27077
22	ARB.ti,ab.	9892
23	(Azilsartan* or Edarbi* or Candesartan* or Amias* or Eprosartan* or Teveten* or Irbesartan* or Losartan* or Cozaar* or Olmesartan* or Sevikar* or telmisartan* or Micardis* or Tolura* or valsartan* or Exforge* or Amlodipine* or sacubitril* or Entresto*).ti,ab.	34238
24	or/14-23	233639
25	13 and 24	97
26	exp hypertension/	710736
27	hypertens*.ti,ab.	627182

28	(elevat* adj2 blood adj pressur*).ti,ab.	13862
29	(high* adj blood adj pressur*).ti,ab.	25461
30	(increase* adj2 blood pressur*).ti,ab.	23976
31	((systolic* or diastolic* or arterial*) adj2 pressur*).ti,ab.	250324
32	exp diabetes mellitus/	932550
33	(diabete* or diabetic*).ti,ab.	907506
34	exp heart failure/	488702
35	exp congestive cardiomyopathy/	31080
36	exp cardiogenic shock/	25453
37	exp heart ventricle function/	18056
38	forward heart failure/	5627
39	((heart* or cardiac* or myocardial*) adj2 (failure* or decompensat*)).ti,ab.	287423
40	((dilated* or congestive*) adj2 cardiomyopath*).ti,ab.	28233
41	"cardiogenic shock*".ti,ab.	19420
42	((ventricular* or ventricle*) adj2 (failure* or insufficien* or dysfunction*)).ti,ab.	48321
43	lvsd.ti,ab.	1273
44	or/26-43	2332088
45	13 and 44	889
46	25 or 45	943
47	limit 46 to yr="2000 -Current"	919
48	(conference abstract or conference paper or conference proceeding or "conference review").pt.	4497370
49	47 not 48	693
50	47 and 48	226

Note: line 49 was downloaded and added to EPPI. Line 50 was downloaded but not added to EPPI-R to help manage the volume by removing conference papers and abstracts. Line

MEDLINE ALL

Database(s): Ovid MEDLINE(R) ALL 1946 to March 20, 2020

Search Strategy:

#	Searches	Results
1	exp coronavirus/	11392
2	exp Coronavirus Infections/	9675
3	((corona* or corono*) adj1 (virus* or viral* or virinae*)).ti,ab,kw.	611
4	(coronavirus* or coronovirus* or coronavirinae* or Coronavirus* or Coronovirus* or Wuhan* or Hubei* or Huanan or "2019-nCoV" or 2019nCoV or nCoV2019 or "nCoV-2019" or "COVID-19" or COVID19 or "CORVID-19" or CORVID19 or "WN-CoV" or WNCoV or "HCoV-19" or HCoV19 or CoV or "2019 novel*" or Ncov or "n-cov" or "SARS-CoV-2" or "SARSCoV-2" or "SARSCoV2" or "SARS-CoV2" or SARSCov19 or "SARS-Cov19" or "SARSCov-19" or "SARS-Cov-19" or Ncovor or Ncorona* or Ncorono* or NcovWuhan* or NcovHubei* or NcovChina* or NcovChinese*).ti,ab,kw.	17413
5	(((respiratory* adj2 (symptom* or disease* or illness* or condition*)) or "seafood market*" or "food market*") adj10 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)).ti,ab,kw.	455
6	((outbreak* or wildlife* or pandemic* or epidemic*) adj1 (China* or Chinese* or Huanan*)).ti,ab,kw.	167
7	Middle East Respiratory Syndrome Coronavirus/	967
8	("middle east respiratory syndrome*" or "middle eastern respiratory syndrome*" or MERSCoV or "MERS-CoV" or MERS).ti,ab,kw.	4399

9	("severe acute respiratory syndrome*" or SARS).ti,ab,kw.	9458
10	("SARS-CoV-1" or "SARSCoV-1" or "SARSCoV1" or "SARS-CoV1" or SARSCoV or SARS-CoV).ti,ab,kw.	2570
11	or/1-10	30433
12	exp Angiotensin-Converting Enzyme Inhibitors/	43216
13	(("Angiotensin* convert*" or Angiotensinconvert*) adj2 enzyme* inhibit*).ti,ab.	20122
14	((ACE or dipeptidyl* or carboxypeptidase* or peptidyl* or peptidyldipeptide* or kininase*) adj3 inhibit*).ti,ab.	24516
15	(ACE2 adj1 stimulat*).ti,ab.	6
16	ACEI*.ti,ab.	4492
17	(captopril* or Noyada* or enalapril* or fosinopril* or imidapril* or Tanatril* or lisinopril* or Zestril* or moexipril* or perindopril* or Coversyl* or quinapril* or Accupro* or ramipril* or Tritace* or trandolapril*).ti,ab.	25073
18	exp Angiotensin Receptor Antagonists/	23307
19	(Angiotensin* adj4 (antagonist* or blocker* or blocking*)).ti,ab.	18678
20	ARB.ti,ab.	4825
21	(Azilsartan* or Edarbi* or Candesartan* or Amias* or Eprosartan* or Teveten* or Irbesartan* or Losartan* or Cozaar* or Olmesartan* or Sevikar* or telmisartan* or Micardis* or Tolura* or valsartan* or Exforge* or Amlodipine* or sacubitril* or Entresto*).ti,ab.	22024
22	or/12-21	90797
23	11 and 22	40
24	exp Hypertension/	251499
25	hypertens*.ti,ab.	422572
26	(elevat* adj2 blood adj pressur*).ti,ab.	10087
27	(high* adj blood adj pressur*).ti,ab.	17218
28	(increase* adj2 blood pressur*).ti,ab.	18073
29	((systolic* or diastolic* or arterial*) adj2 pressur*).ti,ab.	181836
30	exp Diabetes Mellitus/	418243
31	(diabete* or diabetic*).ti,ab.	612568
32	exp heart failure/	119092
33	cardiomyopathy, dilated/	15509
34	shock, cardiogenic/	8321
35	exp ventricular dysfunction/	36752
36	cardiac output, low/	5485
37	((heart* or cardiac* or myocardial*) adj2 (failure* or decompensat*)).ti,ab.	174772
38	((dilated* or congestive*) adj2 cardiomyopath*).ti,ab.	18144
39	"cardiogenic shock*".ti,ab.	10888
40	((ventricular* or ventricle*) adj2 (failure* or insufficien* or dysfunction*)).ti,ab.	29914
41	lvsd.ti,ab.	513
42	or/24-41	1399814
43	11 and 42	480
44	23 or 43	510
45	limit 44 to yr="2000 -Current"	478

Web sources - COVID-19

Website

Name	Centre for Evidence-based medicine (CEBM) COVID-19 Evidence Service
URL	https://www.cebm.net/oxford-covid-19/
Search terms	Browsed the list – this was published at noon on 23 March 2020
How the results were selected	By title
Results	Aronson J; Ferner E (2020) Angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers in COVID-19 https://www.cebm.net/angiotensin-converting-enzyme-ace-inhibitors-and-angiotensin-receptor-blockers-in-covid-19/

Website	
Name	World Health Organization Global research on coronavirus disease (COVID-19)
URL	https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov
Search terms	Angiotensin ACEI ACE2 dipeptidyl ARB Captopril Enalapril Imidapril Tanatril Lisinopril moexipril perindopril quinapril ramipril trandolapril Azilsartan Candesartan Eprosartan Irbesartan Losartan Olmesartan Telmisartan Valsartan Sacubitril
How the results were selected	Downloaded the full WHO database as a csv file. Searched within that file using Excel for the terms above. Marked the ones that had relevant titles and were not already uploaded to EPPI so as not to create new duplicates. Searched for these by doi. Collected these references in Zotero and exported a ris file from there and uploaded to EPPI.
Results	20 results

Analyst recommendation	
Name	Paper suggested by the technical team added to review.
URL	Palmieri L et al. (2020) Characteristics of COVID-19 patients dying in Italy. Report based on available data on March 20th, 2020 https://www.epicentro.iss.it/coronavirus/bollettino/Report-COVID-

	2019_20_marzo_eng.pdf

URL	http://www.nephjc.com/news/covidace2

Website	
Name	MHRA Central Alerting System
URL	https://www.cas.mhra.gov.uk/Home.aspx
Search terms	Browsed the most recent issues
How the results were selected	Title of the letter
Results	None added

Updates	
Tue 24 March 2020	New paper released in JAMA – sent to review team but was not added to the review because it did not meet the inclusion criteria. Patel A & Verma A (24 Mar 2020) COVID-19 and Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers What Is the Evidence? JAMA doi: 10.1001/jama.2020.4812

Appendix C: Evidence selection

A literature search was conducted which identified 905 references (see search strategy for full details). These references were screened using their titles and abstracts and 43 references were obtained and assessed for relevance. Of these, 2 are included in the evidence summary.

The 41 excluded references are listed in the following table.

Study reference
Al Ghamdi, Mohammed, Alghamdi, Khalid M, Ghandoora, Yasmeen et al. (2016) Treatment outcomes for patients with Middle Eastern Respiratory Syndrome Coronavirus (MERS CoV) infection at a coronavirus referral center in the Kingdom of Saudi Arabia. BMC infectious diseases 16: 174
Al-Tawfiq, Jaffar A, Hinedi, Kareem, Ghandour, Jihad et al. (2014) Middle East respiratory syndrome coronavirus: a case-control study of hospitalized patients. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 59(2): 160-5
Alanazi, Khalid H, Abedi, Glen R, Midgley, Claire M et al. (2020) Diabetes Mellitus, Hypertension, and Death among 32 Patients with MERS-CoV Infection, Saudi Arabia. Emerging infectious diseases 26(1): 166-168
Alqahtani, F Y, Aleanizy, F S, Ali El Hadi Mohamed, R et al. (2018) Prevalence of comorbidities in cases of Middle East respiratory syndrome coronavirus: a retrospective study. Epidemiology and infection: 1-5
Aronson J and Ferner E (2020) Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers in COVID-19.
Badawi, Alaa and Ryoo, Seung Gwan (2016) Prevalence of comorbidities in the Middle East respiratory syndrome coronavirus (MERS-CoV): a systematic review and meta-analysis. International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases 49: 129-33
Bloomgarden, Zachary T (2020) Diabetes and COVID-19. Journal of diabetes 12(4): 347-348
Booth, Christopher M, Matukas, Larissa M, Tomlinson, George A et al. (2003) Clinical features and short-term outcomes of 144 patients with SARS in the greater Toronto area. JAMA 289(21): 2801-9
Cao, Bin, Liu, Zheng-yin, Wang, Meng-zhao et al. (2003) [Clinical diagnosis, treatment and prognosis of elderly SARS patients]. Zhongguo yi xue ke xue yuan xue bao. Acta Academiae Medicinae Sinicae 25(5): 547-9
Chan, J W M, Ng, C K, Chan, Y H et al. (2003) Short term outcome and risk factors for adverse clinical outcomes in adults with severe acute respiratory syndrome (SARS). Thorax 58(8): 686-9
Chen, C, Chen, C, Yan, J T et al. (2020) [Analysis of myocardial injury in patients with COVID-19 and association between concomitant cardiovascular diseases and severity of COVID-19]. Zhonghua xin xue guan bing za zhi 48(0): e008
Deng, Sheng-Qun and Peng, Hong-Juan (2020) Characteristics of and Public Health Responses to the Coronavirus Disease 2019 Outbreak in China. Journal of clinical medicine 9(2)
Diaz, James H (2020) Hypothesis: angiotensin-converting enzyme inhibitors and angiotensin receptor blockers may increase the risk of severe COVID-19. Journal of travel medicine
Dodek, Peter (2004) Diabetes and other comorbidities were associated with a poor outcome in the severe acute respiratory syndrome. ACP journal club 140(1): 19
Esler, Murray and Esler, Danielle (2020) Can angiotensin receptor-blocking drugs perhaps be harmful in the COVID-19 pandemic?. Journal of hypertension
Fang, Lei; Karakiulakis, George; Roth, Michael (2020) Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection?. The Lancet. Respiratory medicine

Garbati, Musa A, Fagbo, Shamsudeen F, Fang, Vicky J et al. (2016) A Comparative Study of Clinical Presentation and Risk Factors for Adverse Outcome in Patients Hospitalised with Acute Respiratory Disease Due to MERS Coronavirus or Other Causes. PloS one 11(11): e0165978
Gu, J. and Quin, S. (2003) Three factors resulting in death of SARS patients with diabetes mellitus. Chinese Medical Journal 116(9): 1340
Gurwitz, David (2020) Angiotensin receptor blockers as tentative SARS-CoV-2 therapeutics. Drug development research
Hakawi, A., Rose, E.B., Biggs, H.M. et al. (2019) Middle East respiratory syndrome coronavirus, Saudi Arabia, 2017-2018. Emerging Infectious Diseases 25(11): 2149-2151
Huang, Chaolin, Wang, Yeming, Li, Xingwang et al. (2020) Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet (London, England) 395(10223): 497-506
Kuster, Gabriela M., Pfister, Otmar, Burkard, Thilo et al. SARS-CoV2: should inhibitors of the renin–angiotensin system be withdrawn in patients with COVID-19?. European Heart Journal
Leung, Char (2020) Clinical features of deaths in the novel coronavirus epidemic in China. Reviews in medical virology: e2103
Li, Bo, Yang, Jing, Zhao, Faming et al. (2020) Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China. Clinical research in cardiology : official journal of the German Cardiac Society
Li, Chun-sheng and Pan, Shi-fen (2003) [Analysis and causation discussion of 185 severe acute respiratory syndrome dead cases]. Zhongguo wei zhong bing ji jiu yi xue = Chinese critical care medicine = Zhongguo weizhongbing jijiuyixue 15(10): 582-4
Matsuyama, Ryota, Nishiura, Hiroshi, Kutsuna, Satoshi et al. (2016) Clinical determinants of the severity of Middle East respiratory syndrome (MERS): a systematic review and meta-analysis. BMC public health 16(1): 1203
Nassar, M S, Bakhrebah, M A, Meo, S A et al. (2018) Middle East Respiratory Syndrome Coronavirus (MERS-CoV) infection: epidemiology, pathogenesis and clinical characteristics. European review for medical and pharmacological sciences 22(15): 4956-4961
Palmieri L (2020) Characteristics of COVID-19 patients dying in Italy. Report based on available data on March 20th, 2020.
Roncati, Luca, Gallo, Graziana, Manenti, Antonio et al. (2020) Renin-angiotensin system: the unexpected flaw inside the human immune system revealed by SARS-CoV-2. Medical Hypotheses: 109686
Vandroux, D, Allou, N, Jabot, J et al. (2018) Intensive care admission for Coronavirus OC43 respiratory tract infections. Medecine et maladies infectieuses 48(2): 141-144
Wong, Wing-Wai, Chen, Te-Li, Yang, Su-Pen et al. (2003) Clinical characteristics of fatal patients with severe acute respiratory syndrome in a medical center in Taipei. Journal of the Chinese Medical Association : JCMA 66(6): 323-7
Wu, Chaomin, Chen, Xiaoyan, Cai, Yanping et al. (2020) Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA internal medicine
Xu, W.-Y., Wang, S.-W., Guo, T.-K. et al. (2004) Clinical epidemiologic features of patients with severe acute respiratory syndrome accompanied with internal chronic diseases: A retrospective analysis on 680 cases. Chinese Journal of Clinical Rehabilitation 8(21): 4154-4156
Yang, J. M., Meng, X., Xue, F. et al. (2020) [ACE2 in the context of 2019-nCoV infection: friend or foe?]. Zhonghua Xin Xue Guan Bing Za Zhi 48(0): e012
Yang, Jing, Zheng, Ya, Gou, Xi et al. (2020) Prevalence of comorbidities in the novel Wuhan coronavirus (COVID-19) infection: a systematic review and meta-analysis. International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases
Zeinalian, Mehrdad, Salari-Jazi, Azhar, Jannesari, Amin et al. A potential protective role of Losartan against coronavirus induced lung damage. Infection Control & Hospital Epidemiology: 1-6
Zhang, Jin-Jin, Dong, Xiang, Cao, Yi-Yuan et al. (2020) Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. Allergy

Zhang, M Q, Wang, X H, Chen, Y L et al. (2020) [Clinical features of 2019 novel coronavirus pneumonia in the early stage from a fever clinic in Beijing]. Zhonghua jie he he hu xi za zhi = Zhonghua jiehe he huxi zazhi = Chinese journal of tuberculosis and respiratory diseases 43(3): 215-218
Zheng, Ying-Ying, Ma, Yi-Tong, Zhang, Jin-Ying et al. (2020) COVID-19 and the cardiovascular system. Nature Reviews. Cardiology
Zhou, Fei, Yu, Ting, Du, Ronghui et al. (2020) Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet (London, England)
Zumla, A., Hui, D.S., Azhar, E.I. et al. (2020) Reducing mortality from 2019-nCoV: host-directed therapies should be an option. The Lancet 395(10224): e35-e36