COVID-19 and hypertension—evidence and practical management: Guidance from the HOPE Asia Network

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Abstract
There are several risk factors for worse outcomes in patients with coronavirus 2019 disease (COVID-19). Patients with hypertension appear to have a poor prognosis, but there is no direct evidence that hypertension increases the risk of new infection or adverse outcomes independent of age and other risk factors. There is also concern about use of renin-angiotensin system (RAS) inhibitors due to a key role of angiotensin-converting enzyme 2 receptors in the entry of the SARS-CoV-2 virus into cells. However, there is little evidence that use of RAS inhibitors increases the risk of SARS-CoV-2 virus infection or worsens the course of COVID-19. Therefore, antihypertensive therapy with these agents should be continued. In addition to acute respiratory distress syndrome, patients with severe COVID-19 can develop myocardial injury and cytokine storm, resulting in heart failure, arteriovenous thrombosis, and kidney injury. Troponin, N-terminal pro-B-type natriuretic peptide, D-dimer, and serum creatinine are biomarkers for these complications and can be used to monitor patients with COVID-19 and for risk stratification. Other factors that need to be incorporated into patient management strategies during the pandemic include regular exercise to maintain good health status and monitoring of psychological well-being. For the ongoing management of patients with hypertension, telemedicine-based...
INTRODUCTION

The infectious disease caused by the new severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), COVID-19, broke out in Wuhan, China, and spread to almost every country in the world. Millions of people have been infected, many have died, and everyday life has changed completely. The disease is accompanied by range of different symptoms (Figure 1). Rapidly accumulating data show that prognosis for patients with COVID-19 is good in those with mild disease, but severe cases show relatively asymtomatic early progression followed by rapid worsening after symptom onset, culminating in acute respiratory distress syndrome (ARDS) and significant disease manifestations (Figure 2). The presence of SARS-CoV-2 has been detected in multiple organs on autopsy, including the pharynx, lungs, heart, liver, brain and kidneys, highlighting the multorgan tropism of this virus.1

Early clinical experience suggested that older age and the presence of a number of comorbidities, including hypertension, cardiovascular disease, diabetes mellitus and chronic respiratory disease increased the risk of death in patients with COVID-19.2,3 In addition, the renin-angiotensin aldosterone (RAS) system (specifically the angiotensin-converting enzyme 2 [ACE2] protein) has been identified as playing an important role in facilitating entry of coronaviruses, including SARS-CoV-2, into target cells, especially in the lungs.4,5 Therefore, it has been suggested that angiotensin receptor blockers (ARBs) and ACE inhibitors, which affect ACE2 expression, may influence the susceptibility to and severity of infection with SARS-CoV-2.6-11

Hypertension is very common, affecting an estimated 1.39 billion individuals worldwide,12 and the prevalence of hypertension increases with age (affecting approximately 70% of older adults).13 In addition, RAS inhibitors such as ACE inhibitors and ARBs are recommended and widely used for the treatment of hypertension.14-16 However, hypertension is not a single clinical entity, but it instead manifests as a number of different phenotypes. In Asians, the disease is characterized by salt sensitivity, high rates of masked hypertension, exaggerated morning BP surge, and nocturnal hypertension.17 Nearly half of all patients with hypertension worldwide (44%) live in south or east Asia.18

The HOPE Asia Network was established in 2016 and is a member of the World Hypertension League.19,20 The mission of the HOPE Asia Network is to improve the management of hypertension and organ protection toward achieving “zero” cardiovascular events in Asia.19,20 This has become even more relevant in the current pandemic, with high rates of infection in several Asian countries.

This guidance from the HOPE Asia Network summarizes the latest findings on COVID-19 and hypertension, including evidence-based recommendations for the management of hypertension during the current pandemic.

HYPERTENSION AS A RISK FACTOR IN PATIENTS WITH COVID-19

On March 20, 2020, the Italian Institute of Health announced that there had been 3200 COVID-19 deaths in Italy.21 The patients who died had an average age of 78.5 years (median 80 years, range 31-103 years) and 98.7% had at least one comorbidity.21 Hypertension was a common comorbidity in Italian cases, affecting 73.8% of patients, 52% of whom were taking ARBs or ACE inhibitors.21 However,
there are number of factors that could potentially confound a possible relationship between hypertension and severe COVID-19 (Table 1). The first is age: both severe COVID-19 and hypertension are common in the elderly. In addition, the identified risk factors (Table 1) are generally associated with aging and/or vascular disorders, both of which are common in patients with hypertension. Therefore, the risk of developing severe COVID-19 is more likely to be due to underlying vascular endothelial dysfunction and/or organ damage than high blood pressure (BP) per se. ACE2 receptors are expressed by endothelial cells, and post-mortem examinations have detected the presence of viral infection in endothelial cells.

Clinical Question 1 Is hypertension a risk factor for COVID-19?

Pre-existing hypertension appears to be common in patients with severe COVID-19. However, there is little direct evidence to indicate that hypertension itself is a risk factor for infection or aggravation of the disease independent of aging or other COVID-19 risk factors.

3 | THERAPY WITH RENIN-ANGIOTENSIN SYSTEM INHIBITORS

3.1 | Mechanisms linking COVID-19 and ACE2

The spike protein on the surface of SARS-CoV-2 binds to the extracellular domain of transmembrane ACE2, with S protein priming by transmembrane serine protease 2 (TMPRSS2), to gain entry to host

Clinical Question 2 Is it safe to continue treatment with ACE inhibitors or ARBs?

As of early May 2020, there is no clinical data showing that use of ACE inhibitors or ARBs increases the risk of infection with the SARS-CoV-2 virus or worsens the course of COVID-19 disease. Scientific societies including the American Heart Association, European Society of Cardiology, Japanese Circulation Society, and Japanese Society of Hypertension recommend continuation of ACE inhibitor or ARB therapy in patients with hypertension.
ACE2 plays a regulatory role in the RAS, converting angiotensin I (Ang I) into angiotensin 1-9 (Ang 1-9) or angiotensin II (Ang II) into angiotensin 1-7 (Ang 1-7).\(^ {31,32}\) Currently, available data reflect a possible role for ACE2 in heart failure, myocardial infarction, hypertension, and the cardiovascular complications of diabetes mellitus, and preclinical investigations suggest that activation of ACE2 might have the potential to protect against hypertension and cardiovascular disease.\(^ {31,33-35}\) In addition, angiotensin 1-7 appears to counteract the negative effects of Ang II, attenuating inflammation, suppressing vascular permeability and having vasorelaxant effects.\(^ {36-38}\) Furthermore, ACE2 in the lungs and the renin-angiotensin system has been shown to play a role in the pulmonary manifestations of coronavirus infection.\(^ {39}\)

Interaction of Ang II with angiotensin type 1 receptors (AT1R) activates A Disintegrin And Metalloproteinase 17 (ADAM17) on the cell membrane via phosphorylation.\(^ {40}\) In turn, ADAM17 cleaves the precursors of tumor necrosis factor-\(\alpha\) (TNF\(\alpha\)) and interleukin (IL)-6 receptor-\(\alpha\) (IL-6Ra) in the cell membrane to release TNF\(\alpha\) and soluble IL-6Ra.\(^ {41}\) TNF\(\alpha\) activates the nuclear transcription factor system NF-\(\kappa\)B to induce the production of various inflammatory cytokines, including IL-6 (Figure 4).\(^ {42}\) This represents a potential mechanism for the cytokine storm seen in some patients with COVID-19 and highlights the potential for agents blocking cytokine pathways (especially the IL-6-STAT3 axis) in managing COVID-19 related cytokine storm.\(^ {43}\)

The fact that the SARS-CoV-2 virus uses ACE2 as a mechanism to enter and infect cells meant that there was concern that cells with high ACE2 expression would be most susceptible to infection with SARS-CoV-2. Given that ARB and ACE inhibitors have been shown experimentally to increase expression of ACE2 on cell membranes,\(^ {26,44}\) there was much discussion about the potential for higher infection rates and more severe disease in patients being treated with these agents.

### 3.2 | Current clinical evidence

Despite the theoretical possibility that use of RAS inhibitors increases the risk of infection with SARS-CoV-2 and the severity of COVID-19 illness, analyses including patients from the current pandemic indicate that this does not seem to be the case (Table 2). The effect of hypertension or therapy with ACE inhibitors or ARBs has been evaluated in at least three published studies to date (Table 2).\(^ {45-47}\) Reynolds et al looked at history of antihypertensive usage in 12,594 patients undergoing COVID-19 testing in New York, USA.\(^ {47}\) They did not find any association between the use of ACE inhibitors, ARBs, beta-blockers, calcium channel blockers or thiazide diuretics and the likelihood of a positive or negative result on COVID-19 testing.\(^ {46}\) Similar findings were reported in a population case-control study from Italy.\(^ {45}\)

Data from four studies published by early May 2020 also failed to find a significant association between the use of ACE inhibitors or ARBs and COVID-19 test positivity.\(^ {46}\) Similar findings were reported in a population case-control study from Italy.\(^ {45}\)

In one retrospective case series, the proportion of patients using ACE inhibitors or ARBs did not differ significantly between those with severe vs non-severe COVID-19, or between survivors and non-survivors.\(^ {48}\) However, the in-hospital COVID-19 mortality rate was higher in patients with vs without hypertension (21% vs 11%).\(^ {48}\) In the other studies, death rates for patients taking ACE inhibitors and/or ARBs were actually lower than those in patients not receiving these antihypertensive therapies.\(^ {49,50}\) One of the studies from China reported that levels of the inflammatory markers high sensitivity C-reactive protein and procalcitonin were significantly lower in patients with hypertension who were vs were not receiving ACE inhibitors or ARBs.\(^ {49}\)
4 | BIOMARKERS OF COVID-19-RELATED COMPLICATIONS

Clinical Question 3  What are the biomarkers of severe COVID-19?
In addition to ARDS, patients with severe infection can develop myocardial injury and cytokine storm, resulting in heart failure, arteriovenous thrombosis (venous thromboembolism, acute coronary syndrome, cerebral infarction), and acute kidney injury. Biomarkers for these complications are troponin, N-terminal pro-B-type natriuretic peptide (NT-proBNP), D-dimer, and serum creatinine.

High levels of a number of biomarkers are indicative of severe COVID-19 (Table 3). One of the most important biomarkers in patients with COVID-19 is troponin, which indicates the presence of myocardial injury. D-dimer and IL-6 are also important. D-dimer indicates the presence of arterial microthrombus and venous thrombosis (pulmonary embolism and deep vein thrombosis) and disseminated intravascular coagulation (DIC). IL-6 is an inflammatory marker, suggesting the presence of cytokine storm, while NT-proBNP and creatinine are biomarkers of heart failure and renal damage, respectively.

4.1 | Troponin and myocardial injury

There are two possible mechanisms of cardiovascular damage in COVID-19. The first is direct viral infection of myocardial and vascular cells, and the other is a systemic inflammatory reaction (or cytokine storm) (Figure 5). Myocardial injury at the time of admission or due to disease progression is a strong indicator of poor prognosis in patients with COVID-19. Troponin is a highly sensitive and well-known marker of myocardial injury.

A systematic review and meta-analysis of data published between 1 December 2019 and 27 March 2020 including 4189 patients from 28 studies showed a significant trend for higher levels of cardiac biomarkers in patients with more severe COVID-19.\(^{51}\) On meta-regression analysis, the only factor significantly associated with higher levels of cardiac injury biomarkers was the presence of hypertension \((P = .03)\). In addition, more severe COVID-19 markedly increased the risk of acute cardiac injury (risk ratio vs mild disease 5.99, 95% confidence interval [CI] 3.04-11.80; \(P < .001\)). In turn, the risk of COVID-19-related death was significantly increased in the presence of acute cardiac injury (risk ratio 3.85, 95% CI 2.13-6.96).\(^{51}\) Another analysis also reported that patients with severe COVID-19 had significantly higher levels of troponin than those without severe disease (standardized mean difference 25.6 ng/L, 95% CI 6.8-44.5 ng/L).\(^{52}\)

Early data from Wuhan, China, showed that 12% of patients admitted to hospital with COVID-19 had acute cardiac injury.\(^{53}\) Subsequent analyses investigated associations between underlying cardiovascular disease or myocardial injury and mortality in hospitalized patients with COVID-19 \((n = 187)\).\(^{23}\) Patients with vs without myocardial injury (as defined as elevated troponin levels) were significantly older \((74 vs 60 years; \(P < .001\)) and more likely to have hypertension \((59.8% vs 23.4%; \(P < .001\)) during hospitalization, those with myocardial injury had higher rates of ARDS \((58.5% vs 14.7%; \(P < .001\)) and acute renal injury \((8.5% vs 0.3%; \(P < .001\)) and death \((51.2% vs 4.5%; \(P < .001\)) during hospitalization, those with myocardial injury had higher rates of ARDS \((58.5% vs 14.7%; \(P < .001\)) and acute renal injury \((8.5% vs 0.3%; \(P < .001\)) and death \((51.2% vs 4.5%; \(P < .001\)) during hospitalization. The appearance of myocardial injury increased the risk of death by 4.26-fold compared to patients without myocardial damage, independent of cardiac function based on ECG and echocardiography findings (Figure 6).\(^{23,25}\)

**FIGURE 4** Cytokine storm associated with SARS-CoV-2 infection. ACE, angiotensin-converting enzyme; ADAM17, A Disintegrin And Metalloproteinase 17; IL-6Rα, interleukin-6 receptor-α; TMPRSS2, transmembrane serine protease 2; TNFα, tumor necrosis factor-α.
D-dimer is a biomarker that reflects activation of coagulation and fibrinolysis. D-dimer levels of $>$ 2 µg/mL were an independent predictor of in-hospital death in patients hospitalized with COVID-19 in Wuhan, China (hazard ratio 51.5, 95% CI 12.9-206.7; $P < .001$). The 2 µg/mL cutoff had 92% sensitivity and 83% specificity for predicting in-hospital mortality and therefore might be a useful biomarker for predicting outcome and informing treatment decisions in patients with COVID-19. The cumulative rate of thromboembolic events in patients admitted to hospital in Milan, Italy with COVID-19 ($n = 388$) was 21% (28% of those in intensive care and 7% for those not in intensive care) despite use of thromboprophylaxis in all patients admitted to the intensive care unit and three-quarters of those treated on a general ward. About half of all thromboembolic events occurred within 24 hours of hospitalization, and 2% of patients developed
A consensus statement on the prevention and treatment of venous thromboembolism-associated COVID-19 infection has been published. This recommends that patients with COVID-19 undergo assessment for the risk of venous thromboembolism and bleeding and are monitored regularly to facilitate the diagnosis and treatment of venous thromboembolism, and the use of strategies (pharmacologic and/or mechanical) to prevent venous thromboembolism.

5 CLINICAL PATIENT MANAGEMENT IN THE COVID-19 ERA

Key points regarding the clinical management of COVID-19, particularly in patients with hypertension, based on evidence published before May 5, 2020, are shown in Table 4. Data that have been rapidly compiled during the pandemic to date indicate that there are a number of factors and biomarkers that can be used to identify patients with COVID-19 who are at high risk of more severe disease and adverse outcomes, including death. Age seems to be the most important risk factor, especially for COVID-19-related death, and hypertension is the most common comorbidity in COVID-19-positive deceased patients. Other comorbidities such as cardiovascular diseases, smoking, chronic lung disease, chronic kidney disease, and a suppressed immune system also increase the risks associated with COVID-19 infection, especially when multiple comorbidities exist in the same patient. Thorough history taking and baseline assessments are therefore important. Another important screening tool is oxygen saturation, which indicates severe disease if ≤94% on admission. The relevance of ability to

**FIGURE 5** Mechanisms of myocardial injury in patients with COVID-19 (reproduced, with permission, from Clerkin KJ et al, 2020) IL6, interleukin-6; LDH, lactate dehydrogenase

**FIGURE 6** Prognosis in patients with COVID-19, with or without cardiac injury (reproduced, with permission, from Shi et al, 2020)
TABLE 4  Clinical practice guidance for patient management in the COVID-19 era (based on evidence available up to May 5, 2020)

COVID-19 and Comorbidities: Assessment and Management

- Patients with hypertension, especially older individuals and those with other known risk factors, are at increased risk of developing severe symptoms during COVID-19 infection
- High-risk patients, such as those with hypertension, are more likely to develop cardiac injury during COVID-19 infection
- Diabetes mellitus should be carefully managed and these patients need to be closely monitored for the development of myocardial injury and arteriovenous thrombosis
- Consider determining levels of key biomarkers, especially troponin and D-dimer, to get a complete clinical picture and information about prognosis in patients with COVID-19
- Oxygen saturation should be determined at presentation; if oxygen saturation is <94% then COVID-19 should be considered as severe
- COVID-19 progression and cardiovascular status can be monitored by measuring blood pressure and taking the patient’s temperature
- Antihypertensive therapy with ACE inhibitors or ARBs in patients with COVID-19 should be carefully continued, with careful monitoring to detect hypotension and kidney injury
- Unmedicated older COVID-19 patients whose only comorbidity is hypertension can be treated with calcium channel blockers
- Physicians should be aware of physical manifestations of stress (eg, cardiovascular events), even in individuals not infected with COVID-19 (especially those with pre-existing hypertension)

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6 | TELEMEDICINE DURING COVID-19

Strict lockdown and social distancing rules are being enforced in many countries to slow the spread of the novel coronavirus. In addition, a large proportion of “elective” or “non-essential” procedures have been postponed or canceled to allow health care systems to cope with the influx of infectious disease cases. This has created a requirement for a large proportion of health consultations to be conducted remotely. Telemedicine strategies are ideally suited to facilitating patient management in the absence of face-to-face consultations, and the value of this approach (which has otherwise been slow to be widely used in clinical practice) has become clear. One of the hidden “blessings” of the COVID-19 pandemic may be the widespread adoption of telemedicine approaches to improve patient management.

Out-of-office BP monitoring is a recommended approach for the diagnosis and management of hypertension. Therefore, this field of medicine is better placed than many to be able to continue to effectively manage patients during a global pandemic.

New information and communication technology-based home BP monitoring devices that perform automatic, fixed-interval BP measurement during sleep and store or transmit the data could facilitate a novel approach to patient management. Validated wearable technologies for evaluation of home BP might also be useful for patient monitoring and management during the COVID-19 outbreak. Telemedicine-based strategies for managing BP were implemented and used effectively during the aftermath of the Great East Japan earthquake and tsunami in March 2011, highlighting their potential for use during the COVID-19 pandemic to ensure that patients with hypertension have well-controlled BP. This has the potential to help mitigate the negative effects of hypertension on prognosis in patients with COVID-19.
7 | CONCLUSIONS

Patients with hypertension are at increased risk of morbidity and mortality if they become infected with SARS-CoV-2, although this is confounded by other factors such as age and vascular disorders. However, all usual antihypertensive therapy including RAS inhibitors should continue. Physicians need to take a holistic approach to patient management due the wide range of possible complications, and biomarkers can provide important prognostic information. Overall, multidisciplinary management of COVID-19 based on a rapidly growing body of evidence will help ensure the best possible outcomes for patients, including those with risk factors such as hypertension.

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CONFLICT OF INTEREST

All authors report no potential conflicts of interest in relation to this article.

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