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HYPERTENSION COMPENDIUM

Hypertension, a Moving Target in COVID-19

Current Views and Perspectives

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ABSTRACT: Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) associates with a considerable high rate of mortality and represents currently the most important concern in global health. The risk of more severe clinical manifestation of COVID-19 is higher in males and steeply raised with age but also increased by the presence of chronic comorbidities. Among the latter, early reports suggested that arterial hypertension associates with higher susceptibility to SARS-CoV-2 infection, more severe course and increased COVID-19–related deaths. Furthermore, experimental studies suggested that key pathophysiological hypertension mechanisms, such as activation of the renin-angiotensin system (RAS), may play a role in COVID-19. In fact, ACE2 (angiotensin-converting-enzyme 2) is the pivotal receptor for SARS-CoV-2 to enter host cells and provides thus a link between COVID-19 and RAS. It was thus anticipated that drugs modulating the RAS including an upregulation of ACE2 may increase the risk for infection with SARS-CoV-2 and poorer outcomes in COVID-19. Since the use of RAS-blockers, ACE inhibitors or angiotensin receptor blockers, represents the backbone of recommended antihypertensive therapy and intense debate about their use in the COVID-19 pandemic has developed. Currently, a direct role of hypertension, independent of age and other comorbidities, as a risk factor for the SARS-COV-2 infection and COVID-19 outcome, particularly death, has not been established. Similarly, both current experimental and clinical studies do not support an unfavorable effect of RAS-blockers or other classes of first line blood pressure lowering drugs in COVID-19. Here, we review available data on the role of hypertension and its management on COVID-19. Conversely, some aspects as to how the COVID-19 affects hypertension management and impacts on future developments are also briefly discussed. COVID-19 has and continues to proof the critical importance of hypertension research to address questions that are important for global health.

Key Words: angiotensin ■ blood pressure ■ COVID-19 ■ hypertension ■ risk factors

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has revealed as a novel highly virulent coronavirus responsible of a respiratory infection termed coronavirus disease 2019 (COVID-19) which started at the end of 2019 and developed in a planetary pandemic in 2020.[1] COVID-19 is associated with a high rate of mortality and represents currently the top public health concern worldwide. The majority of patients affected by COVID-19 have a favorable clinical outcome during the acute phase of the infection,[2] yet the risk of severe forms of COVID-19 and poor outcomes increases significantly with age, male sex, and the presence of co-existing chronic comorbidities.[3–6]

The presence of hypertension was initially reported in a case series from China in 27% to 30% of patients with COVID-19, while other co-morbidities such as diabetes and coronary heart diseases were observed in 19% and 6% to 8% of patients.[7] Initial reports from China,[7,8] Europe,[9,10] and United States[11,12] showed that arterial hypertension and cardiovascular diseases (CVDs) were associated with increased COVID-19-related deaths. Both conditions together with diabetes were reported as the most frequent comorbidities among severely ill patients admitted to intensive care units, who received mechanical ventilation, or died as compared with patients who had only mild illness.[13,14] Nevertheless, the role of hypertension as a risk factor for the SARS-CoV-2

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Nonstandard Abbreviations and Acronyms

ACE	angiotensin-converting enzyme
ACEI	angiotensin-converting enzyme inhibitor
ADAM17	a disintegrin and metalloprotease 17
Ang	angiotensin
ARB	angiotensin receptor blocker
AT1R	angiotensin type 1 receptor
BP	blood pressure
CCL2	chemokine [C-C motif] ligand 2
CKD	chronic kidney disease
COVID-19	coronavirus disease 2019
CVD	cardiovascular disease
CXCL10	C-X-C motif chemokine 10
HMOD	hypertension-mediated organ damage
IL	interleukin
INF	interferon
MRA	mineralocorticoid receptor antagonist
Nox	NADPH oxidase
NRLP1	neuropilin 1
PURE	Prospective Urban Rural Epidemiology
RAS	renin-angiotensin system
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
TACE	TNF-α converting enzyme
TMPRSS2	transmembrane protease serine subtype 2
TNF	tumor necrosis factor

infection and COVID-19 outcome was not well defined. The frequent association between COVID-19 and hypertension appeared not surprising, in view of the high global prevalence of hypertension.[15–17] Thus, this association does not necessarily imply a causal relationship between hypertension and COVID-19 or its severity. Because hypertension is exceedingly frequent in the elderly,[15] and older people seem to be at higher risk of being infected with SARS-CoV-2 and of experiencing a more severe course and complications of COVID-19.[4,5]

Furthermore, as the therapies commonly used to treat hypertension and CVD usually include ACE (angiotensin-converting enzyme) inhibitors (ACEIs) and angiotensin receptor blockers (ARBs),[16–18] a persistent and intense debate about the withdrawal or maintenance of chronic ACEI/ARB therapy in patients with COVID-19 has developed.[19–21] Indeed, some animal studies available at the beginning of the COVID-19 pandemic suggested a potential upregulation of ACE2 (angiotensin-converting-enzyme 2), that is, the key binding receptor promoting cell entry of SARS-CoV-2 in the respiratory tract,[22] during treatment with renin-angiotensin system (RAS) blockers.[21] Thus, a potential upregulation of ACE2 in the airway tissue of hypertensive patients upon treatment with RAS-blockers might contribute to a higher risk of SARS-CoV-2 infections and possibly to a more progressive course of COVID-19. It is obvious that conclusive data on this topic are required, in view of the high prevalence of hypertension and CVD in patients with COVID-19 and the widespread use of RAS inhibitors.

The objective of the present article is to review the available knowledge and evidence on the role of hypertension for SARS-CoV-2 infection, the development, and disease course of COVID-19. Conversely, the impact of COVID-19 on hypertension management will be discussed.

Because of the huge number of publications related to this topic that continues to grow on a daily basis a comprehensive review, even when restricted to original work, is hard to fulfill and we apologize for articles not explicitly mentioned.

THE ROLE OF THE RAS IN THE LINK BETWEEN HYPERTENSION AND COVID-19

The RAS and ACE2 in Hypertension

Looking at the mechanisms of blood pressure (BP) control from the point of view of a physiologist, the RAS undoubtedly is one of the most important BP regulating systems.[23–25] From a clinician's point of view, this system can be even considered the most important system, because the pharmacological blockade of the RAS is currently the backbone of antihypertensive therapy as evident from the recommendation in current guidelines.[16–18] In addition, RAS blockers play also a dominant role in the treatment of hypertension-mediated organ damage (HMOD), for example, left ventricular hypertrophy and other associated important cardiorenal diseases such as left ventricular dysfunction, heart failure, atherosclerosis, and chronic kidney disease (CKD).[16,24,26] The core of the RAS pathway and its involvement in BP control involves the formation of the most important effector peptide Ang II (angiotensin II). Hence, Ang II is a potent vasoconstrictor, promotes aldosterone synthesis and secretion, thus increasing sodium and water reabsorption and increasing BP.[24] The main axis in the RAS cascade, which is crucial for BP control and aldosterone secretion, concerns the signaling pathway from Ang II to the angiotensin type 1 receptor (AT_1R).[23,25,27] In addition, by inducing prooxidative, proinflammatory, and profibrotic changes the Ang II/AT_1R axis is also involved in cardiorenal remodeling.[21,25,27]

Within the RAS, several other angiotensin peptides are generated. Overall, these peptides are split off from the high-molecular protein angiotensinogen by renin

and are subsequently generated by other enzymes including the ACEs (angiotensin-converting enzymes). The classical ACE generates Ang II as the main effector peptide in the RAS by converting the decapeptide angiotensin I (Ang 1-10) into the octapeptide angiotensin II (Ang 1-8) (Figure 1).[21,25,27]

Twenty years ago, another enzyme, homologous to ACE was identified[28] and named ACE2.[23,29–31] Both ACE2 and ACE are very strongly membrane-bound enzymes.[23,29] On the other hand, smaller soluble molecules for ACE and ACE2 can be generated from the respective membrane-bound forms by cleavage and shedding from the membrane. These soluble forms circulate in blood plasma and other body fluids. Initially, the clinical relevance of ACE2 was considered low because of its potentially minor role within the RAS. The most important difference between ACE and ACE2, which was already described in the discovery, relates to the fact that ACE2 cannot be inhibited by ACEIs.[25,28] This is due to important structural differences between ACE and ACE2, which affect the respective active center of the enzyme and also explain the differences in their functions. Thus, ACE is a dipeptidyl carboxypeptidase and the most important enzyme for the conversion of Ang I to Ang II. ACE2, in contrast, is a mono-carboxypeptidase, which cleaves one amino acid at the end of peptides and forms another peptide from Ang II with only 7 amino acids, that is, Ang-(1-7). In addition, ACE2 can also cleave one amino acid from Ang I to form Ang 1-9 (Figure 1A).

In addition to the BP increasing and potentially harmful Ang II/AT_1R axis, the RAS has at least 2 other counter-regulatory (protective) arms. One arm concerns the signaling pathway via the angiotensin type 2 receptor,[32] which is also mainly activated by Ang II but additionally also by Ang 1-9. The other arm concerns the Mas receptor signaling pathway, which is mainly activated by Ang 1-7.[29] Of interest, ACE2 has a pivotal role as the main enzyme responsible for Ang 1-7 formation. The ACE2/Ang 1-7/Mas receptor axis mediates vasodilation, antioxidant, anti-inflammatory, and antifibrotic protective functions (Figure 1A).[21,27] The potential role for ACE2 in hypertension has been supported by several experimental studies in rodents.[30,31] The co-localization of the *Ace2* locus with a BP quantitative trait locus identified in inbred hypertensive rat models including the stroke-prone spontaneously hypertensive rat and normotensive Wistar-Kyoto rat models[33] appeared initially of interest, although this locus encompassed a huge chromosomal fragment and is still only crudely defined.[34] A possible link between ACE2 and hypertension was further supported by data showing lower expression of *Ace2* mRNA and ACE2 protein expression in the kidneys of these inbred hypertensive rat models.[34] Nevertheless, differential *Ace2* mRNA, ACE2 protein, and ACE2 activity levels in different compartments of the kidney could not be confirmed in subsequent detailed analysis in stroke-prone spontaneously hypertensive rat and Wistar-Kyoto rats.[35]

Other disparate differential expression patterns for ACE2 have been reported in kidney, heart, and brain of different rodent models with primary or secondary hypertension as previously reviewed.[36] Nevertheless, as recently emphasized by Kuriakose et al,[37] several further studies in rodents supported a protective effect of ACE2 in hypertension. Thus, transgenic overexpression of human ACE2 in vascular smooth muscle cells in the genetic background of stroke-prone spontaneously hypertensive rats resulted in increased circulating levels of Ang 1-7 and associated with a significant reduction in BP, cardiac hypertrophy, and vasoconstrictive response to intraarterial administration of Ang II, while endothelial dysfunction of stroke-prone spontaneously hypertensive rat was significantly improved in transgenic animals.[38] Similarly, lentiviral transfer of the murine ACE2 into young spontaneously hypertensive rats (SHR) and Wistar-Kyoto rat lowered the elevated BP in SHR but caused no BP changes in normotensive Wistar-Kyoto rat.[39] In addition, cardiovascular organ damage was reduced in SHR by the lentiviral gene transfer of ACE2. Attenuation of high BP, cardiac and/or vascular damage in rat models was further shown by pharmacological activation of ACE2[40] or administration of recombinant human ACE2.[41] Taken together, these results indicated that the antihypertensive effect of increased vascular ACE2 could be mediated by a combination of increased degradation of Ang II and augmented Ang 1-7 production.[37]

Recently, activation of the ACE2/Ang 1-7/Mas receptor axis in response to ARB treatment was also linked to the improvement of vascular remodeling in resistance arteries in rodent models with hypertension, which was independent from effects mediated the angiotensin type 2 receptor.[42]

ACE2 THE CONNECTING LINK BETWEEN BP REGULATION AND SARS-COV-2 INFECTION

The spectrum of biological functions previously assigned to ACE2[30,31] was considerably extended in 2003 when ACE2 was discovered as a receptor for the binding of the coronary virus SARS-CoV.[43] Thus, viral cell entry into target cells depends on the binding of the spike protein of SARS-CoV to its cellular receptor ACE2, which facilitates viral attachment to the cell surface and cell entry. This provided the foundation of an unexpected novel link between virology and cardiovascular medicine via ACE2 and the RAS. After this relationship had somewhat receded into the background when SARS epidemic in 2002 and 2003 ended, the link between ACE2 and SARS-CoV-2 has currently regained a strong prominence in the context

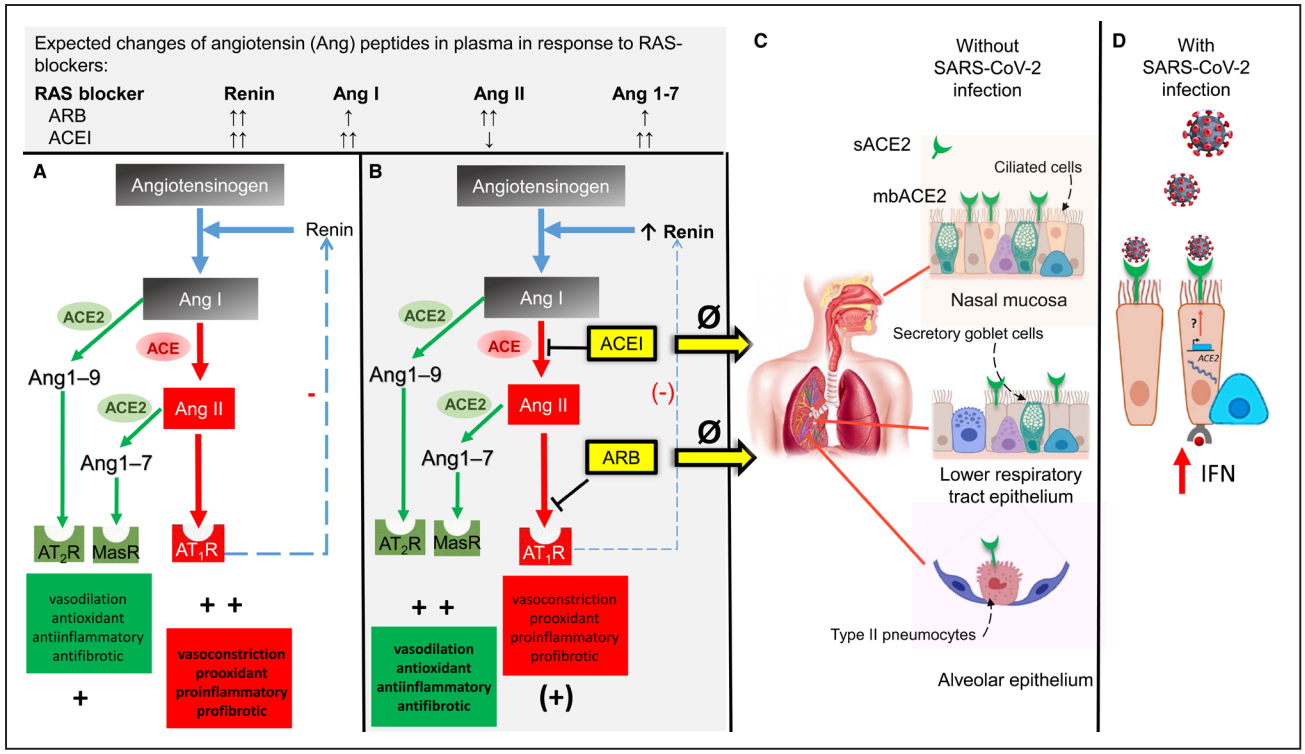

Figure 1. The renin-angiotensin-system (RAS) and its regulation by RAS-blockers in relation to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.

A, Schematic diagram of the RAS showing the role of ACE2 (angiotensin-converting enzyme 2) as a key element in the counter regulatory axis of the RAS (elements in green color, reviewed in the study by Arendse et al[25]). ACE2 counteracts the negative effects of the Ang II (angiotensin II)/angiotensin type 1 receptor (AT1R) axis (red) in the cardiovascular system, the kidneys, and other organs including the lung upon injury, for example, in response to infections in the lung.[30,31] **B**, Pharmacological treatment with ACE inhibitors or ARBs will modulate several components of the RAS either directly or by affecting feedback-loops, for example, strong upregulation of renin.[21] Treatment with RAS-blockers may protect against organ injury, for example, in the lung, by inhibiting the damaging Ang II/AT1R axis and by activation of the protective axis, particularly via the ACE2/Ang 1-7/MasR axis. Available data indicate that *ACE2* mRNA[58] and importantly also ACE2 protein expression[53] are not increased in airway cells of patients treated with ACEIs or angiotensin receptor blockers (ARBs) suggesting that these drugs do not impact on the infectivity of SARS-CoV-2. **C**, ACE2 is expressed in airway epithelial cells as mbACE2 (membrane-bound enzyme) in ciliated cells in the upper and lower respiratory epithelium and in type II pneumocytes in the lung.[52] While studies using single-cell RNA-seq profiling suggested *ACE2* mRNA expression also in secretory goblet cells of the airway, detailed expression analysis at the tissue level did not confirm the presence of neither *ACE2* mRNA nor ACE protein expression in airway goblet cells.[53] mbACE2 is cleaved (shedding) by ADAM17 (not shown) into a soluble form (sACE2) and thereby released in body fluids. After infection, SARS-CoV-2 binds through its viral spike protein to host cell mbACE2 in the respiratory system, thereby promoting viral cell entry and subsequent replication. **D**, The regulation of ACE2 in response to SARS-CoV-2 is still poorly understood.[56] An upregulation of *ACE2* mRNA expression in airway cells of patients infected with SARS-CoV-2 has been shown in several studies.[55,56] The latter has been mechanistically linked to induction of *ACE2* mRNA expression by INF (interferon), while the upregulation of mbACE2 by INF in airway cells of patients with COVID-19 remains to be shown.[56] +, activation; -, inhibition; (), impaired effect; Ø, no effect. MasR indicates Mas receptor.

of the COVID-19 pandemic. This resulted from the finding that ACE2 is also the binding receptor for SARS-CoV-2 responsible for COVID-19.[22,43–45] Accordingly, all cells expressing ACE2 and in addition co-expressing other proteins including the cellular serine protease TMPRSS2 (transmembrane protease serine subtype 2),[22] cathepsin L,[46] furin,[47] NRLP1 (neuropilin-1)[48,49] and potentially other newly identified factors[50] supporting cell entry of SARS-CoV-2 on their cell surface, can potentially take up and replicate SARS-CoV-2.

A systematic and stringent immunohistochemical analysis in human tissues revealed ACE2 expression mainly in enterocytes, renal tubules, gallbladder, cardiomyocytes, male reproductive cells, placental trophoblasts, ductal cells, eye, and vasculature, while the expression in the respiratory tract was largely low.[51] In the latter, ACE2 is expressed in the epithelial cells of the upper (with higher levels) and lower respiratory tract (lower levels), and in the lung predominantly in type II alveolar epithelia (AT-2 cells).[52] Ciliated airway of the upper airway and AT-2 cells are the primary targets for SARS-CoV-2 infection (Figure 1C).[52,53] Interestingly, a recent study using single cell and single nuclei RNA sequencing analysis in human tissues detected *ACE2* mRNA expression also in transient secretory cells of subsegmental bronchial branches together with stronger expression levels of *TMPRSS2*.[54]

Importantly, activation of the Ang II/AT_1R axis contributes not only to remodeling and organ damage in

the cardiovascular system and kidneys but also in the lung.[21,25,27] In several lung injury models (eg, sepsis) in animals, impressive protective effects of the ACE2/Ang 1-7/Mas receptor axis have been demonstrated.[21,55] In contrast, activation of the Ang II/AT_1R axis promotes lung damage. Accordingly, treatment with ACEIs or ARBs may protect the lung.[55]

In airway cells, the SARS-CoV-2 infection itself associates with increased *ACE2* mRNA expression.[56–58] Hence, in epithelial cells obtained from nasopharyngeal and bronchial samples in patients with COVID-19, an average 3-fold increase in *ACE2* expression was found in epithelial cells.[57]This correlated with INF (interferon) signals by immune cells[57] in agreement with a study that revealed the induction of *ACE2* mRNA expression by interferon in human nasal epithelial and lung tissue (Figure 1D).[56] Although preliminary data support also a potential upregulation of ACE2 protein in human airway cells in response to interferon,[56] the upregulation of membrane-bound ACE2 at the luminal surface in airway cells in patients with COVID-19 remains to be shown (Figure 1C). The upregulation of *ACE2* mRNA expression upon SARS-CoV-2 infection was not altered in patients with hypertension and/or by treatment with ACEI or ARB (Figure 1).[58] Moreover, analysis of samples from human donors in a diverse panel of banked tissue demonstrated in nasal ciliary cells that ACE2 protein is not upregulated in patients taking ARB or ACEI (Figure 1C)[53]; ACE2 protein was also not affected by sex, age, or smoking history in this study. Taken together, to the best of our knowledge, and in agreement with a previous statement,[21] convincing evidence for an upregulation of membrane-bound ACE2 in key airway cells responsible for initiation of COVID-19, by hypertension and/or the use of RAS-blockers has not been shown yet (Figure 1B and 1C).

IMPACT OF DYSREGULATED IMMUNOINFLAMMATION IN HYPERTENSION ON COVID-19

Inflammation is a complex process involving multiple cell types and secreted factors, many of which have been linked to hypertension.[59–61] The importance of the immune system in the pathophysiology of hypertension may relate primarily to its effects on inflammation, which is involved not only in BP regulation and thus in the development of hypertension, but also in the initiation and progression of cardiovascular and renal tissue damage/remodeling.[60,62] There is now extensive experimental and also clinical evidence that hypertension is associated with inflammation and immune cell activation, processes that are driven in large part by oxidative stress.[60,63] The latter is characterized by excessive production of reactive oxygen species and an altered oxidation-reduction (redox) state.[60] Important factors involved in BP regulation, such as Ang II, endothelin-1, aldosterone and salt (sodium), induce the activation of Noxs (NADPH oxidases), which are key enzymes in the generation of reactive oxygen species.[60,62,64] The resulting molecular events induce protein oxidation and dysregulated cell signaling, leading to inflammation, cell migration, and immune cell activation, among many other effects.[59–61]

Although it has not yet been proven whether inflammation in humans is causatively related to hypertension or represents a secondary effect of hypertension, it is nevertheless clear that inflammation and the dysregulated immune system are closely linked, and that immunoinflammation plays an important role in hypertension.[60,61] Several factors involved in hypertension including genetic susceptibility,[65] neurohumoral activation,[64,66] salt (sodium),[67–69] and gut microbiome[68,70] among others may promote immunoinflammation in hypertension. Notwithstanding the complexity of the interplay of these factors, it has been suggested that oxidative stress and increased generation of reactive oxygen species represent a common molecular basis linking immunoinflammation in hypertension.[60] Both innate (macrophages, microglia, monocytes, dendritic cells, and myeloid-derived suppressor cells) and adaptive immune cells (CD8+ T cells, CD4+ cells [Th1, Th17 and Treg cells], T cells and B cells) have been shown to play a critical role in hypertension.[62] They produce factors that can promote or inhibit hypertension and, once activated, can generate reactive oxygen species themselves.[60,62] Within the innate immune system, the NLRP3-related inflammasome in monocytes and dendritic cells may be particularly relevant in hypertension.[61,71] The mechanisms of immune cell activation and their effector functions in hypertension, including the complex interplay of different cell types and mediators, are still poorly defined. Nevertheless, the activation of several cytokines has been linked to hypertension in experimental and clinical studies.[72,73] In particular, IL (interleukin)-6 is one of the major cytokines regulating immunoinflammatory responses in hypertension,[73,74] while IL-1β seems not to be involved.[75] In addition, a recent study in the UK Biobank population showed a concordant and potentially causal relationship of lymphocyte count with systolic BP and diastolic BP suggesting a loss of lymphocytes in hypertension.[76] Furthermore, it has been shown that both CD4+ and especially CD8+ cells are dysregulated in hypertension and show increased production of proinflammatory cytokines such as IL-17, IL-7, IL-6, IFN-gamma, and TNF-alpha.[77] In addition, hypertension is associated with a particular immunologic profile of CD8+ cells, which tend to overproduce cytokines and are less efficient in antiviral defense.[77,78] These immune mechanisms also contribute significantly to accelerated end-organ damage. The severity of COVID-19 and risk for clinical deterioration of patients associates also with a pattern of systemic activation of cytokines, that is, a cytokine storm[74,79] that

overlaps with the intrinsic activation of immunoinflammation in hypertension. Thus, increases in IL-2, IL-6, IL-7, granulocyte colony-stimulating factor, CXCL10 (C-X-C motif chemokine 10), CCL2 (chemokine [C-C motif] ligand 2) and TNF (tumor necrosis factor)-α[21,74] have been associated with the severity of COVID-19. Moreover, in parallel with hypertension, loss of lymphocytes is also a major feature of COVID-19.[80] Particularly, SARS-CoV-2-induced immune dysregulation associated with an IL-6-driven inflammatory status with immunosuppressive and inflammatory monocytes and macrophages has been associated with severe forms of COVID-19.[80]

SARS-COV-2 RESPONSES IN AIRWAY CELLS AND HYPERTENSION

Interestingly, a potential dysregulated immunoinflammation state of patients with hypertension or CVD has been recently also documented in cells obtained from nasopharyngeal swabs using single-cell RNA sequencing analysis.[58] The data indicated an activated immunoinflammation state in airway cells from patients with hypertension that was further augmented in patients with the SARS-CoV-2 infection.[58] Moreover, the hyperinflammation status in airway cells correlated with the severity of COVID-19 in agreement with previous findings.[57] In addition, the detected differences between patients treated with either an ACEI or ARBs indicated a more favorable inflammatory transcriptome profile in patients during ACEI treatment.[58] Thus, ACEI treatment was associated with a dampened COVID-19-related hyperinflammation and activated intrinsic antiviral response profile, while patients treated with ARBs exhibited enhanced epithelial-immune cell interactions. However, cautious interpretation of this analysis is warranted as suggested by the authors largely because of the small overall number of patients with COVID-19 (n=32) included in the transcriptome analysis.[58] This seems particularly important against the background of a wide age range (32–91 years) of the included patients with COVID-19 and a variable pattern of additional CVD associated in some but not all patients with hypertension with unclear staging of the comorbidities, for example, for heart failure, that may have confounded the results. The latter could have also affected the interesting finding that viral clearance in nasopharyngeal swaps was delayed in patients treated with ARB as compared with patients treated with ACEIs.[58]

Taken together, our current understanding of dysregulated immunoinflammation in hypertension resulting in a predisposition to hyperinflammatory responses may provide a possible mechanistic link to progression and poorer outcome in COVID-19. In particular, the data suggesting accelerated immune aging in hypertension may support the notion that hypertension may be associated with COVID-19 severity. Of interest, in addition to trajectories over the life course for BP,[81] aging might thus also differentially affect the immunoinflammation status in patients with hypertension. In this regard, as recently indicated,[82] a sexual dimorphism affecting both the innate and adaptive immune system could contribute to the higher mortality risk of male patients[4] in COVID-19, particularly in the context of hypertension with inherent dysregulated immunoinflammation.

ROLE OF HYPERTENSION AND ITS ASSOCIATION WITH AGE, RACE/ETHNICITY, TARGET ORGAN DAMAGE, AND OTHER COMORBIDITIES IN COVID-19

Association With Age and Race/Ethnicity

Hypertension is widely distributed in the world, affecting 25% of the adult population with a peak of prevalence >60% in the elderly population in many countries. This is relevant to COVID-19-related mortality because older people seem to experience more severe forms and complications of COVID-19.[4] The initially reported associations between hypertension and hospitalization rates for COVID-19 in China seem to be in agreement with corresponding population data for hypertension in China.[21] Indeed, in a large database of 20 982 patients with diagnosed COVID-19 infections and information on underlying diseases, the proportion of self-reported hypertension was 12.6%,[83] which is very similar to the population data in China (10.9%) for self-reported hypertension.[84] In a French cohort, it was observed that the high comorbidity rate among patients hospitalized for COVID-19 pneumonia was up to 69% in those aged >65 years.[85]

In a cross-sectional, multicenter, observational study performed in Italy that included >1500 hospitalized patients, hypertension, and antihypertensive therapy did not affect the outcome of COVID-19.[5] Indeed, the prevalence of hypertension among patients with COVID-19 was comparable to the expected prevalence in the general population in Italy, although the median age of patients who died with COVID-19 in Italy was 79 years and 73% of them had known hypertension.[5] Interestingly, the prevalence of other important comorbidities such as diabetes, CKD, and COPD increases also with age.[86] Thus, given that age is one of the most important risk factors for COVID-19, it appears reasonable to conclude that the observed association between hypertension and COVID-19 severity and particularly mortality as reported in several studies is clearly influenced and potentially confounded by the older age of the patients affected by the disease in the different populations. The importance of age for mortality of patients with COVID-19 was highlighted in one report among others,[87,88] that analyzed

data in a large prospective cohort study of >20 000 hospital patients with COVID-19 in the United Kingdom.[4] Among 11 significantly associated risk factors in multivariable Cox proportional hazards model, the hazard ratio for death increased in patients 50 to 59 years old as compared with younger patients from 2.63 ([95% CI, 2.06–3.35], $P<0.001$) to 11.09 ([95% CI, 8.93–13.77]; $P<0.001$) in patients at least 80 years old. In contrast, apart from the role of male sex, the effect size for other comorbidities including chronic cardiac disease, COPD, CKD, or obesity resulted in hazard ratios between 1.13 and 1.51 while the effect of diabetes was not significant and the diagnosis of hypertension even not considered.[4] Another large-scale study from the UK analyzed primary care records from over 17 million adults that were linked to 10 926 COVID-19-related deaths[89] and confirmed again the important role of age, being male, and the impact of ethnicity with higher risk in Black and South Asian people. Of interest, the modestly elevated mortality risk associated with the diagnosis of hypertension after adjustment for age and sex (hazard ratio, 1.09 [95% CI, 1.05–1.14]) changed to a hazard ratio of 0.89 (95% CI, 0.85–0.93) when all variables were included in the statistical analysis with obesity and diabetes largely responsible for this decline in the hazard ratio. However, the authors detected strong evidence for a significant interaction between age and the risk for death in COVID-19, with a significantly higher risk up to the age of 70 years and a lower risk in individuals older than 70 years. They concluded that the reasons for the inverse relationship between hypertension and mortality in older individuals are unclear warranting further investigation, including detailed examination of frailty, comorbidity, and drug exposures in this age group.[89]

It is not surprising that age may represent the most significant risk factor for death due to COVID-19,[89,90] taken into account that also prior human coronaviruses and influenza viruses have been known to impact older people disproportionately.[91] There are very few studies that connect the known mechanisms of aging to the pathogenesis of viruses. However, recent data describing the immunoinflammatory changes and pathology in patients with COVID-19 suggest that immunosenescence and immunoinflammation in aging may represent major drivers in of the higher mortality rates in older patients.[86] Hence the gradual decline in immune function, that is, immunosenescence in older individuals hampers pathogen recognition, alert signaling and clearance, due to deficiencies in both the innate and adaptive immune system.[92] Blacks have a higher prevalence of hypertension than Hispanic, Americans, Whites, Native Americans, and other subgroups defined by race/ethnicity in the United States.[18] Moreover, the control rates of hypertension are lower among non-Hispanic Black adults compared with non-Hispanic White adults,[93] while morbidity and mortality attributed to hypertension are more common in Blacks and Hispanic Americans than in Whites.[18] This indicates that differences in hypertension together with differential patterns of other comorbidities including obesity, diabetes, and CKD could impact on outcome in COVID-19 in specific race/ethnic groups.[94] In the large cohort of 7868 hospitalized patients from the American Heart Association COVID-19 Cardiovascular Disease Registry, Hispanic and non-Hispanic Black patients accounted for 58.5% of all patients hospitalized and bore a greater burden of mortality and morbidity.[95] However, race/ethnicity was not independently associated with worse in-hospital mortality or major cardiovascular events after adjustment. A large cohort study of patients within a large health system in New York City found among patients hospitalized for COVID-19, that Black patients were even less likely than White patients to have severe illness and to die or be discharged to hospice.[94] In agreement with another study focusing on black non-Hispanic and white non-Hispanic patients[12] a study in an health care system in the United States including almost 3.5 Million members, revealed that race among White, Black, Hispanic, and Asian participants was the most important predictor of SARS-CoV-2 infection and hospitalization due to COVID-19 but not for mortality.[96] Thus, it appears that specific race/ethnic groups of patients are not inherently more susceptible to having poorer COVID-19 outcomes than other ethnic groups. Rather, existing structural determinants pervasive for example in Black and Hispanic communities may explain the observed disproportionately higher out-of-hospital deaths and hospitalizations due to COVID-19 in these populations.[94] Nevertheless, whether or not the higher prevalence of hypertension, poorer BP control and susceptibility for HMOD in specific populations might contribute to COVID-19 related outcomes in addition to racial/ethnic disparities should be explored in future research.

ASSOCIATION WITH TARGET ORGAN DAMAGE AND CVD

Endothelial dysfunction due to oxidative stress and inflammation is a major phenotype underlying both the pathogenesis and progression of hypertension.[24] In this regard hypertension could aggravate endothelial damage and dysfunction particularly in patients with severe COVID-19.[97,98] Hence, the vasculature (both venous and arterial) can be also affected in COVID-19 either directly by the SARS-CoV-2 virus[99,100] or indirectly as a result of the systemic inflammatory host response resulting in endotheliitis.[101,102] Endothelial cells are directly linked to the SARS-CoV-2 infection by expression of ACE2/TMPRSS2 and the potential role of SARS-CoV-2-mediated endocytosis and downregulation of ACE2 on cardiovascular complications is currently investigated.[102] Endotheliitis in COVID-19 contributes to systemic endothelial damage including disseminated intravascular

coagulation and cardiovascular complications in COVID-19. Detailed cardiac autopsy studies indicated that lymphomonocytic inflammation in arteries of patients with COVID-19 increases crescentically toward the small vessels suggesting that COVID-19-induced endotheliitis is a small vessel vasculitis not involving the main coronaries.[103] This may also apply to the cerebral vasculature and thus cerebrovascular complications in COVID-19.[104,105] With this in mind, it is understandable that the endothelium represents an important interface between hypertension and COVID-19. As a result, endothelial dysfunction in hypertension and endotheliitis in COVID-19 can mutually potentiate each other and increase the risk of cardiovascular complications in COVID-19.

Moreover, hypertension is frequently associated with other structural HMOD and cardio-renal complications, which are also more prevalent in older persons.[16] Among the various pathophysiological changes in the cardiovascular system, left ventricular hypertrophy and fibrosis is of particular clinical importance and accounts for the increased occurrence of heart failure with preserved ejection fraction[106] This pathological condition is most commonly found in the elderly patients and associates with high cardiovascular morbidity and mortality which are likely underestimated in COVID-19 studies currently reported. It should be noted that the hypertension-induced modifications may render the heart also particularly susceptible to SARS-CoV-2 induced damage[74,107–109] including the development of arrhythmias including atrial fibrillation.[110] Nevertheless, it is important to note that the information on the contribution of hypertension on the manifestations and progression of cardiovascular complications during the course of COVID-19 is scarce (Figure 2). The same applies to the role of hypertension for the progression of CKD in response to or independent from acute kidney injury events in patients with severe COVID-19.[111,112] Moreover hypertension is a well-recognized risk factor for vascular remodeling and vascular stiffness,[113,114] which may contribute to the impact of hypertension on outcomes and mortality in patients with COVID-19. Interestingly, increased arterial stiffness typically seen in older and hypertensive people[114] may exhibit an independent prognostic value for mortality in patients with COVID-19.[115] Thus, it is reasonable to assume that in patients with structural vascular changes, the risk of mortality is increased supporting the link between HMOD and COVID-19 outcomes. On the other hand, hypertension, particularly systolic hypertension, is not only a contributor to increased vascular stiffness but also a consequence of it particularly in the elderly population, which underscores the complex interplay between hypertension and HMOD that might affect COVID-19. Furthermore, as hypertension per se is major risk factor for CVD and major adverse cardiovascular events, most importantly stroke and myocardial infarction, the presence of established CVD in hypertensive patients could clearly impact on cardiovascular outcome in patients with COVID-19. Finally, the presence of other comorbidities that frequently associate with hypertension or contribute to the development and progression of the disease such as obesity[116–118] and diabetes[119,120] may also modify the course of COVID-19 and the independent role of hypertension in the disease. Taken together, the aforementioned observations support the notion that the reported association between hypertension and COVID-19 is in addition to age, likely also to be influenced by the presence of HMOD or target organ damage and CVD that occurred independently from hypertension. Finally, the role of treatment status, type of BP lowering drugs used and achieved BP control needs to be considered. Hence, while the significant role of age and male sex on the course of COVID-19 have been consistently documented,[4,87–89] the independent role of diagnosed, that is, preexisting hypertension, has not been convincingly documented so far.

ROLE OF BP IN PATIENTS PRESENTING WITH COVID-19

Only a few studies considered the role of BP and the role of achieved BP control in hypertensive patients for both the risk of infection with SARS-CoV-2 and the course of COVID-19 and related outcome. In a small retrospective study, high systolic BP but not the diagnosis of hypertension was identified as a covariate in both mortality and survival prediction by using prediction models at the time of hospital admission in a cohort of 157 patients with COVID-19.[121] Another observational, retrospective study analyzed the role of pulse pressure as a surrogate for arterial stiffness in a larger cohort of 12 170 patients admitted to Spanish centers for COVID-19.[115] In this study, elevated systolic BP>140 mm Hg at admission was also identified as a significant predictor for all-cause mortality but only when it associated with higher pulse pressure ≥60 mmHg; the latter was an independent predictor for mortality in patients with COVID-19 (odds ratio, 1.27, P=0.001). Of interest, low systolic BP<120 mm Hg showed the strongest impact of BP phenotypes on risk (odds ratio, 1.48, P=0.001).[115] These data indicate that the limited data so far available on BP phenotypes in patients with COVID-19 represents a major weakness. Thus, more data exploring the role of BP phenotypes for development and outcome in COVID-19 is needed.

IMPACT OF COVID-19 ON HYPERTENSION MANAGEMENT

Lifestyle and Risk Factors

The role of the COVID-19 pandemic on changes in lifestyle may influence BP in a variety of ways and, in the

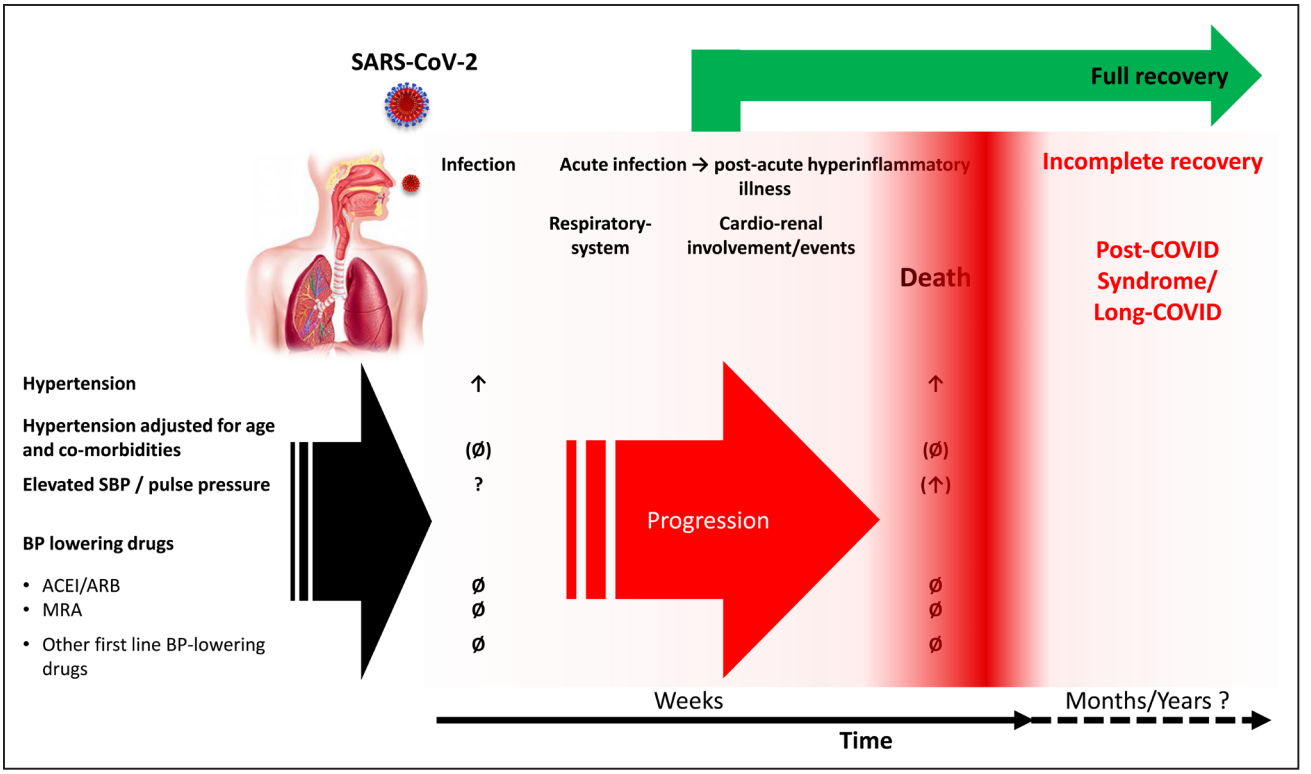

Figure 2. Synopsis of the potential impact of hypertension, blood pressure, and antihypertensive drugs on the risk of infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the course of coronavirus disease (COVID-19).
The overall impact of the parameters shown on the left on the risk of infection with SARS-CoV-2 and the risk of death as shown in available studies are indicated by the symbols. The impact of these parameters on the progression of COVID-19 or the development of long-term sequelae, for example, post-COVID syndrome and long-COVID is unclear and warrants future research; other first-line BP-lowering drugs include calcium channel blockers, thiazide/thiazide-like diuretics, and β-blockers. (), possible effect; Ø, no effect; ↕, increased risk; ?, unclear and/or no data available. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP indicates blood pressure; MRA, mineralocorticoid receptor antagonist; and SBP, systolic blood pressure.

aggregate, possibly rather unfavorably.[122] Several factors that are enhanced during lockdown and/or self-isolation have been identified and include modifications of physical activity, dietary patterns, alcohol consumption, potential increase in body weight, smoking, emotional/psychological stress, changes in sleep patterns, and diurnal rhythms may thus increase BP and promote poor BP control in treated hypertensive patients.[122,123] In addition, physician attitude and health care–related factors associated with delayed diagnosis and increased therapeutic inertia during the COVID-19 pandemic could contribute to poorer control of BP and overall cardiovascular risk.[122] In this regard, specific recommendations have been issued to preserve appropriate lifestyle and patient/physician communication.[122,123]

Therapy With BP-Lowering Drugs

Reflections on the Use of RAS-Blockers in COVID-19

Although, as mentioned above, ACEIs cannot bind and inhibit ACE2, there are several interactions and feedback loops between the individual components in the RAS.[25] The most well-known is the negative feedback between Ang II on renin secretion via AT_1R, which explains the high renin levels under therapy with ACEI and ARB (Figure 1B). Thus, a potential upregulation of ACE2 in the airway tissue of hypertensive patients upon treatment with RAS-blockers might increase the risk of infection with SARS-Cov-2 and contribute to a more progressive course of COVID-19. However, the discussion on the link between ACE2 and the use of RAS blockers was initially mainly driven by animal studies that showed a potential upregulation of ACE2 in cardiovascular organs and the kidney after treatment with RAS blockers (especially ARBs).[21] It appeared that many authors speculating on this link dismissed—among other issues such as concentration-dependent basic pharmacological aspects[20]—to differentiate between the reported effects of RAS blockers on mRNA levels versus membrane-bound ACE2 tissue protein or soluble ACE2 protein levels in body fluids, for example, blood, where the levels are normally low.[20] The latter is generated by cleavage of its membrane-anchor (shedding) by ADAM17 (a disintegrin and metalloprotease 17).[20,124] Activation of the AT1R upregulates ADAM17 and may result in increased soluble ACE2 levels as it has been shown in the brain.[124,125] Thus, the activation of the Ang II/AT1R axis in hypertension or

cardio-renal disease might result in increased activity of ADAM17,[20,124] which may promote shedding of ACE-2 from the membrane, thereby increasing soluble ACE2 and decreasing membrane-bound ACE2. However, these potential links should be noted with caution, since the expression of ADAM17 expression and activity is highly complicated and systemically increased ADAM17 expression does not necessarily enhance its shedding activity in vivo[126] as reviewed in the study by Kawai et al.[127] Nevertheless, ACE2 levels in blood or urine are possibly poor biomarkers for membrane-bound ACE2 and its potential role to modulate infectivity with SARS-CoV-2 in hypertension. On the other hand, this does not preclude a significant role for soluble/circulating ACE-2 as a biomarker for cardiovascular risk[128] as highlighted in a recent analysis in the PURE (Prospective Urban Rural Epidemiology) prospective study.[129]

In this global study, increased plasma ACE2 concentrations were associated with increased risk of total deaths and cardiovascular events including myocardial infarction, stroke, and incident heart failure.[130] As previously documented in patients with heart failure, plasma concentrations of ACE2 were higher in men than in women, but treatment with ACEI or ARB was not associated with higher plasma ACE2 concentrations.[131] In addition, genetic loci that contribute to plasma ACE2 concentrations variations have been identified in men but not in women[132] although a mechanistic link to COVID-19, based on the issues raised above, remains unclear. In this regard, a recent small observational study is of interest that analyzed ACE2 levels in individuals who were admitted to emergency room care with suspected COVID-19. The analysis of several components of the RAS including several angiotensin peptides together with ACE2 concentrations, indicated that the patients who had largely no severe COVID-19 did not exhibit major changes in either RAS activity of ACE2 in plasma.[133]

Among the recent reports that performed tissue expression analysis, Wu et al[134] showed that enalapril or losartan treatment had no effect on *Ace2* mRNA expression in lung, ileum, kidney, or heart tissues in mice. In addition, *Tmprss2* mRNA levels, co-expressed most abundantly in lung and ileum, were also not changed by either RAS blockade.[134] Of interest, the authors could also show that downregulation of angiotensinogen expression by antisense oligonucleotides reduced *Tmprss2* mRNA levels in lungs but did not change *Ace2* expression.[134]

Furin promotes host cell infection by facilitating binding of NRLP1 to SARS-CoV-2 via processing of its spike protein.[135] However, due to its function as proprotein convertase that resides in the trans-Golgi network, furin is also involved in the maturation of several proprotein substrates in the secretory pathway[136] and thereby exhibits also complex interactions with hypertension and the RAS. Furin is for example involved in maturation of ADAM17—also known as TACE (TNF-α converting enzyme)[137]—and thus indirectly linked to ACE2, the RAS, and hypertension.[124] Furthermore, furin plays a key role in the maturation of the epithelial sodium channel (ENaC) subunits linking it again to the RAS and particularly aldosterone, BP, and sodium handling.[138] Based on experimental data, it was recently suggested that ACEI and ARB might enhance furin activity and thus SARS-CoV-2 infectivity by inhibiting protease nexin 1, while the opposite effect is predicted for mineralocorticoid antagonist (MRA).[139] This provides support for future clinical studies investigating the potential protective effects of MRA in COVID-19. In addition to furin, ACE2 itself as well as the other co-factors facilitating cell entry including TMPRSS2 are potential targets for the prevention and/or treatment of COVID-19 as discussed elsewhere.[22,46–50,139]

An important study by Jiang et al[140] evaluated *ACE2* mRNA expression by RNAseq analysis in kidney tissues of 436 patients. The authors showed increasing *ACE2* expression with age but no association between renal expression of *ACE2* and either hypertension or treatment with RAS inhibitors. Another study assessing expression in the heart is of special importance, because a proteomic analysis of ACE2 was performed.[141] The authors analyzed myocardial tissue obtained from the ventricular septum during valve surgery in patients with cardiac hypertrophy. The analysis revealed an increased ACE2 protein abundance (4.76-fold upregulation compared with controls) in the hearts of patients with pressure overload heart disease due to aortic stenosis but not with volume-overload heart disease due to heart failure.[141] Thus, this study prompts further investigations to analyze whether cardiac ACE2 protein is also upregulated in common forms of left pressure overload left ventricular hypertrophy in patients with arterial hypertension, which could impact on the cardiac involvement in hypertensive patients with COVID-19.[141]

Clinical Studies With RAS Blockers in COVID-19

At the beginning of the COVID-19 pandemic, several scientific organizations and societies have consistently recommended to continue RAS-blockers in spite of their at this time still uncertain effects on susceptibility to the SARS-CoV-2 infection and clinical course of COVID-19.[142–147] After this initial phase of concern and uncertainty, multiple observational studies have been presented that evaluated the use of ACEIs and ARBs in patients with COVID-19. The reports show large variations in sample size, robustness in design, and statistical analysis. Among the available reports, 3 case-control studies that were conducted in Europe[148,149] and South Korea[150] are particularly important. In the first study, Mancia et al[148] reported a population-based study from the Lombardy region, Italy, involving 6272 confirmed patients with COVID-19 and 30 759 controls. In this study, the use of ARBs and ACE inhibitors was more frequent among patients with COVID-19 due to their higher prevalence

of CVD as compared with controls who were matched for age, sex, and place of residence. However, in multivariable adjusted analysis, the use of ARBs or ACEI or their combination with other antihypertensive drugs was not significantly associated with the risk of COVID-19 and the severity of COVID-19.[148] In the second report, de Abajo et al[149] conducted a population-based study in the Madrid region, Spain, in 1139 cases of COVID-19 hospital admissions and 11 390 matched population controls. No significant association between the use of ACEI or ARB and the risk of COVID-19 requiring admission to hospital or severity of disease was observed.[149] In the third study, Son et al[150] reported a study from South Korea in which they used the population-based data provided by the Korean National Health Insurance System. Of 16 281 subjects with hypertension, they identified 950 confirmed COVID-19 cases. After case-control matching and multivariable-adjusted conditional logistic regression analysis, exposure to RAS-blockers (95% related to ARB use) had no significant effect on the risk for COVID-19 or hospitalization.[150]

In addition to these, only few case-control studies, multiple single cohort studies, or case series that explored the role of RAS-blockers in COVID-19 have been reported.[151] Among those, an observational analysis reported by Reynolds et al[152] in a cohort of 12 594 patients who were tested for COVID-19 in a large health network in New York City, appears important.[152] In this study, 46.8% of the included patients tested positive for COVID-19 and 17.0% had severe illness. A history of hypertension was present in 34.6% of patients with COVID-19. The authors found no association between the use of RAS-blockers and an increased likelihood of a positive test or the risk of severe illness among patients with COVID-19. Importantly, this applied to both patients with hypertension and without hypertension.[152] Similar findings were also obtained in a retrospective cohort study conducted at the Cleveland Clinic Health System on 18 472 patients tested for COVID-19.[153] A recent meta-analysis of 31 available observational cohort studies provided outcome data on 87 951 patients with COVID-19.[154] The analysis revealed no association between the use of ACEI/ARB and all-cause mortality/severe COVID-19 (risk ratio, 0.94 [95% CI, 0.86–1.03], P=0.20) or occurrence of severe disease (risk ratio, 0.93 [95% CI, 0.74–1.17], P=0.55). Likewise, the analysis of the 3 population-based case-control studies identified no significant association between ACEI/ARB (pooled odds ratio, 1.00 [95% CI, 0.81–1.23], P=0.98) and all-cause mortality/severe disease.[154] Moreover, there was also no differential effect between ACEI and ARB for outcomes. Taken together, it seems that the majority of the studies available thus far documented a neutral effect of the use of either ACEIs or ARBs on both the risk for COVID-19 and severity of the disease including all-cause mortality.[151] In any case, it seems difficult to imagine to establish a cause-effect relation between the use of ACEIs or ARBs and risk for COVID-19 and adverse events in COVID-19 due to the many confounding factors that could play a role for a worse or better prognosis in observational studies.

In contrast to the initial suspicion of a harmful influence or RAS blockers, a protective effect of RAS blockade in COVID-19 could also be considered.[58,149,152,155–158] For example, in a nation-wide Swedish registry study[157] including 1.4 million patients, after adjustment of multiple potential confounders, use of ACEI or ARB was associated with a reduced risk of hospitalization/death for COVID-19 (odds ratio, 0.86 [95% CI, 0.81–0.91]) in the overall population, and with a reduced mortality in COVID-19 cases (hazard ratio, 0.89 [95% CI, 0.82–0.96]). These data are only hypothesis generating and a protective effect of RAS-blockers in COVID-19 requires to be tested in prospective randomized control trials (REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: eg, NCT04493359, NCT04394117, NCT04591210, NCT04312009, NCT04351581, NCT04366050; and DRKS00021732). Two randomized trials addressing the influence of RAS blockers on the course and prognosis of COVID-19 are published. In the BRACE-CORONA trial,[159] 659 hospitalized patients with COVID-19 with hypertension were randomized in a 1:1 ratio to either continuous ACEI/ARB treatment or temporary suspension of treatment for 30 days. The primary outcome was to determine whether ARB/ACEI discontinuation versus continuation affected the number of days alive and out of hospital at 30 days. The patients interrupting ACE inhibitors/ARBs were on average alive and out of the hospital for 21.9 days as compared with 22.9 days for those continuing therapy (average difference between groups was −1.1 days; mean ratio, 0.95 [95% CI, 0.90–1.01]; P=0.09). Thus, withdrawal of ACEI/ARB therapy in patients hospitalized for COVID-19 has no impact on the short-term prognosis of the disease. Some limitations of the study should not go unmentioned.[160,161] First, the overall number of patients was low and the study statistically probably somewhat underpowered. Second, the patients were relatively young (median age 55.1 years) and only a few were taking ACE inhibitors (17%). In addition, the overall risk of the patients was rather low because 57% had mild disease and 43% had at most moderate disease, and the mortality rate was 2.7% (9 deaths in each treatment arm). Consistent results were reported in the REPLACE COVID trial[162,163] in which 152 patients with hypertension (mean age, 62 years; 45% women) were randomized to continue or discontinue ACEI/ARBs. Again, there were no significant differences between groups in the incidence of the primary outcome, consisting in a global rank score of time to death, duration of mechanical ventilation or extracorporeal membrane oxygenation, time to renal replacement, or inotropic vasopressor therapy and multiorgan

dysfunction during hospitalization. These results support the current view to maintain ACEI/ARBs during COVID-19 hospitalization in patients with hypertension, since these compounds do not promote worse outcomes and the opposite may reveal true, as it is currently investigated in the trial RAMIC (Ramipril for the treatment of COVID-19), which investigates the potential benefits of ramipril 2.5 mg compared with placebo in improving survival, reducing intensive care unit admissions or use of mechanical ventilation support in 560 patients admitted to hospital for severe COVID-19 (NCT04366050). Similarly, 2 randomized controlled trials are investigating the effect of the ARB losartan (NCT04312009) or the MRA spironolactone (NCT04345887) versus placebo in patients admitted to hospital for COVID-19.

Role of Other Antihypertensive Drugs

The primary intention and end point in most reported studies was related to the role of ACEIs and ARBs (ie, RAS-blockers) in COVID-19 and did not primarily address the role of MRA, although this was intended in the title of some studies when referring to blockers of the renin-angiotensin-aldosterone system.[148,152] Nevertheless, the role of MRA and other first-line antihypertensive drug classes, including calcium channel blockers (CCBs), thiazides/thiazide-like diuretics, and β-blockers was also assessed, despite these analyses received much less attention.[164] In the study by Mancia, only a few (3.8%) of the COVID-19 cases were treated with MRA and no significant effect on COVID-19 was found in adjusted analysis. Since several exogenous/environmental as well as endogenous (eg, emotional stress)[122] can further trigger the activation of sympathetic system in hypertensive patients with COVID-19, the use of β-blockers may provide beneficial effects as suggested.[152,165] In the cohort study from New York City, United States, reported by Reynolds,[152] the authors investigated in addition to RAS-blockers also all other classes of first line BP-lowering drugs. Similarly to the findings obtained for RAS-blockers, no substantial increase in the likelihood of a positive test for COVID-19 or in the risk of severe COVID-19 among patients who tested positive was found in association with the use of CCB, thiazide diuretics or β-blockers. However, in separate analysis of the different end points, individuals treated with β-blockers had a marginally lower likelihood of a positive COVID-19 test than patients not treated with these agents.[152] In contrast, a slightly higher likelihood of severe illness associated with the previous use of CCBs was obtained.[152] Among the case-control studies that investigated primarily the role of RAS-blockers as summarized above no significant association with the other first-line BP-lowering drugs in separate analysis for each drug class[148] or for combination therapy with RAS-blockers[149] and the investigated COVID-19 related outcomes was found. Treatment with loop diuretics was apparently associated with an increased risk of COVID-19.[148] Nevertheless, the use of loop diuretics in this cohort could reflect the existence of more severe comorbidities such as heart failure or advanced CKD, the severity of which could not be appropriately quantified in the study.[148] The latter highlights again the important role of potential confounding by the pattern and severity of comorbidities in these analyses.

CONCLUSIONS AND FUTURE DIRECTIONS

Hypertension is the most common comorbidity in middle-aged and older adults who represent as well the population carrying the heavier burden of fatal COVID-19 cases. Nevertheless, at this time, there are no consistent proofs that hypertension is an independent risk factor for worse outcomes in patients with COVID-19. A possible beneficial/harm effect using the pivotal ACEIs or ARBs first-line BP-lowering drugs had become controversial for the management of hypertensive patients at the beginning of the current COVID-19 pandemic.[19–21] The prevailing evidence currently supports that these RAS inhibitors are safe and should not be discontinued for fear of an increased risk of COVID-19. This reinforces previous statements presented by several national and international cardiovascular and hypertension scientific societies[142–147] to recommend the continued use of antihypertensive medications and in particular of ACEIs/ARBs in patients with COVID-19.

Many knowledge gaps (Figure 2) remain to fill with regard to the relationship between hypertension and its management in relation to COVID-19. It is unclear how much physician and health care–related factors associated with delayed diagnosis and increased therapeutic inertia will contribute to poorer BP control and thus increased cardiovascular risk during the COVID-19 pandemic. This applies also to the effects of hypertension on the long-term outcome of patients after acute COVID-19 disease with regard to either full recovery (healing)[166] or the development of long-term sequelae[167,168] (Figure 2). The latter could be driven by aggravated endothelial dysfunction due to COVID-19 induced endothelial damage and endotheliitis[102] or other acquired cardiovascular injuries during acute COVID-19. There are as well interesting perspectives that were widened during COVID-19 pandemic and lock-down of the population. The COVID-19 outbreak in fact induced rough challenges in providing health care including delayed care delivery for patients with cardiovascular pathologies that were afraid to attend hospitals or even outpatient practice for hypertension care.[122] To afford these unexpected hurdles in the prevention and care of patients, technological advances were developed to provide new innovative solutions, in particular, regarding the use of telemedicine or telehealth applictions.[169–172] This appears highly appropriate for the management of

chronic diseases including hypertension.[122,169,173] Remote care may result in multiple benefits by reducing resource use in health care systems, improving appropriate access to care, while minimizing the risk of infections by reducing exposure and direct transmissions.[174] Consequently, the use of remote care using telehealth applications might have also positive psychological impact on patients by providing a safer access to care givers.[175] In addition, physicians who are in quarantine can employ these services to assist their patients remotely.[176] Intensive further development of telehealth technology will undoubtedly take place and has certainly received a significant boost from the current requirements and experiences during the COVID-19 pandemic. This will require the development of tailored approaches for hypertension care and suitable training of health care professionals involved. Currently, telemedical care appears already as a very welcome by-product in hypertension management as many doctors experienced during the COVID-19 pandemic. Furthermore, COVID-19, driven by the various links and controversies summarized in this review, seems to have provided a powerful stimulus to hypertension research. Hopefully, this trend will continue and help close the bitter gap[177] that has emerged in recent years compared with general biomedical research.[178] COVID-19 has and continues to proof the critical importance of hypertension research to address questions that are important for global health.

ARTICLE INFORMATION

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