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Review

Counter-regulatory renin-angiotensin system in hypertension: Review and update in the era of COVID-19 pandemic

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ABSTRACT

Cardiovascular disease is the major cause of mortality and disability, with hypertension being the most prevalent risk factor. Excessive activation of the renin-angiotensin system (RAS) under pathological conditions, leading to vascular remodeling and inflammation, is closely related to cardiovascular dysfunction. The counter-regulatory axis of the RAS consists of angiotensin-converting enzyme 2 (ACE2), angiotensin (1–7), angiotensin (1–9), alamandine, proto-oncogene Mas receptor, angiotensin II type-2 receptor and Mas-related G protein-coupled receptor member D. Each of these components has been shown to counteract the effects of the overactivated RAS. In this review, we summarize the latest insights into the complexity and interplay of the counter-regulatory RAS axis in hypertension, highlight the pathophysiological functions of ACE2, a multifunctional molecule linking hypertension and COVID-19, and discuss the function and therapeutic potential of targeting this counter-regulatory RAS axis to prevent and treat hypertension in the context of the current COVID-19 pandemic.

Abbreviations: ADAM17, A Disintegrin and Metalloproteinase 17; ACEI, ACE inhibitors; AC, Adenylate cyclase; AGT, Angiotensinogen; Alamandine-HPβCD, Alamandine/2-hydroxypropyl-β-cyclodextrin; atRA, All-trans retinoic acid; AMPK, AMP-activated protein kinase; AT1R, Ang II type-1 receptor; ARB, Ang II type-1 receptor blockers; AT2R, Ang II type-2 receptor; Ang I, Angiotensin I; Ang II, Angiotensin II; ACE, Angiotensin-converting enzyme; ACE2, Angiotensin-converting enzyme 2; AD, Aspartate decarboxylase; ANP, Atrial natriuretic peptide; BP, Blood pressure; BK2R, Bradykinin B2 receptor; Bdkrb2$^{-/-}$, Bradykinin B2 receptor-deleted; CaMKII, Calcium/calmodulin-dependent protein kinase II; CCB, Calcium channel blockers; CPA, Carboxypeptidase A; CVD, Cardiovascular disease; CTSL, Cathepsin L; CNS, Central nervous system; CSF, Cerebrospinal fluid; C21, Compound 21; COVID-19, Coronavirus disease 2019; DOCA, Deoxycorticosterone acetate; DES, Diethylstilbestrol; DIZE, Diminazene aceturate; D-Pro, D-Pro^{7}-Ang (1-7); DUSP, Dual specificity phosphatase; eNOS, Endothelial nitric oxide synthase; EDR, Endothelium-dependent relaxation; eQTL, Expression quantitative trait loci; GPCRs, G protein-coupled receptors; GI, Gastrointestinal; HAECs, Human aortic endothelial cells; long COVID, Long-term consequence of COVID-19; MrgD, MAS-related GPR family member D; MAP, Mean arterial pressure; mACE2, Membrane-bound ACE2; MKP1, Mitogen-activated protein kinase-phosphatase 1; MrgDR, MrgD receptors; MI, Myocardial infarction; NHE1, Na^{+}/H^{+} exchanger-1; NET, NE transporter; NAM, Negative allosteric modulator; NRLP1, Neuropilin-1; NEP, Neutral endopeptidase; NO, Nitro oxide; NE, Norepinephrine; NFAT, Nuclear factor of activated T-cell; PVN, Paraventricular nucleus; PDGF-BB, Platelet-derived growth factor-BB; PRCP, Prolyl carboxypeptid ase; PEP, Prolyl oligopeptidase (prolyl endopeptidase); PLZF, Promyelocytic zinc finger protein; PGI_2, Prostacyclin; PAH, Pulmonary arterial hypertension; ROS, Reactive oxygen species; RBD, Receptor-binding domain; rACE2, Recombinant ACE2 protein; rACE2-Fc, rACE2 and the immunoglobulin fragment Fc segment; rhACE2, Recombinant human ACE2 protein; RSNA, Renal sympathetic nerve activity; RAS, Renin-Angiotensin System; RVLM, Rostral ventrolateral medulla; SARS, Severe acute respiratory syndrome; sc-RNAseq, Single-cell RNA-seq; SM, Smooth muscle; sACE2, Soluble ACE2; sGC, Soluble guanylate cyclase; SHRs, Spontaneously hypertensive rats; SHP1, Src homology 2-containing protein-tyrosine phosphatase-1; THOP1, Thiocyanate oligopeptidase; TMPRSS2, Transmembrane protease serine isoform 2; 2K1C, Two-kidney-one-clip; VSMCs, Vascular smooth muscle cells; XNT, Xanthone; β-AIBA, β-aminoisobutyric acid.

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1. Introduction

Globally, cardiovascular disease (CVD) is the major cause of mortality and disability, with hypertension being the most prevalent risk factor [1]. The Renin-Angiotensin System (RAS) is one of the critical hormonal systems in human cardiovascular homeostasis and an essential player in the regulation of blood pressure, fluid and electrolyte balance, and systemic vascular resistance [2]. Excessive activation of the RAS under pathological conditions leads to vascular remodeling and inflammation, which is closely associated with cardiovascular dysfunction. RAS consists of several important enzyme-mediated conversions and ligand-receptor binding pathways. Since the discovery of renin in 1898, research on RAS components has been a hot topic over the past 100 years, including their participation in the regulation of both cardiovascular function and pathologies, and also as effective therapeutic targets in the prevention and treatment of CVD [3]. In the classical RAS, renin cleaves liver-derived angiotensinogen into decapeptide angiotensin I (Ang I) which is subsequently converted to the highly physiologically active octapeptide angiotensin II (Ang II) by angiotensin-converting enzyme (ACE). By binding to angiotensin receptors, Ang II exerts pathophysiological effects such as elevating blood pressure, promoting cardiac and vascular remodeling, and interrupting renal water-sodium balance, which in turn leads to hypertension, end-stage organ failure, atherosclerosis, and heart failure [4].

The discovery of the core non-canonical RAS component, angiotensin-converting enzyme 2 (ACE2), opened a new window for studying the counter-regulatory arm of the RAS [5]. There is substantial evidence that the products of ACE2, including angiotensin (1–7), angiotensin (1–9) and alamandine, generate opposite effects of Ang II, suggesting the balance of the RAS and its counter-regulatory arm is critical in cardiovascular physiopathology. Moreover, the severe acute respiratory syndrome (SARS) outbreak in 2003 and the Coronavirus disease 2019 (COVID-19) outbreak in 2019 brought to the attention of scientists another vital role of ACE2, the binding receptor for coronaviruses SARS-CoV and SARS-CoV2 entering cells. In particular, to date (Oct 1, 2022), there have been over 600 million confirmed cases of COVID-19 worldwide, including 6.5 million deaths, reported to WHO (https://covid19.who.int/), while variants of the virus are still rampant. Hypertension and COVID-19 are closely associated, as hypertension aggravates the negative consequence of viral infection, while the long-term consequence of COVID-19 (Long COVID) also includes new-onset hypertension [6,7]. Therefore, the counter-regulatory RAS may have important pharmacological potential as a therapeutic target against viral infection and for treating Long COVID.

In light of the emergence of numerous studies evaluating the pathophysiological effects and signaling pathways elicited by the counter-regulatory RAS, in this review, we aimed to summarize and provide an update on the current understanding of the complex regulation of the non-canonical RAS in hypertension. We highlighted the roles of ACE2, a multifunctional molecule linking hypertension and COVID-19, and discussed the pharmacological investigation of the counter-regulatory RAS axis against hypertension in the context of the ongoing COVID-19 pandemic.

2. Counter regulatory RAS components and pathways in hypertension

2.1. Angiotensin-converting enzyme 2 (ACE2)

ACE2, a type 1 integral membrane glycoprotein mainly expressed in vascular endothelial cells and renal tubular epithelium, is the first recognized homolog of human ACE [8]. The catalytic metallopeptidase unit located in the extracellular domain of ACE2 shares 42% sequence identity (61% sequence similarity) with the catalytic domain of ACE [5]. Nevertheless, ACE2 differs from ACE in that it works as a carboxypeptidase rather than a dipeptidase; thus, ACE2 activity cannot be inhibited by typical ACE inhibitors [9]. Ang II appears to be the major substrate for ACE2 [5,9,10], while other peptides, such as Ang I, vasoactive bradykinin (1–8), des-Arg-kallidin, apelin-13 and apelin-36 as well as other possible substrates might also have a relatively low affinity to be degraded by ACE2 [5,11,12]. So far, as a decarboxylase, ACE2 has been known to catalyze the following three reactions: a) cleavage of Ang II to Ang (1–7), b) breakdown of Ang I to Ang (1–9), and c) cleavage of Ang A (an analog of Ang II) to alamandine. Fig. 1 illustrates the relationships among the major members of the counter-regulatory RAS, which consists of core enzyme-mediated peptide conversions and ligand-receptor binding pathways.

The relationship between ACE2 gene variations and the risk of hypertension in different ethnic populations has been the focus of numerous genetic association studies. One of the first studies to show a link between ACE2 polymorphisms and hereditary hypertension is the Leeds Family Study [13]. Variants rs2285666 (genotype GG, AA), rs1978124 (genotype GG) and rs2106809 (genotype TT, T) have been reported to be associated with a higher risk of hypertension in at least two different ethnic groups, but these studies did not sufficiently represent the generalizability of the link across ethnicity [14–23].

ACE2 is dynamically expressed across the progression of hypertension associated with RAS activation. In spontaneously hypertensive rats (SHRs), renal tubular expression of ACE2 decreases with the onset of hypertension and remains low compared to control rats, while it is highly expressed at birth in these rats [24]. Although there are no appreciable differences in cardiac ACE2 activity between neonatal SHRs and WKY rats, adult SHRs have much lower cardiac ACE2 expression and activity than age-matched WKY rats did [25–29]. However, salt loading has no effects on the cardiac ACE2 gene or activity in SHRs or salt-sensitive Sabra rats [30,31]. When assessing the involvement of ACE2 in hypertension, the discrepancies in observed alterations bring attention to the importance of the strain and model used.

The ACE2 gene corresponds to a specific quantitative trait locus on chromosome X that was previously found as a quantitative locus for blood pressure in preclinical models of hypertension [32]. Moreover, in clinical studies, patients with hypertension had higher serum ACE2 activity compared to healthy individuals, which indicates the association between increased blood pressure and elevated ACE2 activity due to a possible compensatory response [33,34]. Indeed, several preclinical models of hypertension have shown that the upregulation of ACE2 has an anti-hypertensive effect [25,35–38]. The elevated blood pressure can be decreased by lentiviral or adenoviral overexpression of ACE2 via increasing the expression of the components of the counter-regulatory RAS, such as Ang (1–7), MasR and Ang II type 2 receptor (AT2R) [25,36,39]. Likewise, recombinant human ACE2 protein (rhACE2) administration attenuated acute Ang II infusion-induced hypertension and was associated with the rebalance of plasma Ang II and Ang (1–7) levels [38,40]. It also reduced plasma and renal cortex levels of Ang II in diabetic Akita mice, which was linked to reduced blood pressure and postponed development of diabetic nephropathy [41]. Although the effects of intravenous rhACE2 administration in healthy subjects were well tolerated with low immune response and increased plasma ACE2 without affecting blood pressure or heart rate [42], studies examined the efficacy of this genetic ACE2 overexpression to reduce blood pressure in hypertensive patients are currently still lacking.

Reduced expression of ACE2 has been linked to CVDs in a variety of animal models, which is largely attributed to the imbalance of the production of Ang II and Ang (1–7). ACE2 deficiency is associated with the upregulation of putative atherosclerotic mediators, such as cytokines and adhesion molecules [43]. In ApoE$^{-/-}$ mice, ACE2 depletion is associated with increased plaque accumulation [44–46]. Low levels or complete knockout of ACE2 can lead to elevated Ang II levels, which eventually results in hypertension. Downregulation of ACE2 has also been implicated in the pathogenesis of cardiac dysfunction and central hypertension. A severe cardiac contractility defect, an increased Ang II level, and the upregulation of hypoxia-induced genes in the heart were

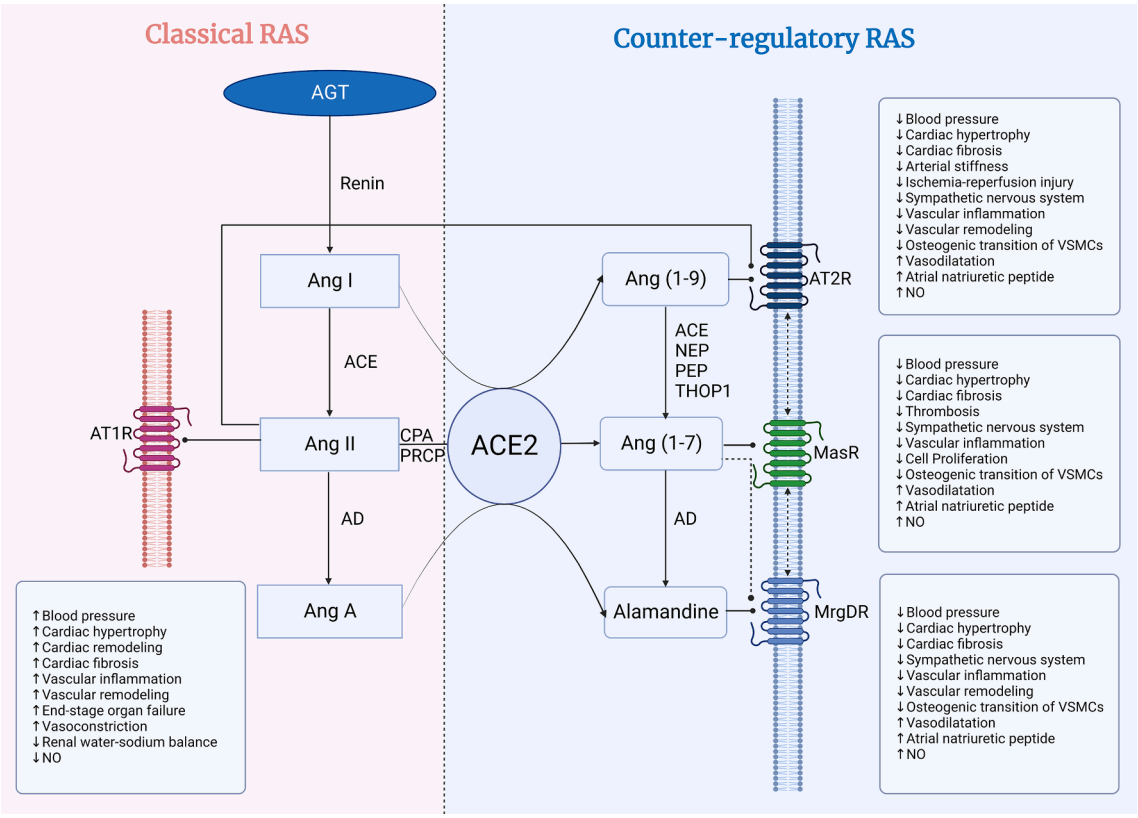

Fig. 1. Classical and counter-regulatory renin-angiotensin system (RAS). Left: The classical RAS pathway. Angiotensinogen (AGT) can be cleaved by renin to form angiotensin I (Ang I). Ang I is converted by angiotensin-converting enzyme (ACE) to generate angiotensin II (Ang II). Ang II activates the Ang II type-1 receptor (AT1R) and the Ang II type-2 receptor (AT2R). The activation of AT1R leads to increased blood pressure, cardiac hypertrophy and fibrosis, vascular inflammation and remodeling, end-stage organ failure, decreased nitric oxide (NO) bioavailability and interrupted renal water-sodium balance. Moreover, Ang II can also produce angiotensin A (Ang A) with the action of aspartate decarboxylase (AD). **Right:** The counter-regulatory RAS pathway. Angiotensin-converting enzyme 2 (ACE2) is considered as the core component of the counter-regulatory arm of the RAS, catalyzing the following three reactions: a) cleavage of Ang II to Ang (1–7); b) breakdown of Ang I to Ang (1–9); and c) cleavage of Ang A to alamandine. Alternatively, Ang(1–7) can be formed from Ang (1–9) cleavage by ACE, neutral endopeptidase (NEP), prolyl endopeptidase (PEP) and thiocyanate oligopeptidase (THOP1). Alamandine can also be generated from Ang (1–7) catalyzed by AD. Ang (1–7) binds to Mas receptor (MasR) to elicit vasoprotective effects, including lowered blood pressure, reduced cardiac hypertrophy and fibrosis, thrombosis, inflammation, cell proliferation, inhibits the sympathetic nervous system and osteogenic transition of vascular smooth muscle cells (VSMCs), but promotes vasodilatation, the release of atrial natriuretic peptide, and NO production. By binding to AT2R and Mas-related G protein-coupled receptor member D (MrgDR), respectively, Ang (1–9) and alamandine exhibit cardioprotective effects, such as enhanced vasodilatation, reduced blood pressure, and improved cardiac hypertrophy and fibrosis. Illustration was created with BioRender.com.

observed in mice with targeted ACE2 disruption [32,47]. In rat brain areas, ACE2 gene deletion leads to impaired baroreflex sensitivity and autonomic function [48]. In particular, the downregulation of ACE2 in the rostral ventrolateral medulla (RVLM) [37], the periventricular nucleus (PVN) [39], the hypothalamus as well as the cerebrospinal fluid (CSF)[49,50], were reportedly associated with elevated blood pressure in different hypertensive animal models including SHRs, Ang II-induced and deoxycorticosterone acetate (DOCA) salt-induced hypertension.

In addition to the previously described membrane-bound ACE2 (mACE2) that is expressed in a tissue- or cell-specific manner, another ACE2 in the circulation, soluble ACE2 (sACE2), can be formed by cleavage of the extracellular domain of the full-length ACE2 catalyzed by A Disintegrin and Metalloproteinase 17 (ADAM17), a member of the exonuclease family. sACE2 has a similar carboxymonopeptidase function to mACE2 as part of the protective branch of RAS, which cleaves the carboxyl-terminal amino acid phenylalanine Ang II and hydrolyses it into the vasodilator Ang (1–7). sACE2, found in plasma and urine, is considered as a biomarker of cell death since it is released from the cytoplasmic membrane into the circulation when tissues are injured in CVDs, such as coronary artery disease [51,52], myocardial infarction (MI) [52], heart failure [53,54], atrial fibrillation [52,55], and aortic stenosis [56–58]. Moreover, aging, metabolic syndromes like obesity, hypertension, insulin resistance, and dyslipidemia are also closely associated with elevated plasma sACE2 level or activity [34,58,59], implying that sACE2 assessment could be a valuable diagnostic and prognostic indicator for patients with cardiometabolic diseases. Although the increase in sACE2 may also signify a compensatory response to harmful stimuli, it is yet unclear whether this process was driven by increased local synthesis or enhanced tissue shedding. By contrast, the increases in serum ACE2 level and activity following therapeutic intervention in patients with acute decompensated heart failure or hypertension were linked to positive clinical outcomes, providing more evidence in favor of therapeutic strategies to raise ACE2 in a variety of diseases [34,60]. However, additional mechanistic investigation into the dynamics of the sACE2 in physiopathological progress is needed in both animals and humans.

2.2. *Ang (1–7)-MasR*

In 1988, Santos et al. first discovered that Ang (1–7) could be converted from Ang I or Ang II in an ACE-independent manner [61], suggesting that Ang (1–7) is a new bioactive product of the RAS. In light of the discovery that ACE2 is the key enzyme for the hydrolysis of Ang II to form Ang (1–7) [8], the pathways of Ang (1–7) production to date are: (1) cleavage of Ang I by endopeptidases including thiocyanate oligopeptidase (THOP1), neutral endopeptidase (NEP) and prolyl

oligopeptidase (also known as prolyl endopeptidase, PEP); (2) hydrolysis of Ang II by carboxypeptidases, including ACE2, carboxypeptidase A (CPA) and prolyl carboxypeptidase (PRCP); (3) cleavage of Ang (1–9) by ACE, NEP and PEP [9,62–64], while Ang (1–9) is the intermediate product generated by cleavage of Ang I by ACE2. Furthermore, among those pathways, ACE2-mediated hydrolysis of Ang II is the predominant one to produce Ang (1–7) with the highest catalytic efficiency.

The binding receptor for Ang (1–7) is Mas receptor (MasR), a bioactive peptide encoded by the MAS1 gene. In the 1980s, MAS1 was initially identified as a human oncogene based on its ability to induce tumorigenicity of NIH 3T3 cells in nude mice [65,66]. MasR belongs to a member of G protein-coupled receptors (GPCRs) with a predicted seven transmembrane segment structure. MasR is predominantly expressed in the brain and testis, while moderate levels are detected in the heart, kidney, and blood vessels [67].

Through the stimulation of MasR, Ang (1–7) activates the NO-soluble guanylate cyclase (sGC) pathway, subsequently triggering vasoprotective effects both in vitro and in vivo. For example, in human endothelial cells which express MAS, Ang (1–7) mediates endothelial nitric oxide synthase (eNOS) activation and NO production via a PI3K/AKT-dependent pathway, which was confirmed in Mas-transfected Chinese hamster ovary cells [68]. Additionally, in different vasculature of different species, Ang (1–7) exerts a vasodilatory effect via the release of endothelium-derived NO [69–79], but it is still confined to certain vascular beds [80,81]. The cellular effects of Ang (1–7) are diminished in MAS-KO human endothelial cells, and the vasodilatory function of Ang (1–7) is also lost in aortic rings and mesenteric arteries from Mas-KO mice [82–85]. Apparent endothelial dysfunction in FVB/N Mas-deficient mice suggests a crucial role of the Ang (1–7)-Mas axis in the regulation of endothelial function [86,87]. Interestingly, a phosphoproteomics study showed that Ang (1–7) produces an antiproliferative action in human aortic endothelial cells (HAECs) by activating the downstream FOXO1 transcription factor, a well-known negative regulator of the AKT signaling pathway [88]. Nevertheless, other studies indicate that Ang (1–7) may function through the hetero-oligomeric complex of MasR and Ang II type-1 receptor (AT1R), and MasR can antagonize the actions of AT1R [89,90].

In addition to the vasodilator effect, the Ang (1–7)-MasR axis also activates other downstream cascades to inhibit cardiovascular pathological processes, including antihypertrophic, antiproliferative and antithrombotic actions. The vast majority of the research on Ang (1–7) or the MasR agonists in the heart focuses on its cardioprotective effects, such as improved arrhythmias and post-ischemic cardiac function [91–95]. In cardiac fibroblasts, signaling molecules, such as Src homology 2-containing protein-tyrosine phosphatase-1 (SHP1) [96] and dual specificity phosphatase (DUSP) [97,98], are found to be the targets of the Ang (1–7)-MasR activation, which consequently suppresses the activities of mean arterial pressure (MAP) kinases (ERK1/2 and p38) and attenuates the Ang II-induced synthesis of mitogenic prostaglandins. At high atrial pacing, Ang (1–7)-MasR activation also stimulates the secretion of atrial natriuretic peptide (ANP) via the PI3K-Akt pathway and the activation of Na^+/H^+ exchanger-1 (NHE1) and calcium/calmodulin-dependent protein kinase II (CaMKII) to decrease cardiac hypertrophy [99]. Treatment of cardiomyocytes with Ang (1–7) prevented Ang II-induced hypertrophy through inhibiting calcineurin/nuclear factor of activated T-cell (NFAT) signaling cascade via PI3K-AKT-NO-cGMP-dependent pathway [92]. The increased NO release promoted by Ang (1–7) was mediated through the activation of eNOS and neuronal nitric oxides synthase (nNOS) [100,101].

In vascular smooth muscle cells (VSMCs), Ang (1–7) inhibits cell proliferation through the release of prostacyclin (PGI_2), which subsequently increases the production of cAMP and the activation of cAMP-dependent protein kinase (PKA) and attenuates ERK1/2 activation [102]. The Ang (1–7)-MasR axis also restores the reduced expression of lineage markers, including smooth muscle (SM) α-actin, SM22α, calponin and smoothelin, and inhibits the osteogenic transition of VSMCs [103].

As for the antithrombotic effect, Ang (1–7)-MasR decreases thrombosis in bradykinin B2 receptor-deleted ($Bdkrb2^{-/-}$) mice by increasing plasma NO and PGI_2 to reduce platelet spreading and glycoprotein VI activation [104]. Acute or chronic oral treatment with Ang-(1–7)-CyD, a modified Ang (1–7) in the oral formulation, can increase plasma Ang (1–7) concentration, promotes an antithrombotic effect in SHRs [105], and this striking effect is absent in $Mas^{-/-}$ mice [106].

Apart from the local protective effects in the cardiovascular system, Ang (1–7) functions as an important neuromodulator, particularly in the hypothalamus, dorsomedial and ventral medulla, and areas involved in the tonic and reflex control of arterial pressure and heart rate [107–111]. In situ central Ang (1–7) infusion decreases blood pressure in transgenic hypertensive rats, DOCA salt-induced hypertensive rats, aldosterone/NaCl induced hypertensive rats, fructose-induced metabolic syndrome rats, two-kidney-one-clip (2K1C)-operated rats with renovascular hypertension, and stress-induced hypertensive rat [112–117]. The Ang (1–7)-MasR axis regulating blood pressure in the nervous system is linked to several central effects, such as elevated NOS activity, increased NO generation in the brain, enhanced release of arachidonic acid and vasopressin, decreased norepinephrine (NE) bioavailability, and suppression of oxidative stress. For example, Ang (1–7) upregulates hypothalamic NOS as a compensatory and protective mechanism to combat hypertension in SHRs [117]. It also acts as a neuromodulator to balance the stimulatory effects of Ang II by reducing presynaptic NE synthesis and release in the hypothalamus [118], which is mediated through the bradykinin/NO-dependent mechanism [118,119]. Ang (1–7)-MasR activation induces a chronic stimulatory effect on neuronal NE transporter (NET) expression via PI3K/Akt and Erk1/2-dependent pathways, indicating that Ang (1–7)-MasR axis regulates a presynaptic mechanism in maintaining appropriate synaptic NE levels under hypertensive conditions [120,121]. Fig. 2 (left) illustrates the signaling transduction cascades mediated by Ang (1–7)-MasR.

2.3. Ang (1–9)-AT2R

Ang I is cleaved by ACE2 and NEP to produce Ang (1–9) and Ang (1–7), respectively [122]. However, Ang (1–9) is less abundantly investigated compared to Ang (1–7). Ang (1–9) is hydrolyzed more slowly than Ang (1–7), and Ang (1–7) can also be synthesized from Ang (1–9) by the action of ACE [5]. Ang (1–9) is thought to reduce Ang II levels because it competes with Ang I as a substrate for the active site of ACE, thereby increasing Ang (1–7) levels and stimulating bradykinin release in endothelial cells [123]. The receptor for Ang (1–9) is now found to be the AT2R which is another binding receptor for Ang II. Thus, Ang (1–9) can compete with Ang II to activate AT2R to trigger urinary natriuretic response and NO production, thereby regulating vasodilatory effects and lowering blood pressure [124,125]. This peptide has several cardioprotective effects, such as protecting cardiomyocytes from cell death induced by ischemia–reperfusion injury and attenuating inflammation, cardiac hypertrophy, and fibrosis [124,126].

Although AT1R mediates most of the recognized Ang II actions, AT2R-mediated actions in the cardiovascular system are complicated. AT2R is a member of the GPCR superfamily that functions by coupling G_i [122]. There is evidence that AT2R-mediated actions are distinct from and often opposite to those of AT1R. Since AT2R is less expressed in healthy adult tissues than AT1R, the role and cellular signaling of AT2R are less characterized than those of AT1R [127–130]. Most of the studies performed in the last decade show that activation of AT2R leads to a protective response to prevent the development of pathological processes such as inflammation, activation of the sympathetic nerve, cell apoptosis, autophagy, cardiac fibrosis, and arterial stiffness [130]. Meanwhile, AT2R stimulation activates defense mechanisms in the heart, including cardiac regeneration, vasodilation of coronary microvessels and compensatory hypertrophy of cardiomyocytes [130]. AT2R-deficient mice show elevated basal blood pressure and elevated blood

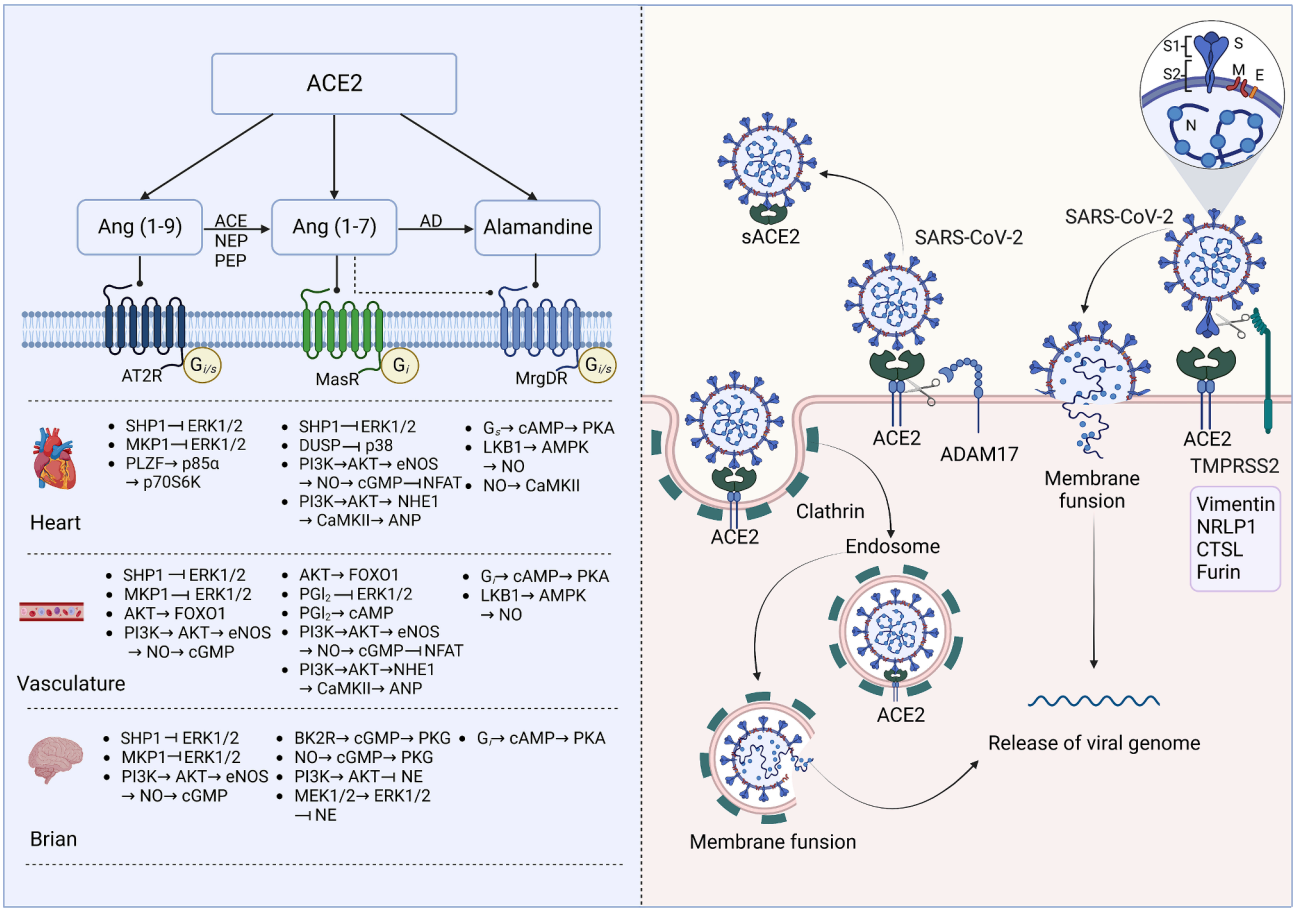

Fig. 2. Signal transduction mechanisms of the counter-regulatory RAS and process of SARS-CoV-2 entry into the host cell. Left: Signal transduction cascades of the three principal axes of the counter-regulatory RAS in the heart, vasculature, and brain. **a)** ACE2-Ang (1–9)-AT2R: Stimulation of AT2R is coupled with $G_{i/s}$, leading to the activation of Src homology 2-containing protein-tyrosine phosphatase-1 (SHP1) /mitogen-activated protein kinase-phosphatase 1 (MKP1) to inhibit extracellular signal-regulated kinase 1/2 (ERK1/2). Moreover, stimulation of AT2R triggers the activation of transcription factor promyelocytic zinc finger protein (PLZF), thereby promoting the expression of ribosomal protein S6 kinase β1 (p70S6K) and PI3K regulatory subunit p85α. **b)** ACE2-Ang (1–7)-MasR: MasR activation stimulates SHP1 and dual specificity phosphatase (DUSP), subsequently suppressing ERK1/2 and p38. In addition, the PI3K-Akt pathway triggered by Ang (1–7)-MasR activates Na^+/H^+ exchanger-1 (NHE1) and calcium/calmodulin-dependent protein kinase II (CaMKII), leading to the increased secretion of atrial natriuretic peptide (ANP). The norepinephrine transporter (NET) in the central nervous system can be inhibited by the PI3K-Akt pathway. Moreover, Ang (1–7)-MasR activation can inhibit calcineurin/nuclear factor of activated T-cell (NFAT) signaling via PI3K-AKT-NO-cGMP-dependent pathway. **c)** ACE2-Alamandine-MrgDR: Alamandine-MrgDR activation functions through the $G_{i/s}$ dependent cAMP-PKA pathway to induce NO production in the heart and vasculature. **Right:** The process of SARS-CoV-2 invasion of the host cell via a membrane-bound ACE2 receptor. The Spike glycoprotein (S protein) of SARS-CoV-2 binds to human ACE2 on the cell membrane through the S1 subunit containing the receptor-binding domain (RBD). A disintegrin and metalloproteinase 17 (ADAM17) mediates a proteolytic shedding of ACE2 to form sACE2 that can be released into extracellular cellular space. Viral membrane fusion with the host cell is activated upon binding through two distinct pathways: a) The intact ACE2 or its transmembrane structural domain is internalized along with the virus by clathrin-dependent endocytosis; b) In the presence of transmembrane proteins and transmembrane protease serine isoform 2 (TMPRSS2) and other co-transmembrane proteins, such as vimentin, neuropilin-1 (NRLP1), cathepsin L (CTSL), furin-like proteases (Furin), the S protein of SARS-CoV-2 is cleaved to trigger membrane fusion and cellular uptake of the virus. The host cell machinery promotes the release of the viral RNA into the cytoplasm for replication and translation. Illustration was created with BioRender.com.

pressure responsiveness after Ang II infusion [131,132]. In addition, in transgenic mice overexpressing AT2R in VSMCs, long-term infusion of Ang II completely abolished the AT1R-induced elevated blood pressure [133].

Signaling through AT2R can directly inhibit the activation of AT1R triggered by Ang II, which is the first example of a GPCR acting as a receptor-specific antagonist [134]. Stimulation of AT2R triggers protein synthesis via activating the transcription factor promyelocytic zinc finger protein (PLZF) and subsequently promoting the expression of ribosomal protein S6 kinase β1 (p70S6K) and p85α subunit of PI3K [135]. In VSMCs, cardiomyocytes, neuronal cells and fibroblasts, AT2R activation also inhibits ERK1/2 by activating SHP1 [136] and mitogen-activated protein kinase-phosphatase 1 (MKP1) [137]. In addition, the PI3K/AKT-eNOS-NO-cGMP pathway can be activated to induce vasodilation via Ang (1–9) binding to AT2R [135,138,139], or via the heterodimerization between AT2R and bradykinin B2 receptor (BK2R) [140]. The vasodilating effect mediated by NO-cGMP triggered by AT2R activation has been reported in the aorta, coronary, cerebral, mesenteric, uterine, and renal arteries [141–144]. Moreover, Ang (1–9)-AT2R activation can also inhibit platelet-derived growth factor-BB (PDGF-BB)-induced VSMC dedifferentiation via the AKT/FOXO1 pathway [145].

However, the signaling upon activation of the Ang (1–9)-AT2R axis remains incompletely understood. Crystal structural study on AT1R and AT2R suggested that, rather than binding to G proteins or β-arrestins [146], activation of this axis forms different heterodimers between AT2R and other receptors, including BK2R [140], AT1R [147] and MasR [148]. This may also account for the tissue specificity of the signaling mediated by the Ang (1–9)-AT2R axis. For instance, Ang (1–9)-dependent activation of AT2R in cardiac myocytes increases AKT phosphorylation, whereas it is reduced in VSMCs [145,149]. The administration of Ang (1–9) reduces blood pressure in several hypertensive animal models [124,145,150]; however, whether it is applicable in

hypertensive patients remains unknown. The mechanisms of Ang (1–9)-AT2R activation involved in blood pressure reduction mainly include increased endothelium-dependent vasodilatation [124,150], improved renal function [124], elevated ANP release [139], restored natriuresis, as well as reduced vascular remodeling and inflammation [145]. Fig. 2 (left) summarizes the signaling transduction cascades mediated by Ang (1–9)-AT2R.

2.4. Alamandine-MrgDR

Differing from Ang (1–7) only in the *N*-terminal alanine instead of aspartate residue, the recently discovered heptapeptide alamandine can be produced via two pathways: (1) Ang (1–7) by decarboxylation of its *N*-terminal aspartate to alanine and (2) Ang II is processed by aspartate decarboxylase (AD) to produce Ang A, an octapeptide with only one amino acid difference from Ang II [151]. Ang A can be further cleaved to alamandine by ACE2 [152]. Alamandine and Ang (1–7) have many similarities in their physiological functions, such as vasodilatory and anti-hypertensive actions by activating the NO pathway [153]. For example, both induce endothelium-dependent relaxation (EDR) in aortic rings isolated from FVB/N mice [152]. Unlike Ang (1–7), alamandine counteracts the vasoconstriction induced by its precursor Ang A without affecting Ang II-induced vasoconstriction [154], indicating that the first alanine residue of alamandine is critical for competitor recognition. The vasoreactivity induced by alamandine also varies in different blood vessels. In the rabbit, alamandine enhanced EDR in the thoracic aorta and iliac artery, but it inhibited EDR in the renal artery [154].

The binding receptor of alamandine is the MAS-related GPR family member D (MrgD). MrgD receptor (MrgDR), widely expressed in tissues throughout the body, was originally identified in primary injurious sensory neurons in rodents and humans to regulate neuropathic pain [155–157]. In the cardiovascular system, MrgDR is found to be expressed in atherosclerotic plaques, SM cells and endothelial cells [154]. MrgDR is a natural endogenous receptor for alamandine both in vitro and ex vivo. The stimulation of MrgDR-transfected cells with alamandine produces and releases NO [152]. Meanwhile, MrgDR has been shown to have other ligands, including β-alanine, β-aminoisobutyric acid (β-AIBA), and diethylstilbestrol (DES) [158,159]. Interestingly, MrgDR can be activated by Ang (1–7) as its second receptor involving adenylate cyclase (AC), cAMP, and protein kinase A (PKA) signal cascade [160,161]. However, except alamandine and Ang (1–7), the presence of other MrgDR ligands like β-alanine fails to elicit any vasoactive response and even competitively inhibits alamandine-induced vasodilatation [152].

Like Ang (1–7), alamandine has been found to attenuate hypertension in SHRs and renal vascular hypertensive rats, which involves local vascular tone regulation as well as a central regulatory effect [152,162,163], but the mechanism of its anti-hypertensive effect is complicated. Alamandine also appears to exert several beneficial effects, including anti-hypertrophy, anti-remodeling, anti-fibrosis, anti-oxidation, and anti-inflammation [164–170]. Long-term administration of alamandine to isoproterenol-treated Wistar rats is associated with reduced accumulation of collagens and fibronectin in the heart [171]. A recent study showed that alamandine alleviated high-salt diet-induced hypertension and renal dysfunction via inhibiting the PKC/reactive oxygen species (ROS) signaling pathway, thereby suppressing apoptosis of renal tubular cells [172]. Different types of G proteins, such as G_s, G_q and $G_{i,}$ can be coupled to MrgDR, which is dependent on ligand selectivity and cell specificity [173]. High-dose almandine increases cAMP concentrations in primary mesangial and endothelial cells via MrgDR coupling G_s protein [174]. Interestingly, in aortic rings isolated from New Zealand white rabbits, almandine can reverse vascular dysfunction induced by hyperhomocysteine, which is through the G_i-coupled PKA pathway [175]. In PVN, Alamandine-MrgDR activation functions through the G_i dependent cAMP-PKA pathway, subsequently increases blood pressure and sympathetic outflow [163]. However, activation of this axis prevents Ang II-induced cardiac hypertrophy via LKB1 dependent-AMP-activated protein kinase (AMPK)–NO pathway [176]. Alamandine also stimulates cardiomyocytes from hypertensive rats to contract vigorously by activating CaMKII in a NO-dependent manner [177]. Fig. 2 (left) demonstrates the signaling transduction cascades mediated by alamandine-MrgDR.

3. The role of counter-regulatory RAS to link hypertension and COVID-19

3.1. ACE2 in SARS-CoV-2 infection

COVID-19 is an acute respiratory disease caused by SARS-CoV-2. Entry into the host cell is the initial step of a viral infection. The structure of the coronavirus consists of the viral envelope (E), membrane (M), nucleocapsid (N), and spike (S) proteins. The S-glycoprotein on the viral envelope can bind to ACE2, which is recognized as the specific functional receptor for SARS-CoV, on the host cell membrane [178]. SARS-CoV-2 has been confirmed to bind to ACE2 as a cellular receptor in a similar way but with a 10- to 20-fold higher binding affinity than SARS-CoV, which leads to a higher pathogenic effect [179,180]. The S glycoprotein of SARS-CoV-2 binds to human ACE2 on the cell membrane through the S1 subunit containing the receptor-binding domain (RBD) [180–182]. Viral membrane fusion with the host cell is activated upon binding. The intact ACE2 or its transmembrane structural domain is internalized along with the virus by endocytosis, and viral RNA is subsequently released into the cytoplasm for replication and translation by the host cell machinery [183]. Several transmembrane proteins, including A disintegrin and metalloprotease 17 (ADAM17), clathrin, transmembrane protease serine isoform 2 (TMPRSS2), cathepsin L (CTSL), vimentin, furin-like proteases, neuropilin-1 (NRLP1) and other newly identified factors are potentially involved in the binding and membrane fusion process [184–193]. Interestingly, the crystal structure demonstrates that the receptor function of ACE2 and S-glycoprotein binding process is independent with the peptidase domain of ACE2 [181], which is also observed in other coronavirus-receptor binding models, such as MERS-CoV to DPP4, HCoV-229E to APN [194–196]. Fig. 2 (right) displays the process of SARS-CoV-2 virus infection of host cells.

Although COVID-19 is primarily a respiratory disease, it is well-known that its progression can cause acute or subacute cardiovascular damage and inflammation. The variation of ACE2 expression levels in different organs could reflect the potential risk of SARS-CoV-2 infection. Immunohistochemical and single-cell RNA-seq (sc-RNAseq) analysis reveals the abundant expression of ACE2 in the lung, heart, esophagus, kidney, bladder, vasculature, and ileum, and located specific cell types (i.e., type II alveolar cells, enterocytes, proximal renal tubules, ileum and esophagus epithelial cells, placental trophoblasts, ductal cells, cardiomyocytes, endothelial cells, and bladder urothelial cells) [197,198]. In the respiratory system, ACE2-enriched nasal ciliated cells are the main targets for SARS-CoV-2 replication in the early stage of infection [199,200]. While in the lower lung, ACE2 is predominantly expressed on type II alveolar epithelial cells, indicating that the lungs are vulnerable to SARS-CoV-2 infection, which leads to severe respiratory symptoms [197,199]. Through blood circulation, the cell-free and macrophage phagocytosis-associated virus can spread from the lungs to other organs with high ACE2 expression. Autopsy studies confirmed the SARS-CoV-2 presence within the myocardium, colon, and kidney [201,202]. Most patients with severe COVID-19 also have multi-organ damage, including acute lung injury, acute kidney injury, heart injury, liver dysfunction, and pneumothorax [203], suggesting that organ involvement and injury are closely related to receptor distribution in vivo.

However, it remains debatable whether ACE2 expression level links to a risk factor or the cause of the severity of COVID-19 due to the dynamics of ACE2 expression profile in different genetic backgrounds, ethnicity, organs, genders, ages, degrees of obesity, medication, and

several comorbidities, such as CVD and metabolic syndrome [204]. Expression quantitative trait loci (eQTL) analysis for ACE2 variants across different populations suggests higher allele frequencies associated with higher ACE2 tissue expression level in East Asian compared to European populations [205]. Genome-wide association *meta*-analysis also showed a causal effect or positive association of elevated liver or circulating ACE2 levels on COVID-19 susceptibility, severity, and clinical outcomes [206,207]. The relatively lower ACE2 expression in nasal and bronchial epithelial cells in children may account for the lower incidence and milder symptoms of COVID-19 in the youngest [208,209]. However, there has been evidence of both positive and negative correlations between ACE2 expression and advanced age [210–212].

Many COVID-19 comorbidities, such as hypertension, T2DM and chronic obstructive pulmonary diseases, are characterized by a shift in the ratio of ACE/ACE2 in both directions, as well as either increased or decreased ACE2 expression or activity, so the relationship between ACE2 expression/activity in these comorbidities and the COVID-19 susceptibility, severity, and clinical outcomes seems paradoxical. Although ACE2 overexpression has shown a protective effect in a lung injury model in mice [213], ACE2 mRNA expression is increased unexpectedly in the lungs of patients with comorbidities associated with severe COVID-19 [214]. Several epidemiological studies showed that hypertension was moderately associated respectively with severity and mortality for COVID-19 [215–218]; however, ACE2 expression levels in patients with hypertension decrease as the disease progresses as previously mentioned. To address this controversy, some investigators have used theoretical models to account for the severity of COVID-19 based on different ACE2 thresholds [219,220]; some researchers propose that the limited expressed local ACE2 in the lung predominately serves as the SARS-CoV-2 receptor and is dysregulated in COVID-19, while highly expressed proinflammatory prolyl oligopeptidase, which has a significantly lower efficiency in converting Ang II to Ang (1–7), contributes to vascular inflammation and dysfunction induced by viral infection [221,222]. However, more clinical and experimental investigations are still needed to confirm this causal relationship.

Studies of ACE2 concentration and activity in circulation are gradually converging from the initial controversy. The ACE2 mRNA level in circulating blood cells (mainly monocytes) and sACE2 concentration from COVID-19 patients were initially found to be lower in prolonged viral shedders than that in healthy controls [223]. By contrast, a few trials did not find evidence for altered ACE2 as well as other RAS components [224]. However, more recent studies demonstrate that sACE2 level or activity is significantly positively associated with the severity of COVID-19, indicating that sACE2 could be a useful biomarker for predicting the risk of severe disease [225–230]. The infection of lung epithelial cells by various SARS-CoV-2 variants can be neutralized by soluble rhACE2 [231]. However, Yeung et al. revealed a new mechanism of sACE2-mediated cell entry of SARS-CoV-2 via interaction with virus dependency factors such as AT1R or AVPR1B [232]. Based upon that, rACE2 has been explored in clinical trials as a possible treatment for COVID-19 [231,233,234].

Given that ACE2, as one of the key counter-regulators of the RAS in regulating cardiovascular physiology, is also an important host receptor that mediates viral binding and triggers the infection, it is obvious that it can become a straightforward and rational research target. However, the causal relationship between the changes in ACE2 levels and the severity and prognosis of COVID-19 is still controversial to some extent. More investigation of the differences between transcriptional and translational levels of ACE2 is needed, as well as the development of specific antibodies against ACE2 isoforms of different lengths.

3.2. Hypertension and COVID-19

The relationship between hypertension and COVID-19 is bidirectional. On the one hand, initial studies have shown that hypertension is one of the most commonly associated comorbidities seen in patients with severe COVID-19 pneumonia during the early outbreak of COVID-19 [216,235]. Reports from China, Europe, and the United States have validated the positive association of arterial hypertension with increased COVID-19-related mortality [216,236–240], although this association does not necessarily imply a causal relationship between hypertension and COVID-19 or its severity. On the other hand, as the pandemic continues and the population of patients recovering from acute COVID-19 grows, the syndromes of Post-acute COVID-19 or Long COVID have been characterized by persistent symptoms and delayed or long-term complications beyond four weeks from the onset of symptoms [241,242]. The new onset or the aggravating pre-existing cardiometabolic syndromes caused by COVID-19 are attracting the attention of scientists and physicians.

Many large-scale epidemiological studies have revealed that hypertension is an independent risk factor for the SARS-CoV-2 infection and severe COVID-19 outcome. The first large-scale data analysis on 1590 laboratory-confirmed hospitalized patients from 575 hospitals found that hypertension was the most prevalent comorbidity (16.9%) [236]. The case fatality rate is 6% in patients with hypertension compared to the overall 2.3% [243]. Many other single-center and multicenter cohort studies also provided clinical evidence of the effect of hypertension on the progression of severe COVID-19 [236,243–248]. In the COVID-19 diagnosed cohort, hypertensive patients had more hospitalizations and higher mortality rates than those without hypertension; in the COVID-19 hospitalized cohort, hypertensive patients were more likely to develop acute respiratory distress syndrome, severe inflammatory response, acute cardiac injury, and arrhythmias with higher mortality rate [249–252]. Notably, almost all epidemiological studies have shown that the mortality of COVID-19 and the prevalence of hypertension increase with advancing age.

Furthermore, long-term hypertension and COVID-19 can damage multiple target organs, such as exacerbated myocardial injury, which implies that the mechanisms of the interaction between hypertension and COVID-19 are complex and may be linked with comorbidities. The pathological mechanisms that link hypertension and COVID-19 are yet to be fully elucidated, but they could be potentially related to imbalanced RAS, dysregulated immunoinflammation, and gut microbiome dysfunction.

First, the dysregulation of the RAS, which is characterized by the overactivated ACE-Ang II-AT1R axis in parallel with the inhibition of the counter-regulatory arm of RAS, is proposed to be the underlying mechanism leading to severe COVID-19 outcome in hypertension. The internalization of membrane-bound ACE2, which occurs as SARS-CoV-2 binds to the host cell membrane, leads to the concurrent loss of ACE2′s catalytic activity [253]. This results in not only the upregulation of Ang II and overactivity of the conventional ACE-Ang II-AT1R axis but the decrease in Ang (1–7) as well as the protective effect of the unconventional ACE2-Ang (1–7)-MasR axis. Excessive Ang II can promote endothelial dysfunction and cytokine storm, which in turn contribute to the pulmonary, inflammatory, and hematological complications of COVID-19 [254–256].

Second, extensive experimental and clinical evidence has shown that hypertension is associated with inflammation and immune cell activation, although it has not been elucidated whether this association is causally linked through a direct or indirect regulation [257,258]. It has been shown that innate immune cells (macrophages, microglia, monocytes, dendritic cells, and myeloid-derived suppressor cells), as well as adaptive immune cells ($CD8^+$ T cells, $CD4^+$ T cells, and B cells), play significant roles in the development of hypertension [259]. For example, both $CD4^+$ and especially $CD8^+$ cells are dysregulated and tend to overproduce proinflammatory cytokines in hypertension, and also show less efficiency in antiviral defense [260,261]. So far, a small number of cytokine mediators, such as interleukins (IL-6, IL-7, IL-17), TNF-α, INF-γ, have been discovered in regulating immunoinflammatory responses in hypertension as well as the accelerated end-organ damage [260,262–265]. On the other hand, SARS-CoV-2 infection activates both

innate and adaptive immune responses and triggers the release of proinflammatory factors, which leads to hyperinflammation or "cytokine storms" [266,267]. The multi-organ damage caused by this uncontrolled innate response and impaired adaptive immune response determines the severity of COVID-19 and the risk for clinical deterioration of patients. The immunoinflammatory status of hypertensive patients could exacerbate COVID-19 severity has been studied in several epidemiological and experimental research. A limited-size of cohort study demonstrated a distinct inflammatory predisposition of immune cells in patients with hypertension that correlated with critical COVID-19 progression [268]. The dynamic immunological profile analysis of hypertensive COVID-19 patients found that T lymphopenia, in particular the prolonged activation and exhaustion of $CD8^+$ T cells, is associated with critical or severe COVID-19 cases [269].

Lastly, ACE2 is most abundantly expressed in the gastrointestinal (GI) tract at both mRNA and protein levels; it also serves as a key regulator of intestinal homeostasis [270]. GI symptoms, including diarrhea, nausea, and vomiting, are very common in COVID-19 patients [271–273]. As the secondary site of viral infection, ACE2 expression on surface cells of the small intestine may mediate the invasion and amplification of the virus and activation of GI inflammation [274–276]. Interestingly, hypertension is also associated with GI inflammation and increased intestinal permeability [277], and intestinal dysbiosis is thought to be one of the causal factors for hypertension in both animal models and patients [278,279]. In addition, the distribution of the gut microbiota in hypertensive and COVID-19 patients also indicates some intriguing correlations. The fecal abundance of the Bacteroidetes species was inversely correlated with COVID-19 severity as well as the fecal viral load of SARS-CoV-2 [275,280], and the subjects with pre-existing hypertension and other cardiometabolic diseases were characterized by a low abundance of Bacteroides species and had the highest COVID-19 mortality and morbidity [281–283]. As a result of gut leakiness and wall pathology brought on by hypertension, SARS-CoV-2 infection can become more severe. In turn, SARS-CoV-2 infection deteriorates the function of the gastrointestinal tract.

Although hypertension is linked to an increased risk of severe COVID-19 and higher mortality, the effects of COVID-19 on pre-existing and newly diagnosed hypertension are still incompletely understood. Elevated BP and even spontaneous hypertension were observed in COVID-19 patients with respiratory failure during the hospitalization [284–286], and individuals with pre-existing hypertension were also found to have worsening BP outcomes, severe respiratory symptoms and excessive inflammatory response [218,287]. A recent prospective case-control study in hospitalized patients also shows that COVID-19 pneumonia individuals have a higher probability of a persistent elevated BP [288]. These studies suggest that the SARS-CoV-2 infection-triggered respiratory failure and modulation of the RAS may increase BP, which is likely explained by the positive correlation between plasma Ang II level and COVID-19 severity [289]. However, a retrospective and prospective cohort study showed that COVID-19 had no lasting effects on systolic or diastolic BP [290]. Additionally, an unexpected rise in plasma Ang (1–7) and a parallel decline in plasma Ang II were observed in another cohort study [291]. It is important to note that all of those controversial findings came from research with a small sample size of hospitalized COVID-19 patients representing a small portion of the total infected population. Another major challenge in determining the relationship between hypertension and COVID-19 is the lack of blood pressure information prior to hospital admission. Although a large-scale longitudinal study in the US showed that blood pressure among US adults increased during the COVID-19 pandemic, the rise in the number of cases of hypertension was probably related to stress or alterations in lifestyle during the pandemic [287,292].

SARS-CoV-2 is prone to mutations due to continuous transmission. As the pandemic continues, SARS-CoV-2 variants of B.1.1.7 (Alpha), B.1.351 (Beta), P.1 (Gamma), B.1.617.2 (Delta) and B.1.1529 (Omicron) alternated as the dominant pathogen in the world accompanied by increasing transmissibility. Hypertension remains a significant risk factor for COVID-19 severity brought on by different SARS-CoV-2 variants, but only limited studies have investigated the relationship between hypertension and infection with these variants. Although the COVID-19 severity and mortality rate associated with Omicron infections declined significantly compared to the previous variants, a recent study showed those infected with variant Omicron were older and had significantly more frequent comorbidities, including hypertension [293], which is probably due to the remarkably higher transmissibility and immune evasion ability.

The cardiometabolic complications of Long COVID have been reported widely [294–307]. We mechanistically investigated that COVID-19 induces new-onset metabolic disorders and found that SARS-CoV-2 infection modulated several secreted metabolic factors contributing to the perturbation of glucose and lipid metabolism [308,309]. Nevertheless, the majority of the studies in patients who had recovered from acute symptoms for more than a month, which were limited to case reports and retrospective observational studies, paradoxically displayed the link between COVID-19 and aggravated hypertension or an elevated risk of new-onset hypertension. In two confirmed COVID-19 patients enrolled cohort studies, BP was significantly higher in the post-COVID-19 period than upon admission [285,286], and Ang II signaling upregulation driven by SARS-CoV-2 infection might play a critical role in the progression of new-onset hypertension [285]. Another retrospective study also demonstrated that arterial hypertension following SARS-CoV-2 infection, either newly verified or worsened existing, was a relatively common occurrence [310]. However, some cross-sectional research showed that COVID-19 did not influence blood pressure, particularly in young subjects [311–314]. To resolve these discrepancies and clarify the pathophysiological effect on the BP of Long COVID, additional clinical and animal investigations are required, and exploring the mechanisms underlying cardiovascular manifestations among patients with Long COVID is warranted. [294,315].

In the context of COVID-19, blood pressure control and antihypertensive medication in hypertensive patients warrant special consideration. The safety and efficacy of the first-line BP-lowering drugs, including beta-blockers [316], thiazide diuretics [317], RAS blockers [318–321] and calcium channel blockers [322], have been evaluated in COVID-19 patients with hypertension. After a brief controversy during the early days of the COVID-19 outbreak, a consensus has been reached that patients with coexisting COVID-19 and hypertension should be actively treated with anti-hypertensive drugs to control their blood pressure. In addition to the blood pressure-lowering benefits, the findings from retrospective and preclinical studies suggested that these reagents may reduce the morbidity and mortality of COVID-19 patients. For example, alpha- and beta-adrenergic receptor antagonists may reduce the risk of hyperinflammation characterized by profound elevation of many proinflammatory cytokines in patients with severe COVID-19 [316,323,324]. The use of calcium channel blockers nifedipine and amlodipine was associated with improved survival and decreased risk of intubation and mechanical ventilation in elderly patients hospitalized for COVID-19; the underlying mechanisms may include inhibition of post-entry replication of SARS-CoV-2 [322,325]. The diuretic spironolactone may protect against COVID-19 by inhibiting TMPRSS2, reducing the cytokine storm and lessening organ injury [317,326,327]. Overall, there is growing observational evidence that the application of anti-hypertensive agents in patients with COVID-19 and hypertension morbidities is safe and even has additional benefits, but the mechanisms underlying this protective response remain largely unknown.

3.3. RAS and counter-regulatory RAS in COVID-19

Although SARS-CoV-2 infection may lead to RAS imbalance, it is still imperative to understand whether all RAS component-related pathways are affected by COVID-19. However, the existing results remain

controversial. Ang II was shown to facilitate SARS-CoV-2 infection in human bronchial cells by upregulating ACE2 [328]. Nevertheless, in COVID-19 patients' plasma, there was no change in the levels of Ang I, Ang II, and Ang (1–7) [329]. Consistently, Rieder et al. also demonstrated that ACE2, Ang II and aldosterone were not altered in SARS-CoV-2-positive patients [224]. Paradoxically, Wang et al. found that the plasma levels of Ang I and Ang (1–7) or the Ang (1–7)/Ang II ratio were elevated during SARS-CoV-2 infection related to the reduced ACE activity at baseline [330]. Many recent clinical trials have confirmed that there is no significant correlation between the application of RAS inhibitors (ACEIs and ARB) and COVID-19 [331]. These data suggest that different RAS peptides may not be involved in SARS-CoV-2 infection, but further studies are needed to elucidate whether other counter-regulatory peptides have beneficial effects on the sequelae of COVID-19.

The application of RAS inhibitors (ACEIs and ARBs), RAS modulators like AT2R agonists (C21), soluble rhACE2, Ang (1–7), and MasR agonists has been known to prevent organ damage via the rebalancing of the overactivated RAS in hypertension [332]. However, as discussed above, in some COVID-19 cases, the immune response to viral infection is augmented due to the upregulation of the ACE-Ang II-AT1R axis, accompanied by ACE2 downregulation. This imbalance of the RAS results in the overproduction of proinflammatory cytokines, leading to cytokine storm syndrome, which is associated with severe cases and death, as well as with multi-organ damage. Moreover, ACE2 expression is also highly correlated with the use of RAS inhibitors. Therefore, it has been focused on the relationship between COVID-19 and RAS counter-regulation, which is summarized in Table 1.

Animal studies have found that ACEI therapy can increase plasma Ang (1–7) levels, decrease plasma Ang II levels, and increase cardiac ACE2 expression, whereas ARBs can increase the plasma levels of both Ang II and Ang (1–7) as well as the cardiac expression and activity of ACE2 [333]. Therefore, as the COVID-19 pandemic is spreading rapidly, concerns about the medical management of hypertension involving RAS inhibition are raised due to the speculation that the use of ACEIs and ARBs may also increase the risk of infection with SARS-CoV-2 [282]. The initial small sample study (113 hypertensive COVID-19 patients) did show that the patients on ACEIs/ARBs therapy had a higher incidence of in-hospital death than those who were not [334]. Although the later cohort study by Mehta et al. demonstrated that there seemed to be a higher risk of hospitalization admission, ICU admission, or mechanical ventilation required in patients with COVID-19 infection taking ACEIs/ARBs, after using overlap propensity score weighting to adjust for underlying confounding factors such as underlying chronic disease conditions, they concluded that there is no association between ACEIs/ARBs use and COVID-19 test positivity [335]. The subsequent large-scale studies have shown that the RAS inhibition does not contribute to SARS-CoV-2 infection and COVID-19 exacerbation, which suggests the application of ACEIs/ARBs appears to be safe in the setting of SARS-CoV-2 infection and should not be discontinued [254,335–338]. Moreover, randomized trials, such as BRACE CORONA, REPLACE COVID and ACEI-COVID19, also concluded an absence of effect of chronic RAS blockade on the course of COVID-19, as previously observed in observational studies [318,339,340]. Notably, in COVID-19 patients, rather than an increase in the risk of death or serious adverse events, inhibition of classic RAS displayed protective effects, which were confirmed in emerging results. Two retrospective multicenter studies, including 15,504 and 2190 participants hospitalized due to the diagnosed COVID-19, demonstrated that ACEIs/ARBs use was associated with lower in-hospital mortality and improved clinical outcomes [341,342]. Additional observational studies, as well as *meta*-analysis, revealed lower incidences of severe disease among the patients using RAS inhibitors, which further supported these findings [321,343–346]. This discrepancy could be explained by the presence of a number of confounding factors, including a) patients' missing information (lifestyle, body mass index, history of smoking, age $>$ 80); b) the dose and period of ACEIs/ARBs intake; c) the degree and duration of hypertension; d) adherence to anti-hypertensive medication during the various COVID-19 pandemic periods; and e) combined use of ACEIs/ARBs and other anti-hypertensive medication [347]. Moreover, the mechanism of the beneficial outcomes induced by RAS inhibition in COVID-19 is still largely unknown, partly due to the lack of appropriate animal models, which can reflect hypertension caused by the imbalance of ACE/ACE2, exhibit a similar susceptibility to SARS-CoV-2 and comparable pathology as humans, including fever, pulmonary infection, and antibody response and pneumonia symptoms [348].

Since ACE2 blocks the proinflammatory AT1R-mediated action of Ang II, studies have been conducted to see if patients with COVID-19 infection and severe lung injury can benefit from using rhACE2 [42,349]. Monteil et al. have shown that soluble rhACE2 markedly reduced the SARS-CoV-2 load by a factor of 1000–5000 and directly neutralized the virus in engineered human organoids [350]. Moreover, the result of phase II clinical trials NCT04335136 showed an inspiring benefit of APN01 (alunacedase alfa, a clinical grade rhACE2) for severe Ill COVID-19 patients due to the infection by various SARS-CoV-2 variants. It led to significant improvement in several specific areas, including the increase in mechanical ventilator-free days, a reduction in viral RNA load, and a reduced plasma Ang II level accompanied by an enhanced Ang (1–7) and Ang (1–5) level [351,352].

4. Targeting counter-regulatory RAS in hypertension

Over the past decade, there appears to be a shift in the strategies for intervening in RAS activity. The growing evidence on the beneficial effects of counter-regulatory RAS is encouraging researchers to explore the potential of the new therapeutic targets, ACE2 and its relevant signaling pathways, in CVD therapy, rather than to block the classical RAS as has been done with well-known renin inhibitors, ACEIs and ARBs. Based on the knowledge of the core enzyme ACE2 and related three counter-regulation axes, the upregulation of ACE2 and the application of analogs of Ang (1–7)/Ang (1–9)/alamandine or agonists of the corresponding receptors can be a potential therapeutic strategy against hypertension. Fig. 3 illustrates the pharmacological treatment for hypertension in the context of the COVID-19 pandemic, which includes first-line antihypertensive medications and counter-regulatory RAS stimulation.

4.1. *ACE2 as a potential therapeutic target for hypertension*

It is known that several pharmaceutical substances can either activate or inhibit ACE2 activity. Given that ACE2 plays a protective role in the cardiovascular system, seeking out new ACE2 activators is a straightforward route for drug discovery, and boosting ACE2 activity might be a useful therapeutic strategy in the treatment of hypertension. Compounds that can activate ACE2, such as all-trans retinoic acid (atRA), xanthone (XNT), and diminazene aceturate (DIZE, Berenil®, an FDA-approved drug), are employed in current pharmacochemical approaches to boost ACE2 activity [29,353,354]. In vivo treatment with atRA, a biologically active metabolite of vitamin A, can increase cardiac and renal expression of ACE2, reduce blood pressure, and attenuate myocardial damage in SHR [29]. XNT is an ACE2 activator discovered by a virtual screening approach. In vitro studies showed that XNT triggered a conformational change of ACE2 to increase its activity in a dose-dependent manner [354]. Both acute and chronic in vivo administration of XNT can induce a decrease in blood pressure, while chronic infusion increases cardiac ACE2 expression and Ang (1–7) production and reverses cardiac and renal fibrosis in SHRs [28,354]. Another ACE2 activator DIZE decreased the infarct area, attenuated LV remodeling post-MI, and restored the normal balance of RAS in ischemia-induced cardiac injury, whose mechanism is probably related to the increased circulating endothelial progenitor cells, increased engraftment of cardiac progenitor cells, and decreased inflammatory cells in peri-infarct cardiac regions [353,355]. ACE2 priming triggered by XNT and DIZE

Table 1
Effect of RAS inhibitor treatment on clinical outcome of COVID-19 patients with hypertension.

No.	Region	Participants	RAS inhibitors used (% of population)	Description & NCT ID	Main outcomes	PMID
1	Hubei, China	1128 adult inpatients with confirmed COVID-19 and hypertension from 9 hospitals	ACEIs (2.75 %, 31/1128) /ARBs (14.0 %, 158/1128)	Not mentioned	Reduce risk of all-cause mortality in COVID-19 patients with hypertension	32302265
2	Lombardy, Italy	6272 patients with confirmed COVID-19	ACEIs (23.9 %, 1502/6272)/ARBs (22.2 %, 1394/6272)	≥1 prescription during 2019	No association between ACEI/ARB treatment and risk of COVID-19 infection	32356627
3	NY, USA	Patients with COVID-19 records in the New York University (NYU) Langone Health electronic health record	ACEIs (8.32 %, 214/2573); ARBs (10.5 %, 270/2573); ACEIs/ARBs (18.4 %, 473/2573)	Within 18 months before COVID-19 diagnosis	No association between ACEI/ARB treatment and susceptibility to or severity of COVID-19 infection	32356628
4	Wuhan, China	2877 COVID-19 patients admitted to the Huo Shen Shan Hospital	ACEIs/ARBs (6.36 %, 183/2877)	Not mentioned	No association between ACEI/ARB treatment and risk of mortality in COVID-19 patients	32498076
5	Wuhan, China	1178 patients with COVID-19 hospitalized in Wuhan Central Hospital	ACEIs/ARBs (31.8 %, 115/362)	Not mentioned	No association between ACEI/ARB treatment and severity or mortality of COVID-19 patients with hypertension	32324209
6	Tarragona area, Spain	34,936 hypertensive patients under 50 years of age	ACEIs (37.6 %, 77/205)/ARBs (16.1 %, 33/205)	Not mentioned	No association between ACEI/ARB treatment and risk of COVID-19 infection in hypertensive patients	32710674
7	Italy	1761 patients aged 18 to 101 years with confirmed COVID-19	ACEIs (21.9 %, 348/1591) /ARBs (19.3 %, 307/1591)	NCT04331574	No contribution to mortality from COVID-19	32564693
8	Kanagawa Prefecture, Japan	151 patients with COVID-19 in 6 hospitals	ACEIs (1.99 %, 3/151); ARBs (12.6 %, 19/151)	Not mentioned	Reduce poor outcomes in COVID-19 patients with hypertension	32820236
9	4 regions of Italy	Patients > 50 years hospitalized for COVID-19	ACEIs (21.9 %, 171/781) /ARBs (17.0 %, 133/781)	Not mentioned	Reduce risk of mortality in hospitalized COVID-19 patients who previously taken ACEIs/ARBs	33023356
10	A French geriatric unit, France	201 patients hospitalized for COVID-19	ACEIs/ARBs (31.3 %, 63/201)	≥1 week before the onset of infection	Reduce mortality rate in COVID-19 patients	33138935
11	Shenzhen, China	417 COVID-19 patients admitted to the Shenzhen Third People's Hospital,	ACEIs/ARBs (40.5 %, 17/42)	>1 year	Improve clinical outcomes of COVID-19 patients with hypertension	32228222
12	Tehran, Iran	636 patients with COVID-19 referred to Sina Hospital	ARBs (48.0 %, 122/254)	≥7 days after hospital admission	Not worsen clinical outcomes in hypertensive patients during COVID-19 infection	32920644
13	Spain	545 hypertensive patients hospitalized for COVID-19 in a Spanish hospital	ACEI/ARB (30.8 %, 168/545)	≥1 month before hospital admission	Reduce risk of death in COVID-19 hypertensive patients during hospitalization	32949380
14	Italy	4069 patients with SAPS-CoV-2 infection and hospitalized in 34 clinical centers	ACEIs (13.5 %, 549/4069); ARBs (13.3 %, 541/4069); ACEIs & ARBs (0.393 %, 16/4069)	NCT04318418	No association between ACEI/ARB usage and severity or mortality in all COVID-19 patients	32992048
15	Wuhan, China	650 COVID-19 patients admitted to the Public Health Treatment Center of Changsha and Tongji Hospital, Tongji Medical College of Huazhong University of Science and Technology	ACEIs/ARBs (29.4 %, 37/126)	Not mentioned	No contribution to mortality in COVID-19 patients with hypertension	33322988
16	Italy	351 COVID-19 patients in Naples who did not require hospitalization and were treated in an outpatient setting	ACEIs/ARBs (26.8 %, 94/351)	Not mentioned	No causal relationship between hypertension and treatment of hypertension in critically ill patients with COVID-19	33375676
17	USA	1449 hospitalized and non-hospitalized patients from a large comprehensive health care system serving central	ACEIs/ARBs (16.0 %, 84/525)	Within 12 months before COVID-19 test	No effect on severity of COVID-19 infection	33220171
18	Brazil	659 patients hospitalized for mild or moderate COVID-19	ACEIs/ARBs (49.3 %, 325/659)	NCT04364893	No association with the number of days alive and out of the hospital in mild COVID-19 patients	33464336
19	Italy	575 consecutive patients with laboratory-confirmed COVID-19	ACEIs (14.3 %, 56/391)/ARBs (12.3 %, 48/391)	Not mentioned	Reduce mortality risk in COVID-19 patients with ACEI not ARB	32980434
20	Italy	2446 charts of Italian patients admitted for certified COVID-19 in 27 hospitals	ACEIs (35.4 %, 530/1498)/ARBs (29.7 %, 445/1498)	NCT04331574	No effect on chance of recovery in COVID-19 patients	33186327

(*continued on next page*)

Table 1 (*continued*)

No.	Region	Participants	RAS inhibitors used (% of population)	Description & NCT ID	Main outcomes	PMID
					with hypertension or heart failure	
21	USA, Canada, Mexico, Sweden, Peru, Bolivia, and Argentina	152 patients admitted to hospital (20 large referral hospitals) with a clinical presentation consistent with COVID-19 and prescribed ACEI or ARB therapy as an outpatient before the hospital admission	ACEIs/ARBs (49.3 %, 75/152)	NCT04338009	No effect on severity and mortality of COVID-19	33422263
22	France	Almost 2 million patients from the French national health data system	ACEIs (30.1 %, 566023/1882556)/ARBs (50.9 %, 958227/1882556)	≥3 months before study conduction	Reduce risk of hospitalization and death with COVID-19 patients	33423528
23	Italy	2377 charts of Italian COVID-19 patients in hospital	ACEIs/ARB (59.0 %, 827/1402)	NCT04331574	No association between ACEI/ARB administration and anticoagulant treatment effect of COVID-19	34055928
24	USA	Data from the national Veterans Health Administration	ACEIs/ARBs (49.9 %, 2482/4969)	≥3 months before study conduction NCT04467931	Association with a 15 % lower relative risk of COVID-19-related outcomes	33891615
25	Iran	64 patients with COVID-19	Not mentioned	IRCT20151113025025N3	No association between ACEI/ARB treatment and risk of COVID-19 infection in hypertensive patients	34265044
26	Minnesota, USA	117 participants included symptomatic outpatients with COVID-19 not already taking ACE-inhibitors or ARBs, enrolled within 7 days of symptom onset	Not mentioned	NCT04311177	No effect on hospitalization and viral load with COVID-19 patients	34195577
27	Argentina	Patients from 18 years of age hospitalized with COVID-19	ARBs (49.4 %, 78/158)	NCT04355936	Reduce morbidity and mortality in hospitalized COVID-19 patients	34189447

improved endothelial function, which is characterized by endothelial-dependent vasorelaxation response in hypertensive and diabetic rodents by attenuation of oxidative stress [35,356]. However, a few studies questioned the specificity of the known ACE2 activators, as many of the beneficial effects induced by XNT can also be observed in ACE2 knockout animals. Moreover, in a model of Ang II-induced acute hypertension, neither renal nor plasma ACE2 activity was affected by XNT treatment, though it could induce a significant reduction of blood pressure [357]. Recently, by using virtual screening and bioinformatic analysis plus experimental confirmation, we found three FDA-approved drugs, imatinib, methazolamide, and harpagoside, as direct enzymatic activators of ACE2. Unlike previously known ACE2 activators, they remarkably ameliorate COVID-19-induced metabolic complications via elevating ACE2 enzymatic activity and inhibiting viral entry [358].

The application of recombinant ACE2 protein (rACE2) is an alternative direct approach to prime ACE2 in the anti-hypertension investigation. Zhong et al. demonstrated that rhACE2 infusion attenuated Ang II-induced hypertension and pressure-overload-induced myocardial hypertrophy, fibrosis, and diastolic dysfunction without affecting basal systolic blood pressure in control mice [359]. Likewise, sustained elevations in serum ACE2 activity followed by attenuated blood pressure can be accomplished with murine rACE2 administration in Ang II-induced mice [40,360]. In SHRs, diabetic Akita and *db/db* mice, rhACE2 or adenovirus-mediated ACE2 overexpression lowered blood pressure in association with reduced plasma Ang II levels and increased Ang (1–7) [35,38,41]. Moreover, rACE2 also produces a therapeutic effect on pulmonary injury and diabetic nephropathy [41,361]. Administration of rhACE2 was well tolerated by healthy and acute respiratory distress syndrome human subjects [42,349], and the safety and efficacy were confirmed by the non-detectable antibodies to rhACE2 at different time points after the last dose of rhACE2, a dose-dependent increase in plasma ACE2 and no change in blood pressure or heart rate [42]. The clinical trial NCT01597635 results show a single infusion of rhACE2 (GSK2586881, 0.2 or 0.4 $mg{\cdot}kg^{-1}$ intravenously) was well tolerated with significant improvement in cardiac output and pulmonary vascular resistance, associated with improved pulmonary hemodynamics and reduced markers of oxidant and inflammatory mediators in a small number (N = 5) of patients with pulmonary arterial hypertension (PAH) [362]. However, in a recent Phase IIa study (NCT03177603), no consistent or sustained effect on acute cardiopulmonary hemodynamics was observed in participants with PAH receiving background PAH therapy (N = 23). This discrepancy suggests that additional clinical investigation is required to determine the efficacy of rACE2.

The therapeutic potential of chronic use of rACE2 is still restricted partially due to the short plasma half-life of the recombinant protein. Thus, a chimeric fusion protein of rACE2 and the immunoglobulin fragment Fc segment (rACE2-Fc) was constructed to increase its plasma stability but retained full peptidase activity and exhibited a greatly extended plasma half-life in mice [363]. The weekly injections of rACE2-Fc effectively lowered plasma Ang II and blood pressure, associated with meliorated albuminuria and reduced kidney and cardiac fibrosis [363]. Recently, in a stringent K18-hACE2 mouse model challenged with various SARS-CoV-2 variants, rACE2-Fc counteracts murine lethal SARS-CoV-2 infection through direct neutralization and Fc-effector activities with a broadly effective therapeutics capability [364].

The inhibition of ACE2 by pharmacological inhibitors such as MLN-4760 and DX600 aggravated cardiopathy in many animal models. The specific and potent ACE2 inhibitor MLN-4760 (IC_{50} = 0.44 nM) worsens the glomerular injury in streptozotocin-induced diabetic mice in vivo, associated with increased ACE expression [365,366]. In (mRen2) 27 transgenic hypertensive rats, chronic treatment with MLN-4760 exacerbated cardiac hypertrophy and fibrosis [367]. Of note, MLN-4760 increased local cardiac Ang II accumulation while having no effect on plasma Ang II or Ang (1–7) levels [367]. The other ACE2 inhibitor, DX600, a peptide inhibitor with high affinity (K_d = 10.8 nM) and efficacy (IC_{50} = 10.1 nM), is regarded as a partial negative allosteric modulator (NAM) of ACE2 due to its mixed inhibitory characteristics [368]. In vitro, DX600 caused a reciprocal increase in autocrine Ang II and a corresponding decrease in Ang (1–7) in cell culture media [369], and it also increased thrombus formation in SHRs [370,371]. Importantly, ACE2 inhibitors can also increase the risk of SARS-CoV-2 infection and exacerbate COVID-19 outcomes since the conformational change of ACE2 triggered by MLN-4760 increased the affinity of the

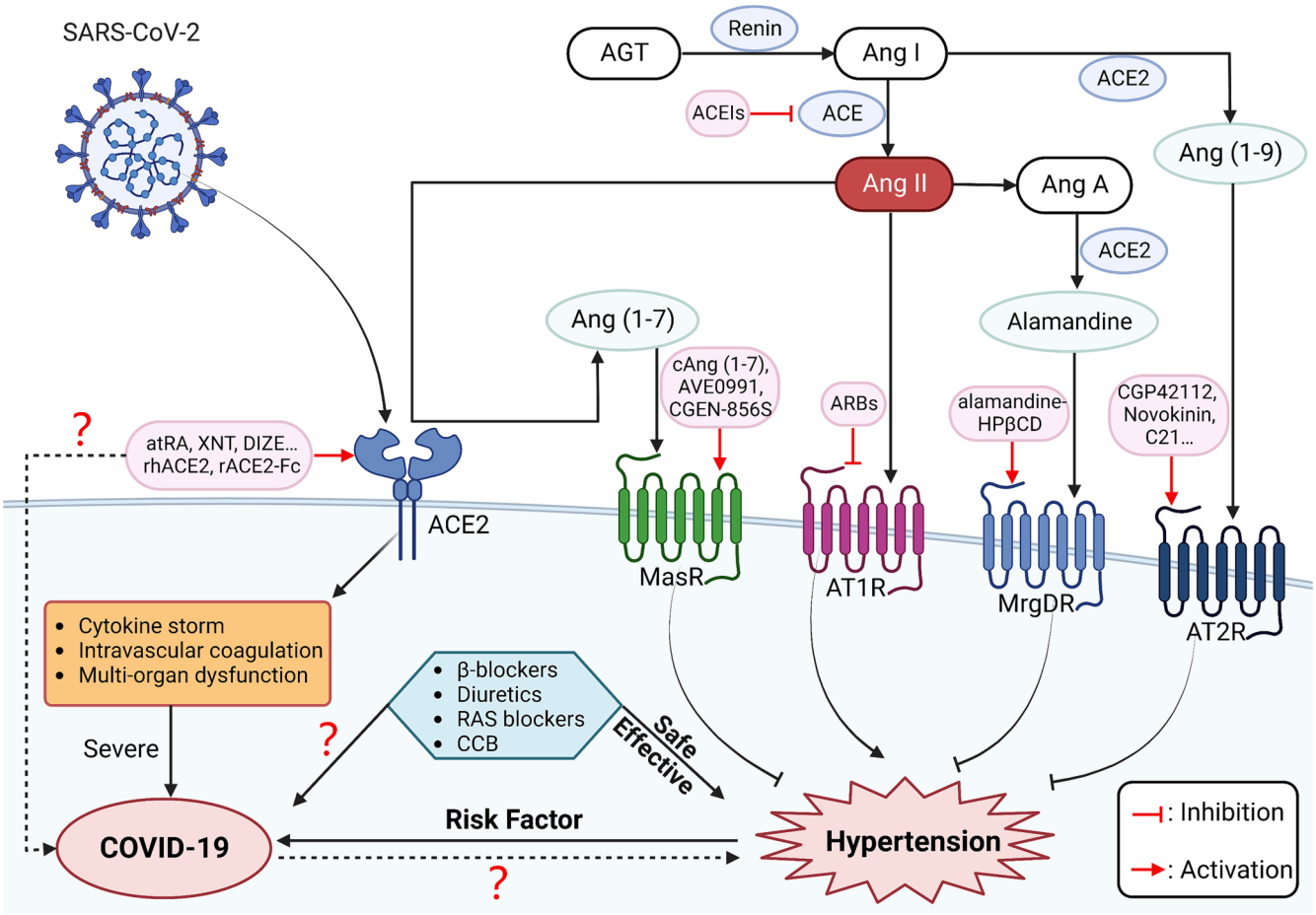

Fig. 3. Hypertension pharmacological treatment in the context of the COVID-19 pandemic. SARS-CoV-2 infection-induced cytokine storm, intravascular coagulation, and multi-organ dysfunction are the leading cause of severe COVID-19. The relationship between hypertension and COVID-19 is bidirectional. Numerous observational studies have confirmed that hypertension is an independent risk factor for SARS-CoV-2 infection and a severe COVID-19 outcome. However, the effects of COVID-19 on both pre-existing and newly diagnosed hypertension are still disputable. The safety and efficacy of the first-line BP-lowering drugs, including beta-blockers, thiazide diuretics, RAS blockers (ACEIs and ARBs) and calcium channel blockers (CCB) have been confirmed in COVID-19 patients with hypertension, some of these agents even provide additional benefits for treating COVID-19, but the mechanisms underlying this protective response remain largely unknown. Pharmacological agents/strategies targeting the counter-regulatory RAS to treat hypertension are highlighted in pink rectangle (artificial agents) and green cycle (natural ligands), including **a)** ACE2 upregulation: all-trans retinoic acid (atRA), xanthone (XNT), diminazene aceturate (DIZE), recombinant ACE2 protein (rACE2), and the immunoglobulin fragment Fc segment infused rACE2 (rACE2-Fc) etc.; **b)** MasR agonists: Ang (1–7), cAng (1–7), AVE0991, CGEN-856S; **c)** AT2R agonists: Ang (1–9), CGP42112, Novokinin, Compound 21 (C21) etc.; **d)** MrgDR agonist: Alamandine, and alamandine-HPβCD. The priming of ACE2 in activity or expression may also provide protection against severe COVID-19. Illustration was created with BioRender.com.

viral S protein's binding to [372].

4.2. Ang (1–7) and MasR agonists

The crucial function of Ang (1–7) in hypertension is to regulate renal blood flow by inducing vasodilatation and counterbalancing the Ang II-induced vasoconstriction. However, both experimental and preclinical studies on the anti-hypertensive effect of Ang (1–7) yielded heterogeneous results, which are related to the drug administration procedure and hypertensive animal models [373,374].

Numerous studies have demonstrated that acute systemic infusion of Ang (1–7) has no effect on blood pressure in either normotensive rats or hypertensive animals, including SHRs and renal hypertensive rats [80,110,375]. Intriguingly, in some of the models, Ang (1–7) synergistically enhanced the hypotensive effect of bradykinin [375,376]. In Ang II-induced hypertensive mice, Ang (1–7) had no effect on elevated blood pressure or on the restoration of blood pressure after cessation of Ang II infusion [40]. However, in Dahl salt-sensitive rats, a decreased MAP and an increased release of PGI_2 and nitric oxide were seen after Ang (1–7) infusion [377,378]. Chronic administration of Ang (1–7) was associated with transient or sustained reductions in blood pressure in SHRs and Dahl salt-sensitive rats but not in DOCA salt-induced hypertensive rats [378–380]. The effects of Ang (1–7) on blood pressure in 2K1C and subtotal-nephrectomy-induced hypertensive rats are inconsistent across different studies [381–383]. Moreover, paradoxical results were obtained in the hypertensive rats administrated with Ang (1–7) to the central nervous system (CNS), which is probably due to the differences in injection sites, administration concentrations, and hypertensive models [83,110,112,384–386].

The clinical trials with Ang (1–7) have also produced conflicting results. Kono et al. first reported that supraphysiologic doses of intravenous Ang (1–7) administration produced a weak pressor response and renin-suppressing actions in healthy men [387]. Nevertheless, in the other study, using the same delivery route, a 3-h infusion of Ang (1–7) (3 pmol/kg/min) did not affect blood pressure or heart rate in healthy people [388]. Intrabrachial Ang (1–7) caused vasodilation in the forearm circulation of normotensive subjects and patients with essential hypertension through a NO-independent pathway [389]. It also antagonized Ang II-induced vasoconstriction and potentiated bradykinin-mediated vasodilation in healthy male subjects [390,391].

Interestingly, intrabrachial Ang (1–7) infusion not only improved insulin-stimulated endothelium-dependent vasodilation but also blunted endothelin-1-dependent vasoconstriction in obese subjects [392]. However, there are two studies showing no significant change in the forearm blood flow in healthy and hypertensive subjects [393,394]. Moreover, intrarenal Ang (1–7) infusion showed an improved renal blood flow as well as glomerular filtration in hypertensive subjects, but those benefits could be attenuated by renal artery stenosis, low sodium intake, and Ang II co-infusion [395–397]. The controversies among those reported preclinical findings call for more clinical investigations to better understand the local and systemic hemodynamic effects of Ang (1–7) in human. There are several ongoing (pre)clinical trials examining the cardiovascular effects of Ang (1–7) pathway activation as shown in Table 2.

Ang (1–7) has several unfavorable pharmacokinetic properties, particularly a very short half-life (~10 s) due to rapid cleavage by peptidases [398,399]. Therefore, biochemical modifications to this heptapeptide were developed to increase its stability and affinity for its receptors. A few MasR agonist and Ang (1–7) formulations have been tested in animals and in preclinical research. The first MasR agonist, AVE0991, a nonpeptide compound that can be used orally, was initially synthesized in 2002 [400]. AVE0991 efficiently mimics the effects of Ang (1–7) on the endothelium, causing significant kinin-mediated activation of eNOS and higher NO release, which subsequently restore vasodilatation in various vascular beds of hypertensive and diabetic animals [401,402]. AVE0991 can also moderate pathological cardiac remodeling and improve baroreflex sensitivity in renovascular hypertensive rats [402], attenuate MI-induced heart failure [403], and prevent Ang II-induced myocardial hypertrophy [404]. It also inhibits monocyte/macrophage differentiation and monocyte transendothelial migration during early stages of atherosclerosis in ApoE$^{-/-}$ mice, displaying anti-atherosclerotic and anti-inflammatory properties [405]. In addition, the results from MasR-deficient mice and the blockade of AVE0991 with Ang (1–7) antagonists (A-779 and D-Pro^7-Ang (1–7) (D-Pro) suggest that its actions are mediated at least in part through MasR [84,406]. To date, the clinical trial of AVE0991 has not been initiated yet [407]. Meanwhile, some other metabolically stable Ang (1–7) analogs, like peptidase-resistant thioether-bridged Ang (1–7) called cAng (1–7), have also been shown to exert vasodilator effects in rat aortic rings and improve cardiac remodeling and endothelial function after MI [408,409]. More recently, another novel nonpeptide MasR agonist, CGEN-856S, was discovered by a computational drug discovery platform [410]. This specific MasR agonist, binding neither to AT1R nor to AT2R, is shown to produce a shallow dose-dependent decrease in MAP of conscious SHRs and to elicit vasodilation in aortic rings and antiarrhythmogenic effects in the isolated rat heart [410].

4.3. Ang (1–9) and AT2R agonists

Ang (1–9) produces potent protective effects in several cardiopathy animal models, but the dosage of the Ang (1–9) used in animal studies is critical to the anti-hypertensive effect. The administration of Ang (1–9) via osmotic micropump at doses of 600 ng/kg/min or higher reduces blood pressure in SHRs [145], and similar effects were also observed in rodents treated with DOCA salt, Ang II-infusion, and in the Goldblatt rats with renal artery clip [124,150]. By contrast, a low dose (100 ng/kg/min) of Ang (1–9) was unable to achieve a hypotensive effect in SHRs [411].

However, the pharmacological application of Ang (1–9) as an antihypertensive agent is still limited due to its unstable pharmacokinetic properties as Ang (1–7). The actual plasma half-life for Ang (1–9) is still unknown. Likewise, the results obtained from animals and preclinical studies are also specious. However, the Ang (1–9)-AT2R axis remains a potential therapeutic target for the treatment of hypertension if the current obstacles can be overcome by focusing on the local synthesis of Ang (1–9), enhancing its stability, or synthesizing small-molecule AT2R agonists [412].

First, engineered adenoviral Ang (1–9) vector transduction boosted local Ang (1–9) levels, reduced cardiomyocyte hypertrophy in vitro, and lessened myocardial injury after MI in vivo [413,414]. However, it has not been demonstrated that this approach reduces blood pressure in hypertensive models yet. Second, the nanoparticle technique is an ideal method for stabilizing Ang (1–9) since it preserves the biological activity of Ang (1–9) after modification with Eudragit® E/alginate or gold nanoparticles [415–417], but this strategy has not yet been evaluated in vivo. Third, studies on various animal models suggest that synthetic AT2R agonists, including that CGP42112, C21, Novokinin, and β-Ile(5)-Ang II, are functionally protective against hypertension. CGP42112 is the first available AT2R agonist that functions both in vitro and in vivo [418,419]. In obese Zucker rats, 2-week subcutaneous osmotic minipump delivery of CGP42112 caused a decreased blood pressure associated with increased urinary sodium excretion [420]. Similarly, intravenous infusion of CGP42112 induces a marked depressor effect together with generalized vasodilatation that was abolished by the co-infusion of the AT2R antagonist PD123319 [421]. C21, a non-peptide small molecule agonist (Vicore Pharma, Gothenburg, Sweden), is another synthetic AT2R agonist that has been studied in both hypertensive animals such as the obese Zucker rat, DOCA salt-induced hypertension rats and SHRs [420,422,423]. The mechanism of C21-mediated blood pressure reduction includes enhancing natriuresis, increasing vasodilation, and inhibiting vasopressin release [424–428]. Additionally, there are a few clinical trials ongoing to evaluate vasodilatation in humans. The short peptide Nnovokinin showed antihypertensive effects in SHR and L-NAME (NOS inhibitor) plus salt-induced hypertensive rats [429–431]. By selectively binding to AT2R, the Ang II derivatives β-Tyr(4)-Ang II and β-Ile(5)-Ang II triggered a reduced blood pressure in conscious SHRs with evoked vasorelaxation [432].

4.4. Alamandine and MrgD agonists

As a new member of the angiotensin family, alamandine has been investigated in a few hypertensive animal models, including SHRs, 2K1C rats, Dahl salt-sensitive rats, and Ang II infusion mice [152,162,164,165,172,433]. Alamandine was firstly found to lower long-term blood pressure by a single dose in SHRs [152]. Moreover, the administration of alamandine via oral and subcutaneous injection attenuates hypertension, alleviates cardiac hypertrophy, and improves LV function in SHRs [164,165]. In renal vascular hypertensive rats, alamandine exhibits a biphasic hemodynamic effect after infusion into different sites of the brain. Microinjection of alamandine at picomole level into the caudal ventrolateral medulla caused a hypotensive effect in 2K1C hypertensive rats [162]. However, microinjection of alamandine into the hypothalamic PVN increased MAP and renal sympathetic nerve activity (RSNA) in both WKY and SHR rats but to a greater extent in SHRs [163]. Interestingly, oral treatment of an inclusion compound of alamandine/2-hydroxypropyl-β-cyclodextrin (alamandine-HPβCD) produced a long-term anti-hypertensive effect in SHRs and attenuated aorta remodeling in the transverse aortic constriction mouse model [152,434].

Cryo-EM has recently revealed the structural insight into the activation mechanism of MrgDR coupled with G_i-protein after β-alanine stimulation [435], but the conformational change of MrgD coupled G_s triggered by alamandine is still unknown. Alamandine competes with β-alanine for binding to MrgDR in vivo, suggesting that they share a similar binding site; however, MrgDR ligands other than alamandine failed to elicit any vasoactive response and even competitively inhibit alamandine-induced vasodilation [152], which indicates that the particular dynamic properties of the receptor-ligand interactions are critical for the downstream signal cascade. Recently, the alamandine glycoside analogs were synthesized and evaluated for their ability to antagonize the MrgDR to produce antinociceptive effects and

Table 2
Pharmacological agents/strategies to treat hypertension targeting the counter regulatory RAS.

Pharmacological approach	Types	In vivo model Used	Clinical Status	Effects	References
atRA	ACE2 agonist	SHRs	N/A	Increase ACE2 protein; reduce blood pressure; attenuate myocardial damage	29
XNT	ACE2 agonist	SHRs; *db/db* mice; streptozotocin-induced diabetic rats	N/A	Increase ACE2 expression/activity; reduce blood pressure; increase Ang (1–7) production; reverse cardiac and renal fibrosis; promote vasorelaxation response by attenuation of oxidative stress	28, 35, 354, 356
DIZE	ACE2 agonist	*db/db* mice; MI rats; ischemic stroke rats; SHRs; streptozotocin-induced diabetic rats	N/A	Decrease the infarct area; attenuate LV remodeling post-MI; restore the normal balance of RAS; promote vasorelaxation response by attenuation of oxidative stress	35, 353, 355, 356
imatinib	ACE2 agonist	high-fat-diet-induced insulin-resistant mice; hACE2 transgenic mice	Phase II NCT04416750	Enhance ACE2 enzyme activity; reduce Ang II/Ang (1–7) ratio; exhibit anti-inflammatory effects; improve aortic glucose and lipid metabolism; ameliorate COVID-19-induced metabolic complications; inhibit spike protein binding to ACE2	358
methazolamide	ACE2 agonist	high-fat-diet-induced insulin-resistant mice; hACE2 transgenic mice	N/A	Enhance ACE2 enzyme activity; reduce Ang II/Ang (1–7) ratio; exhibit anti-inflammatory effects; improve aortic glucose and lipid metabolism; ameliorate COVID-19-induced metabolic complications; inhibit spike protein binding to ACE2	358
rACE2	ACE2 protein	Ang II infused mice; K18-hACE2 mice; healthy participants	Phase II NCT00886353	Attenuate hypertension, myocardial hypertrophy, fibrosis, and diastolic dysfunction; reduce plasma Ang II levels and increase plasma Ang (1–7) levels; sustain elevations in serum ACE2 activity to attenuate blood pressure; improve cardiac output and pulmonary vascular resistance; neutralize SARS-CoV-2 infection	40, 231, 359, 360
rACE2-Fc	ACE2 protein	Ang II infused mice; K18-hACE2 mice	N/A	Improve the pharmacokinetic properties of rACE2; reduce plasma Ang II levels and blood pressure; reduce cardiac fibrosis; counter lethal SARS-CoV-2 infection	363, 364
MLN-4760	ACE2 inhibitor	streptozotocin-induced diabetic mice	N/A	Exacerbate cardiac hypertrophy and fibrosis; increase ACE expression; increase local cardiac Ang II accumulation; increase the risk of SARS-CoV-2 infection; exacerbate COVID-19 outcomes	365, 366, 372
DX600	ACE2 inhibitor	SHRs	N/A	Increase autocrine Ang II and decrease Ang (1–7); increase thrombus formation	369, 370, 371
Ang (1–7)	Ang (1–7) analog	renal hypertensive rats; SHRs; anesthetized rats; Dahl salt-sensitive rats; obese patients; hypertensive patients;	Phase I NCT05189015, NCT03001271	Induce vasodilation and counterbalance the vasoconstriction induced by Ang II; enhance the hypotensive effect of bradykinin; decrease mean arterial pressure; increase release of prostacyclin and nitric oxide; cause vasodilation in the forearm circulation of normotensive subjects and patients with essential hypertension; blunt vasoconstrictor tone; improve renal blood flow and glomerular filtration.	375, 376, 377, 378, 389, 390, 391, 392, 395, 396, 397
cAng (1–7)	Ang (1–7) analog	infarcted rats; isoproterenol-treated rats; MI rats	N/A	Exhibit vasodilatory effects; improve cardiac remodeling and endothelial function	408, 409
AVE0991	MasR agonist	streptozotocin-treated rats; infarcted male Wistar rats; Ang II induced myocardial hypertrophy rats; ApoE$^{-/-}$ mice	N/A	Mimic the effects of Ang (1–7); restore vasodilatation; attenuate heart failure; diminish pathological cardiac remodeling; improve baroreflex sensitivity; prevent Ang II-induced myocardial hypertrophy; exhibit anti-atherosclerotic and anti-inflammatory effects	400, 401, 402, 403, 404, 405
CGEN-856S	MasR agonist	SHRs	N/A	Decrease mean arterial pressure; elicit vasodilation; exhibit anti-arrhythmogenic effects	410
A-779	MasR inhibitor	Mas-deficient mice	N/A	Attenuate Ang (1–7) depressor response in hypertension	84
D-Pro	Mas/MrgD antagonist	Mas-deficient mice cirrhosis and portal hypertension rats	N/A	Block vasorelaxation effects produced by Ang (1–7); compete for the binding of Ang-(1–7) to the cortical supramedullary region; Improve portal hypertension	84, 406, 437
Ang (1–9)	Ang (1–9) analog	Ang II infusion rats; MI rats; C57BL/6 mice with permanent left anterior descending coronary artery ligation; CKD II-III patients with hypertension	NCT01832558	Reduce Ang II levels and increase Ang (1–7) levels; activate AT2R to trigger urinary natriuretic response and NO production; reduce blood pressure; reduce cardiomyocyte hypertrophy; attenuate inflammation, cardiac hypertrophy, and fibrosis; lessen myocardial injury	123, 124, 125, 126, 414

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Table 2 (*continued*)

Pharmacological approach	Types	In vivo model Used	Clinical Status	Effects	References
CGP42112	AT2R agonist	obese Zucker rats; conscious SHRs	N/A	Induce a depressor effect together with generalized vasodilatation; reduce blood pressure by increasing urinary sodium excretion	418, 419, 420, 421
C21	AT2R agonist	SHRs; AT2R knockout mice; Ang II infused rats; AT2R-eGFP mice and heterozygous transgenic eGFP-AVP Wistar rats; healthy participants	Phase I NCT05277922	Reduce blood pressure by enhancing natriuresis, increasing vasodilation, and inhibiting vasopressin release	421, 425, 426, 427, 428
Novokinin	AT2R agonist	SHRs; L-NAME plus salt-induced hypertensive rats	N/A	Exhibit anti-hypertensive effects	429, 430, 431
β-Ile(5)-Ang II	AT2R agonist	conscious SHRs	N/A	Reduce blood pressure with evoked vasorelaxation by selectively binding to AT2R	432
β-Tyr(4)-Ang II	AT2R agonist	SHRs	N/A	Reduce blood pressure with evoked vasorelaxation by selectively binding to AT2R	432
alamandine	alamandine analog	SHRs; LPS-induced myocardial dysfunction mice	N/A	Reduce the long-term blood pressure; attenuate hypertension; alleviate cardiac hypertrophy; improve left ventricular function	152, 164, 165
alamandine-HPβCD	alamandine analog	SHRs; mice with transverse aortic constriction	N/A	Exhibit long-term anti-hypertensive effects; attenuate aorta remodeling	152, 434

Abbreviations: atRA: all-trans retinoic acid; XNT: xanthone; DIZE: diminazene aceturate; rACE2: recombinant ACE2 protein; rACE2-Fc: a chimeric fusion protein of rACE2 and the immunoglobulin fragment Fc segment; D-Pro:D-Pro^7-Ang (1–7); C21: compound 21; alamandine-HPβCD: alamandine/2-hydroxypropyl-β-cyclodextrin; cAng (1–7): peptidase-resistant thioether-bridged Ang (1–7); SHRs: spontaneously hypertensive rats; MI rats: myocardial infarction rats; ApoE$^{-/-}$ mice: apolipoprotein E$^{-/-}$ mice; CKD: chronic kidney disease patients; L-NAME: L-N^G-Nitro arginine methyl ester.

neuropathic pain modulation in vitro [436]. The blockade of MrgDR by D-Pro improved portal hypertension in cirrhotic rats, indicating the major role of MrgDR in the development of cirrhotic portal hypertension [437]. However, due to the absence of a specific structure to explicate the activation process in the cardiovascular system, research on the activation of MrgDR by alamandine and its mimetics to combat hypertension is currently limited.

5. Conclusion

The current evidence supporting the cardiometabolic protective role of the counter-regulatory RAS is encouraging but incomplete, particularly in this COVID-19 era when the dual properties of the core enzyme ACE2 are well recognized. Targeting the counter-regulatory pathways with agonists or stimulators to rescue functional ACE2 and effector peptides may effectively promote the function of this regulatory arm and be a promising therapeutic strategy for the treatment of hypertension and COVID-19. Anti-hypertensive, antiviral, and anti-inflammatory treatments for hypertension and COVID-19 could be personalized based on the commonalities and associations between these two diseases. However, better phenotypic analysis of animal studies and more well-designed interventional trials are needed to understand the Yin and Yang of this complex system in blood pressure regulation as well as in viral infection.

CRediT authorship contribution statement

Hongyin Chen: Investigation, Writing – original draft, Visualization. **Jiangyun Peng:** Investigation, Writing – original draft. **Tengyao Wang:** Investigation, Writing – original draft. **Jielu Wen:** Investigation, Writing – original draft. **Sifan Chen:** Investigation, Supervision, Funding acquisition, Writing – review & editing. **Yu Huang:** Supervision, Funding acquisition, Writing – review & editing. **Yang Zhang:** Conceptualization, Supervision, Funding acquisition, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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