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REVIEW ARTICLE

Hypertension and COVID-19: Current Evidence and Perspectives

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Abstract
Coronavirus disease 2019 (COVID-19) outbreak, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), represents a real challenge for health-care systems worldwide. Male sex, older age and the coexistence of chronic comorbidities have been described as the most relevant conditions associated with a worse prognosis. Early reports suggested that hypertension might represent a risk factor for susceptibility to SARS-CoV-2 infection, a more severe course of COVID-19 and increased COVID-19-related deaths. Nevertheless, the independent role of hypertension remains under debate, since hypertension is often associated with the older age and other cardiovascular (CV) risk factors in the general population, which may also contribute to the SARS-Cov-2 infection and COVID-19. Moreover, the role of antihypertensive drugs, primarily angiotensin-converting inhibitors (ACEIs) and ARBs (angiotensin receptor blockers) in COVID-19 development and outcome appears controversial. Indeed, preclinical studies using these classes of drugs have suggested a potential upregulation of angiotensin-converting-enzyme 2 (ACE2) which is the key binding receptor promoting cell entry of SARS-CoV-2 in the organism. Renin–angiotensin system (RAS) blockers may potentially upregulate ACE2, hence, it has been initially hypothesized that these agents might contribute to a higher risk of SARS-CoV-2 infection and progressive course of COVID-19. However, several clinical reports do not support a detrimental role of RAS blockers in COVID-19, and an intense debate about the withdrawal or maintenance of chronic therapy with ACEi/ARB has been developed. In this review we will discuss the available evidence on the role of hypertension and antihypertensive drugs on SARS-CoV-2 infection and COVID-19 development.

Keywords COVID-19 · High blood pressure · Renin–angiotensin system · ACE2 · MasR · RAS blockers

1 Introduction

The coronavirus disease 2019 (COVID-19) pandemic, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1], poses unprecedented challenges to health-care systems around the world. As of 21st October 2021, there have been more than 240 millions confirmed cases of COVID-19, including 5 millions deaths worldwide [2].

Several reports, over the past months, have shown that hypertension can be associated with the risk of SARS-CoV-2 infection as well as to the development of the worse prognosis of COVID-19 [3–6]. Nevertheless, these assumptions have been challenged and the independent role of hypertension on the risk of infection and the worse outcome of COVID-19 has been mitigated and under debate. In several observational studies hypertension is often associated with other CV risk factors and the older age since these conditions often coexist in the general population worldwide. Indeed, an increased risk of SARS-Cov-2 infection and worse outcomes of COVID-19, consisting in a higher risk of hospitalization, access to intensive care units and mortality, have been shown in the elderly and in individuals affected by comorbidities other than hypertension such as diabetes, previous cardiovascular (CV) and cerebrovascular diseases, obesity, and chronic pulmonary diseases [7–9].

Moreover, the role of the first-line agents for the treatment of hypertension [10–12] including ACE (angiotensin-converting enzyme) inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) appears controversial in COVID-19. Indeed, preclinical studies using these Renin–Angiotensin System (RAS) antagonists have shown a potential induction

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of ACE2 (angiotensin-converting-enzyme 2) upregulation which is the key binding site promoting cell entry of SARS-CoV-2 in the organism [13, 14]. Thus, it has been thought that a putative upregulation of ACE2 in hypertensive patients during treatment with RAS-blockers might potentially contribute to the higher risk of SARS-CoV-2 infections and progressive course of COVID-19. However, several clinical reports do not support the notion of the detrimental role of RAS blockers in COVID-19. Thus, taken into account the widespread use of RAS inhibitors in patients with hypertension and CVD, an intense debate has developed about the withdrawal or maintenance of chronic ACEI/ARB therapy in patients with COVID-19 [15, 16].

In this review we will discuss the available evidence on the role of hypertension and blood pressure (BP) lowering drugs on SARS-CoV-2 infection and disease course of COVID-19.

2 Role of Hypertension and Organ Damage in COVID-19 Outcome

The first case series from China have reported that hypertension is the most common condition in patients affected by COVID-19, ranging from 27 to 30% while other comorbidities were considerably less represented (i.e. diabetes in 19%, coronary artery disease [CAD] in 6–8%) [7, 8]. In an observational study conducted in a cohort of 12,594 patients in New York City, hypertension was reported in a 34.6% [17]. However, hypertension was frequently reported in association with diabetes particularly in patients who experienced a more severe disease course, admitted to intensive care units, and receiving mechanical ventilation or even dying. The association between COVID-19 and hypertension appears not surprising and does not necessarily imply a causal relationship, due to the large prevalence of high-BP worldwide, affecting 25% of the adult population with a peak of prevalence > 60% in the elderly population [18]. Thus, hypertension more frequently occurs in the elderly and in subjects affected by other comorbidities, who are the categories in which the risk of worse outcome of COVID-19 is increased. In a cross-sectional, observational, multicenter, nationwide Italian survey hypertension had higher prevalence in hospitalized patients, however non survivors to COVID-19 had hypertension along with older age, higher Charlson Comorbidity Index, higher prevalence of diabetes, and chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD), coronary artery diseases, and heart failure (HF). Hence, in a multivariate analysis after adjustment for age and other CV risk factors, hypertension did not play an independent role in COVID-19 development and outcome [3, 4]. In a French cohort of more than 87,000 people, cardiometabolic diseases, (including obesity, diabetes, hypertension, dyslipidaemia), CV disease (stroke and stroke sequelae, HF, CAD, cardiac arrhythmias or conduction disorders, valvular heart disease, peripheral artery disease), chronic respiratory diseases and severe CKD were associated to a much higher risk of hospitalization for COVID-19 and of in-hospital mortality. The high comorbidity rate among patients hospitalized for COVID-19 pneumonia was up to 69% in those aged > 65 years [5]. In a large cohort of patients in UK the hazard ratio for death compared to younger subjects increased from 2.63 (95% confidence interval [CI] 2.06–3.35, $P < 0.001$) in patients aged between 50 and 59 years and to 11.09 (95% CI 8.93–13.77; $P < 0.001$) in patients of at least 80 years old, and the influence of hypertension on mortality risk has been demonstrated to be less relevant after adjustment for age and sex, the hazard ratio changing from 1.09 (95% CI 1.05–1.14) to 0.89 (95% CI 0.85–0.93) [9]. Therefore, these observations suggest that hypertension may not play and independent role in SARS-Cov-2 infection and COVID-19, rather, the effect of hypertension on COVID-19 course is influenced by older age and the interaction with other CV risk factors. Interestingly, in a retrospective single-center cohort study at the Seventh Hospital of Wuhan City, China, it has been showed that not the hypertensive status but only elevated systolic BP (SBP) values was associated with death and respiratory distress parameters. High SBP, was identified as a covariate in both mortality and survival prediction models and was present in deceased COVID-19 patients as compared to discharged individuals [19]. This is not surprising, since elevated SBP could be a marker of pre-existing hypertension mediated subclinical organ damage (HMOD, i.e. vascular stiffness), thus representing an important comorbidity factor [20]. Higher SBP could be also due to under-treated or uncontrolled hypertension or may represent a consequence of reduced enzymatic activity of angiotensin converting enzyme-2 (ACE2) caused by the binding of a higher SARS-CoV-2 load. It should be also noted that patients who died were older, and this further highlights the link of age with hypertension in the risk of worse outcome in COVID-19. Consistently, in a large Spanish cohort of 12,170 patients elevated SBP > 140 mmHg at admission has been identified as a predictor of all-cause mortality, particularly when associated with elevated pulse pressure ≥ 60 mmHg (i.e. increased arterial stiffness) [21]. Taken together, these findings suggest that the role of basal and achieved BP control rather than hypertension per se could be considered as a prognostic factor in COVID-19. In such a context, the delay in the diagnosis of hypertension and in the initiation of specific BP-lowering treatments as well as the increase in therapeutic inertia related to the COVID-19 outbreak may have also contributed to the worsening of BP control which may impact on the prognosis of SARS-CoV-2 infection [22, 23]. In this regard, uncontrolled blood pressure values are involved in the development of vascular

remodeling and vascular stiffness, which may contribute to the impact of hypertension on the outcome and mortality in patients with COVID-19 [24, 25]. Hypertension is a major risk factor for endothelial dysfunction and atherosclerosis. Thus, the presence of these subclinical conditions could impact on CV outcome in patients with COVID-19 [20]. Moreover, among the different pathophysiological changes in the CV system in hypertensive patients, left ventricular hypertrophy and fibrosis, associate eventually to HF with preserved ejection fraction (HFpEF), may contribute to the higher susceptibility to SARS-CoV-2-induced damage in the heart, including ischemic damage, and the development of atrial and ventricular arrhythmias [26]. Hypertension may also contribute to the development of CKD, which represents a predisposing condition to the progression of acute kidney injury in patients with severe COVID-19, and may impact on the prognosis [27].

Hence it is reasonable to argue that HMOD may exert an independent prognostic value by increasing the risk of mortality in COVID-19, although this assumption should be further elucidated.

3 Relationship with Vascular Inflammation

The relationship between hypertension and COVID-19 may involve common inflammatory pathways. Indeed, a large body of evidence supports the hypothesis that hypertension is associated with immune activation and oxidative stress, consisting in the production of reactive oxygen species (ROS), increased activity of NADPH oxidases, cell migration and adhesion to endothelial surface [28].

Both innate (i.e. macrophages, microglia, monocytes, dendritic cells, and myeloid-derived suppressor cells) and adaptive immune cells (i.e. CD8+ T cells, CD4+ cells [Th1, Th17 and Treg cells], T cells and B cells) have been shown to favor the development of hypertension in the context of COVID-19, particularly through the activation of the NLRP3-related inflammasome and the secretion of cytokines (e.g. interleukin-6, -7 and -17, interferon [IFN]-gamma, and tumor necrosis factor [TNF]-alpha) [29–32]. These immune mechanisms also contribute significantly to accelerated end-organ damage. Immune dysregulation characterized by the increased levels of interleukin-2, -6 and -7, granulocyte colony-stimulating factor, C-X-C motif chemokine 10, chemokine [C-C motif] ligand 2 and TNF-alpha have been also associated with the severity of COVID-19 [33]. COVID-19 is often associated to cytokine storm resulting in endotheliitis which induces vascular permeability, the secretion of adhesion molecules (such as ICAM-1, VCAM-1), TNF-α, angiopoietin-2, eNOS downregulation, and decreases prostacyclin production. Moreover, it also induces capture of platelets and dysregulation of clotting cascades, thrombin activation, and fibrin production. Glycocalyx disruption and increased release of von-Willebrand factor (VWF) and factor VIII, usually stored in Weibel–Palade body of endothelial cells, have been also proposed as contributing factors of endothelial dysfunction and cloth formation. Conversely, the activation of angiopoietin 2 may countervail and act as an antagonist of Tie2 activation by the angiopoietin 1, and induces anti-inflammatory, anticoagulatory, and antiapoptotic signaling [34]. Intravascular thrombosis and coagulation, in addition, may further damage the endothelium maintaining a vicious circle of endothelial inflammation and dysfunction. Extensive microthrombosis in coronary and pulmonary circulation have been described and are respectively associated to myocardial damage with increased troponin levels and to an unusual dead-space and shunt in the lung contributing to severe hypoxia and respiratory distress [35, 36]. Autoptic analyses of patients who died for COVID-19 showed the presence of thrombi with a diameter of 1–2 mm in pulmonary precapillary vessels and a distorted vascularity with structurally deformed elongated capillaries with sudden changes in caliber and the presence of intussusceptive pillars. Clot formation was also detected in pulmonary arterioles with diffuse alveolar damage and hyaline membranes [37–40].

It should be noted that most of the abovementioned molecular pathways (including immune cells dysregulation, activation of ROS and inflammatory pathways) may be also involved in the pathophysiology of endothelial dysfunction in hypertension which might predispose to SARS-CoV-2 infection [41–45]. These common mechanisms may further contribute to explain the increased vulnerability of hypertensive patients to a more severe disease course when vascular damage occurs, although this hypothesis must be confirmed by future preclinical and clinical studies [20].

4 The Role of Renin–Angiotensin System and RAS Blockers in COVID-19

RAS and, in particular its key effector Ang II, plays a fundamental role in the development of hypertension and its sequelae, contributing to endothelial dysfunction, cell growth, oxidative stress, vasoconstriction and inflammation. Ang II induces hyperplasia and hypertrophy of vascular smooth muscle cells (VSMC) in resistance arteries and increases the production of mitogenic factors such as TGF-β, PDGF (platelet-derived growth factor), EGF (epidermal growth factor), IGF-1 (insulin-like growth factor 1) and of superoxide through the activation of cSrc, PKC, phospholipase A2 (PLA2) and phospholipase D (PLD). Moreover, Ang II enhances NADPH oxidase activity and the generation of ROS [46] which may activate several signaling pathways such as MAPK, JAK-2, STAT, p21Ras,

Pyk-2 (Proline-rich Tyrosine Kinase 2) and AKT, receptor tyrosine kinases such as EGFR (EGF Receptor), IGFR (IGF Receptor 1) and PDGFR, protein tyrosine phosphatases and redox-sensitive transcriptor factors such as Activator Protein 1 (AP)-1 and Hypoxia-inducible factor 1 (HIF-1) [47, 48]. Ang II also stimulates the production of E-selectin and plasminogen activator inhibitor-1 (PAI-1), which may contribute to a prothrombotic state [49].

On the other hand, the activation of complementary protective axes in the RAS may countervail these deleterious effects in the CV system particularly during the use of RAS blockers. These include activation of the type 2 Ang II receptor (AT2R) which exerts a protective role in the CV system, inducing vasodilation, NO production and producing antiproliferative, anti-inflammatory and anti-remodelling effects and the activation of ACE2/Ang-1–7/MasReceptor (MasR) system [50]. The classical ACE, a dipeptidyl carboxypeptidase, converts the decapeptide angiotensin I (Ang 1–10) into the octapeptide angiotensin II (Ang 1–8), which is the main effector of the RAS. Another enzyme, homologous to ACE was identified, and named ACE2 which is a mono-carboxypeptidase, that cleaves one amino-acid at the end of peptides and forms another peptide from Ang II which contains only 7 amino acids, namely Ang (1–7), and cannot be inhibited by ACEi. Ang (1–7) activates the MasR and exerts a protective role on the CV system, mediating vasodilation, antioxidation, anti-fibrotic and anti-inflammatory effects [51–54]. Experimental studies have shown that the activation of ACE-2/Ang (1–7)/MasR axis may counteract, at least in in part, the Ang II effects in the CV system, such a vasoconstriction and cell growth, and may induce favorable effects on the function and structure of aorta and the heart. Furthermore, ACE-2/Ang (1–7)/MasR axis has been demonstrated to play an important role in microvascular protection during selective blockade of the AT1R through the improvement of resistance arteries remodeling via the reduction of ROS production and increased NO bioavailability [50]. MasR expression was significantly increased by Ang (1–7) as well as by ARB, increasing eNOS expression and plasma nitrite. On the other hand, superoxide generation was attenuated by ARB and Ang (1–7). These MasR-mediated actions were independent of AT2R activation and may contribute to the favorable effects of AT1R antagonism on NO bioavailability and microvascular remodeling, independently of AT2R activation and BP control [50].

Animal studies have shown that the development of HMOD is more common in case of a reduced expression of ACE2 mRNA [55–57]. Lentiviral gene transfer of ACE2 reduced CV damage in spontaneously hypertensive rats (SHR) [58]. Consistently, pharmacological activation of ACE2 or administration of recombinant human ACE2 attenuated vascular damage in rat models [59].

Membrane ACE2 is also the key binding receptor promoting cell entry of SARS-CoV-2 in the respiratory tract [60]. In this regard, the RAS inhibitors-mediated increase of ACE2 has generated concern at the beginning of the COVID-19 outbreak due to the hypothesized increased risk of infection and of a more aggressive course of the disease [14]. Several studies, however, have demonstrated that ACE2 expression is low in the respiratory tract [61] and that the ACE2/Ang (1–7)/MasR axis exerts an important protective role against inflammatory lung injury, whereas an increased expression of Ang II and the activation AT1R may favor pulmonary damage [62]. The binding of the SARS-Cov-2 spike protein to ACE2, causing its downregulation, reduces the potentially protective effects during acute inflammation [38]. In animal models the administration of recombinant SARS virus spike protein alone, even in the absence of viral replication, downregulated ACE2 on the surface of pulmonary alveolar cells and concurred to lung injury [63]. In the early phases of COVID-19 outbreak an increasing debate developed on the use (withdrawal or maintenance) of drugs interacting with RAS, in particular angiotensin converting enzyme (ACE) inhibitors (ACEi) and angiotensin receptor blockers (ARBs) [13]. These drugs represent the first line therapy most frequently used in hypertensive patients as recommended by the international guidelines, due to their protective CV activity on the development of HMOD, atherosclerosis, HF, and chronic kidney disease [10–12]. However, on the basis of the abovementioned data, treatment with ACEIs and ARBs may even protect from a severe disease course through the inhibition of the deleterious proinflammatory e effect of AngII as well as through the activation of the protective arms of the RAS. Furthermore, it has been also demonstrated that ACE2 is not upregulated in nasal ciliary cells of patients who received ACEI or ARBs, independently from age, sex and smoking history [64]. In addition, treatment with ACEI has been associated with activation of intrinsic antiviral response [65]. In a study conducted in 436 patients the ACE2 mRNA expression was associated to age, but neither to hypertension nor to treatment with RAS inhibitors [66].

Several observational and cohort studies have shown the non-harmful effect or even the safety of the use of RAS blockers in COVID-19 patients. In an Italian population-based study conducted by Mancia and colleagues, the use of RAS inhibitors was more frequent among the 6272 patients with COVID-19 compared to the 30,759 controls because of the higher prevalence of CV RFs and CVD. However, in multivariable adjusted analysis, the use of ARBs/ACEIs or their combination with other antihypertensive drugs was not significantly associated with the risk of COVID-19 or with a more severe disease course [67].

In another population-based study conducted in Spain on 1139 COVID-19 patients and on 11,390 matched controls, the use of RAS inhibitors was not associated to an increased risk of infection or with hospital admission [68]. In a Korean study, 950 out of 16,281 hypertensive patients experienced COVID-19 disease. Among them, those who were treated with ACEIs or ARBs did not present an increased risk of hospitalization, independently from the use of these drugs for hypertension or other causes after case-control matching and multivariable-adjusted conditional logistic regression analysis [69]. The analysis of these three population-based case–control studies confirmed the absence of significant association between ACEI/ARB (pooled odds ratio 1.00 [95% CI 0.81–1.23], P = 0.98) and all-cause mortality/severe disease [70].

In an observational analysis conducted by Reynolds and colleagues in a cohort of 12,594 subjects who were tested for COVID-19, among whom 46.8% resulted positive and 17.0% had severe illness, no association was found between the use of RAS blockers and an increased likelihood of a positive test or the risk of severe illness [17]. These results have been confirmed by another retrospective cohort study conducted on 18,472 subjects and by a large meta-analysis of 31 studies on 87,951 participants which showed no significant association between treatment with RAS inhibitors and all-cause mortality (risk ratio 0.94 [95% CI 0.86–1.03], P = 0.20) or severe disease (risk ratio 0.93 [95% CI 0.74–1.17], P = 0.55) [71]. In a study conducted by Morales and colleagues, 363,785 patients with hypertension treated with ACEIs or ARBs were compared with 24,8915 subjects who received calcium channel blockers of thiazidic diuretics, showing no association between the used antihypertensive agents, both as monotherapy or associations with other drugs, and COVID-19 diagnosis and hospitalization. Importantly, the direct comparison of ACEIs with ARBs also did not yield any apparent difference [72].

In the randomized BRACE-CORONA trial, 659 hospitalized patients with COVID-19 were assigned to continuation of ACEI/ARB treatment or temporary suspension of the therapy for 30 days. There were no significant differences among group in the primary outcome of the number of days alive and out of hospital at 30 days (21.9 vs 22.9 days in the discontinuation and continuation groups, respectively; average difference − 1.1 days; mean ratio 0.95; 95% CI 0.90–1.01; P = 0.09). However, it should be underlined that the relatively low-risk (57% had mild disease) and young age (mean 55.1 years) of the enrolled population and the low mortality rate (2.7%) may have influenced the achieved results [73].

In the REPLACE-COVID trial 152 patients were randomly assigned to either continue or discontinue RAS-inhibitor therapy, showing no effects on the risk of intensive care unit admission, invasive mechanical ventilatory support and death [74].

In a cohort of hospitalized COVID-19 patients the ARB telmisartan significantly reduced C-reactive protein (CRP) levels and COVID-19 related outcomes, including ICU admission, time to discharge and death, compared to usual care. It should be noted that treatment with telmisartan was started early, within 4 days of symptom onset, and that it was administered at high dosages twice daily, suggesting that RAS inhibition might be adequately obtained with intensive strategies during COVID-19 disease [75].

In the ACEI-COVID trial 204 patients with recent symptomatic SARS-CoV-2 infection and chronically treated with ACEIs or ARBs were randomly assigned to discontinuation or continuation of RAS inhibition for 30 days. There were no significant differences among groups in the primary outcome of the maximum sequential organ failure assessment (SOFA) score within 30 days and in the secondary endpoints of area under the death-adjusted SOFA score (AUCSOFA), mean SOFA score, admission to the intensive care unit, mechanical ventilation, and death [76].

The ongoing RAMIC is assessing the efficacy of treatment with ramipril 2.5 mg for 14 days to decrease ICU admission, mechanical ventilator use and mortality in patients with COVID-19 while also minimizing the risk of transmission and use of personal protective equipment [77].

Consistently, two other randomized trials are exploring the effects of the ARB losartan (NCT04312009) and of the mineralocorticoid receptor agonist spironolactone (NCT04345887) compared to placebo on morbidity and mortality during hospitalization for COVID-19.

In such a context, also angiotensin receptor/neprilysin inhibitors (ARNi), combining the blockade of AT1R and the ability to increase natriuretic peptide levels, which regulate cellular growth and proliferation, preserving endothelial function and integrity as well as vascular tone, might represent a potential therapeutic tool in the treatment of COVID-19 [78].

Thus, on the basis of this evidence, international guidelines and expert consensus have repeatedly recommended to not discontinue treatment with RAS-inhibitors, eventually considering individual risk, comorbidities and the presence of organ damage [79, 80].

5 COVID-19 and Other Antihypertensive Drugs

The role of mineralocorticoid receptor antagonists (MRA) and other first-line antihypertensive drug classes, such as calcium channel blockers (CCBs), thiazides/thiazide-like diuretics, and β-blockers have been also evaluated. In the study by Mancia and colleagues, only 3.8% of patients

received MRA and no differences were observed in disease outcome compared to the control group [67].

It has been suggested that β-blockers may exert protective effects counterbalancing the activation of sympathetic system during COVID-19 disease. Moreover, individuals treated with β-blockers had a marginally lower likelihood of a positive COVID-19 test than patients not treated with these medications. Otherwise, a slightly higher risk of severe illness has been detected in subjects previously treated with CCBs [17].

Treatment with loop diuretics was apparently associated with an increased risk of COVID-19. However, the use of loop diuretics may be related to the existence of more severe comorbidities such as HF or advanced CKD, which may have influenced the results [67]. These findings further underline the important role of potential confounding by the concurrence and severity of comorbidities.

6 Conclusions

Current evidence suggests that even though hypertension is often present in COVID-19 patients, this pathological condition does not play and independent role in SARS-Cov-2 infection and COVID-19 progression. Rather, higher uncontrolled SBP may contribute to a more severe disease course, due to its association with HMOD, including vascular remodelling, which may worsen endothelial dysfunction, endothelial damage and endotheliitis induced by the SARS-Cov-2 infection. Although a large body of evidence supports the safety and even the protective role of the RAS blockers during COVID-19, further randomized clinical trials are required to confirm findings mostly deriving from observational studies and registries.

Finally many knowledge gaps remain to fill-up particularly with regard to the overall impact of hypertension on SARS-CoV-2 infection and the development of long-term sequelae such as post-COVID syndrome and long-COVID. In this perspective, hypertension still represents a "moving target" in COVID-19 management [20].

Declarations

Conflict of Interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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