ORİJİNAL ARAŞTIRMA ORIGINAL RESEARCH

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The Social, Psychological and Clinical Implications of the COVID-19 Pandemic in Cardiovascular Patients Using Angiotensin Converting Enzyme Inhibitor or Angiotensin Receptor Blocker

Anjiotensin Dönüştürücü Enzim İnhibitörü ya da Anjiotensin Reseptör Blokörü Kullanan Kardiyovasküler Hastalarda COVID-19 Pandemisinin Sosyal, Psikolojik ve Klinik Etkileri

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ABSTRACT Objective: The heart expresses angiotensin converting enzyme (ACE)-2 that makes it vulnerable to severe acute respiratory syndrome-coronavirus-2. Besides ACE inhibitors/angiotensin receptor blockers (ARBs) are used for cardiovascular diseases. Although no significant increase in the risk of coronavirus disease-2019 (COVID-19) infection and no increase in the severity of disease in patients receving ACE inhibitor/ARB therapy were shown, it has been noticed that some patients have tendency to stop the use of these agents. The aim of this study is to determine the behavior attitude of the cardiovascular outpatients during pandemic who use ACE inhibitor/ARB and to asses the impact of COVID-19 on them. **Material and Methods:** One hundred outpatients were included. A survey questioning the social, psychological and the clinical implications of COVID-19 was applied to volunteers. To measure the anxiety and despair levels, Beck scorings were used. **Results:** A small number of patients stopped using ACE inhibitors/ARBs. Severe hopelessness and severe anxiety levels were seen in a few patient. Gender, fear of getting sick, thinking to have enough information about COVID-19 and accessibilty to cardiovascular drugs were the factors affecting the Beck scores. Social distancing and cleaning hands are stated as the best measures for protection. Most of the patients preferred primary health clinics for routine controls and a few patient had knowledge about tele-medicine. **Conclusion:** Although a confusion has occured in the public about the use of ACE inhibitors/ARBs, drug release rates were found to be low. The anxiety and disparity levels are subsantially not severe. But it is still important to continue informing patients about the precautions and the use of tele-medicine.

Keywords: COVID-19; angiotensin converting enzyme inhbitor; angiotensin receptor blockers; Beck scores; precautions

ÖZET Amaç: Anjiotensin dönüştürücü enzim [angiotensin converting enzyme (ACE-2)] ekspresyonu, kalbi şiddetli akut solunum sendromu-koronavirüs-2'ye karşı duyarlı yapmaktadır. Bunun yanında birçok kardiyovasküler hastalıkta ACE inhibitörleri/anjiotensin reseptör blokörleri (ARB) kullanılmaktadır. ACE inhibitörü/ARB tedavisi alan hastalarda artmış koronavirüs hastalığı-2019 [coronavirus disease-2019 (COVID-19)] riski ya da hastalığın ciddiyetinde bir artış görülmese de bazı hastaların bu ajanların kullanımını bırakmaya eğilimleri olduğu farkedilmiştir. Bu çalışmanın amacı, pandemi döneminde kardiyoloji polikliniğine başvuran ACE inhibitörü ve ARB kullanan kardiyovasküler hastaların davranış paternlerini belirlemek ve COVID-19'un bu hastalar üzerindeki etkilerini araştırmaktır. **Gereç ve Yöntemler:** Çalışmaya 100 gönüllü hasta dâhil edildi. Hastalara COVID-19'un sosyal, psikolojik ve klinik etkilerini sorgulayan önceden hazırlanmış bir anket uygulandı. Hastaların anksiyete ve umutsuzluk seviyelerini değerlendirmek için Beck ölçekleri kullanıldı. **Bulgular:** Çok az hastanın ACE inhibitörü/ARB kullanımını bıraktığı görüldü. Ciddi anksiyete ve umutsuzluk çok az hastada saptandı. Beck skorlarını etkileyen en önemli faktörlerin cinsiyet, hastalanma korkusu, COVID-19 hakkındaki bilgi düzeyi ve pandemi süresinde kardiyovasküler ilaçları temin edebilme durumu olduğu saptandı. Hastaların COVID-19'dan korunmada, sosyal mesafeyi koruma ve el yıkamayı en önemli önlemler olarak düşündükleri tespit edildi. Bu dönemde rutin kontroller için çoğu hastanın sağlık ocaklarını tercih ettiği ve çok az hastanın tele-tıp uygulaması hakkında bilgi sahibi olduğu tesbit edildi. **Sonuç:** Toplamda ACE inhibitörleri/ARB'lerin kullanımı açısından bir kafa karışıklığı yaşansa da çok az hastanın bu grup ilaçları bıraktığı görülmüştür. Hastalarda anksiyete ve umutsuzluk seviyeleri ciddi düzeyde değildir. Ancak hastalıktan korunmada alınacak tedbirler ve tele-tıp kullanımı konusunda hastaların halen bilgilendirilmesi gerekmektedir.

Anahtar Kelimeler: COVID-19; anjiotensin dönüştürücü enzim inhbitorleri; anjiotensin reseptör blokörler; Beck skoru; önlemler

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Severe acute respiratory syndrome coronovirus (SARS-CoV-2) was first detected in Wuhan, China and it caused Coronavirus disease 2019 (COVID-19). In the begining of March 2021, it was announced as global pandemic.[1] The pandemic of COVID-19 has led to more than 80,430,000 confirmed cases and more than 1,759,000 deaths worldwide. The number of confirmed cases and deaths in Turkey were about 2,118,000 and 19,300 respectively.[2] Elderly and people with an underlying chronic disease were found to be more vulnerable to SARS-CoV-2 and its complications.[3]

It's now known that SARS-CoV-2 uses angiotensin-converting-enzyme-2 (ACE-2) for entry in the host cells.[4,5] Although ACE-2 is mainly found on the surface of type II alveolar epithelial cells, it can be expressed also in heart and other organs.[4-6] Among hospitalized patients with COVID-19, current data suggest that cardiovascular patients have increased risk of mortality and COVID-19 itself can induce many cardiovascular events.[3,7]

On the other hand, ACE-2 receptors are the main regulator of the renin-angiotensin-aldosterone system (RAAS). ACE inhibitors and angiotensin receptor blockers (ARBs) have been used to treat many cardiovascular diseases because they reduce the activity of the RAAS system.[8,9] Although no important increase in the risk of COVID-19 infection and also no significant differences in the severity or mortality of disease in patients receving ACE/ARB therapy were shown, it has been noticed that some patients have tendency to stop the use of these agents.[10,11]

In this period, factors such as anxiety, depression, fear of getting sick, insufficient information can also lead to drug incompatibility. This can affect the natural course of the cardiovascular diseases adversely and also can worsen the prognosis. The aim of this study is to determine the behavior attitude of the cardiovascular outpatients using ACE/ARB therapy and to establish the social, psychological and the clinical implications of COVID-19 in these patients using the results of Beck anxiety and hopelessness inventories.

MATERIAL AND METHODS

This is a survey study performed during COVID-19 pandemic in Turkey. One hundred outpatients who are using ACE inhibitors/ARBs for different cardiovascular diseases were included in the study. The study was performed in a single center in July 2020. A questionnaire was prepared and only volunteers were included. Written informed consent were taken from all the patients and patients below the age <18 were excluded. Questions about the course of their cardiovascular disease and the continuation of the ACE inhibitors/ARBs during pandemic, their knowledge levels about COVID-19 and about taken measures, their acceptance and keeping of measures, their psychological states and the factors affecting their psychology were all asked. For understanding their anxiety and despair levels, we used Beck scorings. In the Beck Anxiety Inventory, we classified patients according to their scores. Scores may range from 0 to 63: Patients with scores from 0 to 7, scores from 8 to 15, scores from 16 to 25 and scores from 26 to 63 were considered to have minimal, mild, moderate and severe anxiety levels, respectively. The Beck Hopelessness Scale is a 20 item self-report inventory. Patients answer 20 items as true or false. Scores ranging from 0 to 3 are considered as normal, scores from 4 to 8, scores from 9 to 14 and scores greater than 14 identify mild hopelessness, moderate hopelessness, and severe hopelessness, respectively.[12]

The study project was confirmed by the Institutional Review Board of Yüksek İhtisas University (no: 2020/07/08, date: 03/07/2020). This study was performed according to the Declaration of Helsinki.

STASISTICAL ANALYSIS

Continuous variables were expressed as mean±SD or median (interquartile range) in the presence of abnormal distribution, and categorical variables as percentages. Comparisons between groups of patients were made using a χ^2 test for categorical variables, an independent samples t test for normally distributed continuous variables, and the Mann-Whitney U test when distribution was skewed. Correlations were evaluted by using Pearson or Spearman correlation tests. SPSS software version 19.0 (SPSS Inc.,

Chicago, IL) were used to perform all statistical procedures. A p value of 0.05 was considered statistically significant.

RESULTS

The properties of the study population was represented in Table 1. The number of the females and males were 38 (38%) and 62 (62%), respectively. The mean age of the study population was 45.1±13.7 (females 43.6±14.6, males 46.7±13.8). Of the patients, 29% had hypertension, 31% of them had heart failure, 33% and 7% of them had congenital heart disease (including patients with residual shunts, valve regurgitations, Fontan circulation and myocardial dysfunction) and coronary artery disease respectively. While 83% of the patients had no other concomitant chronic disease, 1% of them had chronic renal disease, 4% had cancer, 10% had diabetes mellitus and 2% had chronic obstructive pulmonary disease (Table 1). Of the patients, 57 (57%) and 43 (43%) were using ACE inhibitors and ARBs, respectively. Only 9% of the patients stopped using these agents during pandemic. Preference to withdraw the drug was found to be related with the physician decision.

According to the Beck anxiety scoring, 51% of the patients had minimal anxiety. 28%, 14% and 7% of them had mild, moderate and severe anxiety levels, respectively. Minimal, mild, moderate and severe hopelessness levels according to the Beck Hopelessness Scale were found to be 27%, 31%, 33% and 9%, respectively in the study population. There was no statistically significant relation between age, education level and Beck anxiety scoring (p=0.48, p=0.12 respectively). Similiarly, Beck hopelessness scoring had no relation with age, education level and gender (p=0.87, p=0.49, p=0.389, respectively). But Beck anxiety scoring was found to be related with gender (Figure 1). Moderate and severe anxiety levels were determined mostly in female patients (β=-0.637, 95% CI (0.336-0.833), p=0.006) whereas the minimal and mild anxiety levels were seen mostly in males (Table 2). In patients who can easily obtain their cardiovascular drugs, the anxiety scoring was found to be lower (r=-0.083, p=0.004) (Table 2). Of the patients, 92% declared that they have enough information about COVID-19. In this group, anxiety scoring was found to be statistically lower (r=-0.006, p=0.03) whereas hopelessness scoring was found to be higher (r=0.047, p=0.04) (Table 2). In the patients who have a fear of getting sick (49%), Beck anxiety and Beck

TABLE 1: Clinical and demographic properties of the study population.

	n	%	Mean±SD
Age			45.1±13.7
Female			43.6±14.6
Male			46.7±13.8
Gender			
Female	38	38	
Male	62	62	
Hypertension	29	29	
Heart failure	31	31	
CAD	7	7	
ACHD	33	33	
DM	10	10	
CKD	1	1	
COPD	2	2	
Cancer	4	4	
ACE inhibitor	57	57	
ARB	43	43	
Beck anxiety scoring			
Minimal	51	51	
Mild	28	28	
Moderate	14	14	
Severe	7	7	
Beck hopelessness scoring			
Minimal	27	27	
Mild	31	31	
Moderate	33	33	
Severe	9	9	
Best way for protection from COVID-19			
Social distancing	49	49	
Cleaning hands	31	31	
Self-isolation	16	16	
Wearing mask	1	1	
Vaccine (in future)	3	3	
Information tool for COVID-19			
Television	33	33	
Social-media	28	28	
Internet	22	22	
Multifactorial	17	17	

SD: Standard deviation; CAD: Coronary artery disease; ACHD: Adult congenital heart disease; DM: Diabetes mellitus; CKD: Chronic kidney disease; COPD: Chronic obstructive pulmonary disease; ACE: Angiotensin converting enzyme; ARB: Angiotensin receptor blocker.

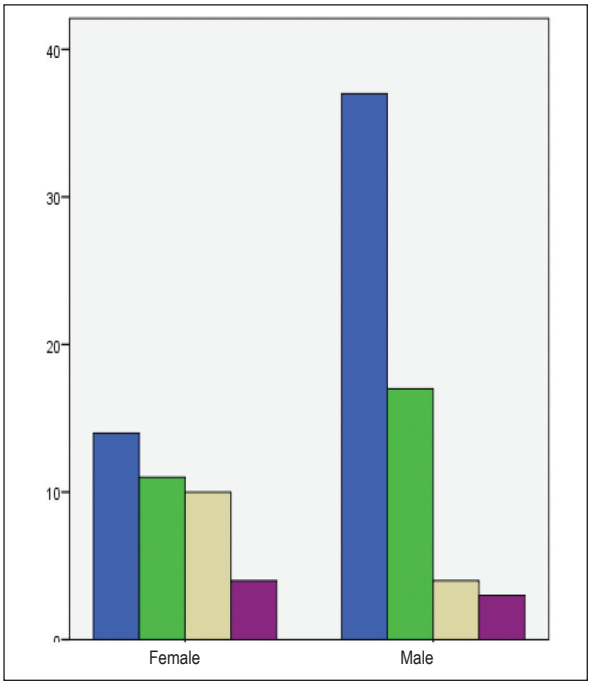

FIGURE 1: Bar-chart for Beck anxiety scoring and gender.
Blue: Minimal anxiety
Green: Mild anxiety
Yellow: Moderate anxiety
Purple: Severe anxiety.

hopelessness scorings were found to be higher (r=0.78, p=0.01 and r=0.57, p=0.003 respectively) (Table 2). Other factors affecting their psychological state were found to be economic stress (20%), social isolation (20%) and future anxiety (11%). Nine patients need psychological support (p=0.54) and one patient need to use an antidepressant medication (p=0.73).

In our study population, 33% of the patients used television, 28% of them used social media, 22% of them used internet and 17% of them used more than one tool to get information about COVID-19; 2% of the patients said that they had no idea about the precatutions for COVID-19; 49% and 31% of the patients indicate that the best ways to protect themselves from SARS-CoV-2 are maintaining social distancing and cleaning hands respectively. 16% of the patients said that self-isolation and only 1% of the patients said that wearing mask is the most important way for protection. Of the patients, 3% of them thought that the vaccine will be effective to protect themselves from COVID-19, 76 patients said that they go outside only for mandatory needs and only 31% of the study population said that they used public transport during this period. Most of the patients said that they didn't come to hospitals for their routine controls in the begining of the pandemic, instead of this they preferred primary health clinics. Only 18% of the patients indicated that they had knowl-

TABLE 2: Effects of different factors on Beck anxiety and Beck hopelessness scorings.

	Beck anxiety scoring		Beck hopelesness scoring	
	r value	p value	r value	p value
Age	-0.093	0.48	0.042	0.87
Gender		0.006*		0.389 +
Education level	-0.14	0.12	-0.103	0.49
Stopping using ACE inh./ARBs	0.046	0.33	-0.41	0.54
Using antidepresssant medication	-0.030	0.97	-0.198	0.49
Need for pschological support	0.24	0.16	0.180.50	
Taking vitamin support	-0.058	0.13	0.074	0.24
Fear of getting COVID-19	0.78	0.01**	0.57	0.003**
Thinking to have enough information about COVID-19	-0.006	0.03***	0.047	0.04***
Patients who obtain cardiovascular drugs easily	-0.083	0.004****	0.131	0.43
Economic stress	0.67	0.65	0.35	0.54
Social isolation	0.033	0.78	-0.038	0.61

*Moderate and severe anxiety levels were determined mostly in female patients; β=-0.637 %95 CI (0.336-0.833) p=0.006; +β=0.191 %95 CI (0.784-1.868) p=0.389; **Patients who have a fear of getting sick Beck anxiety and Beck hopelessness scorings were found to be higher; ***Patients who declared that they have enough information about COVID-19 have lower anxiety scoring, higher hopelessness scoring; ****Patients who obtained cardiovascular drugs easily during pandemic was found to have lower anxiety levels; ACE: Angiotensin converting enzyme; ARB: Angiotensin receptor blocker.

edge about tele-medicine and 54% of them said that they didn't think to use this application because of not having enough information or not hearing the application before.

DISCUSSION

Expressing ACE-2 makes heart undefended to SARS-CoV-2.[8,10] COVID-19 can cause many cardiovascular disorders such as acute coronary sydrome, myocardial injury, arrhytmias, and venous thromboembolism.[13] Furthermore in patients experienced COVID-19, the presence of underlying cardiovascular diseases can increase the mortality.[3,14,15]

Reducing the activity of RAAS system, ACE inhibitors and ARBs have been used in the treatment of many cardiovascular disorders.[8,9] In animal-based studies, ACE-2 expression was shown to increase after using ACE inhibitors and ARBs.[16] In COVID-19, RAS over-activation can be triggered because of the significant down-regulation of ACE-2 and upregulation of Ang-II. The loss of the protective effects of angiotensin-(1-7) can exacerbate the cardiac injuries.[4,10] In this scope, administration of ACE inhibitor/ARBs, can be beneficial in preventing injuries by blocking ACE-2 downregulation-induced hyperactivation of RAAS. In our cohort, these agents were stopped in a few patients. Most of the patients continued to use these agents regularly. Preference to withdraw the drug was found to be related with the physician decision and the most preferred drug instead of a RAAS blocker was found to be a calcium canal blocker. Although minimal or mild increase was observed in the anxiety level of most patients and severe anxiety was observed in 7% of them, none of the patients stopped the use of these drugs due to concerns after reading reports or hearing news from various comminication tools. In this period, although some measurements such as self-isolation, stay-at home orders and also curfew for some age-groups were applied, all of the participians say that they can easily supply their drugs. In our cohort, except in a few patients, we didn't determine any worsening in the course of the cardiovascular disease or in the control of the blood pressure during the pandemic. This may show that measures taken by healthcare system such as drug supply or ease of access to chronic disease medications are important for the control of the underlying cardiovascular disease during the pandemic. No significant increase in the risk of COVID-19 infection and no increase in the severity or mortality of disease in patients receving ACE/ARB therapy were shown during pandemic.[10,11] In this scope, cardiovascular patients should be encouraged by their phsicians to continue the usage of ACE inhibitors/ARBs. In our study especially in the begining of the pandemic, some patients were found to prefer the primary health care centers for their routine controls because of the fear of getting sick in the hospitals. Therefore it can be also benefical to enlighten primary care physicians about the usage and the continuation of ACE inhibitor/ARBs during COVID-19 pandemic.

During the Middle East respiratory syndrome outbreak in 2015, patients were found to have elevated stress levels.[17] Although the broader psychological distress can affect those who have been infected by SARS-CoV-2, increase in the rates of anxiety, depression and other mental health disorders are to be expected in the general population.[18,19] News about deaths, fear of getting sick and may be social distancing and self-isolation all can be impressive factors on the pschology of the general public. In our study, we questioned patients about their anxiety level and degree of despair during the pandemic. We have found that 51% of the patients have minimal anxiety and 28% of the patients have mild anxiety. Only few patients were found to have severe anxiety (7%). Besides, we have found that 33% and 31% of the patients have moderate and mild hopelessness, respectively. In the study of Qiu et al., people with higher education level and those at older age were found to be more affected by the stress during COVID-19 pandemic.[20] Contrary to the findings of this study, we didn't find any association between age and education level, with anxiety and disparity levels.[19] But moderate and severe anxiety were determined mostly in female patients whereas the minimal and mild anxiety levels were seen mostly in males. During this period, nine patients need psychological support and one patient need to use an antidepressant medication. Our findings showed that patients who beleive that they have enough information about

COVID-19 have minimal anxiety and contrarily moderate hopelessness. In our study, we found that the fear of getting sick is the most important factor affecting the psychological state of the patients. The results showed that these patients have higher anxiety and higher despair levels according to Beck scorings. The other factors were found to be economic stress, self-isolation and future anxiety, respectively. In the study of Qui et al., the availability of local medical resources and efficiency of the regional public health system were found to be related with the distess levels during pandemic.[20] Minimal or mild anxiety levels seen in our study population may be related with their ease of access to cardiovascular medications during pandemic. The study findings indicate that multiple factors can lead psychological consequences during COVID-19 outbreak.

Besides taking measures for protecting their physical health, people should pay attention to their mental health as well. In this period, making healthy activities such as physical exercise can improve the ability to cope with this severe situation. Furthermore, being well-informed about this exceptional situation can play an important role on the anxiety and disparity levels. This outlines the importance of having sufficient and correct knowledge about the pandemic.

On the other hand, without comminity acceptance and understanding of measures, succesful control of the disease is impossible. In our study, we questioned the knowledge level of patients about COVID-19 and the patients' acceptance of measures during the pandemic. The result of the study showed that 92% of the patients indicated thet they have adequate information about COVID-19 and they know how to take precautions about the disease; 49% and 31% of the patients indicate that the best way to protect themselves from SARS-CoV-2 is maintaining social distancing and cleaning hands, respectively. Suprisingly, almost none of them is aware of the importance of wearing mask. Although most of the patients claimed to have adequate information about COVID-19, the results of the study showed that they don't know enough about the precautions. In our study, we determined that patients mostly used television, social media and internet as the source of information. Most of them said that they went outside only for the mandatory needs and all of them indicated that they complied the curfew. This can show that comminication tools can be successful in affecting the population for harder precautions. With the increasing number of SARS-CoV-2 affected patients, it will be more important to give brief and clear messages from the comminications tools about the protection ways from COVID-19.

The magnitude and duration of this phenomenon are unpredictable. Our study results showed that patients have some doubts for going to hospitals for routine controls during pandemic. In long term, this can affect the course of the underlying cardiovascular disease. During the pandemic, medical consultations can be made by tele-medicine for mild ilnesses and routine follow-ups. When we asked the study population, we determined that few patients (18%) are informed about tele-medicine and most of them don't think to use it because of not having enough information or not hearing the application before. To decrease the COVID risk of cardiovascular patients, tele-medicine can be a good option.

Our study have some limitations.Small number of patients were included because of the decrease in the number of patients coming to hospitals during pandemic. It is not a multicenter study and only outpatients are included.

CONCLUSION

COVID-19 is one of the most dangerous pandemics the world has ever experienced. Cardiovascular patients are associated with an increased risk of mortality due to COVID-19. One of the most significant management for cardiovascular diseases during pandemic is to continue the use of ACE inhibitors/ARBs.

Prevention with social distancing, mask wearing and cleaning hands is found to be effective. With the increasing number of cases in Turkey, it seems that knowledge about the importance of mask-wearing is not sufficient. It is still important to continue giving brief and clear messages from the comminication tools about the protection ways from COVID-19.

Multiple factors can lead psychological consequences during pandemic. While isolation and quarantine policies are designed to prevent the growth of pandemic, they can increase the intensity of anxiety and despair. Maintaining proper public information may also be of great importance in preventing stress-related psychological troubles. In order to decrease the COVID risk of cardiovascular patients, the health services can encourage and inform the patients to use the tele-medicine approaches.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Meltem Refiker Ege, Ayşenur Feyza Paç, Seçil Sayın, Burcu Demirkan, Yeşim Akın;* ***Design:*** *Meltem Refiker Ege, Ayşenur Feyza Paç, Seçil Sayın, Yeşim Akın, Burcu Demirkan;* ***Control/Supervision:*** *Meltem Refiker Ege, Ayşenur Feyza Paç, Seçil Sayın, Yeşim Akın, Burcu Demirkan;* ***Data Collection and/or Processing:*** *Meltem Refiker Ege, Burcu Demirkan, Seçil Sayın, Yeşim Akın, Ayşenur Feyza Paç;* ***Analysis and/or Interpretation:*** *Meltem Refiker Ege, Ayşenur Feyza Paç, Seçil Sayın, Yeşim Akın, Burcu Demirkan;* ***Literature Review:*** *Meltem Refiker Ege;* ***Writing the Article:*** *Meltem Refiker Ege;* ***Critical Review:*** *Ayşenur Feyza Paç, Yeşim Akın, Burcu Demirkan.*

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