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Cardiovascular Diseases (CVDs) in COVID-19 Pandemic Era

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ABSTRACT

Introduction: COVID-19 is the disease caused by an infection of the SARS-CoV-2 virus, previously known as 2019 Novel Coronavirus (2019-nCoV) respiratory disease. World Health Organization (WHO) declared the official name as COVID-19 in February 2020 and in 11th March 2020 declared COVID-19 as Global Pandemic. In June 6th 2020, over 7 million cases registered in the world, recovered 3.4 million and death over 402.000. **Aim:** The aim of this study is to retreive published papers about COVID-19 infection deposited in PubMed data base and analyzed current results of investigations regarding morbidity and mortality rates as consequences of COVID-19 infection and opinions of experts about treatment of afected patients with COVID-19 who have Cardiovascular diseases (CVDs). **Methods:** It's used method of descriptive analysis of the published papers with described studies about Corona virus connected with CVDs. **Results:** After searching current scientific literature (on PubMed till today is deposited more than 1.000 papers about COVID-19 with consequences in almost every medical disciplines), we have acknowledged that till today not any Evidence Based Medicine (EBM) study in the world. Also, there are no unique proposed ways of treatments and drugs to protect patients, especially people over 65 years old, who are very risk group to be affected with COVID-19, including patients with CVDs. Vaccine against COVID-19 is already produced and being in phases of testing in praxis in treatment of COVID-19 at affected patients, but the opinions of experts and common people whole over the world about vaccination are full of controversis. **Conclusion:** Frequent hand washing, avoiding crowds and contact with sick people, and cleaning and disinfecting frequently touched surfaces can help prevent coronavirus infections are the main proposal of WHO experts in current Guidelines, artefacts stored on a web site. Those preventive measures at least can help to everybody, including also the patients who have evidenced CVDs in their histories of illness. Authors analyzed most important dilemmas about all aspects of CVDs, including etipathogenesis, treatment with current drugs and use of potential discovered vaccines against COVID-19 infection, described in scientific papers deposited in PubMed data base.

Kewywords: COVID-19, CVDs, WHO, ESC Guidelines.

1. INTRODUCTION

COVID-19 is the disease caused by an infection of the SARS-CoV-2 virus, first identified in the city of Wuhan, in China's Hubei province in December 2019. COVID-19 was previously known as 2019 Novel Coronavirus (2019-nCoV), respiratory disease before the World Health Organization (WHO) declared the official name as COVID-19 in February 2020 (1, 2). COVID-19 spreads by contact with respiratory droplets that spread when an infected person coughs or sneezes. Respiratory virus infection is a major source of global pandemics as a consequence of swift human-to-human respiratory tract transmission. Within the past two decades, coronaviruses and influenza viruses have hit the world several times, causing significant mortality, economic loss and global panic. The SARS outbreak in 2002 triggered 916 deaths among more than 8.000 patients in 29 countries, followed by the emergence of MERS in 2012, which resulted in 800 deaths at least, among 2.254 patients in 27 countries (1). Besides coronaviruses, avian and swine influenza remain a concern for global public health in the 2009 H1N1 pandemic alone. There were 18.500 laboratory-confirmed deaths and more than 200.000 deaths from respiratory disease worldwide (1). In late 2019, a cohort of patients presenting with pneumonia of varying

acuity and unknown aetiology in Wuhan, China, heralded the outset of COVID-19. Although COVID-19 appears to have greater infectivity and lower mortality than SARS and MERS, many uncertainties (including route of infection, viral evolution, epidemic dynamics, appropriate antiviral treatment and strategies for disease control) remain. Since there is no cure for this viral disease and a long wait is needed to find a vaccine, a rigorous epidemiological measure was first taken. The largest quarantine in history was made, between 50 and 60 million people in several Chinese cities were quarantined; that included necessary hygiene measures such as: group meetings were canceled, schools closed and travel banned. Some people believe that a later evaluation of all the more modern epidemiological measures will show whether all of them are justified, as experts point to procedures that curb a Severe Acute Respiratory Syndrome (SARS) caused by another type of virus Corona (2-4).

CVDs may become unstable in the setting of viral infection as a consequence of imbalance between infection-induced increasing in metabolic demand and reduced cardiac reserve (6-11). Till the May 31st, 2020, 390.423 persons worldwide died as consequences of COVID-19 infection and total number of infected people was 6,647.258 citizens. Web Portal "Worldometer" announced up-dated picture of global epidemiological facts since of the first registered patient infected with COVID-19 in the world till today, and last number of patients who treated and survived was 3,206.033. From the same source on the May 31st 2020, 3,050.802 patients infected by COVID-19 have been registered in the world including 55.074 cases with worse clinical picture. With COVID-19 pandemic the highest grade of infected cases has been reached in USA with 109.675 died persons, and after USA, Great Britain has been with 39.904, Italy with 33.689 cases, Brasil with 33.038 cases, France with 29.065 cases and Spain with 27.133 cases (5).

2. THE. CARDIOVASCULAR DISEASES (CVD) IN THE COVID-19 ERA

COVID-19 infection is caused by a new beta-coronavirus, which the WHO has called (SARS-CoV-2) - Severe Acute Respiratory Syndrome. Coronavirus 2 is a disease that appeared in December 2019 in the Chinese city Wuhan and began to spread very quickly beyond the borders of China. In a short period of time, it took on all the characteristics of a pandemic and spread exponentially to almost all countries of the world. Early COVID-19 case reports suggest that patients with underlying conditions are at higher risk for complications or mortality - up to 50% of hospitalized patients have a chronic medical illness (40% cardiovascular or cerebrovascular disease). In the largest published clinical cohort of COVID-19 to date, acute cardiac injury, shock and arrhythmia were presented in 7.2%, 8.7%, and 16.7% of patients, respectively (1), with higher prevalence amongst patients requiring intensive care. Initially, the main complications of COVID-19 were thought to be lung-related, then it was quickly observed that COVID-19 is attacking many organs, including the heart muscle, vascular endothelium and the cardiovascular system in general, increasing morbidity and mortality, especially in patients with other cardiovascular risk factors presented (hypertension, diabetes, obesity, cerebrovascular and renal disease). In these patients, the morbidity is 10%. In a significant number of infected patients, severe myocardial damage, malignant arrhythmias and cardiac arrest occurred. It's interesting, SARS-CoV-2 can also lead to neurological symptoms, such as dysgeusia or ageusia, or to the appearance of hyposmia or anosmia (6). The virus damages the nerve endings in the olfactory epithelium and damages the olfactory bulb. Therefore, the virus is neurotropic and can spread along the nerves and then damage them. It happens that the peripheral nerves are also affected, which manifests itself in the form of quadriplegia, and also causes cerebrovascular diseases. So, SARS-CoV-2 is neuroinvasive and can penetrate the brain and lead to neuronal death (6). It is interesting to mention that in 20% of patients, only gastrointestinal symptoms occur in the form of loss of appetite, abdominal pain, nausea and diarrhea. Cardiovascular complications of influenza infection, including myocarditis, acute myocardial infarction and exacerbation of heart failure have been well-recognized during previous historical epidemics and make a significant contribution to mortality. Also, previous coronavirus outbreaks have been associated with a significant burden of cardiovascular comorbidities and complications.

3. COVID-19 IS A SYSTEMIC DISEASE

The afore-mentioned clinical manifestations suggest that COVID-19 is a systemic disease, that it is characterized by numerous tissues and organ damages. The presence of thrombi and microthrombi contributes to the manifestation of various clinical symptoms. At the same time, vascular endothelial dysfunction and coagulopathy occur (7). Inflammation of the endothelium severely impairs its function. The virus not only leads to pneumonia, which in turn causes further complications (4), but also to systemic endothelial inflammation. Namely, the virus directly attacks the endothelial cells of blood vessels. Induce endothelial damage in the small and smallest blood vessels of the lungs and leads to an enhanced inflammatory response by T cells. This is similar to an organ rejection reaction in case of transplantation. During the autopsy, a significant increase in new blood vessels was found in the lungs of the patient with COVID-19, through intussusception angiogenesis. Therefore, there is a comprehensive inflammation of the endothelium of the heart, brain, lungs, kidneys and digestive tract. All of these ones have fatal consequences: severe microcirculation disorders occur that damage of the heart, lead to pulmonary embolism and clog blood vessels in the brain and digestive system. Multiple organ failure occurs, ultimately resulting in death. Systemic inflammation promotes thrombosis. Massive inflammation stimulates the production of cytokines which in the liver leads to the formation of coagulation factors. For example, the level of fibrinogen in a severe patient with COVID-19 is 10-14 g/L, while in a healthy person the value of fibrinogen is 2-4 g/L. Endothelial cells located on the inside of blood vessels have ACE-2 receptors on their surface, which serve as a gateway for SARS-CoV-2. Therefore, the wall of the blood vessel as well as the blood itself is affected at the

same time. This explains why thromboembolic complications occur so frequently, including pulmonary embolism. Many patients have increased D-dimer values as well as cutaneous changes in the limbs, suggesting thrombotic microangiopathy. Diffuse intravascular coagulation and thrombosis of large blood vessels are associated with multisystem organ failure. Renal blood vessels are often involved and ACE-2 receptors are known to be found in the renal tubules. In severe forms of COVID-19 the kidneys are affected in 30%, while in milder forms it's in 5%. Therefore, SARS-CoV-2 not only attacks the lungs, but also affects the blood vessels of all organs. COVID-19 is a systemic inflammation of the blood vessels, so we could see the whole clinical picture as COVID-19 endothelism (8). From the point of view of cardiologists, COVID-19 therapy is directed in two directions: it is necessary to stop the reproduction of the virus at the stage when it is most pronounced and at the same time to protect and stabilize the patient's blood vessels. This is especially true for patients who already have cardiovascular disease and some of the risk factors (hypertension, diabetes, increased cholesterol, obesity, smoking) with reduced endothelial function. It is important to mention that the endothelium of younger patients can more easily resist the attack of the virus. COVID-19 is a primary respiratory disease, but many patients have cardiovascular disease, including the hypertension, acute heart damage and myocarditis. Acute lung damage leads to increased heart rate, which then presents an additional problem, especially for patients with pre-existing heart insuficiency. Cardiovascular disease can be primary if we take into account the activity of the renin-angiotensin system (RAS) and angiotensin converting enzyme (ACE-2), which is also present in the heart itself.

4. COVID-19 AND CARDIOVASCULAR DISEASES

SARS-CoV-2, not only leads to damage of the respiratory system, but also to acute and chronic damage to the cardiovascular system (4). Cardiovascular diseases that were present before a patient was infected with COVID-19 significantly increased, both morbidity and mortality in these patients. This especially refers to the presence of hypertension, diabetes, coronary heart disease and kidney disease. Patients with acute coronary syndrome, who are infected with SARS-CoV-2 virus, have a poor prognosis. In such patients, the functional cardiac reserve is reduced due to myocardial ischemia or necrosis. At the same time, the possibility that these patients will develop heart failure is quite high. Respiratory failure and hypoxia can lead to myocardial damage as well as the reaction of the immune system itself. In Wuhan, according to reports of Chinese physicians, in patients infected with COVID-19 and with acute coronary syndrome, the complete clinical picture was very severe and associated with high mortality (9). If patients already suffer from heart failure, infection with COVID-19 leads to worsening their health condition and not seldomly to death. On the other hand, acute inflammatory responses can lead to ischemia in the presence of pre-existing cardiovascular disease. The inflammatory activity of atherosclerotic plaque in coronary blood vessels becomes even more pronounced during systemic inflammation, which makes atherosclerotic plaque more vulnerable and thus increases the possibility of its rupture. In such a situation, the vulnerable plaque should be stabilized with aspirin, statins, beta blockers, ACE inhibitors, or angiotensin II antagonists (10). Inflammation can lead to endothelial dysfunction and to increased levels of procoagulant factors, which contributes to the forming of an occlusive thrombus and possibly to its rupture. If all these facts are considered, then an intense inflammatory response, along with the already present cardiovascular disease, can contribute to heart damage. Vascular endothelial cell dysfunction in the presence of inflammation, and impaired myocardial function, can lead to cardiac decompensation or to its worsening, if it has been presented before. Myocarditis, pericarditis and arrhythmias can also occur. Rhythm disorders are manifested in the form of bradycardia, tachycardia and paroxysmal atrial fibrillation. The occurrence of myocarditis is the result of focal or global inflammation of the myocardium, necrosis and ventricular dysfunction. Inflammation, by itself, plays an important role in the onset, development and prognosis of cardiovascular disease. The virus can penetrate directly into the myocardium and multiply and lead to its damage, necrosis and apoptosis (programmed cell death). Focal myocarditis should be considered if precordial pain occurs during and after the acute phase of COVID-19, with clinical signs that would suggest that it is a coronary syndrome, but without coronary artery obstruction. C-reactive protein (CRP), as well as other inflammatory cytokines, have become new risk factors. Cardiovascular disease and cardiovascular risk factors represent an independent risk factor for cardiac death.

5. INCREASED TROPONIN VALUES ARE ASSOCIATED WITH POOR PROGNOSIS

Troponin will be released in 8-28% of patients infected with the SARS-CoV-2 virus, indicating that heart damage has occurred. Increased values of troponin and its dynamic increase during hospitalization, shows that the risk of artificial ventilation is increased by 5 times, and the risk of arrhythmias is increased, while mortality is increased by 5 times. All of the above explains the connection between cardiovascular diseases and the occurrence of death in patients suffering from COVID-19. Many patients infected with COVID-19 die from cardiac arrest due to severe hypoxia, multiorgan dysfunction, or systemic inflammation. The occurrence of arrhythmias, such as atrial fibrillation, often occurs as part of COVID-19 cardiomyopathy, among other things, because inflammation is a substrate for the occurrence of arrhythmias (11). Ventricular arrhythmias occur, which can also be an introduction to cardiac arrest. QT prolongation may occur as part of myocarditis, as well as due to the application of chloroquine and hydroxychloroquine, especially if combined with azithromycin. This therapy is currently widely used in many clinics around the world, although the benefits of this therapy are highly debatable and the side effects can be very serious. The latest study, published in May 22nd, 2020 in the Lancet, did not prove the benefit of hydroxychloroquine or chloroquine used as monotherapy or in combination with second-generation macrolides, azithromycin or clarithromycin.

At the same time, there were ventricular arrhythmias and mortality increased.

6. HEART IN A CYTOKINE STORM

Cytokine storm syndrome is a dysregulation of the immune system, and the appearance of severe symptoms that directly endanger the patient's life. When the SARS-CoV-2 virus enters our body, it first seeks protection, then it will reproduce and then spread further. Our cells in the body provide the virus with extraordinary conditions to do all this. As SARS-CoV-2 infiltrates the cells of the respiratory system, it can thus hide better from our immune system and then multiply further. There are special cells in our body called T cells, and they fight infection. When T cells are activated they release cytokines, which further stimulate T cells to form, and then release even more cytokines. A type of T cells - called cytotoxic T cells - are formed.

Cytotoxic cells are such cells that kill infected cells. Cytotoxic cells are chemically oriented to kill and they are ideally to stop the proliferation of viruses such as SARS-CoV2. Cytotoxic T cells only attack infected cells and kill them. The immune response has a chemical indicator that tells a strong immune response to stop in certain moment when the danger is neutralized. At that moment, the cytokine storm is very active and then the system is overloaded and functions no longer properly. The immune system is so irritated that it stops making a difference between an infected cell and a healthy cell and then attacks everything which found in its path. This is a very bad situation for the patient, because, not only does SARS-CoV-2 kill the cells in our body, but so our immune system (12).

Acute myocarditis, cardiac decompensation, or cardiogenic shock can occur during a cytokine storm. Inflammatory cells in the presence of hypercytokinemia infiltrate the heart. There is a release of troponin and an increase in brain natriuretic peptide (BNP). Inflammatory cytokine storm is accompanied by immunopathological changes in the lungs. Patients infected with SARS-CoV-2 mostly die from Acute Respiratory Distress Syndrome (ARDS) (4). This leads to acute pneumonia and to accumulation of fluid in the lungs, which requires intubation and ventilation. Such a severe clinical picture develops six to seven days after the onset of infection. Unfortunately, 40% of patients with acute respiratory distress syndrome do not survive. At the same time, patients die faster from cytokine storms than from infection. During a cytokine storm, death occurs due to the failure of several organs, which explains such a high mortality. Proinflammatory cytokines such as interleukin 6, interleukin 7, interleukin 8, interleukin 17, interleukin 22, interleukin 1beta, and chemokinases such as CCL2, CCL-5 and CCL3, contribute to the development of ARDS. During the cytokine storm, there is an increase in D-dimer, ferritin, lactate dehydrogenase (LDH), CRP, interleukin 1, interleukin 6, tumor necrosis factor alpha (TNF-alpha) and lymphopenia (12). A significant number of people with COVID-19 do not develop a cytokine storm. However, some people have a tendency to develop a cytokine storm, if they possess a specific gene, which allows the immune system to react in a certain way. However, this has not been proven with certainty. This phenomenon of „immune storm" is not completely new. It has been observed in previous coronavirus-related epidemics, namely SARS (Severe acute respiratory syndrome) in 2003 and MERS (Middle East Respiratory Syndrome) in 2012 (1). The phenomenon of „immune storm" can be observed in other viral infections, such as influenza. There are also non-infectious agents that can lead to an „immune storm", for example after an organ transplantation. The cytokine storm is unwanted and one of the most spectacular moments during treatment with CAR-T cells. This method consists of injecting T lymphocytes that have been genetically modified to fight tumors, leukemia or lymphoma.

7. HYPERTENSION AND ANGIOTENTIN CONVERTING ENZYME-2 (ACE-2)

Angiotensin converting enzyme-2 is especially present in the lungs, heart and other tissues. It serves, among other things, as a functional receptor for SARS-CoV-2 virus entry into cells. ACE inhibitors (angiotensin converting enzyme inhibitors) and angiotensin II antagonists (ARBs) are first-line drugs used in the treatment of hypertension, cardiac decompensation, after a myocardial infarction and in chronic kidney disease. Both ACE inhibitors and ARBs lead to increased ACE-2 activity and at the same time, they could lead to increased virus activity. It has been hypothesized that these drugs could lead to worsening of SARS-CoV-2 infection. For now, there is no consensus that the use of ACE inhibitors and ARBs could reduce or increase the risk of developing COVID-19. However, it should be emphasized that so far there are no studies showing that drugs that block the renin-angiotensin system (RAS), such as ACE inhibitors: lisinopril, enalapril, trandolapril, or angiotensin II antagonists such as losartan, candesartan, valsartan, increase ACE -2 in human tissues (13). In addition, there are no animal or human studies to show that drugs that block RAS increase ACE-2 levels in the lungs. In contrast, studies in animals that have been infected with the coronavirus show that ACE-2 plays an important role in protecting the lungs from more serious injuries caused by the virus.

8. HYPERTENSION OFTEN OCCURS WITH COVID-19

According to reports from China, the most common comorbidity in COVID-19 was hypertension, and patients with hypertension required ventilatory support due to severe respiratory complications (1, 20). At the same time, these patients had increased mortality. The mechanism that connects hypertension and COVID-19 is the immune system. Immune system dysregulation occurred in patients with hypertension and COVID-19. Poor blood pressure control in these patients leads to further dysregulation of the immune system in these patients. Hypertension is associated with lymphocytes and CD8 + T cell dysfunction. Immune aging of CD8 + T cells prevents them from effectively resisting viral infection. This contributes to pathological cytokine overproduction. Probably all this could explain the connection between hypertension and COVID-19. It could be assumed that ACE inhibitors and ARBs, leading to better control of hypertension, could, at least in part, establish

better function of the immune system, whose function is compromised (11).

9. DO NOT DISCONTINUE THERAPY WITH ACE INHIBITORS AND ANGIOTENSIN II ANTAGONISTS

In discussions about discontinuing therapy with ACE inhibitors, the European Society of Cardiology, the International Society of Hypertension, the European Society of Hypertension, the European Medicines Agency (EMA) and three American Cardiac Associations: American Heart Association, American College of Cardiology and Heart Failure Society of America, recommend not to stop taking ACE inhibitors and ARBs. Because of these controversial views, a series of ongoing studies will give us an answer as to whether we should stop administering these drugs, or whether they should be given to patients infected with the SARS-CoV-2 virus.

10. HYPERTENSION AND SELF-ISOLATION

Patients who have well controlled hypertension do not require frequent check-ups. Many patients with hypertension due to COVID-19 are in self-isolation in order to reduce the risk of COVID-19 and therefore cannot go for follow-up examinations. These patients need to measure their blood pressure as often as possible at home and continue taking the therapy regularly. In case of an urgent consultation, for example due to an hourly increase in pressure, these patients are recommended a telephone consultation, until they can go to their regular check-ups with the doctor. In addition, hypertension often occurs in the elderly (50% of people over the age of 60 develop hypertension) and at the same time the prevalence of hypertension increases sharply in very old people. The old age of the patient is a very important risk factor for complications in COVID-19 and often with fatal outcome.

11. FACTORS AFFECTING POOR PROGNOSIS IN COVID-19

What are the factors that correlate with a poor patient prognosis? It is evident that patients, younger than 50 years, die significantly less from COVID-19 than older patients. Mortality is especially higher in men older than 70 years (1). Mortality increases with each year of age by 10%. The risk does not increase linearly with age, but exponentially. Men die more than women. This is explained by the fact that circulating ACE-2 is higher in men than in women. At the same time, the values of ACE-2 are higher in diabetics and people with cardiovascular disease. The presence of hypertension, diabetes and coronary heart disease contributes to the patient's poor prognosis. Furthermore, increased D-dimer values are a poor prognostic sign. According to one Chinese study, D-dimer values in survivors were low and were below 1 microgram/L. Among those who died, D-dimer values increased significantly to 42 micrograms/L (14). Continuous increase in D-dimer is a poor prognostic sign. The appearance of lymphopenia and an increase of CRP also do not indicate a good prognosis for the patient (15).

12. COVID-19 THERAPY

The therapy which is currently available in the world, can be divided into supportive, immunosuppressive, antiretroviral and possible new therapies (16). Supportive therapy consists of oxygen administration as well as hemodynamic support. Early intubation and invasive mechanical ventilation are crucial in patients with severe, progressive symptoms and where there is a great need for oxygenation. As heart damage has occurred, as it's mentioned earlier, it is necessary to include therapy given for cardiac decompensation as well as antiarrhythmics. Due to thromboembolic complications, anticoagulant therapy must be included. Antiviral therapy is also included (17-19). From the range of the drugs, Anakinra (Kineret) can be used, which blocks the activity of the specific cytokine interleukin 1 (IL-1). In addition, Tocilizumab (Actemra) is increasingly being used. Tocilizumab blocks the activity of another cytokine, interleukin 6 (IL-6), which is thought to be a key of biological mediator responsible for the cytokine storm. During a cytokine storm, an increase in IL-6 can have severe consequences for the cardiovascular system. Tachycardia, atrial fibrillation, hypotension, and left ventricular dysfunction may occur with concomitant increase in GNP. In a recently published retrospective multicenter analysis in 150 patients from Wuhan, IL-6 was a clinical predictor of mortality in COVID-19 (9). In China, Tocilizumab is approved for use in severe complications with COVID-19 and where IL-6 levels are elevated (17). In Italy, too, Tocilizumab has been used successfully in critically ill patients where complications of COVID-19 have developed. Similar studies with tocilizumab are underway in France, Belgium and Denmark. Other therapeutic options include chloroquine, hydroxychloroquine, lopinavir/ritonavir (Kaletra), ribavirin, favipiravir, intravenous immunoglobulin, and Janus kinase (JAK) inhibition. Inhibition of JAK can affect inflammation and virus entry into cells (18). The already mentioned therapy with corticosteroids and antibiotics is still possible.

13. CAN IMMUNOSUPPRESSIVE THERAPY BE USED IN EACH CASE?

It should be emphasized that immunosuppressive therapy cannot be used in every patient. Suppressing the immune system when the body fights infection can lead to serious side effects and increase the risk of secondary infection (19). In severe forms of COVID-19, Chinese doctors in Wuhan advocate determining laboratory parameters of the cytokine storm. This makes it possible to identify the patients who will benefit most from immunosuppressive drugs and significantly increase the chances of these patients surviving. Effective treatment of a cytokine storm would be the fastest response to reduce mortality in some patients with COVID-19.

Currently, 300 studies are underway examining various therapeutic options with the aim of determining which is the most suitable and most appropriate in the treatment of COVID-19 (20). Under the auspices of the World Health Organization (WHO), several large studies have begun, including the Discovery study. The study will include 3200 patients. Patients are divided into five groups and receive standard therapy given for SARS-CoV2, antiviral therapy

and, among others, the much-lauded hydroxychloroquine. A large Solidarity study is also underway, also sponsored by the WHO. In Solidarity study several therapeutic options are compared, namely remdesivir, lopinavir/ritonavir, lopinavir/ritonavir in combination with interferon beta-1; and chloroquine or hydroxychloroquine.

14. REMDESIVIR I COVID-19

Remdesivir is the focus of clinical trials. A study done with Remdevisir was published in the Lancet (21). It is a randomized, multicenter, double-blind, placebo-controlled study showing that patients receiving Remdesivir recovered more quickly if Remdesivir therapy was started a maximum of ten days after the onset of symptoms. Mortality was 8% in the Remdesivir group and 11% in the placebo group. In short, it is important that Remdesivir is superior to placebo and that it reduces recovery time in patients with COVID-19. At the present time, we need prospective, randomized, and placebo-controlled studies, which will provide us an answer - what is the real role and importance of Remdesivir is in the treatment of COVID-19. There are currently 5 other studies with Remdesivir underway. The EMA in its latest release recommends that Remdesivir can be used as a compassionate use in very severe patients (22). The term compassionate use refers to the use of a drug that has not yet been approved and which is used outside clinical studies under very strictly controlled conditions. This allows the patient to access a drug that is still in the developmental stage. However, Remdesivir is not yet registered in European Union countries (2, 22, 23).

15. VACCINES AGAINST COVID-19

Even before the COVID-19 vaccine is found, national leaders are faced with the dilemma of whether to immunize as much of the population as possible or whether compulsory vaccination carries the risk of movement, which is already prone to conspiracy theories about pharmaceutical companies and government authoritarian tendencies? Preliminary results from a study conducted by the Vaccine Confidence Project and ORB International, in Europe in early April, 2020, while the infection was still on the rise, show that resistance to the vaccine is particularly strong in countries that have managed to avoid the worst pandemic (2, 23-25).

In Switzerland, where immunologists suggested mass vaccination as early as October last year, 20 % of respondents said they did not want to be vaccinated. In Austria, skepticism about the vaccine is at a similar level, as 18 % of respondents said they would refuse the vaccination, according to world media (2).

The number of Germans who answered positively to the question about the vaccine against COVID-19 from mid-April to mid-May, fell from 79 % to 63 %. In the UK, ORB International conducted a survey on May 6th and 7th, and 10 % of respondents said they did not want to be vaccinated.

Four European governments (of Italy, Germany, France and The Netherlands) for their citizens has signed contract with British Pharmaceuthical company "AstraZeneca" to supply the region with its potential vaccine against the coronavirus - the British drugmaker's latest deal to pledge its drug to help combat the pandemic. The contract is for up to 400 million doses of the vaccine, developed by the University of Oxford, which will be produced until the end of the year 2020, as announced Minister of Haelth of Italy, Roberto Speranza. The deal is the first contract signed by Europe's Inclusive Vaccines Alliance (IVA), a group formed by France, Germany, Italy and the Netherlands to secure vaccine doses for all member states as soon as possible (2).

But, virologists weigh evidence and often come up with somewhat contradictory advice, while public health authorities need weeks to formulate their messages (21, 24).

16. CONCLUSION

Patients with CVDs must be observed by health professionals (specialists of cardiology, family practitioners, epidemiologists, etc) with special preventive measures regarding COVID-19 infection (1). The severity of the primary respiratory syndrome and risk of adverse outcomes is increased in patients infected with COVID-19 and with pre-existing cardiovascular diseases.

Patients with coronary artery disease and heart failure may be at particular risk as a result of coronary plaque rupture, secondary to virally induced systemic inflammation, and rigorous use of plaque stabilizing agents (aspirin, statins, beta-blockers and angiotensin-converting enzyme inhibitors) has been suggested as a possible therapeutic strategy (1, 3, 25).

Electrocardiographic changes and troponin elevation may signalyzing the underlying myocarditis, and echocardiography frequently demonstrates subclinical left ventricular diastolic impairment (with a higher likelihood of the need for mechanical ventilation in those patients with systolic impairment and reduced ejection fraction) (1). Pro-coagulant effects of systemic inflammation may increase the likelihood of stent thrombosis and assessment of platelet function and intensified anti-platelet therapy should be considered in those patients with a history of previous coronary intervention.

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