Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Journal of Molecular and Cellular Cardiology 144 (2020) 47–53

Contents lists available at ScienceDirect

Journal of Molecular and Cellular Cardiology

journal homepage: www.elsevier.com/locate/yjmcc

Original article

SARS-CoV-2 receptor ACE2-dependent implications on the cardiovascular system: From basic science to clinical implications

Sonja Groß[a], Christopher Jahn[a], Sarah Cushman[a], Christian Bär[a,b], Thomas Thum[a,b,*]

[a] Institute of Molecular and Translational Therapeutic Strategies, Hannover Medical School, Hannover, Germany
[b] REBIRTH Center for Translational Regenerative Medicine, Hannover Medical School, Hannover, Germany

ARTICLE INFO

Keywords:
COVID-19
SARS-CoV-2
ACE2
Cardiovascular disease

ABSTRACT

The current COVID-19 pandemic started several months ago and is still exponentially growing in most parts of the world – this is the most recent and alarming update. COVID-19 requires the collaboration of nearly 200 countries to curb the spread of SARS-CoV-2 while gaining time to explore and improve treatment options especially for cardiovascular disease (CVD) and immunocompromised patients, who appear to be at high-risk to die from cardiopulmonary failure. Currently unanswered questions are why elderly people, particularly those with pre-existing comorbidities seem to exhibit higher mortality rates after SARS-CoV-2 infection and whether intensive care becomes indispensable for these patients to prevent multi-organ failure and sudden death. To face these challenges, we here summarize the molecular insights into viral infection mechanisms and implications for cardiovascular disease. Since the infection starts in the upper respiratory system, first flu-like symptoms develop that spread throughout the body. The wide range of affected organs is presumably based on the common expression of the major SARS-CoV-2 entry-receptor angiotensin-converting enzyme 2 (ACE2). Physiologically, ACE2 degrades angiotensin II, the master regulator of the renin-angiotensin-aldosterone system (RAAS), thereby converting it into vasodilatory molecules, which have well-documented cardio-protective effects. Thus, RAAS inhibitors, which may increase the expression levels of ACE2, are commonly used for the treatment of hypertension and CVD. This, and the fact that SARS-CoV-2 hijacks ACE2 for cell-entry, have spurred controversial discussions on the role of ACE2 in COVID-19 patients. In this review, we highlight the state-of-the-art knowledge on SARS-CoV-2-dependent mechanisms and the potential interaction with ACE2 expression and cell surface localization. We aim to provide a list of potential treatment options and a better understanding of why CVD is a high risk factor for COVID-19 susceptibility and further discuss the acute as well as long-term cardiac consequences.

1. Introduction

Since the coronavirus disease (COVID-19) is still an emerging pandemic with more than 2.1 million confirmed cases worldwide [1], special focus is currently directed towards the understanding of why people are hospitalized, receive intensive care, and frequently die as a consequence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Mortality rates seem particularly high when patients suffer from distinct comorbidities. First studies were initiated mainly on Chinese cohorts, as China is the suspected point of origin of COVID-19. These studies indicate that patients subjected to intensive care units (ICU) frequently show hypertension, diabetes and/or cardiovascular diseases (CVD) [2,3]. These patients demonstrate much higher mortality rates compared with patients that are free of these comorbidities [4–7]. While higher mortality rates among CVD patients are also associated with other respiratory diseases (especially influenza virus-induced flu or previous SARS epidemics), the question was put forward, whether people treated for heart-related illness are more prone to SARS-CoV-2 viral infection, based on first epidemiological evidence, but particularly based on the presumed upregulation of the SARS-CoV-2 entry receptor. While this association is currently heavily discussed, and will be also be a subject of this review, latest epidemiological studies coming from Europe at least underpin the greater risk for a critical disease progression in this group of patients [8,9]. Therefore, we here aim to outline the mechanisms influencing the cardiac system because of its central implications in the COVID-19 course. We further highlight currently investigated and upcoming therapy options for COVID-19 patients with cardiac disease conditions.

* Corresponding author at: Hannover Medical School, Institute of Molecular and Translational Therapeutic Strategies, Germany.
E-mail address: thum.thomas@mh-hannover.de (T. Thum).

https://doi.org/10.1016/j.yjmcc.2020.04.031
Received 9 April 2020; Received in revised form 21 April 2020
Available online 30 April 2020

1.1. COVID-19 pandemic, what do we know so far?

The emerging pandemic, originating from a **CO**rona**VI**rus **D**isease outbreak at the end of 20**19** (COVID-19), is based on a positive-sense single-stranded RNA virus probably originating from bats and/or pangolins [10–12]. The first local outbreak was reported in Wuhan, a small but heavily populated region in China, subsequently spreading rapidly around the world within three months [5–7]. While the proposed incubation period can last over two weeks, symptoms might already occur five to six days after a COVID-19 infection [1,13]. A substantial number of asymptomatic courses have been reported. To properly address the prevalence, transmission, hospitalization and mortality rates of SARS-CoV-2, it will be of utmost importance to determine the number of asymptomatic cases (including those who are currently infected and recovered). Accordingly, several cross-sectional studies were already launched to determine the presence of anti-SARS-CoV-2 antibodies. Preliminary results from the Heinsberg-Study (named after a town that was the first COVID-19 hotspot in Germany) suggest that around 15% of 500 people chosen at random showed an antibody response [14]. In symptomatic cases, flu-like symptoms range from fatigue, coughing and shortness of breath, to fever as well as gastrointestinal disorders. Less common symptoms are upper respiratory-related signs such as sneezing and a sore throat [7,15,16]. When the symptoms first appear, a relatively rapid spread of the virus towards the lungs might cause severe pneumonia, which then frequently requires an oxygen supply or mechanical ventilation [17]. The progression of a COVID-19 infection towards this critical phase should be urgently avoided if possible, because at this stage there is not only serious damage to the lungs but to the heart due to pre-existing CVDs making COVID-19 a life-threatening infection. In the past two months, unjustified attempts were made to place the number of cases and estimated mortality rates of COVID-19 into perspective by comparing it to influenza [18,19]. The major differences revoking such comparison are: firstly, a suspected high prevalence for asymptomatic disease spreaders; secondly, a prolonged incubation period compared to common seasonal influenza viruses; and thirdly, an extended disease progression, reflected by an average ICU stay of 15 days with a minimum of 10 days in Italy [13,20]. Altogether, this establishes the basis for the COVID-19 outbreak and the fast spread of this pandemic.

A critical disease progression of SARS-CoV-2 infected patients is supposed to be initiated by the inability of the immune system to prevent the spreading of viruses to the lungs. This can rapidly lead to pneumonia evidenced by typical visible features in computed tomographic analyses [21,22]. Delayed clinical treatment of those critical patients causes not only an undersupply of oxygen in the lungs, but additionally causes cardiac ischemia [23,24]. Lung and heart damage is further promoted by an over-reaction of the immune system associated with a pronounced cytokine storm [5,25]. Clinical features include extremely elevated levels of interleukin 6 (IL-6) and ferritin [3,25,26], which are also well-known markers for sepsis. The latest guidelines therefore recommend first measuring basic blood parameters in order to assess the state of infection and adjust medication accordingly, even if SARS-CoV-2 infection has not yet been confirmed [27,28]. This can accelerates the treatment, which might then limit critical manifestations.

1.2. CVD as a risk factor for COVID-19

The involvement of the cardiovascular system in severe COVID-19 courses is already undisputed, but the specific underlying mechanisms remain to be explored. One proposed mode of action is related to a direct infection of cardiomyocytes (CMCs) by SARS-CoV-2 during the critical phase that leads to the development of myocarditis [29,30]. To date, there is no indisputable evidence for myocarditis in deceased COVID-19 patients, which requires confirmation through a biopsy or an autopsy. Therefore, to address whether inflammation of the cardiac muscle contributes to the observed heart failure (HF), additional investigations are still necessary. A second assumption that is currently pursued, is that an over-activated immune system is predominantly contributing to SARS-CoV-2-induced heart damage. Subsequent to cardiac ischemia as a consequence of pneumonia and the associated acute respiratory distress syndrome (ARDS) [7,31,32], CMC damage and death induces a variety of pro-inflammatory mechanisms, which in turn spiral out of control and further promote loss of CMCs [33]. Hence, a secondary induced cardiac injury seems to be quite likely, although specific evidence is still lacking owing to the currently tense clinical situation. However, these ideas are strongly endorsed by previous studies investigating the SARS-CoV outbreak in 2002 or later on the MERS-CoV-associated epidemic in 2012 [34,35], where acute myocarditis and heart failure have also been reported [36]. Similar long-term implications on the cardiovascular system as observed in a study for SARS-CoV can only be suggested [37].

Considering the multiple effects on the heart, it can already be assumed that previous CVDs would lead to an unfavorable progression of COVID-19. Interestingly, the drastically increased mortality rate in patients with pre-existing or new cardiac injuries is associated with elevated serum levels of troponin T (TnT), a biomarker for cardiac damage. Indeed, the study of Guo et al. points out that CVD patients without significantly raised TnT serum levels only represent a slightly increased mortality compared to patients without CVD [23,38]. Therefore, in the case of expected cardiac damage due to distinct comorbidities or severe disease progression, TnT levels should always be strictly monitored, but also critically interpreted since some medications and interventions themselves can cause an upregulation of TnT [39–41]. Together with other biomarkers such as the inflammatory cytokines IL-6 and Ferritin as well as D-dimers [26,33,42,43], TnT may be used to predict the outcome of the SARS-CoV-2 infection and aid in clinical decision making for the best possible treatment options, which ultimately help to reduce COVID-19 mortality [44,45].

1.3. COVID-19 and the renin-angiotensin-aldosterone system

The most prevalent comorbidities include hypertension, diabetes, cardiovascular but also pulmonary dysfunctions, cancer, nephrological disorders and cerebrovascular diseases [2–6,9,46]. Published statistics vary between different countries, mainly because of small cohorts, different prevalence of these diseases and inadequate testing of potentially SARS-CoV-2 infected patients. In general, various organ systems are believed to participate in COVID-19 due to the widespread expression of the primary SARS-CoV-2 entry receptor, angiotensin-converting enzyme 2 (ACE2) [47]. ACE2 is an important regulator of the renin-angiotensin-aldosterone system (RAAS), which systemically influences the vasculature and blood pressure via distinct hormones. This endocrine system additionally regulates the fluid and electrolyte balance in the kidneys. Briefly, the peptide prorenin is cleaved in the kidneys and activated renin is then released into the blood stream where it in turn activates angiotensinogen, which is converted into angiotensin I and finally into angiotensin II (AngII). Specific angiotensin-converting enzymes (ACEs), mainly expressed on renal and pulmonary epithelium, facilitate this activation cascade. The vasoconstrictive angiotensin II is the major driver of the blood pressure-increasing response, when the juxtaglomerular apparatus in the kidneys detects critically low blood pressure [48]. Thus, dysregulation of this fine-tuned system results in hypertension and heart failure as well as chronic kidney disease [49,50]. Specific ACE inhibitors (ACE-I) and angiotensin receptor blockers (ARBs) are the first choice as an antihypertensive drug [49,51]. However, ACE2 is a well-characterized negative regulator of the RAAS system as it converts AngII into the vasodilatory fragment Ang 1–7, which simultaneously decreases the AngII concentration to further facilitate the antihypertensive effect [52,53]. ACE2 is located on the cell surface e.g. in the renal, cardiac, pulmonary and gastrointestinal systems [54], providing an explanation for the

observed symptoms of COVID-19. In the following part of this review, we will highlight potentially connective mechanisms of SARS-CoV-2 and the dysregulated presentation of ACE2 with the described clinical features in the context of cardiac injury.

1.4. The role of ACE2 in COVID-19

The central role of ACE2 in cardiac physiology and pathology, as well as the fact that it acts as the major entry receptor for both SARS-CoV and SARS-CoV-2 suggests that it is a promising therapeutic target [47,55]. Receptor binding is facilitated through the viral spike protein that is processed by the protease TMPRSS2 [47]. Then, the spike protein interacts with the extracellular domain of ACE2, which triggers clathrin-dependent endocytosis of the complex [47,55,56]. Interestingly, this interaction is remarkably enhanced in patients suffering from hypertension or coronary heart disease as well as in diabetic or other comorbid conditions [57–59]. While elevated plasmin or plasminogen levels have already been associated with patients suffering from these medical conditions, the impact of these increased levels on viral infections was only very recently highlighted by Ji et al. [60]. The viral spike protein is cleaved at a furin site, which is not present in SARS-CoV, by the furin protease plasmin, thereby increasing the cellular uptake of viral particles and enhancing its pathogenicity [56,60]. Furthermore, there is an association of elevated plasmin levels with the strong induction of D-dimer as a product of hyper-fibrinolysis, which is an additional critical parameter of severe COVID-19 progression [42,43,61].

Once the virus enters the cell, the viral RNA is released and the host-cell's cellular programs are utilized for viral replication. In addition to producing infectious progeny, several mechanisms of the SARS-CoV-2 infection and replication influence ACE2 expression and presentation. Firstly, internalization of the receptor is accompanied by a reduced availability on the cell surface. Secondly, so far unknown viral mediators inhibit *ACE2* and concurrently induce *ADAM metallopeptidase domain 17* (*ADAM-17*) gene expression [53,62]. The membrane-bound metalloprotease is involved in processing the tumor necrosis factor α (TNFα), but is also functioning as a “sheddase” by releasing anchored receptors and cytokines [63]. As a physiological regulator of the RAAS system, ADAM-17 mediates cleavage of ACE2, pointing towards its direct involvement in COVID-19 [53]. Thirdly, not only the release of TNFα [63], but also processing of different important pro-inflammatory cytokines such as interleukin 4 (IL-4) and interferon γ (IFNγ) is accomplished [62,64,65]. The latter two act directly on *ACE2* expression via autocrine pathways [65], further promoting the downregulation of ACE2 on the cellular surface of infected cells, and might secondary imply an imbalance of T cell responses and over-reaction of the immune system by provoking a cytokine storm (Fig. 1).

1.5. ACE2 as clinical target in the treatment of COVID-19

The consequences of SARS-CoV-2 infection alone are already an enormous stress for the body. Considering that many patients suffer from pre-existing illness and elderly people present a compromised immune system [2,3,66], the severity and the potential life-threat of a SARS-CoV-2 infection becomes very clear. The treatment plan of CVD patients regularly includes inhibitors of the RAAS, namely ACE-I and ARBs. Recently, upregulation of ACE2 has been associated with RAAS inhibitor medication [67–69]. The point was recently raised that the susceptibility in those patients is even increased based on high viral loads that were detected in patients with poor outcomes [30,70]. A broad spectrum of institutions and scientist have discussed this topic extensively as treatment guidelines were and are still required very urgently because of the rapidly growing number of cases. Summarizing the most important aspects of this ongoing discussion, antihypertensive drugs should not be discontinued if there is no medical necessity, as uncontrolled blood pressure or clinical instability is a superior high-risk factor for severe complications [71]. So far, there is no evidence of increased susceptibility of hypertensive patients; on the contrary, studies in Chinese cohorts suggest an even lower estimated prevalence of COVID-19 in blood-pressure controlled subjects compared to the distribution of high blood pressure in the population in general [31,46]. Indeed, a retrospective study of hospitalized COVID-19 patients with hypertension identified a lower risk of all-cause mortality in patients under ACE-I and ARB treatment [72]. Moreover, a cardio-protective activity of ACE2 has been previously described in different animal models and clinical studies of heart diseases [73–75], concluding that an even desirable effect might be achieved through this medication. Therefore, a clinical trial was initiated at the end of February aiming to re-raise ACE2 levels without risking increased infection rates. Here, soluble human recombinant ACE2 (rhACE2) infusions were planned in a COVID-19 patient cohort consisting of 24 participants [76]. The conceptual idea is that the non-membrane-bound receptor functions as a trap for viral particles by intercepting SARS-CoV-2, thereby preventing binding to cell surface-located ACE2 and the subsequent infection. Whether this proposed mode of action is only effective in the early phase of infection remains an open question to date. It is generally conceivable that every drug or clinical intervention leading to a decreased viral load might result in an improved outcome combined with reduced long-term complications. However, for non-declared reasons, the promising pilot study has been recently withdrawn as indicated at www.clinicaltrials.gov (NCT number: NCT04287686) [76]. Nevertheless, the pharmaceutical company APEIRON Biologics AG announced a large phase II clinical study a few days ago. They plan to treat 200 COVID-19 patients in Austria, Germany and Denmark with APN01, synonymous for rhACE2 [77]. Importantly, preclinical models reinforce the potential benefit of this treatment. Monteil et al. demonstrated that SARS-CoV-2 infection of engineered human organoids, more precisely blood vessel and kidney organoids, is significantly limited when soluble hrACE2 is applied. In this approach, the group of Penninger specifically investigated the infection-limiting effects at early stages of COVID-19, thus substantiating the previous hypothesis [78]. Altogether, despite the current lack of evidence of efficacy in humans, first studies support the use of rhACE2 to decrease viral load [53,78]. Additional cardio-protective effects of the treatment are also conceivable, although it is questionable whether non-membrane anchored plasma ACE2 can completely fulfil the protease function [63]. To sum up, rhACE2 appears to offer great potential to improve the outcome of COVID-19 patients and minimize adverse chronic damages to the lung, heart and additional organ systems and therefore, the results of the first clinical trials are eagerly anticipated.

1.6. Alternative therapeutic approaches

Recently, diverse therapeutic approaches have been considered and several clinical trials have already begun. There is an intriguing variety of proposed pharmacological interventions, which arose from intensive research, the collaboration of many working groups and scientific journals around the globe. There are many possible targets in addition to ACE2, thus combined therapies may be possible and probably even more potent. Here, we highlight some of these therapeutic strategies, which have a special focus on adjuvant therapies to prevent cardiac injury. As mentioned above, high plasmin/plasminogen levels are often abundant in distinct comorbidities, and can therefore serve as a predictive biomarker for risk assessment [60]. It has already been demonstrated in vitro that specific protease inhibitors impair viral entry and based on these results [42], first protease inhibitors are administered in COVID-19 patients in China [79,80]. In this context, the study of Hoffmann et al. revealed that the protease TMPRSS2 is critically involved in SARS-CoV-2 cell entry, so that specific inhibitors or antibodies might have a beneficial effect [47]. Antiviral activity has also been shown for Remdesivir, an inhibitor of the viral RNA polymerase, currently used in the clinics. While compassionate use of this nucleotide

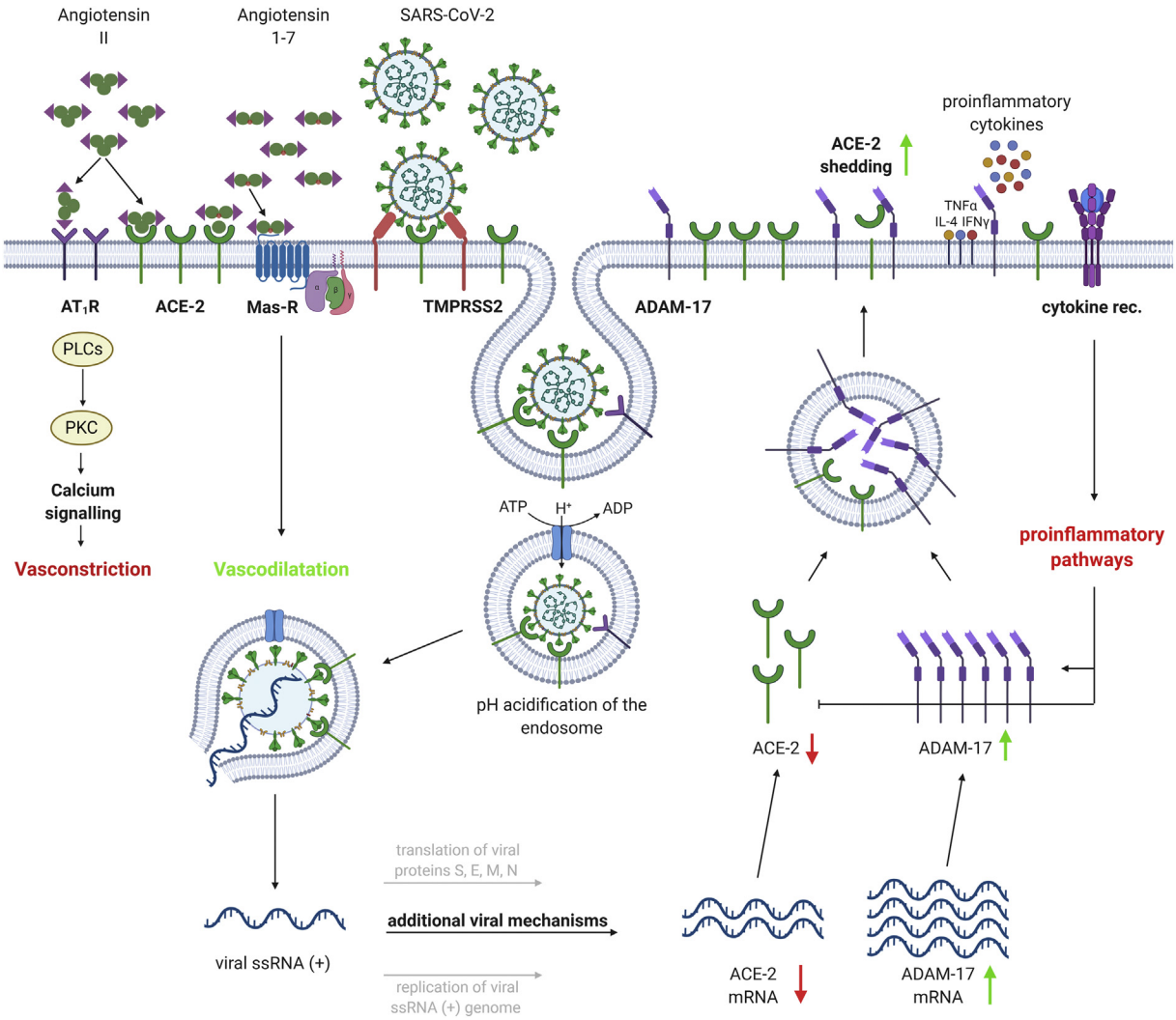

Fig. 1. Overview about the role of ACE-2 during SARS CoV-2 infection.
Angiotensin II can either bind to the angiotensin II receptor type I (AT_1-R), where it induces vasoconstriction via the phospholipase C (PLC), proteinkinase C (PKC) pathway, or be processed by angiotensin converting enzyme 2 (ACE2) to generate angiotensin 1–7. Afterwards, angiotensin 1–7 can bind to the MAS-receptor (Mas-R), which induces a signaling cascade subsequently leading to a vasodilatory effect. During SARS CoV-2 infection, viral spike protein (S) on the surface of the virus binds to ACE2. After processing of the S-protein by the endogenous transmembrane serine protease 2 (TMPRSS2), the viral particle is endocytosed and acidification of the endosome leads to viral and cellular membrane fusion and release of viral single-stranded RNA (ssRNA) into the cytosol. There, the ssRNA is replicated and translated into viral proteins (N, M, E and S). Additional viral mechanisms facilitate the downregulation of endogenous *ACE2* and upregulation of *ADAM metallopeptidase domain 17* (*ADAM-17*) expression. After vesicular transport to the cell surface, ADAM-17 facilitates its role as a "sheddase" and cleaves the extracellular domain of ACE2. Moreover, increased extracellular cytokine concentrations (TNFα, IFNγ, IL-4) lead to the activation of cellular proinflammatory pathways by different cytokine receptors. These pathways further support virus-induced downregulation of ACE2 and upregulation of ADAM-17.

analogue improved the outcome in 36 out of 53 COVID-19 patients, placebo-controlled and randomized trials are required to assess the therapeutic efficacy [81]. Indeed, such studies further testing Remdesivir but also several other therapeutic candidates are currently ongoing. Table 1 provides a comprehensive overview of potential COVID-19 therapeutics including their mode of action and their implication for the cardiovascular system.

2. Conclusion

When the world health organization (WHO) announced COVID-19 as an international emergency at the end of January and declared it a pandemic in March 2020 [82], several efforts were already made to understand the diagnosis and prognosis of this respiratory syndrome. Noteworthy, there are regional differences in COVID-19 severity, which seem to reflect on socio-economic parameters and the readiness of the healthcare systems to cope with such a challenge. Whether COVID-19 has direct or indirect effects to the young or aged cardiovascular system is poorly understood so far because we are only at the beginning of monitoring the COVID-19. This includes specific biomarker discovery to predict patients at very high risk as well as superior imaging tools to monitor cardiac remodeling and inflammation (e.g. MRI). Especially ACE2 abundancy is of high interest in context of SARS-CoV-2 and a potential impact on cardiac tissue; however, insufficient number of cases has been reported so far to draw reliable conclusion and rhACE2 is rather considered a therapeutic strategy to limit viral infection, which will be now investigated in phase-II clinical trials. In addition, clinical association studies in the early, mid and late phase of COVID-19 are urgently needed to discuss standard care, in particular for HF patients who seem to be at highest risk for a severe course of COVID-19.

Declaration of Competing Interest

The authors declare no conflict of interest in relation to this

Table 1
Potential COVID-19 therapeutics currently under clinical investigation.

Therapeutic	Mechanism	Initial usage	Cardiac implementation
Inhibition of the viral cell entry and virus spreading			
Camostat mesylate	1. Inhibitor of serine proteases, especially transmembrane protease serine subtype 2 (TMPRSS2), 2. Protease important for SARS-CoV2 S-protein cleavage for viral membrane fusion.	Therapeutic against pancreatitis Inhibition of pancreatic fibrosis	• Additional function: Inhibition of monocyte activation and reduced TNFα-production, • Reduction of detrimental proinflammatory mechanisms in the heart.
Antiproteases (anti-plasmin)	1. Inhibition of endogenous proteases responsible for SARS-CoV2 S-protein cleavage into S1- and S2-subunit (TMPRSS2, Cathepsin B/L, **plasmin**) 2. Increased plasmin during SARS-CoV2 leads to increased fibrin degradation products (FDPs), hyperfibrinolysis and reduced platelet conc.		• Disturbed blood coagulation may lead to hemophilia or thrombosis, • anti-proteases directed against plasmin could reverse those effects • Plasmin additionally induces hypertension by activation of Na^+-retention
Chloroquine phosphate Hydroxychloroquine	1. Interference with the pH-dependent endosome-mediated entry of SARS-CoV2 by increasing the pH of acidic vesicles 2. Interference of the sialic acid biosynthesis pathway via inhibition of quinone reductase 2, which leads to a disturbed glycosylation of viral entry receptor ACE-2 3. Interference with post-translational modification of viral proteins (proteases) 4. Inhibition of IFNα- and IL-6 expression (anti-inflammatory effect)	Therapeutic against malaria Hydroxychloroquine: therapeutic against rheumatoid arthritis	• Treatment with chloroquine/hydroxychloroquine leads to a drug-induced QT-interval prolongation. • Consequence: torsades de pointes (TdP) tachycardia and increased risk of arrhythmic • high-risk especially when combined with azithromycin treatment (s. below) • thorough QT-monitoring necessary
Umifenovir (Arbidol)	1. Membrane fusion inhibitor by interaction with hemagglutinin of influenza A 2. Exact mechanism for treatment of SARS-CoV2 not elucidated	Therapeutic against influenza A	• protection against other viral infections with heart tropism like Coxsackie virus B5
Soluble human recombinant ACE2 (hrACE2)	Neutralization of SARS-CoV2 via competitive binding of hrACE2, decelerated virus entry and spread		• SARS-CoV2 infection and resulting ACE2-downregulation = increased AngII conc. and thereby hypertension and vasoconstriction • Soluble hrACE2 rescues ACE2 function in lung and heart
Inhibition of the viral RNA-synthesis			
Remdesivir	Nucleosid-analogue for the selective inhibition of the viral RdRp	Therapeutic against Ebola virus	• Increases lung function and decreases viral load • Recent studies only show moderate improvement in severe case patients (larger cohorts necessary to evaluate effectivity)
Lopinavir/Ritonavir	Protease-inhibitor: Most likely inhibits viral 3-chemotrypsine-like protease	HIV-protease inhibitor	• Effectivity against SARS-CoV2 questionable • Side effects: hypertriglyceridemia, hypercholesterinemia, hypertension
Ribavirin	Nucleosid-analogue for the inhibition of the viral RdRp	Therapeutic against hepatitis C, etc.	• Effectivity against SARS-CoV2 questionable
Favipiravir	Nucleosid-analogue for the selective inhibition of the viral RdRp	Therapeutic against influenza and ebola virus	• Decreased fever duration • Increased clearance of viral particles
Immunotherapeutic, Immunosuppressive			
Interferons [IFN-α]	Induction of the expression of antiviral genes and the antiviral immune response		• Inflammation • No benefit in mortality during clinical studies
Anakinra	Immunosuppression by inhibition of IL-1-R	Attenuation of cytokine storm in CAR-T cell therapy	• Anti-inflammatory effect in the heart
Toclizumab/Siltuximab	Immunosuppression by inhibition of IL-6-R (Toclizumab) and IL-6 (Siltuximab)	Attenuation of cytokine storm in CAR-T cell therapy	• Anti-inflammatory effect in the heart
other immunothe rapeutics: Azithromycin	Stimulation of host antiviral response through the induction of interferons and IFN-stimulated genes (ISGs)	Macrolide antibiotic against bacterial infections (e.g. *P. aeruginosa*)	• Azithromycin leads to a drug-induced QT-interval prolongation via inhibition of iKr • Consequence: torsades de pointes (TdP) tachycardia • Increased risk of arrhythmic death
Anti-hypertension therapeutics and potential SARS-CoV2 vaccines			
ACE-inhibitors AT_1-antagonists (Losartan)	Inhibition of ACE-1 leads to: 1. less angiotensin II 2. increased levels of ACE-2 (controversial). 3. ACE-2 product angiotensin 1–7 has a vasodilatory effect		• Increased ACE-2 level initially might result in a higher viral uptake • Withdrawal of ACE-inhibitors might be detrimental, since Ang II might be responsible for acute lung injury • ACEII possesses cardioprotective effect
monoclonal neutralizing AB	1. SARS-CoV2 specific Abs isolated from convalescent patients 2. Cross-reactivity of mABs from SARS and MERS		• Risk of immunopathogenic liver reaction by antibody-dependent enhancement of the disease

manuscript.

Acknowledgment

We acknowledge Dr. Jan Fiedler for fruitful discussions and proofreading of this review. This work was supported by the REBIRTH Center for Translational Regenerative Medicine of Hannover Medical School and by the Deutsche Forschungsgemeinschaft, DFG (KFO311 to TT and TRR267 to CB and TT).

References

[1] World Health Organization (WHO), Coronavirus Disease 2019 (COVID-19) Situation Report – 89, https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200418-sitrep-89-covid-19.pdf?sfvrsn=3643dd38_2.
[2] J. Yang, Y. Zheng, X. Gou, K. Pu, Z. Chen, Q. Guo, et al., Prevalence of comorbidities in the novel Wuhan coronavirus (COVID-19) infection: a systematic review and meta-analysis, Int. J. Infect. Dis. 94 (2020) 91–95.
[3] F. Zhou, T. Yu, R. Du, G. Fan, Y. Liu, Z. Liu, et al., Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study, Lancet 395 (2020) 1054–1062.
[4] S. Wan, Y. Xiang, W. Fang, Y. Zheng, B. Li, Y. Hu, et al., Clinical features and treatment of COVID-19 patients in northeast Chongqing, J. Med. Virol. (2020).
[5] C. Huang, Y. Wang, X. Li, L. Ren, J. Zhao, Y. Hu, et al., Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China, Lancet 395 (2020) 497–506.
[6] D. Wang, B. Hu, C. Hu, F. Zhu, X. Liu, J. Zhang, et al., Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China, JAMA 323 (11) (2020) 1061–1069.
[7] N. Chen, M. Zhou, X. Dong, J. Qu, F. Gong, Y. Han, et al., Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study, Lancet 395 (2020) 507–513.
[8] COVID-19 Surveillance Group. Characteristics of COVID-19 patients dying in Italy Report based on available data on March 20th, 2020. https://www.epicentro.iss.it/coronavirus/bollettino/Report-COVID-2019_20_marzo_eng.pdf.
[9] LEOSS. Lean European Open Survey on SARS-CoV-2 Infected Patients - Statistics. https://leoss.net/statistics/.
[10] P. Zhou, X.-L. Yang, X.-G. Wang, B. Hu, L. Zhang, W. Zhang, et al., A pneumonia outbreak associated with a new coronavirus of probable bat origin, Nature 579 (2020) 270–273.
[11] D. Benvenuto, M. Giovanetti, A. Ciccozzi, S. Spoto, S. Angeletti, M. Ciccozzi, The 2019-new coronavirus epidemic: evidence for virus evolution, J. Med. Virol. 92 (2020) 455–459.
[12] P. Liu, W. Chen, J.-P. Chen, Viral Metagenomics revealed Sendai virus and coronavirus infection of Malayan pangolins (Manis javanica), Viruses 11 (2019).
[13] World Health Organization (WHO), Q&A on coronaviruses (COVID-19): How long does it take after exposure to COVID-19 to develop symptoms? https://www.who.int/emergencies/diseases/novel-coronavirus-2019/question-and-answers-hub/q-a-detail/q-a-coronaviruses, (2020).
[14] H. Streeck, G. Hartmann, M. Exner, M. Schmid, Vorläufiges Ergebnis und Schlussfolgerungen der COVID-19 Case-ClusterStudy (Gemeinde Gangelt), https://www.land.nrw/sites/default/files/asset/document/zwischenergebnis_covid19_case_study_gangelt_0.pdf.
[15] Centers for Disease Control and Prevention, Coronavirus Disease 2019 (COVID-19) - Symptoms of Coronavirus, https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fabout%2Fsymptoms.html.
[16] X.-S. Wei, X. Wang, Y.-R. Niu, L.-L. Ye, W.-B. Peng, Z.-H. Wang, et al., Clinical characteristics of SARS-CoV-2 infected pneumonia with Diarrhea, SSRN Journal (2020).
[17] Centers for Disease Control and Prevention, Coronavirus Disease COVID-19 (2019) 20.03.20 https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html.
[18] World Health Organization (WHO). Q&A: Similarities and differences – COVID-19 and influenza. https://www.who.int/news-room/q-a-detail/q-a-similarities-and-differences-covid-19-and-influenza.
[19] M. Barnes, A.E. Heywood, A. Mahimbo, B. Rahman, A.T. Newall, C.R. Macintyre, Acute myocardial infarction and influenza: a meta-analysis of case-control studies, Heart 101 (2015) 1738–1747.
[20] European Society of Anesthesiology, Analysis of the number growth of ICU patients with Covid-19 in Italy and Lombardy, (2020) https://www.esahq.org/esa-news/analysis-of-the-number-growth-of-icu-patients-with-covid-19-in-italy-and-lombardy/.
[21] Y. Wang, C. Dong, Y. Hu, C. Li, Q. Ren, X. Zhang, et al., Temporal changes of CT findings in 90 patients with COVID-19 pneumonia: a longitudinal study, Radiology 200843 (2020).
[22] M. Dreher, A. Kersten, J. Bickenbach, P. Balfanz, B. Hartmann, C. Cornelissen, et al., Charakteristik von 50 hospitalisierten COVID-19-Patienten mit und ohne ARDS, Dtsch. Arztebl. Int. 2020 (2020) 271–278.
[23] T. Guo, Y. Fan, M. Chen, X. Wu, L. Zhang, T. He, et al., Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19), JAMA Cardiol. (2020).
[24] S. Shi, M. Qin, B. Shen, Y. Cai, T. Liu, F. Yang, et al., Association of Cardiac Injury With Mortality in Hospitalized Patients With COVID-19 in Wuhan, China, JAMA Cardiol (2020).
[25] C. Yang, Z. Jin, An acute respiratory infection runs into the Most common non-communicable epidemic-COVID-19 and cardiovascular diseases, JAMA Cardiol. (2020).
[26] T. Liu, J. Zhang, Y. Yang, H. Ma, Z. Li, J. Zhang, et al., The Potential Role of IL-6 in Monitoring Severe Case of Coronavirus Disease 2019, (2020).
[27] Ärzteblatt, Intensivmediziner veröffentlichen Empfehlungen zur Therapie von COVID-19-Patienten, https://www.aerzteblatt.de/nachrichten/111046/Intensivmediziner-veroeffentlichen-Empfehlungen-zur-Therapie-von-COVID-19-Patienten.
[28] Robert Koch-Institut, Hinweise zu Erkennung, Diagnostik und Therapie von Patienten mit COVID-19, https://www.rki.de/DE/Content/Kommissionen/Stakob/Stellungnahmen/Stellungnahme-Covid-19_Therapie_Diagnose.pdf?__blob=publicationFile.
[29] R.M. Inciardi, L. Lupi, G. Zaccone, L. Italia, M. Raffo, D. Tomasoni, et al., Cardiac involvement in a patient with coronavirus disease 2019 (COVID-19), JAMA Cardiol. (2020).
[30] Y.-Y. Zheng, Y.-T. Ma, J.-Y. Zhang, X. Xie, COVID-19 and the cardiovascular system, Nat. Rev. Cardiol. 17 (2020) 259–260.
[31] W.-J. Guan, Z.-Y. Ni, Y. Hu, W.-H. Liang, C.-Q. Ou, J.-X. He, et al., Clinical characteristics of coronavirus disease 2019 in China, N. Engl. J. Med. 382 (2020) 1708–1720.
[32] Q. Ruan, K. Yang, W. Wang, L. Jiang, J. Song, Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China, Intensive Care Med 46 (5) (2020) 846–848.
[33] P. Mehta, D.F. McAuley, M. Brown, E. Sanchez, R.S. Tattersall, J.J. Manson, COVID-19: consider cytokine storm syndromes and immunosuppression, Lancet 395 (2020) 1033–1034.
[34] World Health Organization (WHO), Summary of probable SARS cases with onset of illness from 1 November 2002 to 31 July 2003, (2003) https://www.who.int/csr/sars/country/table2004_04_21/en/.
[35] World Health Organization (WHO), Background and summary of novel coronavirus infection – as of 30 November 2012, (2020) https://www.who.int/csr/disease/coronavirus_infections/update_20121130/en/.
[36] T. Alhogbani, Acute myocarditis associated with novel middle east respiratory syndrome coronavirus, Ann Saudi Med 36 (2016) 78–80.
[37] Q. Wu, L. Zhou, X. Sun, Z. Yan, C. Hu, J. Wu, et al., Altered lipid metabolism in recovered SARS patients twelve years after infection, Sci. Rep. 7 (2017) 9110.
[38] R.O. Bonow, G.C. Fonarow, P.T. O'Gara, C.W. Yancy, Association of Coronavirus Disease 2019 (COVID-19) with myocardial injury and mortality, JAMA Cardiol. (2020).
[39] Cardiology Magazine, Troponin and BNP Use in COVID-19, https://www.acc.org/latest-in-cardiology/articles/2020/03/18/15/25/troponin-and-bnp-use-in-covid19.
[40] B. Harvell, N. Henrie, A.A. Ernst, S.J. Weiss, S. Oglesbee, D. Sarangarm, et al., The meaning of elevated troponin I levels: not always acute coronary syndromes, Am. J. Emerg. Med. 34 (2016) 145–148.
[41] L. James, J.R. Januzzi, Causes of Non ACS Related Troponin Elevations, https://www.acc.org/latest-in-cardiology/articles/2014/07/18/13/16/causes-of-non-acs-related-troponin-elevations.
[42] S.S. Adam, N.S. Key, C.S. Greenberg, D-dimer antigen: current concepts and future prospects, Blood 113 (2009) 2878–2887.
[43] T. Fuchs-Buder, P. de Moerloose, B. Ricou, G. Reber, C. Vifian, L. Nicod, et al., Time course of procoagulant activity and D dimer in bronchoalveolar fluid of patients at risk for or with acute respiratory distress syndrome, Am. J. Respir. Crit. Care Med. 153 (1996) 163–167.
[44] S. Poe, R.H. Vandivier-Pletsch, M. Clay, H.R. Wong, E. Haynes, F.G. Rothenberg, Cardiac troponin measurement in the critically ill: potential for guiding clinical management, J. Investig. Med. 63 (2015) 905–915.
[45] M.B. Rivara, E.K. Bajwa, J.L. Januzzi, M.N. Gong, B.T. Thompson, D.C. Christiani, Prognostic significance of elevated cardiac troponin-T levels in acute respiratory distress syndrome patients, PLoS One 7 (2012) e40515.
[46] Z. Wang, Z. Chen, L. Zhang, X. Wang, G. Hao, Z. Zhang, et al., Status of hypertension in China: results from the China hypertension survey, 2012-2015, Circulation 137 (2018) 2344–2356.
[47] M. Hoffmann, H. Kleine-Weber, S. Schroeder, N. Krüger, T. Herrler, S. Erichsen, et al., SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor, Cell 181 (2) (2020) 271–280.
[48] M.K. Ames, C.E. Atkins, B. Pitt, The renin-angiotensin-aldosterone system and its suppression, J. Vet. Intern. Med. 33 (2019) 363–382.
[49] L. Ghazi, P. Drawz, Advances in understanding the renin-angiotensin-aldosterone system (RAAS) in blood pressure control and recent pivotal trials of RAAS blockade in heart failure and diabetic nephropathy, F1000Res 6 (2017).
[50] S. Iravanian, S.C. Dudley, The renin-angiotensin-aldosterone system (RAAS) and cardiac arrhythmias, Heart Rhythm. 5 (2008) S12–S17.
[51] C.A. Romero, M. Orias, M.R. Weir, Novel RAAS agonists and antagonists: clinical applications and controversies, Nat Rev Endocrinol 11 (2015) 242–252.
[52] S. Keidar, M. Kaplan, A. Gamliel-Lazarovich, ACE2 of the heart: from angiotensin I to angiotensin (1-7), Cardiovasc. Res. 73 (2007) 463–469.
[53] R.A.S. Santos, W.O. Sampaio, A.C. Alzamora, D. Motta-Santos, N. Alenina, M. Bader, et al., The ACE2/angiotensin-(1-7)/MAS Axis of the renin-angiotensin system: focus on angiotensin-(1-7), Physiol. Rev. 98 (2018) 505–553.
[54] I. Hamming, W. Timens, M.L.C. Bulthuis, A.T. Lely, G.J. Navis, H. van Goor, Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first

step in understanding SARS pathogenesis, J. Pathol. 203 (2004) 631–637.
[55] A.J. Turner, J.A. Hiscox, N.M. Hooper, ACE2: from vasopeptidase to SARS virus receptor, Trends Pharmacol. Sci. 25 (2004) 291–294.
[56] Y. Chen, Y. Guo, Y. Pan, Z.J. Zhao, Structure analysis of the receptor binding of 2019-nCoV, Biochem. Biophys. Res. Commun. 525 (2020) 135–140.
[57] K.B. Buhl, C.S. Oxlund, U.G. Friis, P. Svenningsen, C. Bistrup, I.A. Jacobsen, et al., Plasmin in urine from patients with type 2 diabetes and treatment-resistant hypertension activates ENaC in vitro, J. Hypertens. 32 (2014) 1672–1677.
[58] P. Svenningsen, G.R. Hinrichs, R. Zachar, R. Ydegaard, B.L. Jensen, Physiology and pathophysiology of the plasminogen system in the kidney, Pflugers Arch. 469 (2017) 1415–1423.
[59] H. Zheng, X. Liu, N.M. Sharma, Y. Li, R.U. Pliquett, K.P. Patel, Urinary Proteolytic activation of renal epithelial Na + channels in chronic heart failure, Hypertension 67 (2016) 197–205.
[60] H.-L. Ji, R. Zhao, S. Matalon, M.A. Matthay, Elevated plasmin(ogen) as a common risk factor for COVID-19 susceptibility, Physiol. Rev. 100 (2020) 1065–1075.
[61] B. Zhang, X. Zhou, Y. Qiu, F. Feng, J. Feng, Y. Jia, et al., Clinical Characteristics of 82 Death Cases with COVID-19, (2020).
[62] K. Wang, M. Gheblawi, G.Y. Oudit, Angiotensin converting enzyme 2: a double-edged sword, Circulation (2020) (epub ahead of print).
[63] D.W. Lambert, M. Yarski, F.J. Warner, P. Thornhill, E.T. Parkin, A.I. Smith, et al., Tumor necrosis factor-alpha convertase (ADAM17) mediates regulated ectodomain shedding of the severe-acute respiratory syndrome-coronavirus (SARS-CoV) receptor, angiotensin-converting enzyme-2 (ACE2), J. Biol. Chem. 280 (2005) 30113–30119.
[64] H. Kanzaki, F. Shinohara, M. Suzuki, S. Wada, Y. Miyamoto, Y. Yamaguchi, et al., A-Disintegrin and metalloproteinase (ADAM) 17 enzymatically degrades interferon-gamma, Sci. Rep. 6 (2016) 32259.
[65] A. de Lang, A.D.M.E. Osterhaus, B.L. Haagmans, Interferon-gamma and interleukin-4 downregulate expression of the SARS coronavirus receptor ACE2 in Vero E6 cells, Virology 353 (2006) 474–481.
[66] J.P. Schatzmann Peron, H. Nakaya, Susceptibility of the Elderly to SARS-CoV-2 Infection: ACE-2 Overexpression, Shedding and Antibody-Dependent Enhancement (ADE), (2020).
[67] C.M. Ferrario, J. Jessup, M.C. Chappell, D.B. Averill, K.B. Brosnihan, E.A. Tallant, et al., Effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockers on cardiac angiotensin-converting enzyme 2, Circulation 111 (2005) 2605–2610.
[68] Y. Ishiyama, P.E. Gallagher, D.B. Averill, E.A. Tallant, K.B. Brosnihan, C.M. Ferrario, Upregulation of angiotensin-converting enzyme 2 after myocardial infarction by blockade of angiotensin II receptors, Hypertension 43 (2004) 970–976.
[69] T. Karram, A. Abbasi, S. Keidar, E. Golomb, I. Hochberg, J. Winaver, et al., Effects of spironolactone and eprosartan on cardiac remodeling and angiotensin-converting enzyme isoforms in rats with experimental heart failure, Am. J. Physiol. Heart Circ. Physiol. 289 (2005) H1351–H1358.
[70] J. Guo, Z. Huang, L. Lin, J. Lv, Coronavirus disease 2019 (COVID-19) and cardiovascular disease: a viewpoint on the potential influence of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers on onset and severity of severe acute respiratory syndrome coronavirus 2 infection, J. Am. Heart Assoc. 9 (2020) e016219.
[71] G. de Simone, Position Statement of the ESC Council on Hypertension on ACE-Inhibitors and Angiotensin Receptor Blockers, https://www.escardio.org/Councils/Council-on-Hypertension-(CHT)/News/position-statement-of-the-esc-council-on-hypertension-on-ace-inhibitors-and-ang.
[72] P. Zhang, L. Zhu, J. Cai, F. Lei, J.-J. Qin, J. Xie, et al., Association of Inpatient use of angiotensin converting enzyme inhibitors and angiotensin II receptor blockers with mortality among patients with hypertension hospitalized with COVID-19, Circ. Res. (2020) (epub aheah of print).
[73] A.R. Hemnes, A. Rathinasabapathy, E.A. Austin, E.L. Brittain, E.J. Carrier, X. Chen, et al., A potential therapeutic role for angiotensin-converting enzyme 2 in human pulmonary arterial hypertension, Eur. Respir. J. 51 (2018).
[74] A. Khan, C. Benthin, B. Zeno, T.E. Albertson, J. Boyd, J.D. Christie, et al., A pilot clinical trial of recombinant human angiotensin-converting enzyme 2 in acute respiratory distress syndrome, Crit. Care 21 (2017) 234.
[75] Z. Zou, Y. Yan, Y. Shu, R. Gao, Y. Sun, X. Li, et al., Angiotensin-converting enzyme 2 protects from lethal avian influenza a H5N1 infections, Nat. Commun. 5 (2014) 3594.
[76] ClinicalTrial.gov, Recombinant Human Angiotensin-converting Enzyme 2 (rhACE2) as a Treatment for Patients With COVID-19, https://clinicaltrials.gov/ct2/show/NCT04287686?cond=COVID-19&draw=2.
[77] APEIRON Biologics AG, APEIRON Biologics Initiates Phase II Clinical Trial of APN01 for Treatment of COVID-19, https://www.apeiron-biologics.com/wp-content/uploads/2020/04/20200402_APEIRON_Phase-2-EU-trial_APN01_ENG.pdf.
[78] V. Monteil, H. Kwon, P. Prado, A. Hagelkrüys, R.A. Wimmer, M. Stahl, et al., Inhibition of SARS-CoV-2 infections in engineered human tissues using clinical-grade soluble human ACE2, Cell (2020) (S0092-8674(20)30399, epub ahead of print).
[79] S.G.V. Rosa, W.C. Santos, Clinical trials on drug repositioning for COVID-19 treatment, Rev. Panam. Salud Publica 44 (2020) e40.
[80] H. Chen, Z. Zhang, L. Wang, Z. Huang, F. Gong, X. Li, et al., First Clinical Study Using HCV Protease Inhibitor Danoprevir to Treat Naive and Experienced COVID-19 Patients, (2020).
[81] J. Grein, N. Ohmagari, D. Shin, G. Diaz, E. Asperges, A. Castagna, et al., Compassionate use of Remdesivir for patients with severe Covid-19, N. Engl. J. Med. (2020) (epub ahead of print).
[82] World Health Organization (WHO), WHO Director-General's opening remarks at the media briefing on COVID-19, (2020) https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19—11-march-2020.