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VIEWPOINT

Treat or not treat COVID-19 with combined renin–angiotensin system and neprilysin inhibition: Have we found a solution?

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Since 2019, coronavirus disease 2019 (COVID-19) has affected millions of individuals worldwide, leading to multiple deaths and numerous long-term multiorgan sequelae. In patients with COVID-19, cardiovascular diseases, including heart failure (HF), are common and associated with an increased risk for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections[1] and high mortality rates.[2] Epidemiological data revealed that prevalent HF was an independent predictor of increased in-hospital mortality[2]: in an Italian cohort, nearly 42% of patients with known HF who had been hospitalized with COVID-19 died during hospitalization.[2] Although SARS-CoV-2 infection affects primarily the respiratory system, infected individuals can develop multiple de-novo cardiovascular complications, including HF,[3] arrhythmia, acute coronary syndrome or (peri-) myocarditis.[4] Persistent cardiac injury, defined as long-term high-sensitivity cardiac troponin T (hs-cTnT) elevation or persistent abnormalities in cardiac magnetic resonance[3]—even after the primary SARS-CoV-2 infection was cured—has been described.[3] Proposed underlying mechanisms include activation of inflammatory and thrombotic cascades,[1] direct viral infiltration or emerging/worsening of underlying baseline myocardial structural or atherosclerotic abnormalities.[1]

In a detailed review of the European Society of Cardiology task force for the management of COVID-19,[5,6] the dysregulation of angiotensin-converting enzyme (ACE)/ACE2 system due to direct SARS-CoV-2 interaction is highlighted as one of the central pathways.[7] In brief, SARS-CoV-2 binds to the ACE2 receptor—located among others on myocytes—to mediate cellular internalization (*Figure 1*).[7,8] Thus, viral infiltration can lead to inflammation, cardiac fibrosis and direct cardiac damage by microvascular and macrovascular dysfunction (e.g. myocarditis with consequent arrhythmias or HF).[5] In combination with immune over-reactivity or 'cytokine storm', these processes can destabilize atherosclerotic plaques resulting in acute coronary syndrome.[5]

All these described changes can result in HF with preserved ejection fraction (HFpEF)—particularly in those patients with underlying risk factors as hypertension, obesity or diabetes—or unmask subclinical preexisting HFpEF.[9] Consecutively, its adequate diagnostics and treatment are essential.[9] As quantitative markers of cardiomyocyte injury and haemodynamic myocardial stress measurement of hs-cTnT and N-terminal pro-B-type natriuretic peptide (NT-proBNP) should not be delayed. These biomarkers are common, accurate and easy to perform. In cohort studies, they were independently associated with adverse outcome in acute COVID-19,[3,10] as well as in long-term cardiac injury,[3] strengthening their relevance for precise prognostic risk stratification.

At the beginning of the pandemic, arterial hypertension was rapidly revealed as one of the most prevalent risk factor for COVID-19-associated cardiovascular events.[2,11] As renin–angiotensin system inhibitors (RASi), including ACE inhibitors (ACEi) or angiotensin receptor blockers (ARBs), are the basis for antihypertensive (and HF) treatment and are known to increase the tissue levels of ACE2, they have been claimed to be responsible for adverse outcomes in individuals with arterial hypertension and COVID-19.[11] It was stated that the treatment with RASi may promote SARS-CoV-2 infection, therefore being detrimental in patients who are exposed to SARS-CoV-2.[11] But up to now, this hypothesis has not been confirmed and epidemiological studies showed that there is no clear evidence that ACEi or ARBs affect the risk of SARS-CoV-2 infection.[12] On the contrary, randomized controlled trials on patients on RASi hospitalized for SARS-CoV-2 infection showed that stopping the treatment with ACEi or ARBs resulted in a rise of natriuretic peptides and increasing the risk of acute HF compared to treatment continuation.[13] Additionally, it has been shown that the discontinuation of ACEi and ARBs (and beta-blockers) increases the risk of adverse outcomes (*Table 1*).[12–17] In a meta-analysis compromising data of 11 randomized controlled trials which enrolled a total of 1838

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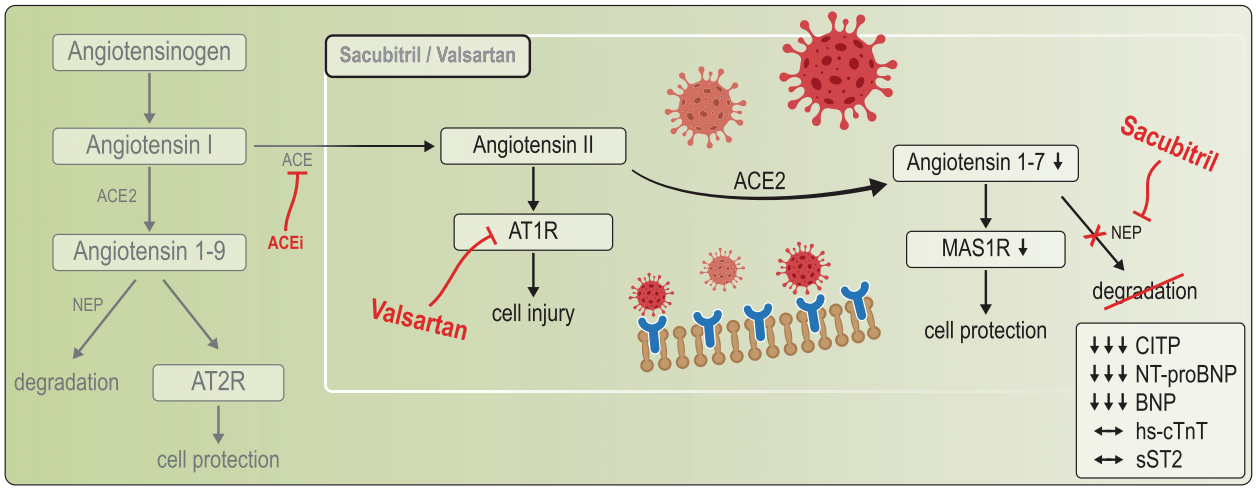

Figure 1 Hypothetical protective mechanisms of sacubitril/valsartan treatment in COVID-19-induced cardiac injury. SARS-CoV-19 entry into cell via angiotensin-converting enzyme 2 (ACE2) downregulates the ACE2 expression and results in higher levels of angiotensin II.[7] Angiotensin II can directly lead to cardiac cell injury by binding to the AT1 receptor (AT1R). Treatment with valsartan hampers this pathway. Angiotensin II is then inactivated by the remaining ACE2 to angiotensin 1–7 that is cardiac cell protective itself. To stop angiotensin 1–7 degradation by neprilysin, its inhibition by sacubitril is of importance.[7] In general, neprilysin levels are higher during inflammation than in physiological circumstances,[8] strengthening the need for neprilysin's potent inhibition in COVID-19 (and over respiratory infections) induced cardiac injury. ACEi, angiotensin-converting enzyme inhibitor; BNP, B-type natriuretic peptide; CITP, carboxy-terminal telopeptide of collagen type I; hs-cTnT, high-sensitivity cardiac troponin T; MAS1R, MAS1 receptor; NEP, neprilysin; NT-proBNP, N-terminal pro-B-type natriuretic peptide; sST2, soluble suppression of tumorigenicity 2.

participants, continuation versus discontinuation of RASi showed no difference in all-cause mortality and a non-significant reduction in acute myocardial infarction, but an increased risk of acute kidney injury.[18] While trials focusing on sodium–glucose cotransporter 2 inhibitors in COVID-19 showed a treatment benefit[19] and those on mineralocorticoid receptor antagonists[20] were neutral, data on sacubitril/valsartan (angiotensin receptor–neprilysin inhibitor [ARNI]) are sparse.[21] Sacubitril increases neprilysin-degraded peptides, such as natriuretic peptides and angiotensin 1–7 by neprilysin inhibition. These peptides are associated with anti-inflammatory, antihypertrophic and antifibrotic effects.

Based on the hypothesis that treatment with ARNI can protect SARS-CoV-2 infected individuals against long-term cardiac injury,[7] the PARACOR-19 trial[14] has been conducted. High-sensitivity cardiac troponin T, soluble suppression of tumorigenicity 2 (sST2) and NT-proBNP were measured at baseline, at least 4–16 weeks after SARS-CoV-2 infection, followed by a 12-week-period of ARNI therapy compared to placebo. The treatment with ARNI failed to lower high levels of hs-cTnT and sST2 following SARS-CoV-2 infection from baseline to week 12, but it resulted in significant reduction of both NT-proBNP levels (−167 pg/ml [mean] from baseline to week 12) and systolic blood pressure (−19 mmHg [mean] from baseline to week 12) due to decreasing cardiac wall stress and reduced afterload. Although there was various discussion about ACE2 and RASi treatment in the past, treatment with ARNI was safe in the present trial. In a subgroup analysis, cardiac magnetic resonance was performed at baseline and at week 12 without any significant differences between the intervention group and the control arm. Unfortunately, the trial was underpowered (42 participants included; subgroup analysis included 18 participants in total only), ARNI treatment was only started 69 (54–90) days (median 25th–75th) after proven COVID-19 infection, the interventional period of only 12 weeks was relatively short and less than half of the participants had residual COVID-19 symptoms at time of enrolment. Additionally, echocardiographic data as well as clinical symptoms such as dyspnoea (New York Heart Association stages) or angina pectoris (Canadian Cardiovascular Society stages) had not been captured, but left ventricular ejection fraction <40% had been an exclusion criterion. The randomized participants in PARACOR-19 were at low cardiovascular risk (only 14% had been hospitalized for COVID-19, 30% in the intervention arm had known hypertension, 30% diabetes and 14% prevalent cardiovascular diseases). In this analysis, ARNI failed to lower hs-cTnT. These data are in contrast to previously published post-hoc analysis of the PARAGON-HF trial. In over 4000 participants with known HFpEF, a reduction of 9% of hs-cTnT in the ARNI treatment arm compared to the valsartan treatment arm has been observed from baseline to week 16.[22] The hs-cTnT reduction was significantly associated with a lower cardiovascular event rate, leading to the author's conclusion that hs-cTnT may be helpful in identifying individuals with HFpEF who are more likely to benefit from ARNI treatment.

Maybe these treatment effects would have been observed by earlier treatment implementation (during acute SARS-CoV-2 infection) or by focused treatment in those with early concomitant cardiac symptoms. Hence, strategies for appropriate treatment for

Table 1 Relevant randomized controlled trials concerning discontinuation versus continuation of renin–angiotensin system inhibitors in COVID-19 infection with >40 participants

Author	Trial	Randomization	No. of participants	Main inclusion criteria	Intervention period	Primary endpoint	Main results	Natriuretic peptides	hs troponin I or T
Sharma *et al.*,[13] 2022	RAAS-COVID-19	Discontinuation vs. continuation of RASi	46	Mild or moderate COVID-19 infection + treatment ≥1 month with ACEi or ARB	7 days	Global rank score	6 ([SD] 6.3) vs. 3.8 (SD 2.5); $p = 0.60$	BNP: +16.7% vs. −27.5%	hs troponin I −20.3% vs. −14.1%
Greene *et al.*,[14] 2024	PARACOR-19	ARNI vs. placebo	42	Recovered acute COVID-19 infection +1 CV risk factor	12 weeks	hs troponin T and sST2	hs troponin T: 1.10 (95% CI 0.92–1.33) sST2: 0.98 (0.78–1.24)	NT-proBNP: −167 pg/ml vs. 1 pg/ml	hs troponin T: 0.8 ng/L vs. 0.3 ng/L
Bauer *et al.*,[15] 2021	ACEI-COVID	Discontinuation vs. continuation of RASi	204	COVID-19 infection + treatment ≥1 month with ACEi or ARB	30 days	SOFA score	Median (IQR) 0.00 (0.00–2.00) vs. 1·00 (0.00–3.00); $p = 0.12$	n/a	n/a
Cohen *et al.*,[16] 2021	REPLACE COVID	Continuation vs. discontinuation of RASi	152	COVID-19 infection + use of ACEi or ARB as an outpatient	5 days	Global rank score	73 (IQR 40–110) vs. 81 (38–117)	n/a	n/a
Lopes *et al.*,[17] 2020	BRACE-CORONA	Discontinuation vs. continuation of RASi	659	Mild to moderate COVID-19 infection + treatment with ACEi or ARB prior to hospitalization	30 days	No. of days alive and out of the hospital through 30 days	HR 0.95 (95% CI 0.90–1.01)	8% vs. 3.9% above the ULN	7.6% vs. 11.9% above the ULN

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; BNP, B-type natriuretic peptide; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; hs, high-sensitivity; IQR, interquartile range; n/a, not available; NT-proBNP, N-terminal pro-B-type natriuretic peptide; RAAS, renin–angiotensin–aldosterone system; RASi, renin–angiotensin system inhibitor; SD, standard deviation; SOFA, sequential organ failure assessment; sST2, soluble suppression of tumorigenicity 2; ULN, upper limit of normal.

COVID-19-associated cardiac injury are still missing and require further investigation.

Nevertheless, the results of PARACOR-19 strengthen the safety of ARNI intake in recently SARS-CoV-2 infected patients with residual hs-cTnT elevation. These results could be transferred to other respiratory virus infections—as influenza or respiratory syncytial virus—that were also associated with myocardial involvement and increased cardiovascular outcome.[20]

We congratulate the authors for having completed their randomized hypothesis-generating trial and helping us to find evidence for treatment options in COVID-19-associated cardiovascular diseases.

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