

# 19. Perindopril and Losartan

*by* Meity Ardiana

---

**Submission date:** 13-Oct-2023 09:34AM (UTC+0800)

**Submission ID:** 2193354315

**File name:** 19.\_Perindopril\_and\_Losartan.pdf (210.29K)

**Word count:** 3823

**Character count:** 21116

M. ARDIANA<sup>1</sup>, I.G.R. SURYAWAN<sup>1</sup>, H.O. HERMAWAN<sup>1</sup>, P.M. HARSOYO<sup>1</sup>,  
I.M. SUFIYAH<sup>1</sup>, A.R. MUHAMMAD<sup>2</sup>, B.S.I. ZAINI<sup>2</sup>

## PERINDOPRIL AND LOSARTAN ATTENUATE PRO-COAGULATION FACTORS IN HUMAN ADIPOCYTES EXPOSED TO SARS-COV-2 SPIKE PROTEIN

<sup>1</sup>Cardiology and Vascular Medicine Department, Medical Faculty of Airlangga University - Dr. Soetomo General Hospital, Surabaya, Indonesia;  
<sup>2</sup>Medical Faculty of Nahdlatul Ulama Surabaya University, Surabaya, Indonesia

Thrombotic events are highly prevalent in coronavirus disease 2019 (COVID-19), especially in patients presenting with risk factors of adverse outcomes such as obesity. Recently, the associations between the angiotensin converting enzyme 2 (ACE2) pathway and thrombosis have been reported. Angiotensin-converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARBs) are widely used cardiovascular pharmacologic agents that upregulate ACE2 levels. An observation of the alterations in pro-coagulation factors after exposure to ACEIs and ARBs may provide valuable insight into the thrombosis mechanism and how it may relate to ACE2. This study used adipose tissue harvested from an obese male donor was isolated and exposed to perindopril, losartan, and ACE2 recombinant as binding assay, following exposure with 10 nm of SARS-CoV-2 S1 spike protein. After 48 hours, tissue factor (TF) and plasminogen activator inhibitor-1 (PAI-1) as pro-coagulation factors as well as ACE2 levels and binding evaluated. The results shows TF level was significantly reduced in Perindopril group compared to control (4.834; p=0.005), while a non-significant reduction was observed in Losartan group (5.624; p=0.111). However, Losartan group showed a better reduction of PAI-1 levels (2.633; p<0.001) than Perindopril group (3.484; p=0.001). These findings were consistent with the observations in ACE2 recombinant group, suggesting that both drugs lowered the bindings of ACE2 and SARS-CoV-2 spike proteins. This study indicated that both perindopril and losartan may attenuate pro-coagulation factors in human adipocytes exposed to SARS-CoV-2 spike proteins, and therefore showcased a potential role of ACE2 in the mechanism of COVID-19-related thrombosis. Further investigation in non-COVID-19 populations should commence and may be of value to expanding this potential in general cardiovascular diseases.

**Key words:** coronavirus disease 2019, perindopril, losartan, angiotensin converting enzyme 2, SARS-CoV-2 S1 spike protein, thrombosis, angiotensin II receptor blockers, adipocytes, tissue factor, plasminogen activator inhibitor-1

### INTRODUCTION

The pandemic coronavirus disease 2019 (COVID-19) has caused high mortality and morbidity throughout the world, especially in COVID-19 infections with severe symptoms (1). Endothelial dysfunction increases the risk of thromboembolic complications in COVID-19 patients (2, 3). An increase in coagulation and platelets (tissue factor (TF) and plasminogen activator inhibitor-1 (PAI-1)) was observed in earlier trials by Al-Tamimi *et al.*, particularly in COVID-19 patients with moderate to severe symptoms (4). Additionally, tissue plasminogen activator (TPA) and PAI-1 promote spontaneous fibrinolysis, which is substantially correlated with mortality in certain COVID-19 patients, according to Zuo *et al.* (5). Furthermore, endothelial cells can release proinflammatory cytokines, like tumor necrosis factor-alpha (TNF- $\alpha$ ), interleukin-1 (IL-1), and interleukin-6 (IL-6), which in turn increase PAI-1, as well as TF expression in the endothelial layer (6).

The use of cardiovascular medications like ACEIs and ARBs in cases of COVID-19 is controversial whether they have a therapeutic effect or the exact opposite. Some early studies suggested that renin-angiotensin-system (RAS) inhibitors might increase the risk of severe COVID-19 infection. This was based on the observation that the virus uses the ACE2 receptor to enter cells, and RAS inhibitors can increase the expression of ACE2. Baral's meta-analysis found no evidence to support the advice of medical societies that using ACEIs, or ARBs increased the risk of multivariable-adjusted mortality and serious adverse events in COVID-19 patients who also had hypertension or numerous comorbidities (7). The latter occurs because not all ARBs or ACEIs consistently affect the expression of ACE2 (8). On the other hand, the prevention of cytokine storms and increased ACE2 is one of the effective approaches to prevent severe symptoms of COVID-19 (9). Perindopril, an ACEI, and losartan, an ARB, have demonstrated to promote ACE2 expression (10). However, no studies have been conducted on the effects of these medications on coagulation and platelet factors. Therefore, it is necessary to determine the role of these drugs on coagulation and platelets in adipocyte exposed to SARS-CoV-2.

### MATERIALS AND METHODS

*Primary culture of adipocyte*

<sup>13</sup> This research is an experimental *in vitro* study, with a post-test only Control group design, conducted in the biosafety level 2 (BSL 2) laboratory at the Department of Physiology of the Faculty of Medicine, Brawijaya University in Malang City, Indonesia.

This study used adipose tissue from visceral abdomen obtained from an obese male donor of around 30–50 years of age. The adipose tissue was isolated enzymatically, according to Carswell *et al.* (11). The adipocytes were isolated using collagenase type 1 and grown in a media of alpha-minimum essential medium (a-mem) with the addition of supplements like penicillin, streptomycin, and platelet rich plasma (PRP). Incubation was performed at 37°C in a 5% CO<sub>2</sub> environment.

#### <sup>46</sup> SARS-CoV-2 subunit S1 spike protein exposure to adipocyte

This study used the SARS-CoV-2 S1 spike protein 10 nm subunit, based on previous studies that tested the effect of SARS-CoV-2 protein on the stimulation of human immune cells (12). 10 nm subunit of SARS-CoV-2 S1 spike protein was added into 100 µL of cells suspension per well and incubated overnight.

#### Administration of losartan and perindopril

<sup>10</sup> Adipocyte cells are divided into 5 groups. The first group is a Negative Control group. The second group is a group which exposes to SARS-CoV-2 S1 spike protein as a Positive Control group. The third group is the Losartan group which given 0.7 µM of losartan (13). The fourth group is Perindopril group which given 0.5 µM of perindopril (14). The fifth group is given 100 µg/mL of ACE2 recombinant (15).

#### <sup>11</sup> Angiotensin converting enzyme 2-spike protein binding assay

<sup>21</sup> A binding test kit was used to gauge how losartan, perindopril and ACE2 recombinant affected the interaction between the SARS-CoV-2 spike protein and ACE2. Reagents were made by combining 100 mL of 100 × ACE2 protein concentrate with 1.25 µL of losartan, perindopril or ACE2 recombinant. The relevant SARS-CoV-2 spike protein-coated wells were filled with each test substance, and they were then incubated at 4°C overnight. Each well was washed four times with 300 mL of wash buffer before being incubated with 100 mL of detection antibody for an hour at room temperature. Following more washing, 50 mL of stop solution, 100 mL of TMB substrate, and 100 mL of HRP-conjugated anti-IgG were progressively added to each well. At 450 nm, the solution absorbance was immediately measured.

#### Measurement of tissue factor and plasminogen activator inhibitor-1

ACE2 levels was carried out 48 h after administration of perindopril and losartan (13, 14). The sample was then given a human tissue factor antibody (BTLAB/E1195Hu) from the ELISA kit (BT LAB, Shanghai, China) and then incubated for 48 h. The results were evaluated with an ELISA Reader at λ 450 nm. The same procedure was followed during the PAI-1 examination, but a human plasminogen activator inhibitor antibody (BTLAB/E1159Hu) was used instead. Each group was run in triplicate to maintain data validity.

#### Statistical analysis

<sup>38</sup> Data obtained and analyzed using SPSS 23.0. One-way ANOVA was used to compare the groups. The difference was considered to be significant if  $p < 0.05$ .

## RESULTS

<sup>41</sup> We assessed the impact of SARS-CoV-2 spike protein on adipocyte cell ACE2 level *in vitro*. SARS-CoV-2 S1 spike protein exposure was successfully carried out on adipocyte culture after 48 hours of incubation. The results showed that SARS-CoV-2 S1 spike protein exposure could increase ACE2 levels (80.31) compared to baseline (14.48) ( $p < 0.001$ ). We used perindopril and losartan to define the role of ACEIs/ARBs on ACE2 levels in infected adipocyte cells. Different results were shown by the Perindopril and Losartan groups. Adipocytes with losartan admission showed a higher ACE2 level (150.98) than the Control groups ( $p < 0.001$ ). In contrast, the Perindopril group demonstrated significantly lower ACE2 levels (47.54) than the Control groups ( $p < 0.001$ ). If we compare the Perindopril and Losartan groups, both have significant differences ( $p < 0.001$ ). To determine the binding of the SARS-CoV-2 spike protein to the ACE2 receptor, we used the recombinant ACE2 protein as a competitor. The results showed that the ACE2 protein recombinant had lower ACE2 levels than the Positive Control ( $p < 0.001$ ) and was not significantly different from the baseline ( $p = 0.516$ ). Next, we assessed the differences in ACE2 levels between Perindopril and Losartan groups compared to the recombinant ACE2 protein. The ACE2 protein recombinant differed significantly from the Perindopril or Losartan group ( $p < 0.001$ ). The mean of each variable is shown in Table 1.

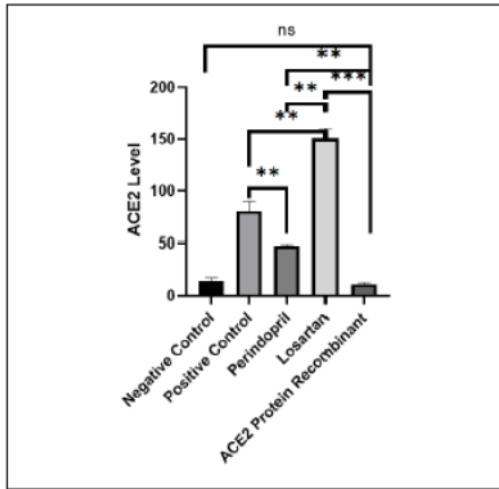


Fig. 1. Effect of administration of perindopril, losartan and ACE2 protein recombinant in ACE2 levels.

Table 1. Mean and standard deviation of angiotensin-converting enzyme 2 (ACE2), tissue factor (TF), and plasminogen activator inhibitor-1 (PAI-1) levels in each group.

Groups	Replication (n)	ACE2 (ng/mL)		Tissue factor (ng/mL)		PAI-1 (ng/mL)	
		Mean $\pm$ SD	Min-Max	Mean $\pm$ SD	Min-Max	Mean $\pm$ SD	Min-Max
Negative control (baseline)	3	14.48 $\pm$ 2.756	11.73–17.24	2.993 $\pm$ 0.641	2.43–3.69	1.956 $\pm$ 0.076	1.88–2.03
Positive control	3	80.312 $\pm$ 9.312	71.00–89.62	6.857 $\pm$ 0.228	6.60–7.02	4.865 $\pm$ 0.115	4.75–4.98
Perindopril	3	47.54 $\pm$ 1.36	46.05–48.71	4.843 $\pm$ 0.396	4.43–5.22	3.484 $\pm$ 0.252	3.22–3.72
Losartan	3	150.98 $\pm$ 9.47	141.37–1160.32	5.624 $\pm$ 0.606	5.01–6.22	2.633 $\pm$ 0.269	2.40–2.93
ACE2 protein recombinant	3	11.107 $\pm$ 1.577	10.13–12.93	4.121 $\pm$ 0.437	3.76–4.61	3.375 $\pm$ 0.443	3.10–3.89

The study showed that SARS-CoV-2 S1 protein spike exposure can also increase TF levels (6.857) compared to baselines (2.993) ( $p < 0.001$ ). The Perindopril group was able to reduce the TF value (4.843) significantly compared to the control ( $p = 0.005$ ). Conversely, losartan was able to decrease the value of TF (5.624) compared to the Positive Control, but the difference was not particularly significant ( $p = 0.111$ ). There was no discernible difference in TF values between the Perindopril and Losartan groups ( $p = 0.772$ ). To determine the impact of binding between the SARS-CoV-2 spike protein and the ACE2 receptor on pro-coagulation factors, we used the recombinant protein ACE2 that competes for binding to the ACE2 receptor. The results showed that the ACE2 protein recombinant had lower TF levels (4.121) than the positive control ( $p < 0.001$ ). Next, we assessed the difference in the ability of the Perindopril and Losartan groups to the recombinant protein ACE2 in reducing TF levels. The results showed that the Perindopril group had TF levels that were not much different from the recombinant ACE2 protein group ( $p = 0.09$ ). In contrast, the Losartan group had higher TF levels than the recombinant ACE2 protein group with a significant difference ( $p = 0.004$ ).

Table 2. Summary of p-values of ACE-2, TF, PAI-1 in all groups.

Comparison Test	ACE-2	TF	PAI-1
	p value	p value	p value
Negative Control vs. Positive Control	<0.0001	<0.0001	<0.0001
Negative Control vs. Perindopril	0.0005	0.0061	0.0003
Negative Control vs. Losartan	<0.0001	0.0004	0.0654
Negative Control vs. ACE2 Protein Recombinant	0.9578	0.0983	0.0005
Positive Control vs. Perindopril	0.0005	0.0033	0.0006
Positive Control vs. Losartan	<0.0001	0.065	<0.0001
Positive Control vs. ACE2 Protein Recombinant	<0.0001	0.0003	0.0003
Perindopril vs. Losartan	<0.0001	0.345	0.019
Perindopril vs. ACE2 Protein Recombinant	0.0002	0.4153	0.9864
Losartan vs. ACE2 Protein Recombinant	<0.0001	0.0232	0.0406

Other results show that SARS-CoV-2 S1 protein spike exposure can increase PAI-1 levels (4.865) compared to baseline (1.956) ( $p < 0.001$ ). The Perindopril-administered groups were able to

lower PAI-1 levels (3.484) compared to the Control group ( $p=0.001$ ), but the Losartan-administered groups did so more effectively (2.633) ( $p<0.001$ ). Compared to Perindopril group, the Losartan group was proven to significantly reduce PAI-1 levels ( $p=0.028$ ). Compared with the recombinant ACE2 protein group, the Perindopril group had PAI-1 levels that were not much different ( $P=0.624$ ). In contrast, the Losartan group had lower PAI-1 levels than the recombinant ACE protein, with a significant difference (0.006). The comparison of each group describes in Fig. 2.

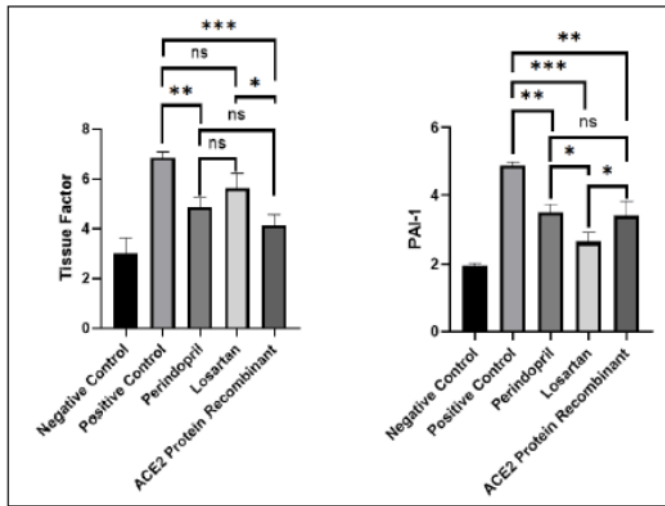


Fig. 2. Effect of administration of perindopril, losartan and ACE2 protein recombinant in TF and PAI-1 levels.

12

To prove the role of ACE2 on tissue factor and PAI-1 levels, in our study examines the correlation between ACE2, tissue factor and PAI-1 levels. The results show there is a strong significant correlation between ACE2 levels with tissue factor ( $p=0.01$ ), but the other results show that there is no correlation between ACE2 levels with PAI-1 ( $p=0.735$ ). The correlation of ACE2, TF, and PAI-1 described in Table 3.

Table 3. Pearson correlation between ACE2 levels to TF and PAI-1.

		Dependent variable	
		Tissue factor	PAI-1
ACE2 level	Pearson correlation	0.640	0.096
	Sig (2-tailed)	0.01*	0.735
	N	15	15

14

\*Correlation is significant at the 0,05 level (2-tailed) with strong correlation

## DISCUSSION

Our research showed that the adipocyte cells given the SARS-CoV-2 S1 protein spike have a significant increase in ACE2 levels compared to baseline. Patel *et al.* showed the same evidence in their research on ACE2 plasma activity in COVID-19 patients; ACE2 activity was proven to increase during SARS-CoV-2 exposure and to continue increasing afterwards (16). Increased ACE2 levels are related to an increase in shedding from infected cells and are associated with the downregulation of membrane bound ACE2 (17).

Perindopril seem to take on opposite roles in our study, previous studies found that the administration of a single dose of Lisinopril caused a significant increase in ACE2 compared to the positive control (18), but in our study the ACE2 expression is increase in Perindopril administration group but not as high as positive control. Another study of human alveolar cells showed a sharp increase in the expression of the ACE2 gene, 24 h after giving Captopril (19). While on Losartan there is a significant increase and higher than the positive control. The difference between the effects of perindopril and losartan in our research is allegedly related to the way each therapy modulates ACE2. Although both ACEIs and ARBs directly affect ACE2, they may have different impacts on ATII. ACEIs work by reducing circulating ATII, while ARBs increase free ATII levels in the circulation (20, 21). The three mechanisms by which ATII affects ATII type 1 receptors to reduce ACE2 regulation are as follows: 1) ATII decreases ACE2 expression by inducing ERK1/2 or p38 MAPK; 2) ATII causes ACE2 shedding from the cell surface by disintegrin and metalloprotease ADAM17; 3) ATII causes the internalization of ACE2 to enter the cell (22).

ACE2 plays an important role in preventing increased TF exposure and PAI-1 levels, thereby inhibiting an increase in extrinsic path activation and decreased fibrinolysis. Both are responsible for

the incidence of thrombotic complications in COVID-19 patients (23). TF activation causes a disruption of fibrin disposal, disseminated intravascular coagulation (DIC), consumption of fibrin, and a decreased platelet count (24). A prothrombotic condition is linked to the inhibition of the ACE2/AT1-7/MasR axis because ACE2 stimulates tissue plasminogen activator (tPA). The endothelium and smooth muscle cells produce and secrete PAI-1 in response to ATII via the AT1R (25). However, there was no appreciable difference between losartan and the positive control in terms of lowering TF levels. We presume that the functional distinctions between ACEIs and ARBs also affects TF regulation via the function of ATII (20, 21). Nevertheless, in our research, there was no significant difference in effect between the ACEI and the ARB in reducing TF levels.

Endothelial PAI-1 is produced by the molecules that cause endothelial cell damage, including TNF, TGF, ATII, and thrombin (26). Adipose tissue is the major source of circulating PAI-1 (27). This clarifies how obesity raises the risk of thromboembolism, hospitalization, and COVID-19-related death (28). Our results also showed that PAI-1 levels significantly increase in the positive control groups compared to baseline. The drugs perindopril and losartan were successful in significantly lowering PAI-1 levels. These findings indicate that ACEI/ARBs can help prevent thrombotic problems, particularly in COVID-19 patients. ACEI decreases the amount of PAI-1 through the suppression pathway of extracellular matrix (ECM) (29). While losartan managed to reduce PAI-1 levels more significantly, in Rosselli's study (30) it was also proven that losartan reduced PAI-1 better than other drugs in the ARB group (Telmisartan). This is due to the mechanism of action of the drug, it was demonstrated that both losartan and telmisartan produce a rightward shift of the AngII dose-response curve; however, the maximal response is unaffected by surmountable antagonists, such as losartan, whereas it is reduced by insurmountable antagonists, such as Telmisartan, leading to a nonparallel displacement of the AngII response curve.

Our study simultaneously responds to previous cohort research queries by examining the potential influence of ACE2 and ARB therapy on the occurrence of thrombotic events in COVID-19 patients (31). We looked at the difference between the effects of perindopril and losartan, finding that losartan is actually more effective at reducing PAI-1 than perindopril, with a significant difference. Our study is the first to compare an ACEI and ARB in adipocyte cells that have been exposed to the SARS-CoV-2 S1 protein spike. Some speculation exists regarding the relationship between ARBs and an increase in free ATII, which is considered capable of causing fibrinolytic instability and plaque rupture (32). Further research is needed to establish how far the role of ARBs can contribute to the potential prevention of thromboembolism complications.

ACEIs and ARBs have different pathways in modulating ACE2. Losartan and perindopril both have the ability to lower TF levels, but only Perindopril shows significant differences to the control. Additionally, perindopril and losartan were successful in significantly lowering PAI-1 levels when compared to positive controls, but losartan reduced PAI-1 levels more extensively compared to perindopril. This reduction in PAI owing to ACEI/ARBs may have an effect on the lowering of thrombotic complications, notably in COVID-19 infection.

6

**Acknowledgement:** This work was supported by the Ministry of Research, Technology, and Higher Education of Indonesia to I Gde Rurus Suryawan (279/UN3.15/PT/2021).

53

**Conflict of interests:** None declared.

## REFERENCES

1. World Health Organization. WHO Coronavirus Disease (COVID-19) Dashboard With Vaccination Data [Internet]. World Health Organization. 2021 [cited 2022 Apr 30]. p. 1-5. Available from: <https://covid19.who.int/>
2. Bompard F, Monnier H, Saab I, et al. Pulmonary embolism in patients with COVID-19 pneumonia. *Eur Respir J* 2020; 56: 2001365. doi: 10.1183/13993003.01365-2020
3. Criel M, Falter M, Jaeken J, et al. Venous thromboembolism in SARS-CoV-2 patients: Only a problem in ventilated ICU patients, or is there more to it? *Eur Respir J* 2020; 56: 2001201. doi: 10.1183/13993003.01201-2020
4. Al-Tamimi AO, Yusuf AM, Jayakumar MN, et al. SARS-CoV-2 infection induces soluble platelet activation markers and PAI-1 in the early moderate stage of COVID-19. *Int J Lab Hematol* 2022; 44: 712-721.
5. Zuo Y, Warnock M, Harbaugh A, et al. Plasma tissue plasminogen activator and plasminogen activator inhibitor-1 in hospitalized COVID-19 patients. *Sci Rep* 2021; 11: 1580. doi: 10.1038/s41598-020-80010-z
6. Senchenkova EY, Russell J, Kurmaeva E, Ostanin D, Granger DN. Role of T-lymphocytes in angiotensin II-mediated microvascular thrombosis. *Hypertension* 2011; 58: 959-965.
7. Baral R, Tsampasian V, Debski M, et al. Association between renin-angiotensin-aldosterone system inhibitors and clinical outcomes in patients with COVID-19: a systematic review and meta-analysis. *JAMA Netw Open* 2021; 4: e213594. doi: 10.1001/jamanetworkopen.2021.3594
8. Bian J, Li Z. Angiotensin-converting enzyme 2 (ACE2): SARS-CoV-2 receptor and RAS modulator. *Acta Pharm Sin B* 2021; 11: 1-12. doi: 10.1016/j.apsb.2020.10.006
9. Tang Y, Liu J, Zhang D, Xu Z, Ji J, Wen C. Cytokine storm in COVID-19: the current evidence and treatment strategies. *Front Immunol* 2020; 11: 1708. doi: 10.3389/FIMMU.2020.01708
10. Deshotels MR, Xia H, Sriramula S, Lazartigues E, Filipeanu CM. Angiotensin II mediates angiotensin converting enzyme type 2 internalization and degradation through an angiotensin II type I receptor-dependent mechanism. *Hypertension* 2014; 64: 1368-1375.
11. Carswell KA, Lee MJ, Fried SK. Culture of isolated human adipocytes and isolated adipose tissue. *Methods Mol Biol* 2012; 806: 203-214.
12. Dosch SF, Mahajan SD, Collins AR. SARS coronavirus spike protein-induced innate immune response occurs via activation of the NF- $\kappa$ B pathway in human monocyte macrophages *in vitro*. *Virus Res* 2009; 142: 19-27.
13. Ferrario CM, Jessup J, Chappell MC, et al. Effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockers on cardiac angiotensin-converting enzyme 2. *Circulation* 2005; 111: 2605-2610.
14. Huang ML, Li X, Meng Y, et al. Upregulation of angiotensin-converting enzyme (ACE) 2 in hepatic fibrosis by ACE inhibitors. *Clin Exp Pharmacol Physiol* 2010; 37: e1-e6. doi: 10.1111/j.1440-1681.2009.05302.x

15. Monteil V, Kwon H, Prado P, *et al.* Inhibition of SARS-CoV-2 infections in engineered human tissues using clinical-grade soluble human ACE2. *Cell* 2020; 181: 905-913.e7.
16. Patel S, Juno J, Lee WS, *et al.* Plasma Ace2 activity is increased in patients recovered from Sars-Cov-2 infection: implications for the prolonged consequences of Covid-19. *J Hypertens* 2021; 39:e394. doi: 10.1097/01.HJH.0000749140.12677.66
17. Patel SK, Juno JA, Lee WS, *et al.* Plasma ACE2 activity is persistently elevated following SARS-CoV-2 infection: implications for COVID-19 pathogenesis and consequences. *Eur Respir J* 2021; 57: 2003730. doi: 10.1183/13993003.03730-2020.2003730
18. Brooks SD, Smith RL, Moreira AS, Ackerman HC. Oral lisinopril raises tissue levels of ACE2, the SARS-CoV-2 receptor, in healthy male and female mice. *Front Pharmacol* 2022; 13: 798349. doi: 10.3389/fphar.2022.798349
19. Wu C, Ye D, Mullick AE, *et al.* Effects of renin-angiotensin inhibition on ACE2 (angiotensin-converting enzyme 2) and TMPRSS2 (transmembrane protease serine 2) expression: insights into COVID-19. *Hypertension* 2020; 181: 29-30.
20. Aronson JK, Ferner RE. Drugs and the renin-angiotensin system in covid-19. *BMJ* 2020; 369: m1313. doi: 10.1136/bmj.m1313
21. Vaduganathan M, Vardeny O, Michel T, McMurray JJ, Pfeffer MA, Solomon SD. Renin-angiotensin-aldosterone system inhibitors in patients with Covid-19. *N Engl J Med* 2020; 382: 1653-1659.
22. Kriszta G, Kriszta Z, Vancsa S, *et al.* Effects of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers on angiotensin-converting enzyme 2 levels: a comprehensive analysis based on animal studies. *Front Pharmacol* 2021; 12: 619524. doi: 10.3389/fphar.2021.619524
23. Gue YX, Gorog DA. Reduction in ACE2 may mediate the prothrombotic phenotype in COVID-19. *Eur Heart J* 2020; 41: 3198-3199.
24. Acanfora D, Ciccone MM, Scicchitano P, Acanfora C, Casucci G. Sacubitril/valsartan in COVID-19 patients: the need for trials. *Eur Heart J Cardiovasc Pharmacother* 2020; 6: 253-254.
25. Bednarsz K, Borek A, Drzymala F, Rachwal K, Gabryel B. Pharmacological protection of vascular endothelium in acute COVID-19. *J Physiol Pharmacol* 2022; 73: 167-177.
26. Han M, Pandey D. ZMPSTE24 regulates SARS-CoV-2 spike protein-enhanced expression of endothelial PAI-1. *Am J Respir Cell Mol Biol* 2021; 65: 300-308.
27. Samad F, Pandey M, Loskutoff DJ. Regulation of tissue factor gene expression in obesity. *Blood* 2001; 98: 3353-3358.
28. Hendren NS, de Lemos JA, Ayers C, *et al.* Association of body mass index and age with morbidity and mortality in patients hospitalized with COVID-19. *Circulation* 2021; 143: 135-144.
29. Shinosaki T, Miyai I, Nomura Y, Kobayashi T, Sunagawa N, Kurihara H. Mechanisms underlying the ameliorative property of lisinopril in progressive mesangiolipid nephritis. *Nephron* 2002; 91: 719-729.
30. Rosselli MS, Burgueno AL, Carabelli J, Schuman M, Pirola CJ, Sookoian S. Losartan reduces liver expression of plasminogen activator inhibitor-1 (PAI-1) in a high fat-induced rat nonalcoholic fatty liver disease model. *Atherosclerosis* 2009; 206: 119-126.
31. Lupi L, Adamo M, Inciardi RM, Metra M. ACE2 down-regulation may contribute to the increased thrombotic risk in COVID-19. *Eur Heart J* 2020; 41: 3200-3200.
32. Dezsi CA, Szentés V. Effects of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers on prothrombotic processes and myocardial infarction risk. *Am J Cardiovasc Drugs* 2016; 16: 399-406.

Received: February 5, 2023

Accepted: June 30, 2023

Author's address: Dr. I Gde Rurus Suryawan, Cardiology and Vascular Medicine Department, Medical Faculty of Airlangga University - Dr. Soetomo General Hospital, Surabaya, Indonesia. e-mail: igde.rurus.s@fk.unair.ac.id

## 19. Perindopril and Losartan

---

### ORIGINALITY REPORT

---

17%

SIMILARITY INDEX

11%

INTERNET SOURCES

15%

PUBLICATIONS

2%

STUDENT PAPERS

---

### PRIMARY SOURCES

---

1 [academic.oup.com](https://academic.oup.com) Internet Source 1%

---

2 [scholar.unair.ac.id](https://scholar.unair.ac.id) Internet Source 1%

---

3 [www.msjonline.org](http://www.msjonline.org) Internet Source 1%

---

4 Farahnaz Motamedi-Sedeh, Akbar Khorasani, Mohsen Lotfi, Seyed Morteza Moosavi, Arash Arbabi, Seyed Maede Hosseini. "Immune Responses Following Administration of Whole Gamma Irradiated SARS-CoV-2 Vaccine Stabilized With Disaccharide Trehalose on Syrian Hamster Model", Research Square Platform LLC, 2023  
Publication <1%

---

5 [cardiab.biomedcentral.com](https://cardiab.biomedcentral.com) Internet Source <1%

---

6 [repository.unp.ac.id](https://repository.unp.ac.id) Internet Source <1%

---

[www.minervamedica.it](http://www.minervamedica.it)



7

Internet Source

&lt;1 %

8

Saeideh Zareei, Reza Homayounfar, Mohammad Mehdi Naghizadeh, Elham Ehrampoush, Zohre Amiri, Maryam Rahimi, Lida Tahamtani. "Dietary Pattern in Patients with Preeclampsia in Fasa, Iran", Shiraz E-Medical Journal, 2019

Publication

&lt;1 %

9

[randr19.nist.gov](http://randr19.nist.gov)

Internet Source

&lt;1 %

10

[repository.ub.ac.id](http://repository.ub.ac.id)

Internet Source

&lt;1 %

11

Haoran Zhang, Panjing Lv, Jingrui Jiang, Yahui Liu, Ruixi Yan, Sainan Shu, Bing Hu, Han Xiao, Kun Cai, Shuai Yuan, Yan Li. "Advances in developing ACE2 derivatives against SARS-CoV-2", The Lancet Microbe, 2023

Publication

&lt;1 %

12

Katrin Schäfer, Stavros Konstantinides. "Adipokines and thrombosis", Clinical and Experimental Pharmacology and Physiology, 2011

Publication

&lt;1 %

13

[phcogj.com](http://phcogj.com)

Internet Source

&lt;1 %

14

[uir.unisa.ac.za](http://uir.unisa.ac.za)

Internet Source

&lt;1 %

15

Agnieszka M. Murakami, Katsuhiko Nagatomo, Ichiro Miyoshi, Shirou Itagaki, Yasutaka Niwa, Manabu Murakami. "A novel binding site between the voltage-dependent calcium channel CaV1.2 subunit and CaVβ2 subunit discovered using a new analysis method for protein–protein interactions", *Scientific Reports*, 2023

Publication

&lt;1 %

16

Fabio Angeli, Martina Zappa, Gianpaolo Reboldi, Monica Trapasso, Claudio Cavallini, Antonio Spanevello, Paolo Verdecchia. "The pivotal link between ACE2 deficiency and SARS-CoV-2 infection: One year later", *European Journal of Internal Medicine*, 2021

Publication

&lt;1 %

17

Mei Peng, Jia He, Ying Xue, Xue Yang, Shao Liu, Zhicheng Gong. "Role of Hypertension on the Severity of COVID-19: A Review", *Journal of Cardiovascular Pharmacology*, 2021

Publication

&lt;1 %

18

Devasahayam Arokia Balaya Rex, Sumaithangi Thattai Arun Kumar, Prashant Kumar Modi, Thottethodi Subrahmanya Keshava Prasad. "Broadening COVID-19 Interventions to Drug Innovation: Neprilysin

&lt;1 %

Pathway as a Friend, Foe, or Promising  
Molecular Target?", OMICS: A Journal of  
Integrative Biology, 2021

Publication

19

Submitted to University of Queensland

Student Paper

<1 %

20

globalhealthmedicine.com

Internet Source

<1 %

21

wjgnet.com

Internet Source

<1 %

22

En-tong Yi, Rui-xia Liu, Yan Wen, Cheng-hong  
Yin. "Telmisartan attenuates hepatic fibrosis  
in bile duct-ligated rats", Acta Pharmacologica  
Sinica, 2012

Publication

<1 %

23

Ibrahim Al-Hashmi, John Decoteau, Hans-  
Jurgen Gruss, Maria Zielenska et al.

"Establishment of a Cytokine-Producing  
Anaplastic Large-Cell Lymphoma Cell Line  
Containing the t(2;5) Translocation: Potential  
Role of Cytokines in Clinical Manifestations",  
Leukemia & Lymphoma, 2009

Publication

<1 %

24

Ismael Chehaibou, Jean-Pierre Hubschman,  
Sundeep Kasi, Daniel Su et al. "Spontaneous  
Conversion of Lamellar Macular Holes to Full-  
Thickness Macular Holes: Clinical Features

<1 %

and Surgical Outcomes", Ophthalmology  
Retina, 2021

Publication

---

25

Niki Lee, Julie Wang, Rowena Brook, Paul Monagle, Geoffrey Donnan, Harshal Nandurkar, Prahlad Ho, Hui Yin Lim. " The evaluation of overall hemostatic potential assay in patients with -19 infection ", International Journal of Laboratory Hematology, 2022

Publication

---

<1 %

26

S.C.L Koh, V Dramusic, S Shan Ratnam. "The effects of long-term hormone-replacement therapy on coagulation, fibrinolysis and inhibitors in postmenopausal women", International Journal of Gynecology & Obstetrics, 1998

Publication

---

<1 %

27

Tom W. van de Berg, Mark M. G. Mulder, Teba Alnima, Magdolna Nagy et al. "Serial thrombin generation and exploration of alternative anticoagulants in critically ill COVID-19 patients: Observations from Maastricht Intensive Care COVID Cohort", Frontiers in Cardiovascular Medicine, 2022

Publication

---

<1 %

28

[pubs.asahq.org](https://pubs.asahq.org)

Internet Source

---

<1 %

29

[www.karger.com](http://www.karger.com)

Internet Source

&lt;1 %

30

Anamika Gupta, Rizwan Qaisar, Rabih Halwani, Meganathan Kannan, Firdos Ahmad. "TFPI and FXIII negatively and S100A8/A9 and Cystatin C positively correlate with D-dimer in COVID-19", *Experimental Biology and Medicine*, 2022

Publication

&lt;1 %

31

Ismail Sami Mahmoud, Yazun Bashir Jarrar, Walhan Alshaer, Said Ismail. "SARS-CoV-2 entry in host cells-multiple targets for treatment and prevention", *Biochimie*, 2020

Publication

&lt;1 %

32

Miklós Fagyas, Zsolt Fejes, Renáta Sütő, Zsuzsanna Nagy et al. "Circulating ACE2 activity predicts mortality and disease severity in hospitalized COVID-19 patients", *International Journal of Infectious Diseases*, 2021

Publication

&lt;1 %

33

[aging-us.com](http://aging-us.com)

Internet Source

&lt;1 %

34

[indjaerospacemed.com](http://indjaerospacemed.com)

Internet Source

&lt;1 %

35

[pea.lib.pt.e.hu](http://pea.lib.pt.e.hu)

Internet Source

&lt;1 %

36	<a href="http://vitamindwiki.com">vitamindwiki.com</a> Internet Source	<1 %
37	<a href="http://www.bmj.com">www.bmj.com</a> Internet Source	<1 %
38	<a href="http://www.hindawi.com">www.hindawi.com</a> Internet Source	<1 %
39	<a href="http://www.jpp.krakow.pl">www.jpp.krakow.pl</a> Internet Source	<1 %
40	<a href="http://www.medrxiv.org">www.medrxiv.org</a> Internet Source	<1 %
41	<a href="http://www.science.org">www.science.org</a> Internet Source	<1 %
42	Gael B. Morrow, Nicola J. Mutch. "Past, Present, and Future Perspectives of Plasminogen Activator Inhibitor 1 (PAI-1)", <i>Seminars in Thrombosis and Hemostasis</i> , 2022 Publication	<1 %
43	Marieta P Theodorakopoulou, Maria-Eleni Alexandrou, Afroditi K Boutou, Charles J Ferro, Alberto Ortiz, Pantelis Sarafidis. "Renin–angiotensin system blockers during the COVID-19 pandemic: an update for patients with hypertension and chronic kidney disease", <i>Clinical Kidney Journal</i> , 2021 Publication	<1 %

44

Metodi V. Stankov, Markus Hoffmann, Rodrigo Gutierrez Jauregui, Anne Cossmann et al. "Humoral and cellular immune responses following BNT162b2 XBB.1.5 vaccination", Cold Spring Harbor Laboratory, 2023

Publication

&lt;1 %

45

Sonia Tamanna, Eugenie R. Lumbers, Saije K. Morosin, Sarah J. Delforce, Kirsty G. Pringle. "ACE2: a key modulator of the renin-angiotensin system and pregnancy", American Journal of Physiology-Regulatory, Integrative and Comparative Physiology, 2021

Publication

&lt;1 %

46

Bonnie Ky, Douglas L. Mann. "COVID-19 Clinical Trials: A Primer for the Cardiovascular and Cardio-Oncology Communities", JACC: Basic to Translational Science, 2020

Publication

&lt;1 %

47

Chawanun Charnsil. "Comparing stigma toward depression in physicians and the general population and its impact on seeking mental health treatment: a cross-sectional study", Research Square Platform LLC, 2023

Publication

&lt;1 %

48

Cristian-Mihail Niculae, Adriana Hristea, Ruxandra Moroti. "Mechanisms of COVID-19

&lt;1 %

## Associated Pulmonary Thrombosis: A Narrative Review", Biomedicines, 2023

Publication

---

49

Deepak Atri, Hasan K. Siddiqi, Joshua Lang, Victor Nauffal, David A. Morrow, Erin A. Bohula. "COVID-19 for the Cardiologist: A Current Review of the Virology, Clinical Epidemiology, Cardiac and Other Clinical Manifestations and Potential Therapeutic Strategies", JACC: Basic to Translational Science, 2020

Publication

---

<1 %

50

Jean-Philippe Desilles, Mialitiana Solo Nomenjanahary, Arturo Consoli, Véronique Ollivier et al. "Impact of COVID-19 on thrombus composition and response to thrombolysis: Insights from a monocentric cohort population of COVID-19 patients with acute ischemic stroke", Journal of Thrombosis and Haemostasis, 2022

Publication

---

<1 %

51

Jordan Loader, Frances C. Taylor, Erik Lampa, Johan Sundström. "Renin-Angiotensin Aldosterone System Inhibitors and COVID-19: A Systematic Review and Meta-Analysis Revealing Critical Bias Across a Body of Observational Research", Journal of the American Heart Association, 2022

Publication

---

<1 %



52

R. L. KLEIN. "Glycation Does Not Alter LDL-Induced Secretion of Tissue Plasminogen Activator and Plasminogen Activator Inhibitor-1 from Human Aortic Endothelial Cells", Annals of the New York Academy of Sciences, 06/01/2005

Publication

<1 %

53

[hdl.handle.net](http://hdl.handle.net)

Internet Source

<1 %

Exclude quotes Off

Exclude matches Off

Exclude bibliography On

# 19. Perindopril and Losartan

---

## GRADEMARK REPORT

---

FINAL GRADE

GENERAL COMMENTS

**/100**

---

PAGE 1

---

PAGE 2

---

PAGE 3

---

PAGE 4

---

PAGE 5

---

PAGE 6

---