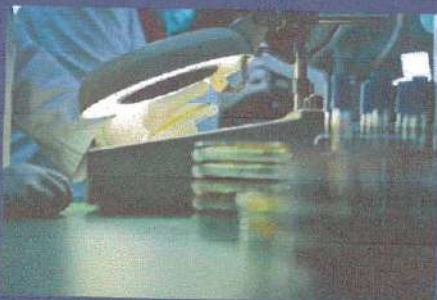


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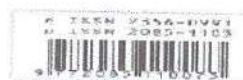
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# Indonesian Journal of Tropical and Infectious Disease

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## Review Article

### COVID-19 and Endothelial Dysfunction: Biomarkers and Potential Drug Mechanisms

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#### ABSTRACT

Since the first report of pneumonia outbreak in Wuhan by the end of 2019, Coronavirus Disease 2019 (COVID-19) has become a global pandemic; causing millions of deaths globally and affecting the rest of worldwide population. The disease is caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), which enters hosts by inhabiting Angiotensin-Converting Enzyme-2 (ACE-2) receptors expressed in the endothelium layer of not only the respiratory tracts, but also various organs in the body. COVID-19 has been reported to trigger multiple cardiovascular manifestations. Since endothelial dysfunction plays an important role in cardiovascular events and the endothelium is heavily involved in COVID-19 pathophysiology, it is important to investigate their associations and previously established drug potencies to improve endothelial functions as possible treatment options for COVID-19. In this review, we summarize endothelial dysfunction biomarkers involved in COVID-19 and drugs that have shown potential endothelial protective properties to better understand the incidence of endothelial dysfunction in COVID-19 and its future treatment. We searched in PubMed, Wiley Online Library, EBSCO, ScienceDirect databases for literatures containing following keywords: "Endothelial dysfunction", "COVID-19", and "biomarkers". Eligible publications were then assessed and studied to comprise our literature review. A total of 96 studies matched our criteria and provided scientific evidences for our review. Materials were then compiled into a review summarizing endothelial biomarkers involved in COVID-19 and potentially repurposed drugs targeting endothelium for COVID-19. Various endothelial dysfunction biomarkers were found to be elevated in COVID-19 and is found to be related to its severity, such as adhesion molecules, selectins, PAI-1, and von Willebrand Factors. Multiple drugs targeting the endothelium are also potential and some are under investigation for COVID-19.

**Keywords:** COVID-19, endothelial dysfunction, SARS-COV-2, biomarkers

#### ABSTRAK

Sejak pertama kali pelaporannya sebagai wabah pneumonia di Wuhan pada akhir 2019, Corona Virus disease 2019 (COVID-19) telah menjadi pandemi global yang menyebabkan jutaan kematian dan memengaruhi populasi di seluruh dunia. Penyakit ini disebabkan oleh SARS-CoV-2 yang menginfeksi sel inang dan berikatan dengan reseptor angiotensin-converting enzyme-2 (ACE-2) yang diekspresikan lapisan endotel saluran pernapasan serta berbagai organ lain dalam tubuh. COVID-19 telah dilaporkan dapat menimbulkan berbagai manifestasi gangguan kardiovaskular. Mengingat peran penting disfungsi endotel yang berperan dalam kejadian kardiovaskular dan patofisiologi COVID-19, maka penting menyelidiki hubungan di antaranya. Selain itu, perlu dilakukan telaah mengenai potensi obat yang sebelumnya telah terbukti memperbaiki fungsi endotel sebagai pilihan terapi yang digunakan untuk COVID-19. Pada studi ini, kami memaparkan beberapa biomarker disfungsi endotel yang terlibat pada COVID-19 dan obat-obatan yang melindungi endotel sebagai terapi potensial COVID-19 di masa mendatang. Kami melakukan pencarian di database PubMed, Perpustakaan Online Wiley, EBSCO, dan ScienceDirect untuk literatur yang berisi kata kunci berikut: "Disfungsi endotel", "COVID-19", dan "biomarker". Publikasi yang memenuhi syarat kemudian dinilai dan ditelaah untuk menyusun tinjauan pustaka. Sebanyak 96 publikasi memenuhi kriteria dan memberikan

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bukti ilmiah untuk tinjauan pustaka ini. Materi kemudian disusun menjadi ulasan yang merangkum biomarker-biomarker endotel yang terlibat dalam COVID-19 dan obat-obatan dengan target endotel yang potensial. Berbagai biomarker disfungsi endotel ditemukan meningkat pada COVID-19 dan terkait dengan tingkat keparahannya, seperti molekul adhesi, selektin, PAI-1, dan Faktor von Willebrand. Beberapa obat yang menargetkan endotel juga ditemukan memiliki potensi dengan beberapa tengah diinvestigasi lebih lanjut sebagai terapi COVID-19.

**Kata kunci:** COVID-19, disfungsi endotel, SARS-CoV-2, biomarka

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## INTRODUCTION

In December 2019, a novel corona virus was isolated from the respiratory tract epithelial layer of a patient with pneumonia of unknown cause in Wuhan, China. By November 2020, the Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2), and its consequential disease, Coronavirus Disease 2019 (COVID-19), has now infected more than 46 millions of people all over the world and caused more than 1.2 million global death.<sup>1</sup>

Beside instigating substantial pulmonary disturbances such as pneumonia and acute respiratory distress syndromes, COVID-19 is known to trigger extrapulmonary responses, including cardiovascular manifestations. Several reported cardiovascular manifestations of COVID-19 include myocardial ischemia, arrhythmia, and even cardiogenic shock.<sup>1,2</sup>

Endothelial dysfunction is a significant contributor of various cardiovascular diseases mechanism. Endothelial cells play a major role in maintaining blood tissue non-thrombogenicity, regulating thrombosis, thrombolysis, thrombocyte adherence, vascular tone, and blood flow.<sup>1</sup> Any disturbance of endothelial function may trigger a progression of cardiovascular problems.<sup>3</sup>

SARS-CoV-2 exploits Angiotensin-Converting-Enzyme-2 (ACE-2) as a receptor to attack human cells. ACE-2, a main target component in various cardiovascular diseases mechanism and drugs, is widely expressed in both respiratory endothelial layers and vascular endothelial layers. Therefore, it is important to learn of the endothelial involvement in COVID-19 related cardiovascular function alterations as well as the changes of biomarkers it comprises.<sup>1,2</sup>

## DISCUSSION

### SARS-CoV-2 related endothelial changes

The innermost part of the vascular system is comprised of a single layer of endothelial cells called endothelium. A healthy endothelium maintains blood fluidity through platelet reactivity regulation, coagulation, and smooth thrombolysis by synthesizing and responding to vasoactive molecules accordingly.<sup>2</sup> The endothelium, alongside its primary immunoregulatory properties, also plays an important role in maintaining dynamic interactions between pro-coagulant and fibrinolytic factors within the vascular system. In its inactive state, the endothelium acts as a barrier that separates pro-thrombotic subendothelial layers and procoagulant factors carried within the circulation.<sup>3</sup>

SARS-CoV-2 directly affects the endothelial cells due to the high expression of ACE-2 receptors and Transmembrane Protease, Serine 2 (TMPRSS2) enzyme. After being bound by SARS-CoV-2, ACE-2 receptors are internalized such that the diminishing number of ACE-2 in endothelial cells promotes inflammation and thrombosis, triggered by subsequent hyperactivity of local Angiotensin-II (Ang-II). The decrease of ACE-2 receptors also reduces a number of conversions it normally mediates, including Angiotensin 1-7 from Ang-II, which acts as a vasoactive ligand of the MAS receptor. This causes reduction of MAS receptor activation and induction of pro-inflammatory phenotypes through the increase of type-1 Angiotensin receptor (AT<sub>1</sub>R) activation. Furthermore, the decrease of ACE-2 receptor prevents the degradation of des-Arg-9-



Bradykinin (DABK) into inactive peptides, which subsequently raises prothrombotic signals through bradykinin receptors (BKR) activation.<sup>4,5</sup>

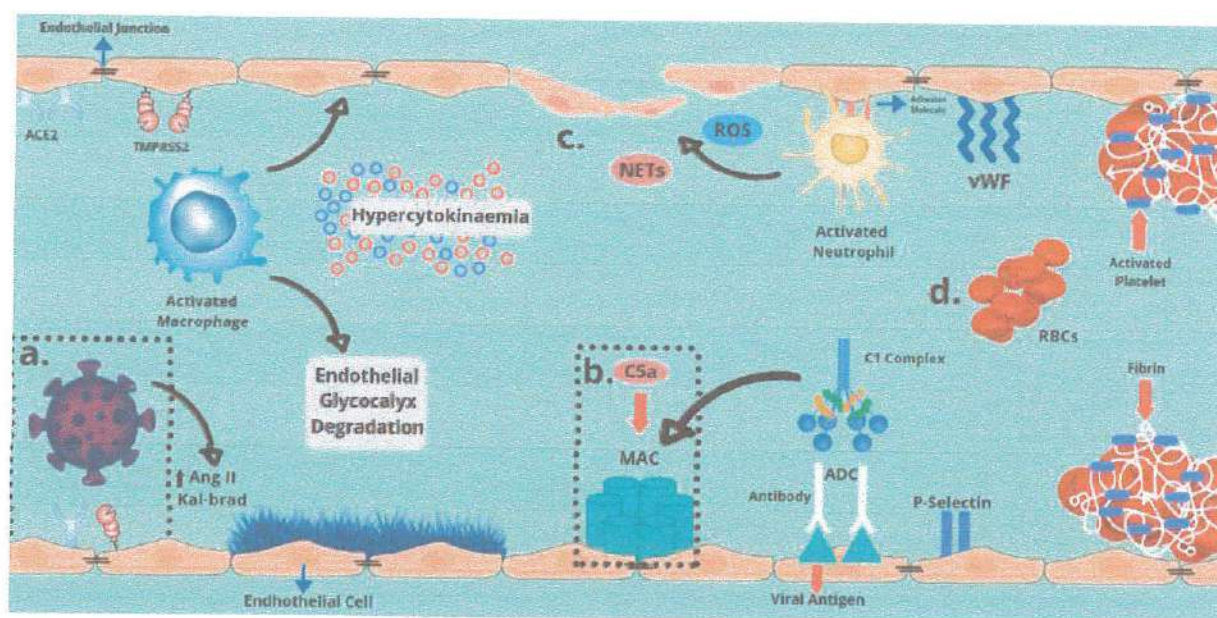
Endothelial activation and subsequent dysfunction is marked by imbalance of endothelium-released vasomotor factors, expressions of inflammatory cytokines and chemokines, expression and secretion of selectins and adhesive molecules as well as modulation of local thrombotic pathway.<sup>6</sup> The release of cytokines and pro-inflammatory chemokines by activated macrophages augments the vicious circle of vascular integrity, coagulation, and thrombosis disturbances through reduction of endothelial glycocalyx, activation of coagulation system, and dampening of anticoagulation mechanism. Endothelial cell adhesive phenotypes induced by pro-inflammatory cytokines and chemokines promote neutrophil infiltration, producing large quantity of histotoxic components such as reactive oxygen species (ROS) and Neutrophil Extracellular Traps (NETs).

Endothelial activation is the transition of static phenotype to a specific phenotype involving responses to host immunity.<sup>5</sup> Endothelial cells activation causes an increase of inflammatory cytokines and adhesion molecules, triggering releases of leukocyte, adhesion, and migration

to subendothelial chambers, constituting fundamental process of atherosclerotic lesion initiation, progress, and destabilization.<sup>5</sup> Activated endothelial cells begin coagulation process by expressing P-selectin, von Willebrand factor (vWf), and fibrinogen, causing massive platelet binding, formation of fibrin and clotting of Red Blood Cells (RBC), which finally results in systemic thrombosis and Disseminated Intravascular Coagulation (DIC).<sup>4</sup>

### Measurable biomarkers of endothelial activation and dysfunction

Activated endothelial cells express increased levels of E-selectin, P-selectin, Interleukin Adhesion Molecule 1 (ICAM-1), and Vascular Cell Adhesion Molecule 1 (VCAM-1). Upregulations of E-selectins, ICAM-1, and VCAM-1 are mediated at transcription level. E-selectin induces the rolling of circulatory leukocytes. VCAM-1 and ICAM-1 induces strong adhesion by binding Very Late Antigen 4 (VLA4) and Leukocyte Function Antigen-1 (LFA-1). After strong adhesion, leukocyte migrates through endothelial cells into its underlying tissues. Among these molecules, the adhesion molecules (ICAM-1 and VCAM-1), selectins (E-selectin and P-selectins), plasminogen activator inhibitor-1 (PAI-1), and



**Figure 1.** Alterations of endothelial, systemic coagulation and thrombotic functions due to SARS-CoV-2 infection.<sup>6</sup>



von Willebrand Factor (vWF) are easily obtained from the circulation and well measured by commercial immunoassays.<sup>5</sup>

### **Adhesion molecules**

Endothelial dysfunction can be detected by the increase of circulating cellular adhesion molecules (CAM), including ICAM-1 and VCAM-1. ICAM-1 and VCAM-1 are minimally expressed in inactive endothelial cells. However, these expressions can be augmented by activation of cytokines and endotoxin liposaccharides. Thrombin and histamine stimulations selectively induce endothelial P-selectin expression, whereas cytokines and liposaccharides stimulations induce E-selectins expression.<sup>7,8</sup>

Studies have shown that endothelial cellular adhesion markers, VCAM-1 and ICAM-1, are increased in COVID-19 patients compared to control group.<sup>9</sup> These markers were also found significantly higher in severe COVID-19 infections, associating the severity of COVID-19 infection with increase of serum VCAM-1 and ICAM-1.<sup>9</sup> Likewise, the recovery of severe COVID-19 infections was also associated with a decrease of serum VCAM-1 and ICAM-1 levels over time. Therefore, it could be inferred that according to the study, the increase of endothelial cellular adhesion molecule expression is correlated with the presence of COVID-19 and its severity, as well as indicating a contribution to patient's coagulopathy state.<sup>9</sup> To further support this, a previous postmortem study had demonstrated a marked endothelial dysfunction in COVID-19 patients with significant increase of ICAM-1.<sup>10</sup>

### **Selectins**

Besides VCAM-1 and ICAM-1, endothelial cells also express P-selectin and E-selectin. P-selectin is a cellular adhesion molecule stored inside the endothelium and thrombocytes which would be rapidly deployed into plasma membrane upon activation.<sup>11</sup> As infection progresses, P-selectin increases platelet aggregation and platelet-endothelium interaction. Soluble P-selectin (sP-selectin) is produced through enzymatic release of mobilized P-selectins during

inflammation.<sup>12</sup> Experiments with genetically engineered rat in pro-coagulant state revealed high level of sP-selectin expressions. On the other hand, sP-selectin was also proven to be a significant marker of several inflammatory and pro-coagulopathy disorders, including systemic inflammatory responses.<sup>11,14,15</sup> Most recent study showed increase of sP-selectin in COVID-19 cases, further supporting the theory of COVID-19 being an endothelial dysfunction disorder.<sup>16</sup>

E-selectin can also provide as markers of endothelial dysfunction. E-selectin (CD62E) is a leukocyte adhesion molecule that is expressed by activated endothelial cells. Endothelial cells of normal skin and bone marrow or in the case of infantile hemangioma constitutively express E-selectin, in contrast with endothelial cells from other tissues that do not.<sup>18,19</sup> However, these expressions are tightly regulated by inflammatory cytokines. Soluble E-selectins (sE-selectin) are released during inflammation and has long been proposed as a biomarker of endothelial dysfunction, especially in cases of sepsis.<sup>20</sup> Therefore, increased circulating sE-selectin alongside mRNA increase confirm the presence of endothelial dysfunction in COVID-19 as well as a linear correlation with its severity. Smadja *et al.* found in their study that there was an increase of E-Selectin level in COVID-19 patients. This strengthens the theory of endothelial dysfunction in COVID-19.<sup>21</sup>

### **Plasminogen activator inhibitor-1 (PAI-1)**

Procoagulant condition formed by endothelial activation can also be measured from alterations of balance between tissue plasminogen activator (t-PA) and its endogen, plasminogen activator inhibitor-1.<sup>22</sup> Plasminogen activator inhibitor-1, also known as endothelial PAI, is a serine protease inhibitor (serpin) which serves as main inhibitor of t-PA and urokinase type plasminogen activator (u-PA), a fibrinolytic agent with recent additional non-fibrinolytic properties reported.<sup>23-26</sup> While also secreted by other tissues such as adipose tissue, PAI-1 is mainly produced by endothelium. Increase of PAI-1 is a risk factor of thrombosis and atherosclerosis.<sup>2,22</sup>



One characteristic of COVID-19 is leukocyte sequestration, especially neutrophils, in the pulmonary microvasculature—which contributes to alveolar injury and infinite inflammation.<sup>27</sup> Local pro-inflammatory environment is exaggerated by the formation of NET which results in mass production of pro-inflammatory cytokines.<sup>28</sup> These cytokines trigger endothelial cells activations and possibly promotes release of t-PA and PAI-1.<sup>28,29</sup> Activated endothelial cells expresses raised levels of PAI-1, inhibiting t-PA and u-PA, further instigating hemostasis balance alteration to procoagulant state.<sup>17</sup>

In a study by Zuo, PAI-1 level is found to be raised in COVID-19 patients.<sup>30</sup> This raise has a significant correlation between PAI-1 as well as circulating absolute neutrophil and calprotectin. This supports the presence of endothelial dysfunction in COVID-19.<sup>30</sup> Besides endothelial activation, there is a possibility that direct infection and endothelial cells destruction by SARS-CoV-2 cause a potential release of t-PA and PAI-1.<sup>31</sup>

A study by Kang *et al* revealed that in advanced cases of COVID-19 with severe respiratory dysfunction, the PAI-1 level is significantly higher than sepsis, acute respiratory distress syndrome (ARDS), or even burn cases.<sup>32</sup> The significant increase of PAI-1 in severe cases of COVID-19, which are comparable to ARDS, had shown to induce vascular endothelium destruction. SARS-CoV-2 had also shown to directly infect the vascular endothelium, triggering endothelitis which indicates vascular endothelial destruction in patients with COVID-19.<sup>31</sup> Collectively, this finding suggests that increased PAI-1 level promotes endotheliopathy and coagulopathy in severe cases of COVID-19.<sup>32</sup>

Intensive care patients with severe conditions were reported to have significantly increased level of PAI-1 compared to non-intensive care patients. Data from a study by Nougier clearly demonstrated that balance between coagulation and fibrinolysis diminished in COVID-19 patients in significant hypercoagulability state related to hypofibrinolysis caused by high increase of PAI-1 level.<sup>33</sup> In a study by Blasi, plasma PAI-1 level

was found 3.7 times higher in COVID-19 patients compared to control.<sup>34</sup>

### *Von Willebrand Factor*

Von Willebrand Factor (vWF) is a major multidomain adhesive glycoprotein derived from endothelium, released into circulation by activated endothelial cells.<sup>35,36</sup> vWF binds with platelet glycoprotein Ib $\alpha$ ,  $\alpha$ IIb $\beta$ 3 and endothelial collagen, which activates the platelets and commences platelet aggregation.<sup>35</sup> As a carrier of blood clotting factor VIII, vWF also has an important role in clotting cascade.<sup>37</sup> vWF is synthesized by endothelial cells and megakaryocytes, which is then stored as ultra-large vWF multimers or multimers with large molecular weight within the endothelial Weibel-Palade bodies or platelet  $\alpha$ -granules.

It is well established that pathological alterations of fibrinogen, D-dimer, vWF and P-selectin have important roles in abnormal coagulation and endothelial dysfunction. Both infection and inflammation can increase plasma vWF through activated endothelial cells.<sup>40,41</sup> The majority of vWF originate from endothelial cells. Endothelial cells vWF (EC-vWF), instead of platelet vWF, critically promotes thrombus formation. In accordance, EC-vWF contributes in vWF-dependent atherogenesis by raising platelet adhesion and vascular inflammation.<sup>39</sup> vWF is also a biomarker that is relatively easy to measure.<sup>42</sup>

In healthy individuals, ACE2 transforms angiotensin-II into angiotensin 1-7, which stimulates endothelial cells to produce nitric oxide (NO). NO aids blood vessels in vasodilation and suppressing platelet aggregation. In COVID-19, SARS-CoV-2 occupies ACE2, subsequently raising Angiotensin-II levels. This further enhance vasoconstriction and reduce blood flow. In this process, vWF stored inside Weibel Palade bodies, increasing formation of blood clots.<sup>44</sup>

Activation of EC-vWF in relation of COVID-19 is known as acute phase protein, released from endothelial cells as inflammatory response.<sup>45</sup> In this case, its high level indicates a disturbance of endothelial function.<sup>46</sup> Several studies had been



performed to determine the role of vWF in COVID-19. COVID-19 patients have a documented higher level of vWF, as shown in a study by Blasi.<sup>34</sup> An increased activity of vWF and vWF antigen (vWF:Ag) was also found to be significantly raised in a study by Helms, which revealed a well-defined endothelial inflammation with a very high level of vWF:Ag.<sup>47</sup> Morici *et al.*, in their study, reported a significantly higher vWF in all COVID-19 patients, supporting previous studies.<sup>48</sup> Katneni *et al.* and several other previous publications similarly reported that vWF level was higher in COVID-19 patients.<sup>49-53</sup> In a study by Panigada, the increase of vWF was reported up to 863 U/dL, further supporting evidences of endothelial dysfunction in COVID-19 patients and its potential use as a biomarker in COVID-19.<sup>54</sup>

Fraser, in his study, measured three thrombosis factors and five markers of endothelial cell injury from the plasma using ELISA, showing significant higher levels in intensive care COVID-19 patients compared to healthy individuals.<sup>16</sup> A study by Rauch has also shown evidences of associations between coagulation marker level on admission, amongst which are factor VIII and vWF, with the severity of COVID-19.<sup>55</sup> In other words, increased levels of vWF in COVID-19 patients is a potential biomarker associated with severity

of the disease. Previous studies have shown the ability of pulmonary virus to promote platelet-endothelium interactions through upregulation of endothelial ICAM-1, vWF, and fibronectins, culminating ongoing pulmonary injury.<sup>56</sup>

State of hypoxia also triggers vWF expression and its following detachment from endothelial Weibel-Palade bodies.<sup>57,58</sup> VWF upregulation induced by hypoxia has been associated with the presence of coronary and pulmonary vessels thrombus formation, as well as promoting leukocyte recruitment.<sup>59</sup> Accordingly, hypoxemia state observed in COVID-19 patients induce prothrombotic condition through upregulation of t-PA inhibitor and stimulation of procoagulant endothelial synthesis, including tissue factor and vWF.<sup>57,60-62</sup>

VWF is an acute phase response protein released by activated endothelial cells as a reaction to inflammatory stimuli. This increase in activity of vWF and its antigen level contribute to platelet aggregation. In another study, cases of COVID-19 can cause up to 490% raise of vWF and vWF:Ag level. VWF is a main determinant of platelet adhesion after vascular injury and its resulting blood clot. High vWF:Ag level is an independent risk factor for ischemic stroke and myocardial infarction.<sup>64</sup> Thus, thrombocyte

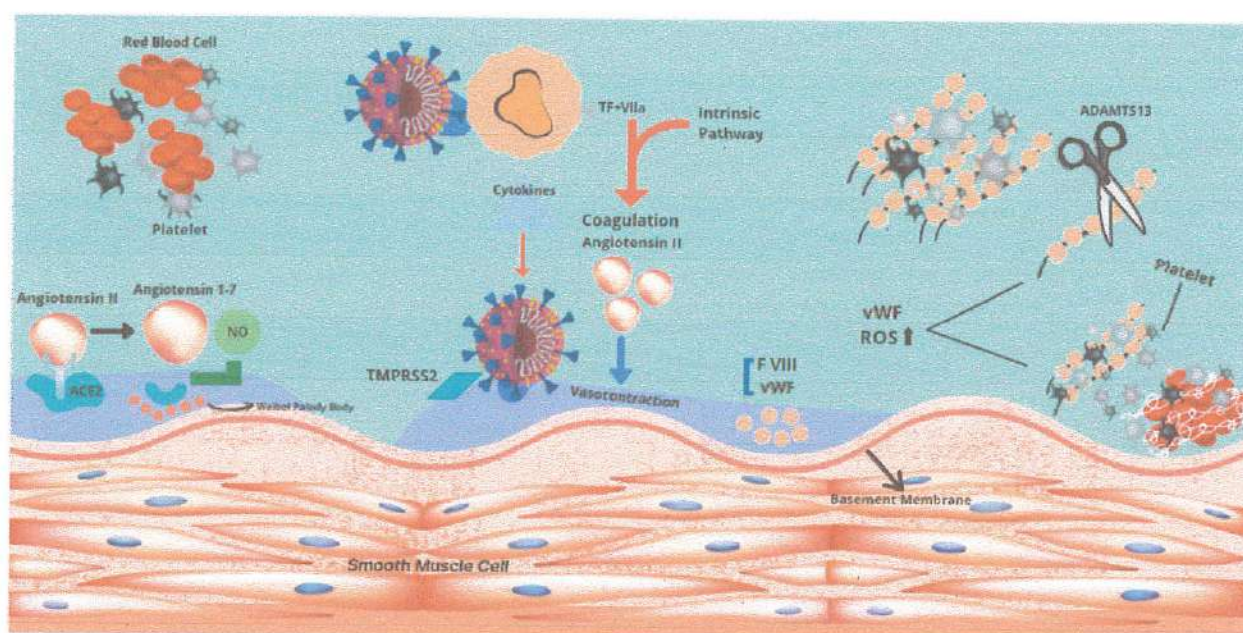


Figure 2. Thrombus formation in COVID-19.



inhibitors can be considered in prevention of cardiovascular events in COVID-19.<sup>65</sup>

### **Potential mechanisms of cardiovascular drugs in COVID-19 related endothelial function repair**

Various experimental and clinical studies have shown multiple currently used of investigated drugs currently can repair endothelial function, although they may have different structures and mechanisms. Among those drugs are Angiotensin Converting Enzymes (ACE) inhibitor (ACEi), Angiotensin-II Receptor Blocker (ARB), statins and antioxidants.

#### **ACEi and ARB**

Evidences have established the role of ACE inhibitors in repairing endothelial functions in animal models with heart failure and in animal models with coronary artery disease.<sup>66,67</sup> ACE inhibitors elevate endothelial functions by reducing Angiotensin-II, while regulating endothelial Nitric Oxide Synthase (eNOS) and inhibiting production of reactive oxygen species (ROS), giving the drug its protective properties for endothelium.<sup>68-70</sup> In the TREND study, quinapril, compared to placebo, repaired endothelial dysfunction in normotensive patients with coronary artery disease.<sup>67</sup> Administration of ARB has shown to improve endothelial function and demonstrate an overall reduction of inflammatory biomarkers, implying its importance in the pathogenesis of atherosclerosis.<sup>71</sup> A previous meta-analysis showed that ACEi improves endothelial function in patients with endothelial dysfunction of multiple causes.<sup>72</sup>

However, despite available studies mentioned, there has not been any consensus related to COVID-19 related endothelial dysfunction and ACEi or ARB as its potential clinical approach. Several available meta-analysis regarding effectivity of ACE inhibitor or ARB administration for endothelial dysfunction in COVID-19 still have differing conclusions.<sup>73,74</sup> Further investigation is necessary, especially considering that ACE-2 receptor is a binding site of SARS-CoV-2.

#### **Statins**

Beneficial effects of statin in endothelial function involves multiple mechanisms. Statins improve endothelial dysfunction due to their LDL lowering properties, considering LDL and OxLDL capability in reducing eNOS.<sup>75,76</sup> Statin improves NO bioactivity by activating eNOS through PI3K/Akt signaling pathway.<sup>80</sup> The benefits of statin for endothelial function is also related with its anti-inflammation and antioxidant properties.<sup>77</sup> Statins provide direct antioxidant effects to LDL through reducing LDL electronegative forms.<sup>78,79</sup>

In 1995, randomized control trial stated that lovastatin can return endothelial function of a coronary artery.<sup>81</sup> Atorvastatin was shown to reduce pro-inflammatory cytokines (TNF- $\alpha$ , IL-1 and IL-6), ICAM-1 and C-reactive protein (CRP) in hypercholesterolemic patients.<sup>82</sup> One study showed that simvastatin produces significant reduction in endothelial dysfunction markers, inflammation, oxidative stress and endothelial apoptosis; in this study, CRP reduction seemed to have been in relation to the lipid lowering property of simvastatin.<sup>83</sup> A meta-analysis showed that statin therapy is associated with significant improvement of both coronary and peripheral endothelial functions.<sup>84</sup> Otherwise, statin elevate endothelial progenitor cells circulation, which contribute in the long-term effects of statin in endothelial function.<sup>85</sup> The combination of ACE inhibitors and statin therapy have also been demonstrating a relaxation effects in coronary vessels, which is largely dependent on endothelial function through NO production.<sup>86</sup>

Several studies reported benefits of statins in COVID-19. Masana *et al.* in their study revealed fewer deaths reported in statin-administered group compared to the non-statin-administered group. It has also been stated that statin therapy should not be halted in hospitalized patients due to lower death rate of SARS-CoV-2 infection patients who took statins before hospitalization.<sup>87</sup> An observational study by Omar *et al.* also reported that, in diabetic patients with COVID-19, statin users have a 12% lower chance of death during hospitalization compared to those who did not.<sup>88</sup> A retrospective cohort in Singapore

linked independent use of statin with lower ICU admission rate.<sup>88</sup> Evidence by Sophia *et al* suggested beneficial use of continuous statin for hospitalized COVID-19 patients, as it correlates with lower chance of invasive mechanical ventilation support.<sup>89</sup> However, there has not been a randomized controlled trial which further supports the use of statins in COVID-19.

### Antioxidant

Several substances such as vitamin C, vitamin E and N-acetylcysteine provide an antioxidant effect through different mechanisms. Vitamin C protects the endothelium by eliminating superoxide, which in turn prevents NO decomposition, lipid peroxidation, platelet and neutrophil activation, as well as upregulation of adhesion molecules.<sup>90,91</sup> Vitamin C scavenges reactive nitrogen species yielded by peroxidase and inhibits myeloperoxidase/H<sub>2</sub>O<sub>2</sub>.<sup>92</sup> Vitamin E acts as lipid soluble antioxidant, clearing radical hydroperoxyl in lipid environment.<sup>93</sup> Meanwhile, the effects of N-acetylcysteine in endothelial dysfunction are related to inhibitions of NADPH oxidase expression, leukocyte adhesion and inflammatory cytokine secretion.<sup>94</sup> N-acetylcysteine also prevents platelet aggregation, which largely depends on vWF and collagen binding in human plasma, and inhibits upregulation of Caveolin-1 as well as strengthening endothelial barrier function in rats.<sup>95</sup> Further investigations may provide useful information regarding antioxidants in the management of endothelial dysfunction related to COVID-19.

### CONCLUSION

SARS-CoV-2 infection, which has caused a global pandemic, involved various clinical manifestations and underlying mechanisms. This virus invades hosts by occupying ACE-2 receptors in endothelium, which signify the important role of endothelium in this disease. Available studies have demonstrated the increase of several endothelial biomarkers such as ICAM-1, VCAM-1, E-Selectin, P-Selectin, PAI-1 and vWF in COVID-19 patients, which

supports the presence of endothelial dysfunction in COVID-19, and could further provide helpful information for the detection of endothelial dysfunction in COVID-19. These findings may also explain the higher chance of individuals with comorbidity to contract COVID-19, with increased severity. Further studies investigating NO levels in COVID-19 is necessary to confirm COVID-19 related endothelial dysfunction.

The use of drugs that has been established to improve endothelial functions may be useful as a baseline therapy in COVID-19. It has also become a point of interest whether a cured COVID-19 patient has an increased risk of cardiovascular diseases in the future due to their endothelial impairment. This topic is potential for future research, and may provide helpful insight in prevention of cardiovascular system events after COVID-19.

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### CONFLICT OF INTEREST

None of the authors had a conflict of interest in this study.

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