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ARTICLE

Acute Coronary Syndrome in Patients with SARS-CoV-2 Infection: Pathophysiology and Translational Perspectives

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Abstract

Acute coronary syndromes (ACS) may complicate the clinical course of patients with Coronavirus Disease 2019 (COVID-19). It is still unclear whether this condition is a direct consequence of the primary disease. However, several mechanisms including direct cellular damage, endothelial dysfunction, in-situ thrombosis, systemic inflammatory response, and oxygen supply-demand imbalance have been described in patients with COVID-19. The onset of a pro-thrombotic state may also be facilitated by the endothelial dysfunction secondary to the systemic inflammatory response and to the direct viral cell damage. Moreover, dysfunctional endothelial cells may enhance vasospasm and platelet aggregation.

The combination of these factors promotes atherosclerotic plaque instability, thrombosis and, consequently, type 1 myocardial infarction.

Furthermore, severe hypoxia due to extensive pulmonary involvement, in association with other conditions described in COVID-19 such as sepsis, tachyarrhythmias, anemia, hypotension, and shock, may lead to mismatch between oxygen supply and demand, and cause type 2 myocardial infarction.

A deeper understanding of the potential pathophysiological mechanisms underlying ACS in patients with COVID-19 could help the therapeutic management of these very high-risk patients.

Keywords: Acute coronary syndromes, Myocardial infarction, Coronary artery disease, Novel coronavirus 2019, COVID-19, SARS-CoV-2, Endothelial dysfunction, Oxidative stress

1. Introduction

After the detection of the first cases in Hubei Province, China, Coronavirus Disease 2019 (COVID-19) spread rapidly worldwide and reached pandemic proportions [1,2].

Although mainly involving the respiratory apparatus, COVID-19 can assume the characteristics of a multi-systemic disease involving many organs and lead to death in 15% of hospitalized patients [3]. Among these systemic effects, cardiovascular involvement is frequently reported and impact negatively on patient clinical outcome [4–13].

Although a clear association between these two conditions has not yet been found, a significant proportion of patients with COVID-19 may be complicated by acute coronary syndromes (ACS) [14,15], this aspect must be hardly considered, since cardiovascular risk factors are widely represented in COVID-19 patients. As reported in other infectious

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diseases, COVID-19 may promote atherosclerotic plaque instability resulting in rupture, thrombus formation and type 1 myocardial infarction (MI) [16,17]. However, in the context of a systemic disease, other factors may contribute to the ACS pathophysiology including cellular damage mediated by the virus or systemic inflammatory response, microvascular thrombosis, endothelial dysfunction and the mismatch between oxygen demand and availability secondary to respiratory involvement [18–22].

The aim of this review is to describe the potential pathophysiological pathways of ACS in COVID-19 patients, focusing on the translational application and on possible therapeutic perspectives.

2. Pathogenesis and transmission of COVID-19

COVID-19 is caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) [23]. The internalization of the virus in the target host cells is mediated by the interaction between the angiotensin converting enzyme 2 (ACE2) receptor expressed by the cells, and the spike (S) protein expressed by the virus [24,25]. In this context, interferon release enhances the expression of further ACE2 receptors on the membranes of nearby pneumocytes and promotes the inflammatory response and the development of interstitial edema, microvascular thrombosis, and alveolar damage, which combined can precipitate the onset of an acute respiratory distress syndrome (ARDS) [26]. Viral transmission occurs through close individual contact and is mediated by respiratory droplets and subsequent inhalation of viral particles [27]. After an average incubation of approximately five days, the early clinical presentations of the disease are similar to other viral respiratory syndromes, including fever, cough, shortness of breath, fatigue, myalgias, headache, and gastrointestinal involvement [1]. The subsequent progression can be extremely wide, varying from asymptomatic or minimally symptomatic to life-threatening or fatal conditions, characterized by systemic inflammatory response syndrome, ARDS, multiple organ failure, and death [4,15,28].

3. The epidemiology paradox of ACS in COVID-19

Although ACS can complicate the clinical course of patients infected by SARS-CoV-2, a dramatic reduction in hospital admissions for ACS was observed during the first phase of the pandemic as demonstrated by the number of urgent or emergent coronary angiography performed [29–33]. Zhang et al. in a study involving 395 STEMI patients reported a halving of the number of primary percutaneous coronary interventions (pPCI) in 2020 compared to 2019 and 2018, and a concomitant increase in the use of fibrinolysis [34]. De Luca et al. also reported a significant reduction of pPCI performed in March and April 2020 compared with the same period of 2019 [35]. As expected, longer ischemia and door-to-balloon times were reported [36]. In contrast, fibrinolysis was frequently preferred as reperfusion strategy in patients with STEMI and COVID-19 [34,37–39].

This change in the rate of hospital admissions for ACS could have several explanations. Surely the governmental restrictive measures such as national lockdowns and the media emphasis on the rapid spread of the pandemic could have played a critical role in making the population more hesitant on seeking medical attention and into underestimating potentially life-threatening conditions. Moreover, the reorganization of health services and pathways has impacted on the efficiency of the emergency system, especially for time-dependent diseases such as STEMI [40]. This could also explain the significant increase in the incidence of out-of-hospital cardiac arrest, the most dreadful complication of ACS, which has been widely described in this period [35,41,42].

In addition, in the context of hospital access flows, it should be considered a substantial reduction in all cause access to the emergency cardiology department, which was more profound when COVID-19 cases increased and less evident during periods in which the epidemic curve tended to flatten [43].

4. Mechanisms of acute coronary syndromes in COVID-19

The characteristics of ACS in patients with COVID-19, such as angiographic evidence of unobstructed coronary arteries, stent thrombosis, multiple thrombotic culprit lesions, and high thrombus burden, suggest distinct pathophysiological pathways [37,44,45]. (Fig. 1). MI may be also the first presentation of SARS-CoV-2 infection and may not correlate with the severity of lung involvement [44,46].

4.1. Hemostatic abnormalities

In hospitalized patients with COVID-19, multiple hemostatic abnormalities have been described and may be related to poorer clinical outcome. The most representative were decreased platelet counts,

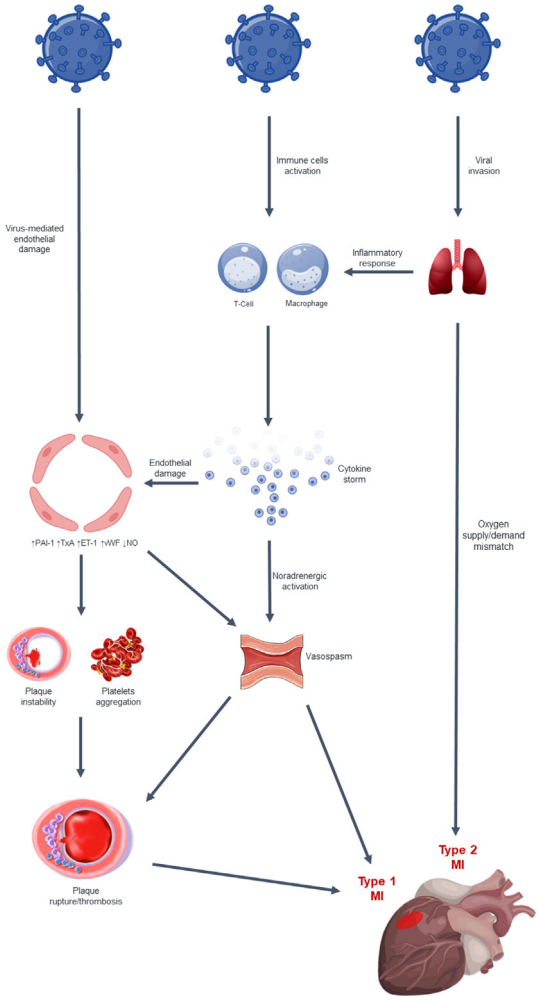

Fig. 1. ***Pathophysiology of ACS in COVID-19****. SARS-CoV-2, through ACE2 receptors, enters inside pneumocytes, macrophages, and endothelial cells. Hypoxia secondary to serious pulmonary involvement, which may escalate into ARDS, may cause type 2 MI due to oxygen supply-demand imbalance. Moreover, the excessive inflammatory response related to infection promotes the release of cytokines such as IL-1, IL-6, IL-7, TNFα, and IFNγ. The cytokine storm can facilitate the onset of endothelial dysfunction with subsequent production of oxidative and prothrombotic factors. Furthermore, the virus can directly damage the endothelium by interacting with its cells. Lastly, the state of hyperinflammation increases the activity of the sympathetic nervous system favoring coronary vasospasm. This context may then enhance atheromatous plaque rupture and platelet aggregation resulting in thrombosis and type 1 MI. ACS, acute coronary syndrome; ACE2, Angiotensin Converting Enzyme 2; COVID-19, Coronavirus Disease 2019; IFNγ, Interferon γ; IL-1, Interleukin 1; IL-6, Interleukin 6; IL-7, Interleukin 7; MI, myocardial infarction; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2; TNFα, Tumor Necrosis Factor α.*

raised d-dimer serum levels, and prolonged prothrombin time [47,48]. Huang et al., in an observational study on hospitalized patients with COVID-19, reported that patients with higher levels of d-dimer were more likely to need intensive cares [49]. A study by Tang et al. also reported increased levels of d-dimer and fibrinogen degradation products, and a slight prolongation of the prothrombin time in patients hospitalized or who died due to severe forms of COVID-19 [50]. Whether these disorders are directly associated to the activity of the virus or are a consequence of an excessive inflammatory response secondary to the infection is yet to be defined [51]. By comparing laboratory blood samples obtained from patients with ARDS due to other causes and patients with ARDS due to SARS-CoV-2, patients with COVID-19 showed a significant increase in procoagulant and acute phase factors suggesting that the cytokine storm (CS) observed in these patients may act as a primary trigger in the development of thrombotic complications [52]. The systemic inflammatory response, through cytokines activity, may facilitate the expression of ultralarge von Willebrand factor multimers (ULVWF) and tissue factor (TF), which take part at various stages in the hemostatic mechanisms, enhancing thrombin production and the development of a procoagulant state [50,53–55]. A potential contributing factor to the development of SARS-CoV-2-related coagulopathy might be the presence of lupus anticoagulant (LA) [53], a condition that typically occurs in inflammatory and infectious disorders where cellular injury may expose phospholipid moieties, that are not usually reachable by the immune system, with consequent activation of the coagulation cascade and thrombus formation [56].

The presence of this procoagulant environment could explain the frequent occurrence of thrombotic complications such as venous thromboembolism (VTE), pulmonary embolism (PE), and ACS in patients with COVID-19 [7,18,22,44]. Furthermore, this patient population seem to have a peculiar phenotype in the development of ACS. Choudry et al., in a cohort of STEMI patients with COVID-19, reported an increased incidence of multiple thrombotic lesions, a higher thrombotic burden, and less successful PCI as assessed by the myocardial blush grade (a marker of myocardial perfusion) after pPCI, compared with a control group of SARS-CoV-2 negative STEMI patients [45,57,58]. In addition, Rodriguez-Leor et al. reported a high incidence of stent thrombosis (4.1%) during the hospitalization in patients with COVID-19 and STEMI [30], an event described in less than 1% in the general STEMI population up to 1 year from the index event [59–63].

4.2. Endothelial dysfunction

Vascular endothelium plays a crucial role in regulating the interaction between the circulatory system and tissues, and it is the main responsible

for preserving vascular homeostasis by regulating vasomotility, immune response, platelet aggregation, coagulation, and vascular permeability. Endothelium can be harmed by several mechanisms, including oxidative stress due to an intracellular increase of superoxide anions, a condition already described in several conditions such as diabetes, hypertension, elderly age, and smoking. Hence, a dysfunctional endothelium will assume a predominantly vasoconstrictive and procoagulant state, promoting the development of ACS [64,65].

Endothelial dysfunction is also a key player in the pathophysiology of COVID-19 complications [66,67]. The endothelium can be impaired either directly by the virus or by the inflammatory response secondary to the infection, leading to venous, arterial, and microvascular thrombosis [21,68]. The endothelium increases the expression and release of TF, von Willebrand factor (vWf), thromboxane and plasminogen activator inhibitor-1 (PAI-1) [69−71] Furthermore, the CS favors the production of superoxide anions with consequent increase in oxidative stress and endothelial damage, creating a vicious loop that can lead to severe vascular complications [72−74]. An increased production and release of endothelin-1 also occurs in these circumstances, with consequent increased vasoconstriction and platelet aggregation [75].

These conditions could be exacerbated in patients with preexisting CV risk factors and CAD, favoring the precipitation toward an ACS or other thrombotic complications.

The role of the endothelium in the development of vascular complications encourages future investigations on endothelium-targeting therapy, including ACE inhibitors (ACEi) and statins [76−79].

4.3. Inflammatory response and cytokine storm

Inflammation is a leading mechanism in the development and progression of atherosclerosis [80]. During the acute phase of a viral infection, the CS can impair the physiological homeostasis by activating platelets, directly damaging the endothelium, and stimulating vasoconstriction by increasing sympathetic activity, facilitating the development of a pro-thrombotic state [16,81]. The interaction between these biological and mechanical agents can disrupt the atheromatous plaque architecture, facilitating the formation of thrombus and the occurrence of acute coronary syndrome [82,83].

An aberrant inflammatory response is typically associated with severe forms of COVID-19 [49,51]. Due to its self-expressing ability, interleukin-1 (IL-1) is the leading facilitator of CS, promoting the development of a self-enhancing inflammatory response [84]. The release of further inflammatory molecules, such as tumor necrosis factor (TNFα), interleukin-6 (IL-6), and various chemoattractant molecules, which facilitate tissue penetration of inflammatory cells is also promoted by IL-1 [85−87]. IL-6 further promotes the production of acute phase reactants, such as fibrinogen and plasminogen activator inhibitor-1 (PAI-1) priming a prothrombotic and antifibrinolytic state. Many studies have consistently reported increased levels of proinflammatory factors, such as IL-1, IL-6, IL-10, IFNγ, granulocyte colony-stimulating factor (G-CSF), monocyte chemoattractant protein (MCP1), macrophage inflammatory protein 1 alpha (MIP1A), platelet-derived growth factor (PDGF), TNFα, and vascular endothelial growth factor (VEGF) in patients with COVID-19, suggesting the possibility of SARS-CoV-2-induced CS [49,88]. Cytokines impair the endothelial function and contribute to the development of thrombotic complications [50,53,89]. This evidence emphasizes the potential usefulness of an individualized therapy targeting these factors [90].

4.4. Oxygen supply/demand imbalance

Approximately 60% of patients with COVID-19 die due to hypoxemic respiratory failure [91]. The hypoxic state, in association with other disorders that may occur in critical COVID-19 patient, including sepsis, tachyarrhythmias, anemia, hypotension, and shock, may facilitate the onset of type 2 MI as a consequence of an imbalance between oxygen supply and demand [6,92]. The characteristics of these patients that are frequently elderly and with multiple comorbidities, justify the a poorer prognosis compared to patients with type 1 MI [93]. the comorbidities and frailty increase the risk of type 2 MI, a and contribute to the high mortality rate of these patients [4].

5. Myocardial infarction with non-obstructive coronary arteries

Non-obstructed coronary arteries have been widely reported in COVID-19 patients suffering an ACS, with a prevalence ranging from 30% to 40% [30,44,46,94] Different mechanisms may be responsible for the pathogenesis of myocardial infarction with non-obstructed coronary arteries (MINOCA), including plaque erosion, microthrombus formation, and coronary vasospasm [44,95,96]. In the context of COVID-19, the mechanisms of MINOCA are probably under-investigated due to difficulties

of performing invasive and noninvasive tests that are time consuming and increase the exposure of the operator to the risk of contagion [97–102]. However, CS seems to be a key player also in MINOCA due to its potential to impair the endothelial integrity and function [103,104].

Takotsubo syndrome (TTS) is a particular condition that mimics ACS [105] clinical presentation and has been reported in 2–4% of hospitalized patients with COVID-19 [15,106–108]. This disease could also lead to severe complications and dramatically impact on the survival of these patients [109–113]. TTS could either be part of the pathophysiological manifestations of COVID-19 or related to the physical and emotional stress characterizing SARS-CoV-2 infection, leading to increased catecholamine levels [114]. Also, the psychological stress associated with COVID-19 spread may have contributed to the occurrence of TTS and justify the high incidence of TTS reported during the pandemic period [115,116].

6. Therapeutic perspectives

The need to limit the exposure of health workers to the risk of contagion has been a major limitation for the management of SARS-CoV-2 positive STEMI patients, particularly during the first peak of the pandemic. Scientific societies have suggested the use of fibrinolysis as primary treatment [117–119]; however, the increased risk of complications due to the delay to myocardial reperfusion does not seem to support this approach over pPCI, which has long been considered the standard of care [36,45,120,121].

On the other hand, in patients with non-STE and/or equivocal ECG presentation, a rapid bedside echocardiogram showing regional wall motion abnormalities play an important role in detecting acute coronary syndromes early and triaging patients for invasive or conservative strategies [5].

Antiplatelet agents may have a particular value in the context of the thrombo-inflammatory syndrome frequently associated with COVID-19. Activated platelets may release several inflammatory mediators that may contribute to CS and [122], by interplaying with inflammatory cells, may further promote endothelial damage and subsequent thrombus formation [123,124]. Therefore, these therapeutic regimens could have pleiotropic effects in this particular STEMI population.

Anticoagulant drugs may also be particularly useful in COVID-19, since they may exert several anti-inflammatory effects. Unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH) can affect the interaction between platelets and neutrophils and decrease the release of inflammatory mediators, such as IL-1β, IL-6, E-selectin, and ICAM-1 [125–127] In addition, heparins also possess direct antiviral effects, including interaction with heparan sulfate, a common component of many viruses essential for interactions with human host cells [128–130], and the ability to induce structural changes in the S1 subunit of SARS-CoV2, preventing virus access into the target cells [128].

However, it is still unclear what is the best anticoagulant molecule and its dosage [131,132]. A recent observational study of 4389 patients demonstrated that those receiving anticoagulant treatment had a lower mortality rate, with no difference between prophylactic and therapeutic dosing [133]. Randomized clinical trials are needed to define the best strategy for these patients, and the choice of antiplatelet/anticoagulant regimens should be individualized for every specific patient, taking into account his ischemic and hemorrhagic risk [134–137]. Table 1 summarizes the main ongoing trials testing antithrombotic and/or anticoagulant therapeutic regimens in patients with COVID-19.

Since endothelial dysfunction plays a prominent role in the development of ACS in the patient with COVID-19, ACEi and statins have been hypothesized to prevent the risk of ischemic complication [77,79].

The ACE2 receptor, used by SARS-CoV-2 to enter into the host cell, is not inhibited by ACEi and may have multiple beneficial effects [138]. These mechanisms are accomplished through several pathways leading to the production of the molecule Angiotensin 1-7 which exert multiple anti-inflammatory, antioxidant, vasodilator, and natriuretic effects [139]. SARS-CoV-2, by binding to ACE2 may interfere with these effects, causing its cleavage from the plasma membrane [140]. Conversely, ACEi may facilitate the overexpression of ACE2 by enhancing the transcription of its mRNA, leading to the extrinsicity of its beneficial effects [141]. Based on this evidence, the use of these medications might provide a viable preventive strategy in patients with COVID-19 at risk of developing ACS.

Statins are widely used in post–MI patients [142] and have shown to be also effective in regulating the inflammatory response at different stages of COVID-9 due to their ability to interfere with the Ras, Rho, and Rac GTPases and leading to a reduction in the expression of various transcription factors like NF-κB [143,144]. They may also enhance nitric oxide production by promoting the expression of eNOS with an overall antioxidant effect that restores normal endothelial homeostasis [145] At platelet level, statins were shown to reduce platelet

Table 1. Ongoing randomized clinical trials investigating antithrombotic regimens in patients with COVID-19.

Study name	Registration number	Population	Treatments	Design	Estimated enrollement (n)	Primary endopoint	Time of FU (days)
PARTISAN	NCT04445623	Non-ICU patients	Prasugrel 10 mg	Randomized, double blind	128	P/F ratio	7
PEAC	NCT04365309	Non-ICU patients	Aspirin 100 mg	Randomized, open label	128	Clinical recovery time The time of SARS-CoV2 overcasting	14 37
ACT-COVID19	NCT04324463	Non-ICU patients	Aspirin Rivaroxaban Colchicine	Randomized, open label, factorial	4000	Colchicine vs. control; Aspirin and Rivaroxaban vs. control: - composite of invasive mechanical ventilation or death - disease progression of 2 points on a 7-points scale Aspirin and Rivaroxaban vs. control: - composite of MACE (MI, stroke, acute limb ischemia, VTE, death).	45
C-19-ACS	NCT04333407	Non-ICU patients	Aspirin 75 mg Clopidogrel 75 mg Rivaroxaban 2.5 mg Atorvastatin 40 mg Omeprazole 20 mg	Randomized, open label	3170	All-cause mortality	30
RESIST	CTRI/2020/07/026791	Non-ICU patients	Aspirin 75 mg Atorvastatin 40 mg	Randomized, open label	800	Clinical deterioration expressed as progression of WHO clinical improvement ordinal score $\geq$6	10
COVID-PACT	NCT04409834	ICU patients	UFH iv Enoxaparin 1 mg/kg Clopidogrel 75 mg UFH sc Enoxaparin 40 mg/0.4 mL	Randomized, open label, factorial	750	Hierarchical composite: death due to venous or arterial thrombosis, pulmonary embolism, clinically evident DVT, type 1 MI, ischemic stroke, systemic embolism, or acute limb ischemia or clinically silent DVT	28

COVID-19, Coronavirus Disease 2019; DVT, Deep Vein Thrombosis; ECMO, Extra Corporeal Membrane Oxygenation; ICU, Intensive Care Unit; MACE, Major Adverse Cardiovascular Events; MI, Myocardial Infarction; P/F, PaO2/FiO2; RRT, Renal Replacement Therapy; SARS-CoV2, Severe Acute Respiratory Syndrome Coronavirus 2; UFH, Unfractionated Heparin; VTE, Venous Thromboembolism.

reactivity and the releasing of proaggregative molecules like thromboxane, isoprostane and TF [146,147]. Similarly to ACEi, statins may also promote the expression of the ACE2 receptor [148]. Recent observational studies have reported that hospitalized patients with COVID-19 treated with statins showed a significantly lower mortality than patients not taking these medications [149,150]. However, their potential efficacy is still controversial [151] and randomized clinical trials are needed to clarify their effectiveness in these patients.

Beta-blockers (β-blockers) have been proposed in patients with COVID-19 to antagonize the hyperinflammatory response [152,153], since beta2-adrenergic receptors are expressed on several immune cells and their activation seems to promote inflammatory activity and cytokines release [154–157]. Therefore, targeting these receptors could be beneficial in counteracting the harmful effects of the inflammatory hyperactivation that occurs in these patients. However, their potential beneficial effect in patients with COVID-19 needs to be proven by randomized studies.

7. Conclusions

ACS may complicate the clinical course of COVID-19. These patients usually present a particular clinical phenotype compared to non-COVID-19 patients, with higher thrombotic burden, presence of multiple thrombotic lesions, poorer success of revascularization procedures, and higher incidence of non-obstructive CAD.

The pathophysiology of STEMI in SARS-CoV-2 positive patients is complex and includes hemostatic abnormalities, excessive inflammatory response, endothelial damage, and a mismatch between oxygen supply and demand. A deep knowledge of these mechanisms may be crucial for the management of these patients, and to plan a proper pharmacological treatment. Antiplatelet agents, anticoagulants, ACEIs, β-blockers, and statins may be helpful for preventing ACS in patients with severe forms of COVID-19, for reducing the risk of adverse events, and improving the patients' clinical outcome.

However, further evidence from randomized studies is needed to substantiate their use in routine clinical practice.

Conflict of Interest

The authors have no commercial or financial relationships that could be construed as a potential conflict of interest.

References

[1] Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020;382(18):1708–20.

[2] Progress report on the coronavirus pandemic. Nature 2020; 584(7821):325.

[3] Silverio A, Di Maio M, Citro R, Esposito L, Iuliano G, Bellino M, et al. Cardiovascular risk factors and mortality in hospitalized patients with COVID-19: systematic review and meta-analysis of 45 studies and 18,300 patients. BMC Cardiovasc Disord 2021;21(1):23.

[4] Shi S, Qin M, Shen B, Cai Y, Liu T, Yang F, et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. JAMA Cardiol 2020;5(7): 802–10.

[5] Citro R, Pontone G, Bellino M, Silverio A, Iuliano G, Baggiano A, et al. Role of multimodality imaging in evaluation of cardiovascular involvement in COVID-19. Trends Cardiovasc Med 2021;31(1):8–16.

[6] Russo V, Di Maio M, Mottola FF, Pagnano G, Attena E, Verde N, et al. Clinical characteristics and prognosis of hospitalized COVID-19 patients with incident sustained tachyarrhythmias: a multicenter observational study. Eur J Clin Invest 2020;50(12):e13387.

[7] Scudiero F, Silverio A, Di Maio M, Russo V, Citro R, Personeni D, et al. Pulmonary embolism in COVID-19 patients: prevalence, predictors and clinical outcome. Thromb Res 2021;198:34–9.

[8] Scudiero F, Silverio A, Muraca I, Russo V, Di Maio M, Silvestro A, et al. Long-Term prognostic impact of right ventricular dysfunction in patients with COVID-19. J Personalized Med 2022;12(2).

[9] Polito MV, Silverio A, Di Maio M, Bellino M, Scudiero F, Russo V, et al. Prognostic implications of right ventricular function and pulmonary pressures assessed by echocardiography in hospitalized patients with COVID-19. J Personalized Med 2021;11(12).

[10] Henein MY, Mandoli GE, Pastore MC, Ghionzoli N, Hasson F, Nisar MK, et al. Biomarkers predict in-hospital major adverse cardiac events in COVID-19 patients: a multicenter international study. J Clin Med 2021;10(24).

[11] Silverio A, Di Maio M, Scudiero F, Russo V, Esposito L, Attena E, et al. Clinical conditions and echocardiographic parameters associated with mortality in COVID-19. Eur J Clin Invest 2021;51(12):e13638.

[12] Polito MV, Silverio A, Bellino M, Iuliano G, Di Maio M, Alfano C, et al. Cardiovascular involvement in COVID-19: what sequelae should We expect? Cardiol Ther 2021;10(2): 377–96.

[13] Russo V, Silverio A, Scudiero F, Micco PD, Maio MD. Preadmission atrial fibrillation in COVID-19 patients: prevalence and clinical impact. Eur J Intern Med 2021;88:133–5.

[14] Piazza G, Campia U, Hurwitz S, Snyder JE, Rizzo SM, Pfeferman MB, et al. Registry of arterial and venous thromboembolic complications in patients with COVID-19. J Am Coll Cardiol 2020;76(18):2060–72.

[15] Giustino G, Croft LB, Stefanini GG, Bragato R, Silbiger JJ, Vicenzi M, et al. Characterization of myocardial injury in patients with COVID-19. J Am Coll Cardiol 2020;76(18): 2043–55.

[16] Corrales-Medina VF, Madjid M, Musher DM. Role of acute infection in triggering acute coronary syndromes. Lancet Infect Dis 2010;10(2):83–92.

[17] Kwong JC, Schwartz KL, Campitelli MA, Chung H, Crowcroft NS, Karnauchow T, et al. Acute myocardial infarction after laboratory-confirmed influenza infection. N Engl J Med 2018;378(4):345–53.

[18] Clerkin KJ, Fried JA, Raikhelkar J, Sayer G, Griffin JM, Masoumi A, et al. COVID-19 and cardiovascular disease. Circulation 2020;141(20):1648–55.

[19] Madjid M, Safavi-Naeini P, Solomon SD, Vardeny O. Potential effects of coronaviruses on the cardiovascular system: a review. JAMA Cardiol 2020;5(7):831−40.
[20] Guagliumi G, Sonzogni A, Pescetelli I, Pellegrini D, Finn AV. Microthrombi and ST-segment-elevation myocardial infarction in COVID-19. Circulation 2020;142(8): 804−9.
[21] Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, et al. Endothelial cell infection and endotheliitis in COVID-19. Lancet (London, England) 2020;395(10234):1417−8.
[22] Bikdeli B, Madhavan MV, Jimenez D, Chuich T, Dreyfus I, Driggin E, et al. COVID-19 and thrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy, and follow-up: JACC state-of-the-art review. J Am Coll Cardiol 2020;75(23):2950−73.
[23] Zhang H, Penninger JM, Li Y, Zhong N, Slutsky AS. Angiotensin-converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor: molecular mechanisms and potential therapeutic target. Intensive Care Med 2020;46(4):586−90.
[24] Wu P, Hao X, Lau EHY, Wong JY, Leung KSM, Wu JT, et al. Real-time tentative assessment of the epidemiological characteristics of novel coronavirus infections in Wuhan, China, as at 22 January 2020. Euro surveillance : bulletin Europeen sur les maladies transmissibles = European communicable disease. Bulletin 2020;25(3).
[25] Wan Y, Shang J, Graham R, Baric RS, Li F. Receptor recognition by the novel coronavirus from Wuhan: an analysis based on decade-long structural studies of SARS coronavirus. J Virol 2020;94(7).
[26] Ziegler CGK, Allon SJ, Nyquist SK, Mbano IM, Miao VN, Tzouanas CN, et al. SARS-CoV-2 receptor ACE2 is an interferon-stimulated gene in human airway epithelial cells and is detected in specific cell subsets across tissues. Cell 2020;181(5):1016−35. e19.
[27] Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. N Engl J Med 2020;382(13): 1199−207.
[28] Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese center for disease control and prevention. JAMA 2020;323(13):1239−42.
[29] Garcia S, Albaghdadi MS, Meraj PM, Schmidt C, Garberich R, Jaffer FA, et al. Reduction in ST-segment elevation cardiac catheterization laboratory activations in the United States during COVID-19 pandemic. J Am Coll Cardiol 2020;75(22):2871−2.
[30] Oriol R-L, Ana Belen Cid A, Armando Pérez de P, Xavier R, Soledad O, Ana S, et al. In-hospital outcomes of COVID-19 ST-elevation myocardial infarction patients. EuroInterven : J EuroPCR Collab Work Group Interven Cardiol Eur Soc Cardiol 2021;16(17):1426−33.
[31] Bonnet G, Panagides V, Becker M, Rivière N, Yvorel C, Deney A, et al. ST-segment elevation myocardial infarction: management and association with prognosis during the COVID-19 pandemic in France. Arch Cardiovasc Dis 2021; 114(5):340−51.
[32] Gluckman TJ, Wilson MA, Chiu ST, Penny BW, Chepuri VB, Waggoner JW, et al. Case rates, treatment approaches, and outcomes in acute myocardial infarction during the coronavirus disease 2019 pandemic. JAMA Cardiol 2020;5(12):1419−24.
[33] Mafham MM, Spata E, Goldacre R, Gair D, Curnow P, Bray M, et al. COVID-19 pandemic and admission rates for and management of acute coronary syndromes in England. Lancet 2020;396(10248):381−9.
[34] Zhang F, Song X, Dang Y. Experience of ST segment elevation myocardial infarction management during COVID-19 pandemic from the mainland of China. Cardiovasc Revasc Med. 2021 Jul;28:92−4.
[35] De Luca G, Verdoia M, Cercek M, Jensen LO, Vavlukis M, Calmac L, et al. Impact of COVID-19 pandemic on mechanical reperfusion for patients with STEMI. J Am Coll Cardiol 2020;76(20):2321−30.
[36] Mahmud E, Dauerman HL, FGP Welt, Messenger JC, Rao SV, Grines C, et al. Management of acute myocardial infarction during the COVID-19 pandemic: a consensus statement from the society for cardiovascular angiography and interventions (SCAI), the American college of cardiology (ACC), and the American college of emergency physicians (ACEP). Catheter Cardiovasc Interven Off J Soc Cardiac Angiogr Interven 2020;96(2):336−45.
[37] Hamadeh A, Aldujeli A, Briedis K, Tecson KM, Sanz-Sánchez J, Al Dujeili M, et al. Characteristics and outcomes in patients presenting with COVID-19 and ST-segment elevation myocardial infarction. Am J Cardiol 2020;131:1−6.
[38] Rashid M, Wu J, Timmis A, Curzen N, Clarke S, Zaman A, et al. Outcomes of COVID-19-positive acute coronary syndrome patients: a multisource electronic healthcare records study from England. J Intern Med 2021;290(1):88−100.
[39] Xiang D, Xiang X, Zhang W, Yi S, Zhang J, Gu X, et al. Management and outcomes of patients with STEMI during the COVID-19 pandemic in China. J Am Coll Cardiol 2020; 76(11):1318−24.
[40] Silverio A, Di Maio M, Ciccarelli M, Carrizzo A, Vecchione C, Galasso G. Timing of national lockdown and mortality in COVID-19: the Italian experience. Int J Infect Dis : IJID Off Pub Int Soc Infect Dis 2020;100:193−5.
[41] Baldi E, Sechi GM, Mare C, Canevari F, Brancaglione A, Primi R, et al. Out-of-Hospital cardiac arrest during the covid-19 outbreak in Italy. N Engl J Med 2020;383(5):496−8.
[42] De Luca G, Suryapranata H, Ottervanger JP, Antman EM. Time delay to treatment and mortality in primary angioplasty for acute myocardial infarction: every minute of delay counts. Circulation 2004;109(10):1223−5.
[43] Tsioufis K, Chrysohoou C, Kariori M, Leontsinis I, Dalakouras I, Papanikolaou A, et al. Correction to: the mystery of "missing" visits in an emergency cardiology department, in the era of COVID-19.; a time-series analysis in a tertiary Greek General Hospital. Clin Res Cardiol 2020; 109(12):1490.
[44] Bangalore S, Sharma A, Slotwiner A, Yatskar L, Harari R, Shah B, et al. ST-Segment elevation in patients with covid-19 - a case series. N Engl J Med 2020;382(25):2478−80.
[45] Choudry FA, Hamshere SM, Rathod KS, Akhtar MM, Archbold RA, Guttmann OP, et al. High thrombus burden in patients with COVID-19 presenting with ST-segment elevation myocardial infarction. J Am Coll Cardiol 2020; 76(10):1168−76.
[46] Stefanini GG, Montorfano M, Trabattoni D, Andreini D, Ferrante G, Ancona M, et al. ST-elevation myocardial infarction in patients with COVID-19: clinical and angiographic outcomes. Circulation 2020;141(25):2113−6.
[47] Lippi G, Favaloro EJ. D-Dimer is associated with severity of coronavirus disease 2019: a pooled analysis. Thromb Haemostasis 2020;120(5):876−8.
[48] Lippi G, Plebani M, Henry BM. Thrombocytopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: a meta-analysis. Clinica chimica acta. Int J Clin Chem 2020;506:145−8.
[49] Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395(10223):497−506.
[50] Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemostasis : JTH. 2020;18(4):844−7.
[51] Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet 2020;395(10229):1033−4.
[52] Masi P, Hékimian G, Lejeune M, Chommeloux J, Desnos C, Pineton De Chambrun M, et al. Systemic inflammatory response syndrome is a major contributor to COVID-19-

associated coagulopathy: insights from a prospective, single-center cohort study. Circulation 2020;142(6):611–4.
[53] Helms J, Tacquard C, Severac F, Leonard-Lorant I, Ohana M, Delabranche X, et al. High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. Intensive Care Med 2020;46(6): 1089–98.
[54] Zhang W, Zhao Y, Zhang F, Wang Q, Li T, Liu Z, et al. The use of anti-inflammatory drugs in the treatment of people with severe coronavirus disease 2019 (COVID-19): the Perspectives of clinical immunologists from China. Clin Immunol 2020;214:108393.
[55] Panigada M, Bottino N, Tagliabue P, Grasselli G, Novembrino C, Chantarangkul V, et al. Hypercoagulability of COVID-19 patients in intensive care unit: a report of thromboelastography findings and other parameters of hemostasis. J Thromb Haemostasis : JTH. 2020;18(7): 1738–42.
[56] Giannakopoulos B, Krilis SA. The pathogenesis of the antiphospholipid syndrome. N Engl J Med 2013;368(11): 1033–44.
[57] van 't Hof AW, Liem A, Suryapranata H, Hoorntje JC, de Boer MJ, Zijlstra F. Angiographic assessment of myocardial reperfusion in patients treated with primary angioplasty for acute myocardial infarction: myocardial blush grade. Zwolle Myocardial Infarction Study Group. Circulation 1998;97(23):2302–6.
[58] Baldi C, Silverio A, Esposito L, Di Maio M, Tarantino F, De Angelis E, et al. Clinical outcome of patients with ST-elevation myocardial infarction and angiographic evidence of coronary artery ectasia. Catheterization and cardiovascular interventions. Off J Soc Cardiac Angiogr Interven 2022;99(2):340–7.
[59] Souteyrand G, Amabile N, Mangin L, Chabin X, Meneveau N, Cayla G, et al. Mechanisms of stent thrombosis analysed by optical coherence tomography: insights from the national PESTO French registry. Eur Heart J 2016; 37(15):1208–16.
[60] Kimura T, Morimoto T, Kozuma K, Honda Y, Kume T, Aizawa T, et al. Comparisons of baseline demographics, clinical presentation, and long-term outcome among patients with early, late, and very late stent thrombosis of sirolimus-eluting stents: observations from the Registry of Stent Thrombosis for Review and Reevaluation (RESTART). Circulation 2010;122(1):52–61.
[61] Galasso G, De Angelis E, Silverio A, Di Maio M, Cancro FP, Esposito L, et al. Predictors of recurrent ischemic events in patients with ST-segment elevation myocardial infarction. Am J Cardiol 2021;159:44–51.
[62] Silverio A, Buccheri S, Venetsanos D, Alfredsson J, Lagerqvist B, Persson J, et al. Percutaneous treatment and outcomes of small coronary vessels: a SCAAR report. JACC Cardiovasc Interv 2020;13(7):793–804.
[63] De Rosa R, Silverio A, Varricchio A, De Luca G, Di Maio M, Radano I, et al. Meta-Analysis comparing outcomes after everolimus-eluting bioresorbable vascular scaffolds versus everolimus-eluting metallic stents in patients with acute coronary syndromes. Am J Cardiol 2018;122(1):61–8.
[64] Gutiérrez E, Flammer AJ, Lerman LO, Elízaga J, Lerman A, Fernández-Avilés F. Endothelial dysfunction over the course of coronary artery disease. Eur Heart J 2013;34(41): 3175–81.
[65] Kitta Y, Obata JE, Nakamura T, Hirano M, Kodama Y, Fujioka D, et al. Persistent impairment of endothelial vasomotor function has a negative impact on outcome in patients with coronary artery disease. J Am Coll Cardiol 2009;53(4):323–30.
[66] Libby P, Lüscher T. COVID-19 is, in the end, an endothelial disease. Eur Heart J 2020;41(32):3038–44.
[67] Goshua G, Pine AB, Meizlish ML, Chang CH, Zhang H, Bahel P, et al. Endotheliopathy in COVID-19-associated coagulopathy: evidence from a single-centre, cross-sectional study. Lancet Haematol 2020;7(8):e575–82.
[68] Klok FA, Kruip M, van der Meer NJM, Arbous MS, Gommers D, Kant KM, et al. Confirmation of the high cumulative incidence of thrombotic complications in critically ill ICU patients with COVID-19: an updated analysis. Thromb Res 2020;191:148–50.
[69] Croce K, Libby P. Intertwining of thrombosis and inflammation in atherosclerosis. Curr Opin Hematol 2007;14(1): 55–61.
[70] Lüscher TF, Vanhoutte PM. Endothelium-dependent contractions to acetylcholine in the aorta of the spontaneously hypertensive rat. Hypertension (Dallas, Tex : 1979) 1986; 8(4):344–8.
[71] Wagner DD. The Weibel-Palade body: the storage granule for von Willebrand factor and P-selectin. Thromb Haemostasis 1993;70(1):105–10.
[72] Loffredo L, Martino F, Zicari AM, Carnevale R, Battaglia S, Martino E, et al. Enhanced NOX-2 derived oxidative stress in offspring of patients with early myocardial infarction. Int J Cardiol 2019;293:56–9.
[73] Xuan Y, Gào X, Holleczek B, Brenner H, Schöttker B. Prediction of myocardial infarction, stroke and cardiovascular mortality with urinary biomarkers of oxidative stress: results from a large cohort study. Int J Cardiol 2018;273:223–9.
[74] Pennathur S, Heinecke JW. Oxidative stress and endothelial dysfunction in vascular disease. Curr Diabetes Rep 2007; 7(4):257–64.
[75] Rafnsson A, Matic LP, Lengquist M, Mahdi A, Shemyakin A, Paulsson-Berne G, et al. Endothelin-1 increases expression and activity of arginase 2 via ETB receptors and is co-expressed with arginase 2 in human atherosclerotic plaques. Atherosclerosis 2020;292:215–23.
[76] Anderson TJ, Meredith IT, Yeung AC, Frei B, Selwyn AP, Ganz P. The effect of cholesterol-lowering and antioxidant therapy on endothelium-dependent coronary vasomotion. N Engl J Med 1995;332(8):488–93.
[77] Shahin Y, Khan JA, Samuel N, Chetter I. Angiotensin converting enzyme inhibitors effect on endothelial dysfunction: a meta-analysis of randomised controlled trials. Atherosclerosis 2011;216(1):7–16.
[78] Flammer AJ, Sudano I, Hermann F, Gay S, Forster A, Neidhart M, et al. Angiotensin-converting enzyme inhibition improves vascular function in rheumatoid arthritis. Circulation 2008;117(17):2262–9.
[79] Penny WF, Ben-Yehuda O, Kuroe K, Long J, Bond A, Bhargava V, et al. Improvement of coronary artery endothelial dysfunction with lipid-lowering therapy: heterogeneity of segmental response and correlation with plasma-oxidized low density lipoprotein. J Am Coll Cardiol 2001; 37(3):766–74.
[80] Libby P, Ridker PM, Hansson GK. Inflammation in atherosclerosis: from pathophysiology to practice. J Am Coll Cardiol 2009;54(23):2129–38.
[81] Ardlie NG, McGuiness JA, Garrett JJ. Effect on human platelets of catecholamines at levels achieved in the circulation. Atherosclerosis 1985;58(1–3):251–9.
[82] Stone PH. Triggering myocardial infarction. N Engl J Med 2004;351(17):1716–8.
[83] Katritsis DG, Pantos J, Efstathopoulos E. Hemodynamic factors and atheromatic plaque rupture in the coronary arteries: from vulnerable plaque to vulnerable coronary segment. Coron Artery Dis 2007;18(3):229–37.
[84] Warner SJ, Auger KR, Libby P. Human interleukin 1 induces interleukin 1 gene expression in human vascular smooth muscle cells. J Exp Med 1987;165(5):1316–31.
[85] Warner SJ, Libby P. Human vascular smooth muscle cells. Target for and source of tumor necrosis factor. J Immunol (Baltimore, Md : 1950) 1989;142(1):100–9.
[86] Wang JM, Sica A, Peri G, Walter S, Padura IM, Libby P, et al. Expression of monocyte chemotactic protein and interleukin-8 by cytokine-activated human vascular smooth muscle cells. Arterioscler Thromb : J Vasc Biol 1991;11(5): 1166–74.

[87] Loppnow H, Libby P. Adult human vascular endothelial cells express the IL6 gene differentially in response to LPS or IL1. Cell Immunol 1989;122(2):493−503.
[88] Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020;395(10223):507−13.
[89] Pons S, Arnaud M, Loiselle M, Arrii E, Azoulay E, Zafrani L. Immune consequences of endothelial cells' activation and dysfunction during sepsis. Crit Care Clin 2020;36(2):401−13.
[90] Bikdeli B, Madhavan MV, Gupta A, Jimenez D, Burton JR, Der Nigoghossian C, et al. Pharmacological agents targeting thromboinflammation in COVID-19: review and implications for future research. Thromb Haemostasis 2020;120(7):1004−24.
[91] Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med 2020;46(5):846−8.
[92] Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, et al. Fourth universal definition of myocardial infarction (2018). Circulation 2018;138(20):e618−51.
[93] Chapman AR, Shah ASV, Lee KK, Anand A, Francis O, Adamson P, et al. Long-Term outcomes in patients with type 2 myocardial infarction and myocardial injury. Circulation 2018;137(12):1236−45.
[94] Popovic B, Varlot J, Metzdorf PA, Jeulin H, Goehringer F, Camenzind E. Changes in characteristics and management among patients with ST-elevation myocardial infarction due to COVID-19 infection. Cathet Cardiovasc Interv : Off J Soc Cardiac Angiogr Interven 2021;97(3). E319-e26.
[95] Rivero F, Antuña P, Cuesta J, Alfonso F. Severe coronary spasm in a COVID-19 patient. Catheterization and cardiovascular interventions. Off J Soc Cardiac Angiogr Interven 2021;97(5). E670-e2.
[96] Nakao M, Matsuda J, Iwai M, Endo A, Yonetsu T, Otomo Y, et al. Coronary spasm and optical coherence tomography defined plaque erosion causing ST-segment-elevation acute myocardial infarction in a patient with COVID-19 pneumonia. J Cardiol Cases 2021;23(2):87−9.
[97] Reynolds HR, Maehara A, Kwong RY, Sedlak T, Saw J, Smilowitz NR, et al. Coronary optical coherence tomography and cardiac magnetic resonance imaging to determine underlying causes of myocardial infarction with nonobstructive coronary arteries in women. Circulation 2021; 143(7):624−40.
[98] Dastidar AG, Baritussio A, De Garate E, Drobni Z, Biglino G, Singhal P, et al. Prognostic role of CMR and conventional risk factors in myocardial infarction with nonobstructed coronary arteries. JACC Cardiovasc Imag 2019;12(10):1973−82.
[99] Collet JP, Thiele H, Barbato E, Barthélémy O, Bauersachs J, Bhatt DL, et al. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J 2021;42(14): 1289−367.
[100] Silverio A, Citro R, Nardi F. Clinical imaging in patients experiencing chest pain. Minerva Cardioangiol 2017;65(6): 601−15.
[101] Citro R, Pontone G, Pace L, Zito C, Silverio A, Bossone E, et al. Contemporary imaging in takotsubo syndrome. Heart Fail Clin 2016;12(4):559−75.
[102] Citro R, Lyon AR, Meimoun P, Omerovic E, Redfors B, Buck T, et al. Standard and advanced echocardiography in takotsubo (stress) cardiomyopathy: clinical and prognostic implications. J Am Soc Echocardiogr : Off Pub Am Soc Echocardiograph 2015;28(1):57−74.
[103] Murase Y, Yamada Y, Hirashiki A, Ichihara S, Kanda H, Watarai M, et al. Genetic risk and gene-environment interaction in coronary artery spasm in Japanese men and women. Eur Heart J 2004;25(11):970−7.
[104] Matta A, Bouisset F, Lhermusier T, Campelo-Parada F, Elbaz M, Carrié D, et al. Coronary artery spasm: new insights. J Intervent Cardiol 2020;2020:5894586.
[105] Parodi G, Scudiero F, Citro R, Silverio A, Bellandi B, Zito C, et al. Risk stratification using the CHA(2)DS(2)-VASc score in takotsubo syndrome: data from the takotsubo Italian network. J Am Heart Assoc 2017;6(9).
[106] Lang JP, Wang X, Moura FA, Siddiqi HK, Morrow DA, Bohula EA. A current review of COVID-19 for the cardiovascular specialist. Am Heart J 2020;226:29−44.
[107] Hegde S, Khan R, Zordok M, Maysky M. Characteristics and outcome of patients with COVID-19 complicated by Takotsubo cardiomyopathy: case series with literature review. Open Heart 2020;7(2).
[108] Dweck MR, Bularga A, Hahn RT, Bing R, Lee KK, Chapman AR, et al. Global evaluation of echocardiography in patients with COVID-19. Eur Heart J Cardiovasc Imag 2020;21(9):949−58.
[109] Citro R, Radano I, Parodi G, Di Vece D, Zito C, Novo G, et al. Long-term outcome in patients with Takotsubo syndrome presenting with severely reduced left ventricular ejection fraction. Eur J Heart Fail 2019;21(6):781−9.
[110] Di Vece D, Silverio A, Bellino M, Galasso G, Vecchione C, La Canna G, et al. Dynamic left intraventricular obstruction phenotype in takotsubo syndrome. J Clin Med 2021;10(15).
[111] Citro R, Bossone E, Parodi G, Carerj S, Ciampi Q, Provenza G, et al. Clinical profile and in-hospital outcome of Caucasian patients with takotsubo syndrome and right ventricular involvement. Int J Cardiol 2016;219:455−61.
[112] Citro R, Bossone E, Parodi G, Rigo F, Nardi F, Provenza G, et al. Independent impact of RV involvement on in-hospital outcome of patients with takotsubo syndrome. JACC Cardiovasc Imag 2016;9(7):894−5.
[113] Citro R, d'Avenia M, De Marco M, Giudice R, Mirra M, Ravera A, et al. Polymorphisms of the antiapoptotic protein bag3 may play a role in the pathogenesis of tako-tsubo cardiomyopathy. Int J Cardiol 2013;168(2):1663−5.
[114] Moady G, Atar S. Takotsubo syndrome during the COVID-19 pandemic, state-of -the- art review. CJC open; 2021.
[115] Jabri A, Kalra A, Kumar A, Alameh A, Adroja S, Bashir H, et al. Incidence of stress cardiomyopathy during the coronavirus disease 2019 pandemic. JAMA Netw Open 2020; 3(7):e2014780.
[116] Ghadri JR, Wittstein IS, Prasad A, Sharkey S, Dote K, Akashi YJ, et al. International expert consensus document on takotsubo syndrome (Part I): clinical characteristics, diagnostic criteria, and pathophysiology. Eur Heart J 2018; 39(22):2032−46.
[117] Jing ZC, Zhu HD, Yan XW, Chai WZ, Zhang S. Recommendations from the peking union medical college hospital for the management of acute myocardial infarction during the COVID-19 outbreak. Eur Heart J 2020;41(19):1791−4.
[118] FGP Welt, Shah PB, Aronow HD, Bortnick AE, Henry TD, Sherwood MW, et al. Catheterization laboratory considerations during the coronavirus (COVID-19) pandemic: from the ACC's interventional council and SCAI. J Am Coll Cardiol 2020;75(18):2372−5.
[119] Daniels MJ, Cohen MG, Bavry AA, Kumbhani DJ. Reperfusion of ST-segment-elevation myocardial infarction in the COVID-19 era: business as usual? Circulation 2020;141(24): 1948−50.
[120] Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 2018;39(2):119−77.
[121] Esposito L, Di Maio M, Silverio A, Cancro FP, Bellino M, Attisano T, et al. Treatment and outcome of patients with coronary artery ectasia: current evidence and novel opportunities for an old dilemma. Front Cardiovasc Med 2021; 8:805727.
[122] Manfredi AA, Ramirez GA, Rovere-Querini P, Maugeri N. The neutrophil's choice: phagocytose vs make neutrophil extracellular traps. Front Immunol 2018;9:288.

[123] Hottz ED, Medeiros-de-Moraes IM, Vieira-de-Abreu A, de Assis EF, Vals-de-Souza R, Castro-Faria-Neto HC, et al. Platelet activation and apoptosis modulate monocyte inflammatory responses in dengue. J Immunol (Baltimore, Md : 1950) 2014;193(4):1864−72.
[124] Zarbock A, Polanowska-Grabowska RK, Ley K. Platelet-neutrophil-interactions: linking hemostasis and inflammation. Blood Rev 2007;21(2):99−111.
[125] Li X, Zheng Z, Li X, Ma X. Unfractionated heparin inhibits lipopolysaccharide-induced inflammatory response through blocking p38 MAPK and NF-κB activation on endothelial cell. Cytokine 2012;60(1):114−21.
[126] Maugeri N, de Gaetano G, Barbanti M, Donati MB, Cerletti C. Prevention of platelet-polymorphonuclear leukocyte interactions: new clues to the antithrombotic properties of parnaparin, a low molecular weight heparin. Haematologica 2005;90(6):833−9.
[127] Qian Y, Xie H, Tian R, Yu K, Wang R. Efficacy of low molecular weight heparin in patients with acute exacerbation of chronic obstructive pulmonary disease receiving ventilatory support. COPD 2014;11(2):171−6.
[128] Mycroft-West C, Su D, Elli S, Li Y, Guimond S, Miller G, et al. The 2019 coronavirus (SARS-CoV-2) surface protein (Spike) S1 Receptor Binding Domain undergoes conformational change upon heparin binding. bioRxiv 2020;Mar: 2:18−48.
[129] Trybala E, Liljeqvist JA, Svennerholm B, Bergström T. Herpes simplex virus types 1 and 2 differ in their interaction with heparan sulfate. J Virol 2000;74(19):9106−14.
[130] Simon AY, Sutherland MR, Pryzdial EL. Dengue virus binding and replication by platelets. Blood 2015;126(3):378−85.
[131] Russo V, Bottino R, D'Andrea A, Silverio A, Di Maio M, Golino P, et al. Chronic oral anticoagulation and clinical outcome in hospitalized COVID-19 patients. Cardiovasc Drugs Ther 2021:1−8.
[132] Russo V, Di Maio M, Attena E, Silverio A, Scudiero F, Celentani D, et al. Clinical impact of pre-admission antithrombotic therapy in hospitalized patients with COVID-19: a multicenter observational study. Pharmacol Res 2020;159:104965.
[133] Nadkarni GN, Lala A, Bagiella E, Chang HL, Moreno PR, Pujadas E, et al. Anticoagulation, bleeding, mortality, and pathology in hospitalized patients with COVID-19. J Am Coll Cardiol 2020;76(16):1815−26.
[134] Silverio A, Galasso G, De Luca G. Consolidating the value of fondaparinux for current treatment of non-ST-elevation acute coronary syndromes. Int J Cardiol 2021 Jul 15;335:21−3.
[135] Silverio A, Di Maio M, Prota C, De Angelis E, Radano I, Citro R, et al. Safety and efficacy of non-vitamin K antagonist oral anticoagulants in elderly patients with atrial fibrillation: systematic review and meta-analysis of 22 studies and 440 281 patients. Eur Heart J Cardiovasc Pharmacother. 2021 Apr 9;7(FI1):f20−9.
[136] Scudiero F, Canonico ME, Sanna GD, Dossi F, Silverio A, Galasso G, et al. Dual antiplatelet therapy with 3(rd) generation P2Y(12) inhibitors in STEMI patients: impact of body mass index on loading dose-response. Cardiovasc Drugs Ther. 2022 Feb 17.
[137] Silverio A, Di Maio M, Buccheri S, De Luca G, Esposito L, Sarno G, et al. Validation of the academic research consortium high bleeding risk criteria in patients undergoing percutaneous coronary intervention: a systematic review and meta-analysis of 10 studies and 67,862 patients. Int J Cardiol 2022;347:8−15.
[138] Rice GI, Thomas DA, Grant PJ, Turner AJ, Hooper NM. Evaluation of angiotensin-converting enzyme (ACE), its homologue ACE2 and neprilysin in angiotensin peptide metabolism. Biochem J 2004;383(Pt 1):45−51.
[139] Simões e Silva AC, Silveira KD, Ferreira AJ, Teixeira MM. ACE2, angiotensin-(1-7) and Mas receptor axis in inflammation and fibrosis. Br J Pharmacol 2013;169(3):477−92.
[140] Kuba K, Imai Y, Rao S, Gao H, Guo F, Guan B, et al. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. Nat Med 2005;11(8): 875−9.
[141] Iyer SN, Chappell MC, Averill DB, Diz DI, Ferrario CM. Vasodepressor actions of angiotensin-(1-7) unmasked during combined treatment with lisinopril and losartan. Hypertension (Dallas, Tex : 1979) 1998;31(2):699−705.
[142] Silverio A, Benvenga RM, Piscione F, Gulizia MM, Meessen J, Colivicchi F, et al. Prevalence and predictors of out-of-target LDL cholesterol 1 to 3 Years after myocardial infarction. A subanalysis from the EYESHOT post-MI registry. J Cardiovasc Pharmacol Therapeut 2021;26(2): 149−57.
[143] Zeiser R. Immune modulatory effects of statins. Immunology 2018;154(1):69−75.
[144] Castiglione V, Chiriacò M, Emdin M, Taddei S, Vergaro G. Statin therapy in COVID-19 infection. Eur Heart J Cardiovasc Pharmacother 2020;6(4):258−9.
[145] Laufs U, La Fata V, Plutzky J, Liao JK. Upregulation of endothelial nitric oxide synthase by HMG CoA reductase inhibitors. Circulation 1998;97(12):1129−35.
[146] Laufs U, Gertz K, Huang P, Nickenig G, Böhm M, Dirnagl U, et al. Atorvastatin upregulates type III nitric oxide synthase in thrombocytes, decreases platelet activation, and protects from cerebral ischemia in normocholesterolemic mice. Stroke 2000;31(10):2442−9.
[147] Violi F, Calvieri C, Ferro D, Pignatelli P. Statins as antithrombotic drugs. Circulation 2013;127(2):251−7.
[148] Tikoo K, Patel G, Kumar S, Karpe PA, Sanghavi M, Malek V, et al. Tissue specific up regulation of ACE2 in rabbit model of atherosclerosis by atorvastatin: role of epigenetic histone modifications. Biochem Pharmacol 2015; 93(3):343−51.
[149] Gupta A, Madhavan MV, Poterucha TJ, DeFilippis EM, Hennessey JA, Redfors B, et al. Association between antecedent statin use and decreased mortality in hospitalized patients with COVID-19. Nat Commun 2021;12(1):1325.
[150] Zhang XJ, Qin JJ, Cheng X, Shen L, Zhao YC, Yuan Y, et al. In-hospital use of statins is associated with a reduced risk of mortality among individuals with COVID-19. Cell Metabol 2020;32(2):176−87. e4.
[151] Russo V, Silverio A, Scudiero F, Attena E, D'Andrea A, Nunziata L, et al. Preadmission statin therapy and clinical outcome in hospitalized patients with COVID-19: an Italian multicenter observational study. J Cardiovasc Pharmacol 2021;78(1):e94−100.
[152] Barbieri A, Robinson N, Palma G, Maurea N, Desiderio V, Botti G. Can beta-2-adrenergic pathway Be a new target to combat SARS-CoV-2 hyperinflammatory syndrome?-lessons learned from cancer. Front Immunol 2020;11:588724.
[153] Vasanthakumar N. Beta-adrenergic blockers as a potential treatment for COVID-19 patients. Bioessays : News Rev Mol Cell Develop Biol 2020;42(11):e2000094.
[154] Wu L, Tai Y, Hu S, Zhang M, Wang R, Zhou W, et al. Bidirectional role of β2-adrenergic receptor in autoimmune diseases. Front Pharmacol 2018;9(1313).
[155] Manni M, Granstein RD, Maestroni G. β2-Adrenergic agonists bias TLR-2 and NOD2 activated dendritic cells towards inducing an IL-17 immune response. Cytokine 2011; 55(3):380−6.
[156] Haldar R, Shaashua L, Lavon H, Lyons YA, Zmora O, Sharon E, et al. Perioperative inhibition of β-adrenergic and COX2 signaling in a clinical trial in breast cancer patients improves tumor Ki-67 expression, serum cytokine levels, and PBMCs transcriptome. Brain Behav Immun 2018;73: 294−309.
[157] Zhou L, Li Y, Li X, Chen G, Liang H, Wu Y, et al. Propranolol attenuates surgical stress−induced elevation of the regulatory T cell response in patients undergoing radical mastectomy. J Immunol 2016;196(8):3460−9.