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The use of antiplatelet agents in patients with new coronavirus infection exampled by acetylsalicylic acid

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Abstract

The outbreak of the new coronavirus infection, which subsequently led to the pandemic, negatively affected preventive and treatment measures in patients with acute and chronic noncommunicable diseases, including cardiovascular diseases (CVDs). Arterial hypertension, diabetes mellitus, chronic kidney disease, coronary heart disease, obesity are the most prevalent diseases in the structure of multimorbidity that aggravate the outcomes in patients with COVID-19.

Patients with COVID-19 and in the absence of CVDs may develop cardiovascular complications, including life-threatening ones. In addition, some therapeutic agents administered at the beginning of the pandemic in experimental settings, such as antimalarial and antiviral drugs, may cause cardiovascular adverse events.

The severe course of COVID-19 is accompanied by the development of inflammatory alveolar lesions. Moreover, endothelial dysfunction also occurs, which leads to micro- and macrothrombosis in the blood vessels. Activation of thrombosis contributes to the development of thrombotic/thromboembolic complications.

Since activated platelets may contribute to the pathogenesis of thrombotic complications, the feasibility of using antiplatelets (acetylsalicylic acid, P2Y12 receptor blockers, dipyridamole) in COVID-19 is currently being studied. The available clinical and scientific data demonstrates the need for a comprehensive approach to the prevention and treatment of new coronavirus infection, which should

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include viral replication management, blocking the release of cytokines and other biologically active substances, endothelial dysfunction, coagulation, fibrinolysis and, most importantly, platelet function.

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Introduction

An outbreak of novel coronavirus infection (COVID-19), first reported on 8 December 2019 in Hubei Province, China, was defined as a pandemic by World Health Organization (WHO) experts on 11 March 2020. The pandemic has had a negative impact on a range of preventive and treatment interventions for patients with acute and chronic non-communicable diseases (CNCDs), including cardiovascular diseases (CVDs). Evidence from prospective and retrospective studies continues to shape our understanding of the long-term effects of COVID-19 and demands further study. It is extremely important to analyse the information on the characteristics of the endothelial thrombo-inflammatory syndrome in COVID-19 and the complex therapy of patients with this disease and high cardiovascular risk, with a focus on the appropriate use of acetylsalicylic acid, which is the subject of this article.

The burden of CVDs in the COVID-19 pandemic era

Arterial hypertension (AH), diabetes mellitus (DM), chronic kidney disease (CKD), coronary heart disease (CHD), and obesity are the most common comorbidities in the structure of multimorbidity and further exacerbate the adverse outcomes of COVID-19 [1]. To date, many investigators have reported that patients with CVDs have an increased risk for a more severe course of COVID-19 and the development of life-threatening complications.

According to Pranata R. et al. AH was associated with an increased combined adverse outcomes, including death, severe COVID-19, acute respiratory distress syndrome (ARDS), intensive care unit (ICU) treatment, and progression of CVD in patients with COVID-19 (odds ratio (OR) 2.11, 95% confidence interval (CI) 1.85-2.40, $p < 0.001$) [2].

A meta-analysis of 30 studies published between February and April 2020, involving 6389 patients with COVID-19, showed that acute myocardial injury and symptomatic heart failure (HF) occur in 15.7% and 11.5% of patients, respectively [3].

The burden of CVD in the COVID-19 pandemic era should be viewed from several perspectives. Patients with cardiovascular risk factors and pre-existing CVDs have a high risk of adverse outcomes; patients with COVID-19 and in the absence of CVDs may develop cardiovascular complications, including life-threatening ones; some therapeutic agents administered early in the pandemic under experimental conditions, such as antimalarials and antivirals, may cause cardiovascular adverse events [4].

The above-mentioned factors contribute to the formation of new phenotypes of major CVDs and related complications, which, among other things, can develop even after a certain period of time after infection, even if the bronchopulmonary system is not involved in the pathological process (Fig. 1).

When talking about the long-term consequences of COVID-19, it is impossible not to mention such a term as "long-term COVID", which confirms the fact that the patient continues to suffer after the acute phase of the disease and clinical recovery. The WHO proposes define the post-COVID-19 state as the persistence of symptoms beyond 3 months after acute SARS-CoV-2 infection, lasting at least 2 months and not explained by another disease [6]. The mechanisms of persistent cardiovascular damage after acute illness are poorly understood. One possible explanation may be a chronic inflammatory response, which in turn may be exacerbated by obesity-related inflammatory signalling, partially controlled by perivascular adipose tissue through the release of adipokines and chemokines, exacerbating endothelial dysfunction through dissociation of endothelial nitric

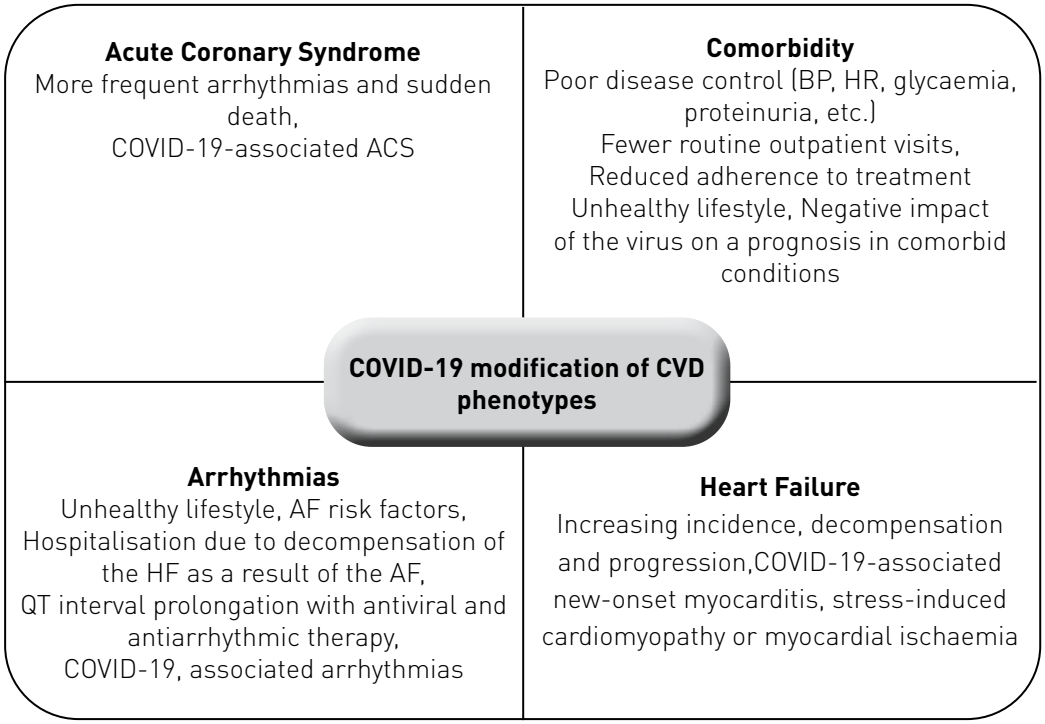

Fig. 1. New CVD phenotypes in the COVID-19 era

oxide synthetase and reactive oxygen species production [7].

COVID-19-associated endothelial thrombo-inflammatory syndrome

To date, sufficient data have been collected to demonstrate the different pathophysiological features and severity of COVID-19 disease in patients, which depend on age, leading risk factors and the presence of comorbidities.

In the severe course of COVID-19 associated with the development of pneumonia, hypoxaemia develops not only due to inflammatory alveolar damage, but also due to endothelial dysfunction leading to micro- and macrothrombosis in the vascular bed [8, 9].

Activation of thrombosis contributes to the development of thrombotic/thromboembolic complications. In addition, the development of microangiopathy with the presence of inflammation and thrombosis at the level of the microcirculatory bed without signs of thromboembolism has been observed, which is explained not only by the activation of thrombosis, but also by the direct effect of the SARS-CoV-2 virus on the endothelium and the rapidly progressing systemic immune inflammation. This results from an imbalance of T-cell activation with unregulated release of pro-inflammatory interleukins (ILs): IL-6, IL-7, IL-22, IL-17, etc., the cytokine storm triggers the processes of "immunothrombosis" leading to multiple organ failure and death [10, 11].

The pathobiology of coronavirus infection involves binding of the SARS-CoV-2 virus to the host angiotensin-converting enzyme 2 (ACE-2) receptor for entering into target cells. In this context, ACE-2 is considered to be an important modulator not only of the pathophysiological processes of several CVDs, including AH, CHD and HF, but also of the severity of symptoms associated with SARS-CoV2 virus infection.

ACE-2 receptors are found throughout the human body, on the airways cells, kidney, oesophagus, bladder, ileum, heart and central nervous system. ACE-2 is a key regulator of the renin-angiotensin system (RAS) and converts angiotensin II to angiotensin 1-7, which has protective vasodilatory and anti-inflammatory properties and counteracts the vasoconstrictive effects of angiotensin II [12, 13].

The SARS-CoV-2 virus binds to the catalytic site of the ACE-2 receptor and interferes with its ability to convert angiotensin II to angiotensin 1-7. As a result, the angiotensin II type 1 (ATR1) receptor, which is normally associated with ACE-2, is dissociated by the SARS-CoV-2 virus, allowing ATR1 to act freely and cause vasodilation, increased vascular permeability,

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oedema and ultimately the severe respiratory and cardiovascular manifestations of SARS-CoV-2 seen in some patients [14].

Evidence of disseminated intravascular coagulation (DIC) and pulmonary embolism is common in COVID-19. In a study by Tang N. [15] of 183 patients, the overall mortality rate was 11.5%; 71.4% of the patients who died and 0.6% of the surviving patients had evidence of disseminated intravascular coagulation during their hospital stay.

The intact endothelium of the vascular bed has so-called thromboresistance, which is caused by a number of factors, including negative surface charge and secretion of the antiaggregant prostacyclin, binding of thrombin by thrombomodullin and inactivation of other procoagulants (plasma factors V, VIII, IX and X), activation of the fibrinolytic system by synthesis of tissue plasminogen activator, production of nitric oxide, etc. [16].

It is important to note that damaged endothelium acts as a procoagulant factor. Adrenaline release and endothelin-1 secretion lead to transient vasospasm at the site of injury, which slows down blood flow and improves the interaction between platelets, coagulation factors and the site of injury. It also contributes to the decreased production of the physiological antiplatelet prostacyclin and increased release of platelet activators, stimulators of platelet adhesion and aggregation: adrenaline, ADP, Willebrand factor, thromboxane A2, platelet aggregation factor, etc. The anticoagulant activity of the endothelium is weakened; thrombomodulin activity, protein S synthesis, antithrombin III activation, tissue factor pathway inhibitor synthesis are reduced.

The work of Bois M. et al. seems to support the concept of microthrombi caused by COVID-19 [17]. In a small group of 15 individuals, the authors observed that postmortem fibrin microthrombi were more common (80%) than acute ischaemic injury (13%) and myocarditis (33%), suggesting a role for thrombosis in aggravating myocardial injury.

Elevated levels of cytokines (IL-1, IL-6, IL-17, IL-22, interferon-γ, tumour necrosis factor-α) may also contribute to myocardial damage, causing endothelial dysfunction, platelet activation, neutrophil recruitment and ultimately a hypercoagulable state [18].

Given the strong association of COVID-19 with increased thrombosis, the renaming of COVID-19 to MicroCLOTS (microvascular COVID-19 lung vessels obstructive thromboinflammatory syndrome) is being considered. The authors believe that in predisposed individuals, alveolar viral injury is followed by an inflammatory response and progressive endothelial thromboinflammatory syndrome with further multiorgan failure and death [19].

Issues in the complex management of patients with COVID-19

One of the main issues discussed in the resolution of the International Expert Council of the Eurasian Association of Therapists and the Russian Society of Cardiology on rehabilitation after COVID-19 was devoted to risk factors (RFs) for thrombosis formation in the post-hospital stage [20].

According to the results of the expert meeting, it was decided to consider COVID-19 as an independent risk factor for thrombosis formation and to include patients with the development of new diseases (CHD, HF, AH, type 2 DM) in the post-hospital period (up to 6 months, according to the available data) in a separate risk group for thrombotic events.

As activated platelets may also be involved in the pathogenesis of thrombotic complications, the appropriate use of antiplatelet drugs (acetylsalicylic acid, platelet P2Y12 receptor blockers, dipyridamole) is currently being investigated in COVID-19. Canzano P. therefore hypothesised that the cytokine storm described in COVID-19 patients may lead to sequential activation of cellular tissue factor (TF)-mediated coagulation, release of procoagulant microvesicles (MVs) and massive platelet activation. COVID-19 plasma added to the blood of healthy volunteers induced platelet activation similar to that observed in vivo. This effect was attenuated by a pre-incubation with tocilizumab, aspirin or a P2Y12 inhibitor [21].

The answer to this question cannot be clear, as antithrombotic therapy in COVID-19 may not only prevent the development of thrombosis and/or thromboembolism, but may also be the part of the pathogenetic treatment of the disease, reducing the severity of clinical manifestations and improving the prognosis. However, it should be noted that COVID-19 is associated with an increased risk of bleeding, which increases with the severity of the disease.

One of the most commonly recommended agents in cardiovascular and cerebrovascular pathology for primary and secondary prevention is acetylsalicylic acid (ASA). The action of ASA is based on the inacti-

vation of cyclooxygenase-1 (COX-1) and COX-2, which influence platelet activation and the action of prostanoids. COX-1 is involved in the conversion of arachidonic acid to prostaglandins and subsequently to thromboxane A2, a potent vasoconstrictor and stimulator of platelet activation and aggregation. COX-1 suppression is an irreversible process and persists throughout the life of the platelet. In addition, ASA acts through the acetylation mechanism to inactivate platelets by inhibiting glycoprotein P-selectin, preventing thrombin generation and increasing fibrinolysis [22, 23].

ASA suppresses the expression of genes involved in the activation of pro-inflammatory cytokines (tumour necrosis factor-α and interleukin-1β) and other mechanisms other than antiaggregation [24]. In particular, interleukin-1ß is the major mediator of platelet-induced activation of endothelial cells, causing enhanced release of chemokines and upregulation of endothelial adhesion molecules, which promotes adhesion of neutrophils and monocytes to the endothelium. The efficacy and safety of ASA administration have been confirmed in numerous trials and meta-analyses, allowing ASA to be considered as a standard of antithrombotic therapy [25-27].

The objective of the Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial was to evaluate the efficacy and safety of aspirin (at a dose of 150 mg/day in addition to standard therapy) in patients hospitalised for COVID-19. The trial was conducted in 177 clinics in the UK, two clinics in Indonesia and two clinics in Nepal. The primary outcome was the occurrence of death within 28 days. The trial was registered on ClinicalTrials.gov (NCT04381936) [28].

Previous searches of the major bibliographic databases such as MEDLINE, Embase, bioRxiv, medRxiv and WHO using the search terms "coronavirus infections", "SARS-CoV-2. mp", "coronavirus" or "CORONAVIRUS.mp", "COVID.mp", "COVID-19.mp", "2019-nCoV.mp", "COVID19.mp", "SARS-CoV2.mp" or "SARS-Cov2. mp" and "aspirin.mp", "aspirin/" or "acetylsalicylic acid/", and for the medRxiv and bioRxiv systems, the term "aspirin" was not found in published randomised controlled trials evaluating the effect of aspirin in the treatment of patients with COVID-19, which prompted the RECOVERY study.

The characteristics of the patients included in the trial are shown in Table 1.

Table 1. **Baseline characteristics of patients**

	Prescribed treatment	
	Aspirin (n = 7351)	**Standard treatment (n = 7541)**
Age, (years)	59.2 (14.1)	59.3 (14.3)
< 70	5658 (77 %)	5786 (77 %)
70–79	1163 (16 %)	1165 (15 %)
⩾ 80	530 (7 %)	590 (8 %)
Gender		
Males	4570 (62 %)	4631 (61 %)
Females*	2781 (38 %)	2910 (39 %)
Ethnicity		
Europeoids	5474 (74 %)	5655 (75 %)
Negroids, Mongoloid and ethnic minorities	1176 (16 %)	1202 (16 %)
Unknown	701 (10 %)	684 (9 %)
Number of days since the onset of the symptoms	9 (7–12)	9 (6–12)
Number of days since hospital admission	1 (1–3)	2 (1–3)
Respiratory support		
None or oxygen therapy	4936 (67 %)	5036 (67 %)
Non-invasive ventilation	2057 (28 %)	2133 (28 %)
Invasive ventilation	358 (5 %)	372 (5 %)
Biochemical parameters		
C-reactive protein, mg/l	88 (47–146)	91 (47–150)
Creatinine, μmol/l	76 (63–93)	76 (62–92)
D-dimer, ng/ml	475 (205–1088)	489 (210–1083)
Pre-existing conditions		
Diabetes mellitus	1588 (22 %)	1659 (22 %)
Cardiovascular diseases	776 (11 %)	788 (10 %)
Chronic pulmonary diseases	1425 (19 %)	1411 (19 %)
Tuberculosis	20 (< 1 %)	21 (< 1 %)
HIV	25 (< 1 %)	21 (< 1 %)
Severe liver diseases†	67 (1 %)	53 (1 %)
Severe kidney failure‡	214 (3 %)	251 (3 %)
Any of the above-mentioned conditions	3154 (43 %)	3247 (43 %)
Use of corticosteroids		
Yes	6906 (94 %)	7109 (94 %)
No	441 (6 %)	425 (6 %)
No data	4 (< 1 %)	7 (< 1 %)
Test result for SARS-CoV-2		
Positive	7140 (97 %)	7327 (97 %)
Negative	87 (1 %)	86 (1 %)
Unknown	124 (2 %)	128 (2 %)

Notes. Data are presented as n (%), mean (SD) or median (IQR).
* Including 58 pregnant women.
† Requiring a constant supervision by a specialist.
‡ Glomerular filtration rate less than 30 ml/мin/1.73 м².

Aspirin (in combination with standard therapy) was not associated with a reduction in mortality compared with standard therapy. Within the first 28 days of hospitalisation, the mortality rate in the aspirin and standard of care groups was 17 % (p = 0.35), and the

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Table 2. **Effect of aspirin prescription on study outcomes**

	Prescribed treatment		OR (95% ДИ)	p
	Aspirin (n = 7351)	Standard treatment (n = 7541)		
Primary outcome				
Mortality within 28 days	1222 (17%)	1299 (17%)	0.96 (0.89–1.04)	0.35
Secondary outcome				
Discharge mean time of a living patient (interquartile range), days	8 (от 5 до > 28)	9 (от 5 до > 28)	—	—
Hospital discharge within 28 days	5496 (75%)	5548 (74%)	1.06 (1.02–1.10)	0.0062
Transition to invasive mechanical ventilation or death*	1473/6993 (21%)	1569/7169 (22%)	0.96 (0.90–1.03)	0.23
Invasive mechanical ventilation	772/6993 (11%)	829/7169 (12%)	0.95 (0.87–1.05)	0.32
Death	1076/6993 (15%)	1141/7169 (16%)	0.97 (0.90–1.04)	0.39
Secondary clinical outcomes				
Use of artificial ventilation	1131/4936 (23%)	1198/5036 (24%)	0.96 (0.90–1.03)	0.30
Non-invasive ventilation	1101/4936 (22%)	1162/5036 (23%)	0.97 (0.90–1.04)	0.36
Invasive mechanical ventilation	296/4936 (6%)	325/5036 (6%)	0.93 (0.80–1.08)	0.35
Successful cessation of invasive mechanical ventilation	135/358 (38%)	135/372 (36%)	1.08 (0.85–1.37)	0.54
Renal replacement therapy	273/7291 (4%)	282/7480 (4%)	0.99 (0.84–1.17)	0.93

Note. RR — The rate ratio for the incidence of death and discharge from hospital within 28 days, and the rate ratio for the transition to invasive mechanical ventilation or death (and its components).
* Excluding patients already on invasive mechanical ventilation at randomisation.

event rates did not differ between the pre-specified subgroups.

However, there was a small but statistically significant increase in the proportion of patients discharged within the first 28 days in the aspirin group (75% vs 74%; OR 1.06; 95% CI 1.02-1.10; p = 0.0062) (Table 2).

Thus, it was concluded that aspirin has a small advantage in the complex therapy of patients with COVID-19, which is not a sufficient reason to include aspirin in the scheme of routine therapy of patients with COVID-19.

Russian scientists analysed the efficiency of interaction of the aspirin molecule with the active centres of a number of proteins of the SARS-CoV-2 virus using the molecular docking method, and it was shown that aspirin is able to inhibit the activity of some of them, which may affect the design of further studies on this drug. The results of this study were published in the Journal of Molecular Structure in March 2022 [29].

The available clinical and scientific data demonstrates the need for a comprehensive approach: to the prevention and treatment of new coronavirus infection, which should include viral replication management, blocking the release of cytokines and other biologically active substances, endothelial dysfunction, coagulation, fibrinolysis and, most importantly, platelet function.

Therefore, ASA, as an inexpensive, widely available, safe and time-tested anti-inflammatory, antithrombotic drug, can be considered as an additional therapeutic option for COVID-19 treatment, especially in the group of patients with cardiovascular pathology. In addition, experts of the European Society of Cardiology confirm the fact of necessity of continuation of ASC intake in persons with chronic coronary syndrome on COVID-19 background for secondary prevention.

Conclusion

Taking into account the available scientific evidence, a comprehensive approach to the prevention and treatment of new coronavirus infections is reasonable, which should include an impact on all pathogenetic mechanisms of the disease development: viral replication, blocking cytokine release, endothelial dysfunction, coagulation, fibrinolysis and, most importantly, platelet function. These data allow us to consider ASC as one of the possible additional treatment options for COVID-19, especially in the group of patients with cardiovascular pathology and high cardiovascular risk.

Conflict of interest: none declared.

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