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Additional evidence against widespread use of inpatient antiplatelet therapy in coronavirus infection: data from a randomized controlled trial

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Activation of thrombogenesis with an increase in microvascular thrombosis, as well as venous and (less often) arterial thrombotic complications with larger blood clots is one of the characteristic features of coronavirus disease 2019 (COVID-19), closely related to its severity and prognosis [1]. At the same time, according to numerous data, along with blood coagulation activation, functional activity of platelets increases [2]. Therefore, it is believed that suppression of platelet function may be one of the targets of therapeutic interventions for COVID-19.

The retrospective real-world evidence analysis indicates a possible benefit from the use of acetylsalicylic acid (ASA) in COVID-19. Combined results of 6 observational studies published up to April 16, 2021 and including a total of 13993 patients showed a 54% decrease in mortality ($p<0,001$) with prescription of low-dose ASA before hospitalization or after admission to the hospital, and this pattern was maintained in cases where ASA began to be used in the hospital [3]. However, such data do not confirm that the effect is associated with the analyzed intervention, since the compared groups of patients inevitably turn out to be unbalanced in many factors that can affect the prognosis. Attempts to balance them according to known risk factors using various mathematical approaches are far from always successful, since they can additionally distort the result and do not take into account indicators that were not recorded during data collection. Accordingly, the analyses of non-randomized studies are always only a hypothesis that is tested in randomized controlled trials.

In 2021, the results of a prospective multicenter (177 healthcare facilities) international (UK, Indonesia, Nepal) open-label Randomised Evaluation of Covid-19 Therapy (RECOVERY) study were published, including 14892 patients ⩾18 years old, hospitalized with possible or verified COVID-19, which was eventually laboratory confirmed in 97% of cases who did not receive antiplatelet agents [4]. The median time after symptom onset was 9 days. All patients received respiratory support (invasive mechanical ventilation was performed in 5%), corticosteroids – 94%. The use of ASA at a dose of 160 mg/day did not contribute to a decrease in mortality within 28 days. At the same time, in patients who initially had mechanical ventilation, there was no decrease in the number of those who needed ventilatory support or mortality. The incidence of thrombotic complications was 4,6% in the ASA group and 5,3% in the control group ($p=0,07$), and these were mainly venous thromboembolic complications, while the incidence of arterial thrombosis and thromboembolism did not reach 1%. The only benefit of ASA was a reduction in length of stay in hospital by 1 day (ASA group, 8 days; control group, 9 days) and a slightly more frequent discharge of patients alive in the first 28 days – 75 vs 74%, respectively ($p=0,0062$). This was achieved at the cost of a twofold increase in the risk of major GI bleeding (0,8% vs 0,4%, respectively; relative risk, 2,09 ($p=0,0014$)), increased risk of any major bleeding (1,6 vs 1,0%, respectively; relative risk, 1,55 ($p=0,0028$)), including requiring blood transfusion and surgery. However, this clinical trial leaves hope for the possible benefit of ASA at a lower dose (75-100 mg/day), when used earlier in the disease, as well as in hospitalized patients who, for some reason, do not receive anticoagulants.

In January 2022, the results of a prospective multicenter (60 healthcare facilities) international (Brazil, Italy, Spain and the USA) randomized open-label

Accelerating COVID-19 Therapeutic Interventions and Vaccines 4 ACUTE (ACTIV-4a) study were published, including 562 patients hospitalized with laboratory-verified COVID-19, the severity of which did not require treatment in the intensive care unit [5]. The results showed no need for high-flow oxygen therapy at a rate of ⩾20 l/min, non-invasive or invasive mechanical ventilation, infusion of vasopressor or inotropic drugs, extracorporeal membrane oxygenation. For inclusion in the study, following evidence of adverse disease course was required: D-dimer blood concentration at least 2 times higher than the upper reference level or age 60-84 years. Patients <60 years of age were included if they required respiratory support (>2 L/min) or had hypertension, diabetes, estimated glomerular filtration rate <60 ml/min/1,73 m^2, CVD or body mass index >35 kg/m^2. Patients should not have been included later than 72 hours after hospitalization, with an expected discharge within the next 72 hours, if dual antiplatelet therapy was necessary.

The mean age of studied patients was 52,7±13,5 years. At randomization, oxygen therapy was carried out in 88,4% of them, while D-dimer concentration at least 2 times higher the upper reference limit was noted in 41%. Prior CVD (mainly hypertension) was observed in 43,7% of patients in the $P2Y_{12}$ inhibitor group and in 55,8% in the conventional treatment group. At the same time, the cumulative incidence of CVD, in which antiplatelet agents are indicated (coronary artery disease, peripheral atherosclerosis, cerebrovascular disease), was only 6,9%.

Prior to randomization, ASA was received by 15,0% of patients in the $P2Y_{12}$ inhibitor group and 13,4% in the conventional treatment group. At the physician's discretion, after inclusion, ASA could be withdrawaled or continued; in the latter case, it was recommended to use a dose of 80-100 mg/day, and in combination with ticagrelor <100 mg/day. Corticosteroids, remdesivir, and interleukin-6 antagonists were used in 64,1%, 52,1%, and in 2,8% of patients.

All patients had to receive high (therapeutic) doses of heparins. In patients randomized to the $P2Y_{12}$ inhibitor group, at the physician's discretion, ticagrelor was used at a dose of 60 mg 2 times a day (63%) or clopidogrel at a dose of 75 mg/day with a possible first dose of 300 mg (37%) for 14 days or until discharge at an earlier discharge time.

The median duration of $P2Y_{12}$ inhibitor therapy was 6 days (interquartile range, 4-8 days). None of the patients of conventional treatment group received $P2Y_{12}$ inhibitors.

The intervention effectiveness was assessed using a special scale characterizing the number of days without the need for organ support therapy in case of inhospital death (-1 point) or, in survivors, the number of days when respiratory and cardiovascular support was not required up to the 21st days after hospitalization (the higher the final score, the better). The study was stopped after a predetermined futility boundary of adding a platelet $P2Y_{12}$ inhibitor to conventional treatment was reached. At the same time, the median number of days without organ support need in the $P2Y_{12}$ inhibitor group was 21 days (interquartile range, 20-21 days), while in the conventional treatment group – 21 days (interquartile range, 21-21 days), which corresponded to the odds ratio of 0,83 with 95% confidence interval of 0,55-1,25. A similar result was obtained when 69 patients who did not receive therapeutic-dose heparins were excluded from the analysis. The result did not depend on sex, age, intensity of respiratory support at the study inclusion, the presence of obesity (body mass index >30 kg/m^2) and CVD, the initial D-dimer concentration, the use of steroids, ticagrelor or clopidogrel.

There were no significant differences between the groups in the need for organ support therapy, 28-day incidence of thrombotic complications, and inhospital mortality. At the same time, the incidence of thrombotic complications was generally low and amounted to 2,5%.

The primary safety endpoint included major bleeding according to the International Society on Thrombosis and Haemostasis criteria during 28 days. It occurred in 2,0% of patients in the $P2Y_{12}$ inhibitor group and 0,7% of cases in the conventional treatment group (p=0,15).

Therefore, the results of this randomized controlled trial do not justify the widespread use of $P2Y_{12}$ inhibitors in addition to standard COVID-19 therapy, including parenteral administration of high (therapeutic) doses of anticoagulants, in hospitalized patients who do not initially require intensive care. However, this study does not answer the question of its effectiveness with an earlier antiplatelet therapy start (in particular, before hospitalization), as well as with a longer intake of antiplatelet agents. The unexpectedly low incidence of major bleeding is noteworthy, indicating the safety of $P2Y_{12}$ inhibitor therapy in the studied group of patients, despite the simultaneous use of therapeutic-dose heparins and ticagrelor. The incidence of clinically relevant non-major bleeding was not considered in this study.

A segment of the ACTIV-4a trial in hospitalized patients with more severe COVID-19 manifestations is ongoing.

Thus, up-to-date evidence does not support the widespread use of antiplatelet agents for the COVID-19 treatment in addition to parenteral anticoagulants in hospitalized patients. It remains to be hoped that antiplatelet monotherapy may be useful for earlier and/or sufficiently long-term treatment of the disease in patients not receiving anticoagulants, as well as at a higher risk of unfavorable outcome and cardiovascular events. Further randomized controlled trials will answer this question. To date, it seems clear that the available data do not negate the need for antiplatelet therapy in patients with indications for it, as prescribed by current clinical guidelines.

Relationships and Activities: none.

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