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Can low-dose aspirin help the RECOVERY of patients hospitalized with COVID-19?

Giovanna Liuzzo [1,2]* and Carlo Patrono [3]

[1]Department of Cardiovascular Medicine, Fondazione Policlinico Universitario A. Gemelli - IRCCS; [2]Department of Cardiovascular and Pulmonary Science, Catholic University School of Medicine, Largo A. Gemelli, Rome 8-00168, Italy; and [3]Department of Pharmacology, Catholic University School of Medicine, Largo A. Gemelli, Rome 8-00168, Italy

Comment on 'Aspirin in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial' which was published online in *Lancet*. https://doi.org/10.1016/S0140-6736(21)01825-0.

Key Points

- The RECOVERY trial was established as an adaptive, randomized, open-label clinical trial to test a range of potential treatments for patients hospitalized with COVID-19. Between November 2020 and March 2021, the RECOVERY Collaborative Group included 14 892 patients [mean age ± standard deviation (SD), 59 ± 14 years] hospitalized with COVID-19 to assess the efficacy and safety of low-dose aspirin (150 mg once daily) added to usual care when compared with usual care alone.[1] The primary outcome was 28-day all-cause mortality. The vast majority (94%) of patients were also treated with corticosteroids (mostly, dexamethasone) and low molecular weight heparin (LMWH; 34% with a high-dose and 60% with a standard-dose LMWH). Moreover, two-thirds received no respiratory support or simple oxygen and one-third non-invasive ventilation or invasive mechanical ventilation.[1]
- Overall, 1222 (16.6%) of 7351 patients allocated to aspirin and 1299 (17.2%) of 7541 patients allocated to usual care died within 28 days [rate ratio (RR) 0.96; 95% confidence interval (CI), 0.89–1.04; $P = 0.35$). Consistent results were seen in all pre-specified subgroups. Patients allocated to aspirin had a slightly shorter duration of hospitalization (median 8 vs. 9 days), and a significantly higher proportion of patients were discharged from hospital within 28 days, but the effect size was small (75 vs. 74%; RR 1.06; 95% CI, 1.02–1.10; $P = 0.0062$). Among those not on invasive mechanical ventilation at baseline, there was no significant difference in the proportion who progressed to invasive mechanical ventilation or death (21 vs. 22%; RR 0.96; 95% CI, 0.90–1.03; $P = 0.23$).
- The incidence of both venous and arterial thrombotic events was lower [4.6 vs. 5.3%; absolute reduction ± standard error (SE) 0.6 ± 0.4%], whereas the incidence of major bleeding events was higher (1.6 vs. 1.0%; absolute increase 0.6 ± 0.2% SE) in the aspirin group than in the usual care group.

Comment

Pulmonary thrombosis is often observed in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pneumonia, and platelets are primed to spread proinflammatory and procoagulant activities in the systemic circulation of patients with COVID-19.[2] In the clinical setting of SARS-CoV-2 pneumonia, microvascular thrombosis may extend upstream to larger arteries and downstream to pulmonary veins in the severely inflamed tissues.[2] Depending on the dose, aspirin treatment might have beneficial effects in severe COVID-19 through several mechanisms, including inhibition of thromboxane (TX)-dependent platelet activation,[3] down-regulation of cyclooxygenase (COX)-2-dependent inflammation, and reduced formation of neutrophil extracellular traps.[4] Moreover, the surface of platelet aggregates facilitates the assembly of coagulation factors, explaining the prevention of both arterial and venous thrombotic events by low-dose aspirin.[3]

The failure of the RECOVERY trial to meet its primary endpoint of 28-day all-cause mortality might reflect the limited participation of TXA_2-dependent platelet activation in the progression to the fatal respiratory complications of the disease, as suggested by the small numerical differences in several secondary outcomes. In fact, 95% of 2521 deaths were classified as due to COVID-19, with only 30 deaths reported as due to vascular causes (20 in the usual care group and 10 in the aspirin group).[1] As for a direct anti-inflammatory effect of aspirin, this would be limited by the relatively low dose (150 mg) and prolonged dosing interval (once daily), in the light of the short half-life of the drug in the human circulation.[3] Moreover, the

* Corresponding author. Tel: +39 06 30154187, Email: giovanna.liuzzo@unicatt.it

potential clinical read-out of transiently inhibited COX-2 activity in inflammatory cells would be dwarfed by the suppression of COX-2 induction by concomitant corticosteroid treatment.[5] Dexamethasone had been previously shown to significantly reduce 28-day all-cause mortality by 17% in patients hospitalized with COVID-19, supporting an important role of inflammation-mediated lung injury, particularly among those who were receiving either invasive mechanical ventilation or oxygen therapy at randomization.[6]

The modest, non-significant reduction in thrombotic events associated with low-dose aspirin treatment is probably explained by the fact that the vast majority (626 of 735) of these outcomes were episodes of pulmonary embolism, occurring despite concomitant (inadequate?) anticoagulant therapy, with only 80 presumably atherothrombotic events (49 in the usual care group and 31 in the aspirin group).[1] As expected, major bleeds were significantly increased by aspirin therapy (although intra-cranial bleeds were numerically lower), with about three-quarters of the absolute excess in these events being due to gastrointestinal (GI) bleeding.[1] Cytoprotective therapy (e.g. proton-pump inhibitor) was not mentioned among the concurrent treatments or co-medication required by the protocol, although the enrolled patients had at least four risk factors for upper GI bleeding, i.e. advanced age in one-quarter, antiplatelet therapy in one-half, anticoagulant and corticosteroid therapy in the vast majority.

Finally, the reassuring mortality data of the RECOVERY trial in a very high-risk acute medical setting are consistent with the results of a tabular meta-analysis of 14 randomized clinical trials of aspirin for long-term primary prevention,[7] that suggested a small, non-significant benefit of antiplatelet therapy on all-cause mortality of a similar size as recorded in the present study.[1]

In conclusion, based on a large trial with adequate statistical power, low-dose aspirin was not associated with significantly lower 28-day mortality or risk of progressing to invasive mechanical ventilation or death, in patients hospitalized with COVID-19, but produced a small increase in the rate of being discharged alive within 28 days.[1] The latter finding suggests the opportunity of further investigating the underlying mechanism(s) and optimal dose requirement, before testing the reproducibility of these potential beneficial effects of aspirin in new trials.

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