

Could Low Doses Acetylsalicylic Acid Prevent Thrombotic Complications in COVID-19 Patients?

Clinical and Applied
Thrombosis/Hemostasis
Volume 27: 1-4
© The Author(s) 2021
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/10760296211014592
journals.sagepub.com/home/cat



Federico Cacciapuoti, MD, PhD¹ , and Fulvio Cacciapuoti, MD²

Abstract

Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2) can induce inflammatory and thrombotic complications of pulmonary district (interstitial pneumonia), sometimes evolving toward acute respiratory failure. In adults, Acetylsalicylic Acid (ASA) is widely employed at low doses for primary and secondary prevention of cardiovascular diseases (CVD). Apart their anti-thrombotic effect, low ASA doses also exert an anti-inflammatory action. So, when these are assumed for CVD prevention, could prevent both inflammatory reaction and pro-coagulant tendency of Coronavirus-2019 (COVID-19) infection. In addition, some patients receiving ASA are simultaneously treated with Statins, to correct dyslipidemia. But, for their pleiotropic effects, Statins can also be useful to antagonize pulmonary thrombo-inflammation induced by COVID-19. Thus ASA, with or without Statins, employed for CVD prevention, could be useful to avoid or minimize inflammatory reaction and thrombotic complications of COVID-19. But, further studies performed in a wide range are requested to validate this hypothesis.

Keywords

SARS-CoV-2, interstitial pneumonia, acetylsalicylic acid, statins, inflammation, thromboembolism

Date received: 01 March 2021; revised: 25 March 2021; accepted: 14 April 2021.

Introduction

The recent pandemic Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2) may cause some thromboembolic complications¹ and bilateral interstitial pneumonia (Figure 1), until acute respiratory distress. Alveolar inflammation caused by the hyper-production of pro-inflammatory cytokines (cytokines' storm) and interleukins triggers thrombosis and increased coagulation. Multisystemic endothelitis associated with microthrombi formation often complicates the Coronavirus Disease-2019 (COVID-19) course and may be responsible for multi-organ dysfunctions, pulmonary embolism (Figure 2), significant injury in the respiratory tract with high mortality rate.^{2,3}

Acetylsalicylic Acid

It is known that Acetylsalicylic Acid (ASA) at high doses (650 mg to 1 g/day) has anti-thrombotic, anti-pyretic, anti-inflammatory and anti-viral activities⁴⁻⁶ while, at low doses (75 to 325 mg/day), has an anti-inflammatory and anti-thrombotic effect, that can act on pro-coagulant and thromboembolic respiratory events induced by COVID-19.⁷

The efficacy of low doses of ASA (also called Aspirin) as antithrombotic agent has been demonstrated in several trials that evidenced the non-superiority of higher doses compared to lower doses.⁸ Traditionally, the anti-inflammatory dose of Aspirin in humans is 1 gr. (high dose). But, at low doses, Aspirin is able to dampen acute inflammatory response by triggering 15-epi-lipoxin A₄. In turn, this compound acts by inhibiting leukocyte/endothelial attachments.⁹ In addition, low-dose Aspirin reduced vascular inflammation in mice, decreased macrophage foam cell content and increased the stability of atherosclerotic plaque.¹⁰

Thus, low ASA doses are commonly employed for primary and secondary prevention of thrombosis against cardiovascular

¹ Department of Internal Medicine, "L. Vanvitelli" Campania University, Naples, Italy

² Department of Cardiology and Coronary Intensive Care Unit, "V. Monaldi" Hospital, Naples, Italy

Corresponding Author:

Federico Cacciapuoti, Department of Internal Medicine, "L. Vanvitelli" Campania University, Piazza L. Miraglia, 2, 80138 Naples, Italy.
Email: fulvio.cacciapuoti@gmail.com



Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons

Attribution-NonCommercial 4.0 License (<https://creativecommons.org/licenses/by-nc/4.0/>) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (<https://us.sagepub.com/en-us/nam/open-access-at-sage>).

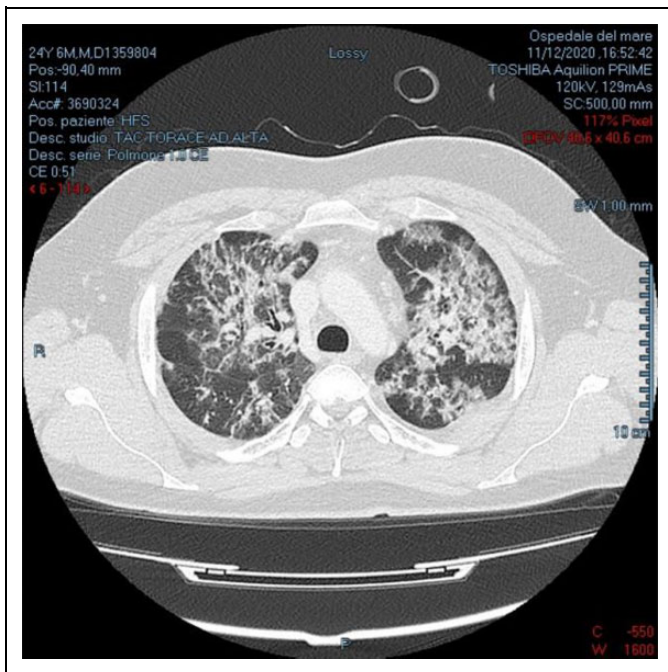


Figure 1. CT showing severe bilateral interstitial pneumonia (“ground glass” opacities) in a patient affected by COVID-19.

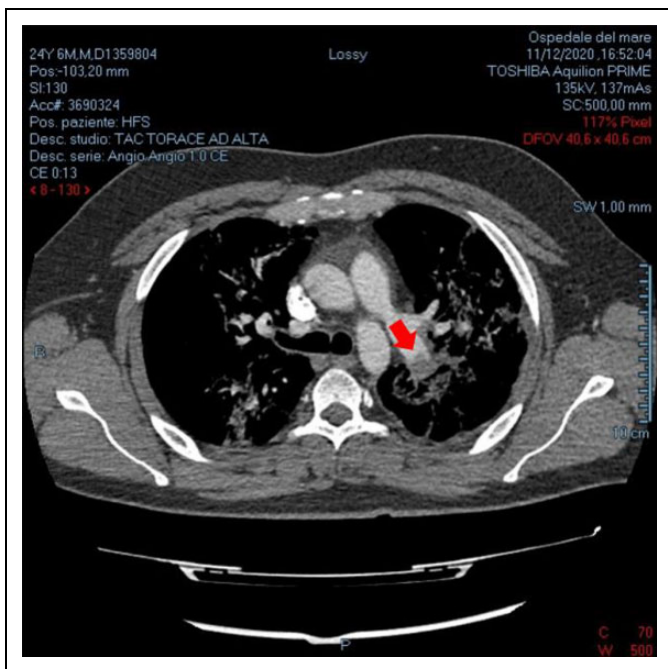


Figure 2. CT of pulmonary thromboembolism (arrow) found in an individual with COVID-19.

disease (CVD).¹⁰⁻¹² But, the potential benefits are offset by potential harms of bleeding when ASA is employed as anti-thrombotic drug for primary CVD prevention.¹³ On the contrary, when ASA is used in patients previously suffering for an acute ischemic event (secondary prevention), the benefits outweigh the potential harms.¹⁴ So, the use of ASA in the primary

prevention of CVD is not approved, even its beneficial effects on the mortality were pointed out.¹⁵ On the contrary, its employment for secondary prevention is widely used.¹⁶

In this review, we hypothesized that low doses of ASA, already assumed for its anti-inflammatory and anti-thrombotic effects on CVD and/or its complications (atherogenic plaques), are also useful for weaken the thrombotic complications induced by COVID-19.⁷

Mechanisms of Action of COVID-19

COVID-19 causes an inflammatory state prevalently located in the cells of pulmonary alveoli. In turn, the infection of alveolar, endothelial cells leads to activation and dysfunction of the endothelium. At the beginning coronavirus enters in the cells through ACE2 receptor by the S spike protein. Subsequently, the endothelial dysfunction favors the shift of the hemostatic balance toward the pro-coagulation starting the pro-thrombotic process.¹⁷ That happens by triggering complex molecular events that leads to inflammation by cytokines’ over-production (cytokine storm). In turn, the condition is responsible for the platelet’s activation, with increased levels of von Willebrand Factor and Factor VIII.

In addition, the increased levels of glycoproteins contribute to thrombin generation and fibrin clot formation. Consequently, an increased thrombotic risk happens, that favors arterial thrombotic events, such as acute myocardial infarction, ischemic stroke and peripheral arterial disease.³

Anti-Thrombotic ASA Effects

Antithrombotic effect of ASA is due to the inhibition of platelets’ function by acetylation of the COX-1 at the functionally important amino acid serine 529. On the other hand, the COX-1 acetylation inhibits TXA-2, a stimulator of platelet reactivity.¹⁸ This inhibition results in anti-thrombotic effect, able to prevent thrombosis on the arterial walls.¹⁹ Most intensively, ASA is employed against arterial thrombosis, while it is not commonly used in venous thrombosis. Nevertheless concerning this topic, some trials (WARFASA, ASPIRE and a recent meta-analysis) evidenced that ASA also reduces venous thrombosis without significantly increasing the risk of bleeding.²⁰⁻²² Really, the most common pro-coagulative event happening in COVID-19 is venous thromboembolism (VTE), while arterial thrombosis seems to have a minor incidence.²³ Some reports also referred on microangiopathies, characterized by microangiopathic hemolytic anemia, thrombocytopenia and organ damage, such as neurological, renal and cardiac dysfunction.^{24,25} It must be also added that pro-coagulation in COVID-19 patients is evidenced by the laboratory findings, showing a thrombocytopenia and an increased D-dimer levels.²⁶

In Figure 3, the mechanism through COVID-19 induces both arterial and venous thrombi are illustrated.

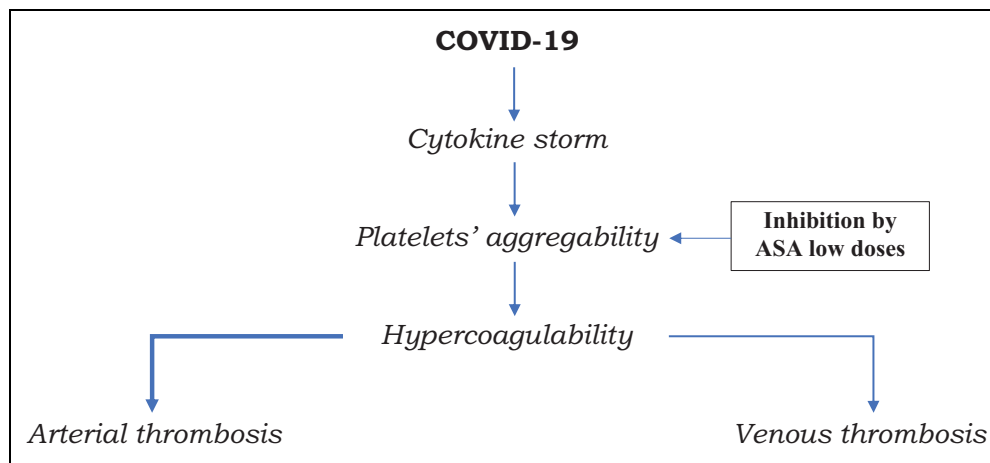


Figure 3. Events following the infection with COVID-19. Inhibition of arterial and venous thrombosis induced by low doses ASA.

Conclusive Remarks

Contrarily to the multiple effects (anti-inflammatory, analgesic, anti-pyretic anti-thrombotic and antiviral action against DNA and RNA viruses) obtained with high ASA doses, low doses have antithrombotic and anti-inflammatory effects only.⁷ Consequently, adult individuals receiving low ASA doses and nowadays affected by SARS-CoV-2, could be protected against possible inflammatory and thrombotic complications. To confirm this hypothesis, a retrospective, observational study performed by the Researches of the Maryland University (US) demonstrated that hospitalized COVID-19 patients who were taking a daily low-dose Aspirin in secondary prevention for CVD had a significantly lower risk of inflammatory and coagulative events compared to those not taking Aspirin.²⁷ Concerning that, in the near future, the RECOVERY II (Randomized Evaluation of COVID-19 thERapY II) trial will be performed to test the effectiveness of low dose Aspirin as anti-inflammatory and antithrombotic drug in the treatment of patients with COVID-19.

Frurthermore, Hydroxy-Methyl-Glutaryl-Coenzyme A reductases (Statins) are other drugs frequently employed in CVD patients, to reduce dyslipidemia.²⁸ Nevertheless, they also could supply some beneficial effects against the complications of COVID-19. These favorable effects depend on their pleiotropic actions, such as anti-thrombotic, anti-inflammatory, anti-oxidative effects and improvement of endothelial dysfunction. Moreover, Statins also induce the upregulation of Angiotensin-Converting Enzyme (ACE)-2 receptor, used for cellular entry of the coronavirus.^{29,30} These beneficial results were confirmed by a recent, retrospective study. But in this case, the higher severity of COVID-19 patients due to the CV comorbidities and treated with statin therapy, frustrated the supposed favorable effects.³¹

Nevertheless, these observations on Aspirin at low doses (with or without Statins) about the favorable effects on the complications of COVID-19 could be confirmed by further studies performed in a wide range.

Abbreviations

SARS-CoV-2, Severe Acute Respiratory Syndrome-Coronavirus-2; COVID-19, Coronavirus Disease-2019; ASA, Acetylsalicylic Acid; RNA, Ribo Nucleic Acid; DNA, DeossiNucleic Acid; CVD, Cardio-Vascular Disease; ACE 2, Angiotensin Converting Enzyme-2; VTE, Venous Thrombo Embolism; COX-1, CycloOXygenase-1; TXA-2, ThromboXane-2; WARFASA, WARFarin and AcetylSalicylic Acid; ASPIRE, ASpirin to Prevent Recurrent Venous Embolism.

Authors' Note

Both authors equally contributed to the study conception and development.


Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iD

Federico Cacciapuoti  <https://orcid.org/0000-0002-0532-3242>

References

1. Giannis D, Ziogas IA, Gianni P. Coagulation disorders in coronavirus infected patients: COVID-19, SARS-CoV-1, MERS-CoV and lessons from the past. *J Clin Virol.* 2020;95:104362.
2. Subramanian S, Sharrer I. Procoagulant activity during viral infections. *Front Biosc (Landmark Ed).* 2018;23:1060-1081.
3. Abdou-Ismail MY, Diamond A, Kapoor S, Arafath Y, Nayak L. The hypercoagulable state in COVID-19: incidence, pathophysiology and management. *Thromb Res.* 2020;194:101-105.
4. Amin AR, Attur RG, Pillinger M, Abramson SB. The pleiotropic function of aspirin: mechanisms of action. *Cell Mol Life Sci.* 1999;56(3-4):305-312.
5. Glatthaar-Saalmuller B, Mair KH, Saalmuller A. Anti-viral activity of aspirin against RNA viruses of the respiratory tract—an in vitro study. *Influenza Other Resp Viruses.* 2017;11(1):85-92.

6. Muller C, Karl N, Ziebuhr J, Pleska S. D3-Lysine acetylsalicylate + glycine impairs coronavirus replication. *J Antivir Antiretrovir*. 2016;8(4):42-50.
7. Bianconi V, Violi F, Fallarino F, Pignatelli P, Sahebkar A, Pirro M. Is acetylsalicylic acid a safe and potentially useful choice for adult patients with COVID-19? *Drugs*. 2020;80(14):1383-1396.
8. Patrono C, Baigent C, Hirsh J, Roth G. Antiplatelet drugs: American College of Chest Physicians Evidence Based Clinical Practice Guidelines (8th ed.). *Chest*. 2008;133(6 suppl):199S-233S.
9. Morris T, Stables M, Hobbs A, et al. Effects of low-dose aspirin on acute inflammatory responses in humans. *J Immunol*. 2009;183(3):2089-2096.
10. Kolber M, Sharif N, Marceau R, Szafran O. Family practice patients' use of acetylsalicylic acid for cardiovascular disease progression. *Can Fam Physician*. 2013;59(1):55-61.
11. O'Brien CW, Jurachek SP, Wee CC. Prevalence of aspirin use for primary prevention of cardiovascular disease in the United States: results from the 2017 National Health Interview Survey. *Ann Intern Med*. 2019;171(8):596-598. doi:10.7326/M19-053
12. Smith SC Jr, Benjamin EJ, Bonow RO, et al. AHA/ACCF secondary prevention and risk reduction therapy for patients with coronary atherosclerotic vascular disease: 2011 update: a guideline from the American Heart Association and American College of Cardiology Foundation. *Circulation*. 2011;124(22):2458. doi:10.1161/CIR.0b013e31835 eb4d
13. Antithrombotic Trialists' (ATT) Collaboration. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomized trials. *Lancet*. 2009;373(9678):1849-1860.
14. Berger JS, Brown DL, Becker RC. Low-dose aspirin in patients with stable cardiovascular disease: a meta-analysis. *Am J Med*. 2008;121(1):43-49.
15. Raju N, Sobierai-Teague M, Hirsh J, O'Donnell M, Eikelboom J. Effect of aspirin on mortality in the primary prevention of cardiovascular disease. *Am J Med*. 2011;124(7):621-629.
16. Byrne R, Colleran R. Aspirin for secondary prevention of cardiovascular disease. *Lancet*. 2020;395(10235):1462-1463.
17. Yun JW, Teah H, Verma S. Endothelial cell control of thrombosis. *BMC Cardiovasc Disord*. 2015;15:130. doi:10.1186/s12872-015-0124-z
18. Rucker D, Dharmoon AS. Physiology, thromboxane A2. In: *StatPearls*. StatPearls Publishing; 2020.
19. Warner TD, Nylander S, Whatling C. Antiplatelet therapy: cyclooxygenase inhibition and the use of aspirin with particular regard to dual anti-platelet therapy. *Br J Clin Pharmacol*. 2011;72(4):619-633.
20. Beccatini C, Agnelli GC, Schenon A, et al. Aspirin for preventing the recurrence of venous thromboembolism. *N Engl J Med*. 2012;366(21):1959-1967.
21. Simes J, Becattini C, Agnelli G, et al. Aspirin for the prevention of recurrent venous thromboembolism. *Circulation*. 2014;130(13):1062-1071.
22. Matharu GS, Kunutsor SK, Judge A, Blom AW, Whitehouse MR. Clinical effectiveness and safety of aspirin for venous thromboembolism prophylaxis after total hip and knee replacement: a systematic review and meta-analysis of randomized clinical trials. *JAMA Intern Med*. 2020;180(3):376-384.
23. Lodigiani C, Iapichino G, Carenzo L, et al. Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy. *Thromb Res*. 2020;191:9-14.
24. Magro C, Mulvey J, Berlin D, et al. Complement associated microvascular injury and thrombosis in the pathogenesis of severe COVID-19 infection: a report of five cases. *Transl Res*. 2020;220:1-13.
25. Gavrilaki E, Brodsky RA. Severe COVID-19 infection and thrombotic microangiopathy: success does not come easily. *Br J Haematol*. 2020;189(6):e227-e230.
26. Ou CQ, He IX, Liu L, et al. China medical treatment expert group for COVID-19. Clinical characteristics of coronavirus disease-2019 in China. *N Engl J Med*. 2020;382(18):1708-1720.
27. Chow JH, Khanna AK, Kethireddi S, et al. Aspirin use is associated with decreased mechanical ventilation, ICU admission, and in-hospital mortality in hospitalized patients with COVID-19. *Anest Anal J*. 2021;132(4):930-941. doi:10.1213/ANE0000000000005292
28. Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS guidelines for the management of dyslipidemias: lipid modification to reduce cardiovascular risk. *Eur Heart J*. 2020;41(1):111-188.
29. Liao JK, Laufs U. Pleiotropic effects of statins. *Annu Rev Pharmacol Toxicol*. 2005;45:89-118.
30. Vaduganathan M, Vardeny O, Michel T, McMurray JJV, Pfeiffer MA, Salomon SD. Renin-angiotensin-aldosterone system inhibitors in patients with COVID-19. *N Engl J Med*. 2020;382(17):1653-1659.
31. Mitacchione G, Schiavone M, Curris A, et al. Impact of prior statin use on clinical outcomes in COVID-19 patients: data from tertiary referred hospitals during COVID-19 pandemic in Italy. *J Clin Lipidol*. 2021;15(1):68-78.