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Antiplatelet Therapy Following Percutaneous Coronary Intervention in Patients Complicated by COVID-19: Implications from Clinical Features to Pathological Findings

Running Title: *Zhou et al.; Antiplatelet Therapy and COVID-19*

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On March 11, 2020, the World Health Organization has officially announced the novel coronavirus disease 2019 (COVID-19) as a global pandemic. Considering an approximately 5 million percutaneous coronary interventions (PCIs) were performed annually worldwide, as well as recent clinical and pathological findings, we therefore raised safety concerns regarding dual antiplatelet therapy (DAPT) on life-threatening bleeding complications among acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infected patients, especially the risk for diffuse alveolar hemorrhage (DAH).

SARS-CoV-2 and SARS-CoV have shared cellular target, i.e., angiotensin converting enzyme 2. When comparing the clinical manifestations, we found that thrombocytopenia (platelet count < 150,000/μL), prolonged thrombin time and elevated D-dimer levels were frequently observed in both infections,[1, 2] suggestive of high likelihood of disseminated intravascular coagulation (DIC) or pre-DIC. Moreover, diffuse alveolar hemorrhage (DAH) was reported as a common finding from lung pathology in SARS and COVID-19 patients.[3, 4]

Although not completely understood, previous findings from influenza pneumonia revealed a mechanistic link between virus infection and the risk for DAH (summarized in **Figure**), which starts from virus replication and dissemination, followed by alveolar endothelial dysfunction, platelet activation, generation of neutrophil-platelet aggregates, neutrophil migration, and fibrin/micro-thrombus formation; if left uncontrolled, these alterations would trigger secondary fibrinolysis, coagulation factors depletion, and consequently DIC and DAH. The term DAH refers to a distinct form of life-threatening pulmonary hemorrhage that originates from pulmonary microcirculation (alveolar arterioles, capillaries and venules), and should be

distinguished from other causes of pulmonary hemorrhage caused by localized abnormalities (bronchiecatasis, malignancy and tuberculosis). Although alveolar hemorrhage can be localized, there are generally multiple areas of involvement, and therefore the term DAH is preferred. In the rapid progressive and life-threatening form of viral pneumonia, the underlying pathological process is often DAH. Collectively, the pathologic and clinical features of COVID-19 are mechanistically linked to high risk for DIC and propensity for DAH.

In addition to thrombosis and hemostasis, emerging evidence supports a putative role of platelets in host defense against infections, which add a greater layer of complexity in evaluating the role of antiplatelet therapy in the setting of viral pneumonia. In this regard, the following three issues should be taken into account when interpreting the impact of antiplatelet therapy on disease progression. First, the timing of administration: as summarized in **Figure**, in the early phase of infection, platelet inhibition may reduce intravascular fibrin and thrombus formation, thereby preventing the ensuing consequences. Supportively, pre-hospital aspirin use, but not post-admission use, was associated lower risk for developing severe acute respiratory distress syndrome (ARDS) and mortality in patients with community-acquired pneumonia. Second, the choice of oral $P2Y_{12}$ inhibitors: despite the fact that all $P2Y_{12}$ inhibitors reduce platelet-leukocyte aggregates and platelet-derived pro-inflammatory cytokines from α-granules, ticagrelor is unique in having the only well-documented additional target of inhibition, the equilibrative nucleoside transporter 1 (ENT1), contributing to inhibition of cellular adenosine uptake. Therefore, ticagrelor confers more potent anti-inflammatory properties via dual inhibition of platelet $P2Y_{12}$ receptor and ENT1. Encouragingly, the XANTHIPPE (Targeting Platelet-Leukocyte Aggregates

in Pneumonia With Ticagrelor; NCT01883869) trial, as well as post-hoc analyses of PLATO study (NCT00391872) and basic researches, provides evidence demonstrating the clinical benefit of ticagrelor in the management of pneumonia by preventing the complications of sepsis and reducing lung injury. Third, the circulating platelet counts: both primary (immune thrombocytopenia) and secondary (enhanced consumption) thrombocytopenia are associated with increased risk for infection (including pneumonia) and worsened clinical outcomes associated with ARDS. Individuals that are thrombocytopenic would lose the ability to deposit fibrinogen and fail to seal the damaged pulmonary vasculature. With regards to clinical significance, current expert consensus warrants proactive measures or even stopping all antiplatelet therapy in patients with a platelet count < 100,000/μL and < 50,000/μL, respectively.

On the contrary, in terms of DAH, when performing a Pubmed searching, emerging evidence suggests DAPT as an important aggravating factor for DAH. Notably, the clinical features of DAH in these case studies could be initially mistaken as pneumonia, due to similarities in clinical manifestations, i.e., coughing, radiographic evidence of mild infiltrations and fever. Given high bleeding risk in patients following PCI complicated by COVID-19, shorter-duration DAPT may be beneficial in this population.

To counterbalance of increased bleeding risk associated with DAPT, emerging findings from large randomized controlled trials provide evidence supports a net benefit of aspirin-free strategies after PCI for patients at low, intermediate and high risk for both ischemia and bleeding, which is mainly driven by the reduction in bleeding events. This strategy reduces the duration of aspirin (1 to 3 months) while allowing for more prolonged use of potent $P2Y_{12}$ inhibitors. When

facing with global challenge of COVID-19 pandemics with insufficient evidence regarding appropriate antithrombotic regimens for patients following PCI, we can only resort to extrapolating from related clinical scenario to assist in decision making. Among patients currently on DAPT, maintaining $P2Y_{12}$ inhibitor monotherpy (preferably ticagrelor) may be scientifically reasonable for patients with PCI performed ≥ 3 months. Due to the lack of convening evidence, for those with PCI performed < 3 months, DAPT should not be discontinued. Notably, considering recent experience from China demonstrating the effectiveness of low molecular weight heparin (LMWH) in reversing DIC in COVID-19,[5] routine practice of the International Society of Thrombosis and Hemostasis DIC scoring system and platelet counting should be warranted daily or more frequently to identify patients who would benefit either from early LMWH administration, or from discontinuation of $P2Y_{12}$ antagonist due to clinically meaningful thrombocytopenia. The situation of trade-off between ischemia and bleeding may be challenging when patients on oral $P2Y_{12}$ inhibitor concomitantly with an indication for LMWH prophylaxis. An alternative approach in this setting would involve utilizing an intravenous $P2Y_{12}$ inhibitor such as cangrelor as bridge therapy.

The COVID-19 pandemic is currently a global disaster, but left a unique opportunity to study the key questions concerning the preventive, therapeutic or even aggravating effects of antiplatelet therapy on viral pneumonia based on non-randomized real-world data. Presently, clinicians need to be cognizant of the pros and cons of antiplatelet therapy in patients complicated by COVID-19.

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Disclosures

The other authors report no conflicts of interest.

References

1. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DSC, Du B, Li LJ, Zeng G, Yuen KY, Chen RC, Tang CL, Wang T, Chen PY, Xiang J, Li SY, Wang JL, Liang ZJ, Peng YX, Wei L, Liu Y, Hu YH, Peng P, Wang JM, Liu JY, Chen Z, Li G, Zheng ZJ, Qiu SQ, Luo J, Ye CJ, Zhu SY, Zhong NS for China Medical Treatment Expert Group for COVID-19. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med*. Feb 28, 2020; doi:10.1056/NEJMoa2002032. [epub ahead of print].
2. Lee N, Hui D, Wu A, Chan P, Cameron P, Joynt GM, Ahuja A, Yung MY, Leung CB, To KF, Lui SF, Szeto CC, Chung S, Sung JJ. A major outbreak of severe acute respiratory syndrome in Hong Kong. *N Engl J Med*. 2003;348:1986-1994. doi:10.1056/NEJMoa030685
3. Lang ZW, Zhang LJ, Zhang SJ, Meng X, Li JQ, Song CZ, Sun L, Zhou YS, Dwyer DE. A clinicopathological study of three cases of severe acute respiratory syndrome (SARS). *Pathology*. 2003;35:526-531. doi:10.1080/00313020310001619118
4. Luo W, Yu H, Guo J, Li X, Sun Y, Li J, Liu L. Clinical pathology of critical patient with novel coronavirus pneumonia (COVID-19). *Preprints*. 2020;2020020407
5. Wang YD, Zhang SP, Wei QZ, Zhao MM, Mei H, Zhang ZL, Hu Y. [COVID-19 complicated with DIC: 2 cases report and literatures review]. *Zhonghua Xue Ye Xue Za Zhi*. March 5, 2020; doi:10.3760/cma.j.issn.0253-2727.2020.0001. [epub ahead of print].

Figure Legend

Figure. The potential pathophysiological evolution of SARS-CoV-2 infection in lung tissue and implications for antiplatelet therapy.

Early antiplatelet therapy, especially $P2Y_{12}$ antagonists, may be beneficial due to their inhibitory effects on platelet activation and generation of neutrophil-platelet aggregates, key mechanisms in both thrombus formation and pulmonary neutrophil recruitment.