JACC: BASIC TO TRANSLATIONAL SCIENCE VOL. 7, NO. 11, 2022

EDITORIAL COMMENT

Cardiovascular Prevention in People Living With HIV

Is There a Rationale to Move Beyond Aspirin?*

Johanne Silvain, MD, PhD,[a] Mathieu Kerneis, MD, PhD,[a] Franck Boccara, MD, PhD[b]

At the end of the year 2019, people living with HIV (PWHIV) in the United States were estimated to be 1.2 million people aged 13 years and older with approximately 35,000 to 40,000 new HIV infections per year. Antiretrovirals (ARTs) have revolutionized the lives of PWHIV, reducing the direct impact of HIV as a cause of premature death and prolonging life expectancy of treated patients. However, PWHIV have an important excess of morbidity and mortality related to cardiovascular diseases. Even in well-treated population of PWHIV taking ARTs, studies found an increased risk of both first and recurrent acute coronary syndromes (ACS) as compared to the risk for the general population.[1,2] The underlying mechanism of this high residual risk of both disease occurrence and recurrent events is multifactorial, including an earlier and higher rate of traditional cardiovascular risk factors (smoking, illicit drug use, diabetes mellitus), metabolic disorders associated with some ARTs, chronic inflammation caused by the virus itself (reservoir cells), and medical inertia caused by potential drug-drug interaction between some ARTs (eg, protease inhibitors, cobicistat) and some cardiovascular therapies (eg, statins, $P2Y_{12}$ inhibitors, warfarin).

Increased platelet reactivity has been associated with the risk of atherothrombotic cardiovascular events and can be considered an integrative cardiovascular risk factor, reflecting not only the impact of the presence of global effect of traditional and nontraditional risk factors but also the adequate response to antiplatelet preventive therapy. Indeed, both "baseline" and "on-treatment" platelet reactivity were found to be associated with recurrent cardiovascular events in PWHIV taking ARTs.[3] The causes of this increased platelet reactivity are complex and are potentially explained by the internalization of the virus into platelets observed in patients with high viral load, the role of hepatitis C and B viruses, and the effects of the higher levels of both proinflammatory cytokines and coagulation markers observed in PWHIV compared with in patients who are uninfected. Some effects are drug related, such as the effect of first generation of protease inhibitors on the purinergic system ectoenzymes of the platelets and the interaction between some ARTs with the cytochrome P450, which are 2 factors implicated in the observed increased on-treatment platelet reactivity and poor response to antiplatelet drugs. Other effects such as the impact of recreational cannabis and/or cocaine use, habits that have been frequently observed in ACS studies involving PWHIV (between 2 and 4 times higher rate of use than in the general population), on platelet reactivity and aggregation remain controversial because of a lack of evidence.

Regardless of the mechanism, the higher risk of cardiovascular atherothrombotic events associated with increased platelet reactivity has been historically prevented by aspirin, which remains the

*Editorials published in *JACC: Basic to Translational Science* reflect the views of the authors and do not necessarily represent the views of *JACC: Basic to Translational Science* or the American College of Cardiology.

From the [a]Sorbonne University, Action Group, Institut National de la Santé et de la Recherche Médicale, Unité de Recherché sur les Maladies Cardiovasculaires, le Métabolisme et la Nutrition, Institut de Cardiologie Hôpital de la Pitié-Salpêtrière (Assistance Publique-Hôpitaux de Paris), Paris, France; and the [b]Sorbonne Université, Groupe de Recherche Clinique number 22, C2MV—Complications Cardiovasculaires et Métaboliques chez les Patients Vivant avec le Virus de l'Immunodéficience Humaine, Institut National de la Santé et de la Recherch Médicale Unité Mixte de Recherche S 938, Centre de Recherche Saint-Antoine, Institut Hospitalo-Universitaire de Cardio-métabolisme et Nutrition Cardiologie, Hôpital Saint Antoine Assistance Publique-Hôpitaux de Paris, Paris, France.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

ISSN 2452-302X https://doi.org/10.1016/j.jacbts.2022.07.007

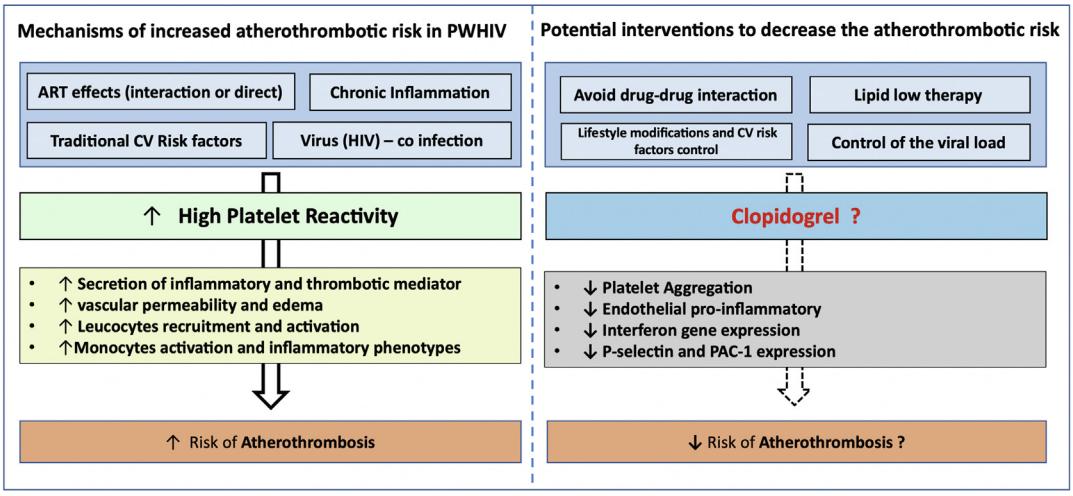
preferred single antiplatelet therapy in PWHIV with asymptomatic atherosclerosis or stable coronary artery disease as well as in the general population. Cardiovascular prevention is a major concern in PWHIV, who are categorized as a high cardiovascular risk population, and consists of the promotion of lifestyle modifications and the prescription of the 2 types of drugs—high intensity statins and antiplatelet therapy—that are effective in reducing their increased cardiovascular risk mostly related to atherothrombotic events.

A preliminary biological randomized trial that compared the effects of 100 mg aspirin, 300 mg aspirin, or placebo suggested that inhibition of cyclooxygenase (COX)-1-mediated platelet activation does not significantly improve HIV-related immune activation and endothelial dysfunction. In this issue of *JACC: Basic to Translational Science,* Marcantoni et al[4] present the results of a new randomized open-label study performed among PWHIV taking ARTs, evaluating for the first time whether a strategy based on clopidogrel would provide better platelet inhibition than aspirin would. In this study the primary measure outcome was platelet aggregation to arachidonic acid (for those assigned to the aspirin group) and adenosine diphosphate (ADP) (for those assigned to the clopidogrel arm) and the secondary measures evaluated platelet activity and the platelet's ability to induce endothelial inflammation in vitro. They compared 3 groups: patients without any antiplatelet therapy (control patients); patients treated for 14 days with aspirin 325 mg loading dose followed by 81 mg/d; or patients treated for 14 days with clopidogrel 300 mg loading dose followed by 75 mg/d. The key findings of this study by Marcantoni et al[4] can be summarized as follows: First, their study demonstrated that despite a broader ability of aspirin to reduce platelet aggregation in response to arachidonic acid and ADP, platelet receptor expression was not affected by aspirin. Second, clopidogrel, which logically decreased ADP (but not arachidonic acid), induced platelet aggregation and also reduced P-selectin and platelet activation complex (PAC)-1-expression, suggesting that platelet activation markers are not solely dependent on COX-1 signaling. Finally, their study provided interesting exploratory findings regarding the ability of antiplatelet therapies to modulate platelet cell effector functions on endothelial cells using an elegant analysis of the proinflammatory transcriptomic signature showing that clopidogrel treatment, as compared to aspirin therapy and no antiplatelet therapy, has the capacity to decrease the platelets' ability to promote endothelial proinflammatory and interferon gene expression.

Marcantoni et al[4] should be congratulated for conducting this small but well-performed biological randomized trial and bringing some additional knowledge to the field of cardiovascular prevention in PWHIV. The demonstration of an interplay between platelet activation and inflammation is probably the most interesting result of the presented work in an era where thromboinflammation has risen as a potential therapeutic target. Their study suggests, almost 30 years after the publication of the CAPRIE (Clopidogrel Versus Aspirin in Patients at Risk of Ischaemic Events) trial, that inhibition of the $P2Y_{12}$ receptor with clopidogrel may provide better benefits in terms of atherothrombotic events prevention for PWHIV than aspirin, which is the standard of care. Unfortunately, sufficient clinical data on the comparison of aspirin versus a $P2Y_{12}$ receptor are not available for PWHIV, and we must compile the results of this hypothesis-generating biological study with existing evidence from studies of the general population. A recent meta-analysis pooling the results of 9 randomized trials (5 with clopidogrel and 4 with ticagrelor) has compared the clinical effect of a monotherapy with a $P2Y_{12}$ inhibitor versus aspirin for secondary prevention in patients with atherosclerotic vascular disease (cardiovascular, cerebrovascular, or peripheral artery disease).[5] In line with the CAPRIE trial, but this time with the additional data of ticagrelor monotherapy, a more potent $P2Y_{12}$ inhibitor than clopidogrel, and with more subjects exposed (n = 61,623), Aggarwal et al[5] found that $P2Y_{12}$ inhibitors, compared with aspirin monotherapy, significantly reduced the risk of major adverse cardiac events by 11% and myocardial infarction by 19% with no significant differences in the risk of stroke or all-cause mortality nor in term of the risk of major bleeding. Importantly, these results were consistent for clopidogrel monotherapy despite the known phenomenon of cytochrome P450 (CYP) 2C19 genetic resistance giving the choice between clopidogrel or ticagrelor as an option for monotherapy instead of aspirin.

All together these data would set, in theory, the ground for specific clinical studies in the high-risk population of PWHIV taking ARTs; however, the small biological and clinical differences observed seem to exclude the use of a clinical endpoints for such comparison. In clinical practice, physicians should be aware that ticagrelor is metabolized by CYP

FIGURE 1 Atherothrombotic Risk and its Prevention in PWHIV



Atherothrombotic risk and its prevention in people living with HIV (PWHIV). ART = antiretroviral; CV = cardiovascular.

3A4/5 and should not be prescribed in PWHIV taking protease inhibitors or cobicistat (potent inhibitors of CYP 3A4/5) because doing so could lead to the risk of major bleeding (increased exposure to ticagrelor). The same contraindication is available for clopidogrel (prodrug) and protease inhibitors or cobicistat but with the opposite pharmacologic effect, leading to a decreased exposure to clopidogrel. Therefore, after an ACS in PWHIV taking a protease inhibitor or cobicistat, the $P2Y_{12}$ of choice associated with aspirin is prasugrel. However, new ARTs such as integrase inhibitors, which are becoming predominantly prescribed, have no potential drug-drug interaction with any $P2Y_{12}$ inhibitors.

Finally, the presented work underlines the increasing role of thromboinflammation as a potential therapeutic target in atherothrombosis prevention. Indeed, besides their "classic" role in aggregation, platelets may also act as important inflammatory mediators, which is particularly true in PWHIV where platelets are more adherent to endothelial cells and monocytes than they are in the general population, leading to a chronic proinflammatory state. Platelets-leucocytes interaction is now recognized as an important trigger for intercellular signaling and synthesis of hemostatic and inflammatory mediators, particularly in chronic viral infections (HIV, hepatitis C virus)[6] or recently demonstrated in acute infection by the SARS-CoV-2 virus leading to a specific endotheliopathy and high level of thromboinflammation with increased acute thrombotic events in patients who are critically ill with COVID-19. Thus, targeting $P2Y_{12}$-mediated platelet reactivity with clopidogrel is a seductive therapeutic alternative to aspirin and represents a promising strategy to reduce proinflammatory platelet-endothelia interactions and the associated risk of atherothrombosis in PWHIV (**Figure 1**). Such effect remains to be verified by more evidence in order to be confirmed; however, it seems there are few (possibly no) disadvantages to using clopidogrel instead of aspirin in this high-risk population.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr Silvain has received grants and personal fees outside the submitted work from AstraZeneca; personal fees from Bayer HealthCare, Boehringer Ingelheim France, BPI France, CSL Behring, Gilead Science, Sanofi-Aventis France, and Zoll; nonfinancial support from Abbott Medical France and Terumo France; and is a stockholder in 4P-Pharma. Dr Kerneis has received personal fees from Bayer HealthCare, Sanofi-Aventis France, and Servier. Dr Boccara has received research grants from Amgen; and lecture fees from Gilead, ViiV Healthcare, Amgen, Sanofi, Merck Sharp & Dohme, NovoNordisk, Novartis, and Servier outside the submitted work.

ADDRESS FOR CORRESPONDENCE: Prof Johanne Silvain, Sorbonne Université, Action Group, Bureau 7, 2ème Étage Institut de Cardiologie, Pitié-Salpêtrière Hospital, 47-83 Boulevard de l'Hôpital, 75013 Paris, France. E-mail: johanne.silvain@aphp.fr. Twitter: @docjohanne.

REFERENCES

1. Boccara F, Lang S, Meuleman C, et al. HIV and coronary heart disease: time for a better understanding. *J Am Coll Cardiol*. 2013;61(5):511–523.

2. Boccara F, Mary-Krause M, Teiger E, et al. PACS Investigators. Acute coronary syndrome in human immunodeficiency virus-infected patients: characteristics and 1 year prognosis. *Eur Heart J*. 2011;32(1):41–50.

3. Hauguel-Moreau M, Boccara F, Boyd A, et al. Platelet reactivity in human immunodeficiency virus-infected patients on dual antiplatelet therapy for an acute coronary syndrome: the EVERE2ST-HIV study. *Eur Heart J*. 2017;38(21):1676–1686.

4. Marcantoni E, Garshick MS, Schwartz T, et al. Antiplatelet effects of clopidogrel vs aspirin in virologically controlled HIV: a randomized controlled trial. *J Am Coll Cardiol Basic Trans Science*. 2022;7(11):1086–1097.

5. Aggarwal D, Bhatia K, Chunawala ZS, et al. $P2Y_{12}$ inhibitor versus aspirin monotherapy for secondary prevention of cardiovascular events: meta-analysis of randomized trials. *Eur Heart J Open*. 2022;2(1):oeac019. https://doi.org/10.1093/ehjopen/oeac019

6. Hottz ED, Quirino-Teixeira AC, Merij LB, et al. Platelet-leukocyte interactions in the pathogenesis of viral infections. *Platelets*. 2022;33(2):200–207.

KEY WORDS aspirin, clopidogrel, endothelium, HIV, platelets