Potential Screening for Cardiologist?

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Platelets play a pivotal role in atherothrombosis, the major cause of cardiovascular (CV) events and CV deaths.[1] Platelets secrete and express a large number of substances that are crucial mediators of coagulation, inflammation, thrombosis, and atherosclerosis.[2] Accordingly, measuring platelet activity by a wide variety of methods has been proposed. However, clinical trials, such as GRAVI-TAS and TRIGGER-PCI, and several observational studies failed to demonstrate the clinical benefit of alternative therapy based on platelet function tests.[3-5] Consequently, measuring platelet activity remains a research tool that is yet to be included in routine clinical decision-making. Additionally, many of these methods are costly, time-consuming, and require specialized equipment. Furthermore, platelets are heterogeneous in size and density. Mean platelet volume (MPV), the most commonly used measure of platelet size, is a marker of platelet size and activity.[6] MPV was routinely available for a relatively low cost in an admission setting. Although there is still uncertainty about the most precise methodology for measuring MPV, it is routinely available in the inpatient and outpatient setting. Elevated MPV was associated with increased platelet aggregation, thromboxane synthesis, β-thromboglobulin release, expression of adhesion molecules,[7] and various comorbidities related to CV risk.[8]

This study,[9] as well as a most laboratories, used ethylene diaminetetraacetic acid (EDTA) for cell count sample anticoagulation. However, several studies reported that MPV values increase due to platelet swelling when EDTA is used as an anticoagulant.[10] Previous study has suggested that MPV can be measured accurately if analysis is performed within 1 h of sampling.[11]

In this issue of the Journal, Hakki et al.[9] reported the results of a retrospective study examining the association between MPV and the risk for subsequent mortality and heart failure (HF)-related hospitalization in 197 stable chronic HF outpatients with reduced ejection fraction and sinus rhythm. Patients were classified into two groups according to threshold MPV levels: group I with MPV ≤ 9.1 fL, and group II with MPV > 9.1 fL. The threshold was derived from receiver-operating characteristic (ROC) curve analysis predicting HF-related hospitalization. Patients with greater MPV experienced significantly more HF-related hospitalization (41% vs. 87%, respectively, p < 0.001), but not CV mortality (21% vs. 24%, respectively, p = 0.649) in the mean follow-up duration of 10 ± 3 months compared to patients with MPV ≤ 9.1 fL.

Why might a higher MPV be associated with greater risk of HF-related hospitalization – but not CV mortality – in patients with stable HF? Several possible explanations should be considered. First, larger platelets are enzymatically and metabolically more active, and have a higher thrombotic potential than smaller platelets, which resulted in microvascular infarction and deteriorating HF.[12] Second, the association between MPV and HF-related hospitalization might be explained by confounding and study design. In the study by Hakki et al.,[9] two groups were classified by the cutoff value of MPV to predict HF-related hospitalization. A different cutoff point to predict CV mortality might generate different results. Further group validation might be required to support the conclusion in this study. Third, the impact of

antiplatelet medication other than aspirin was not evaluated in this study. Additionally, limited CV deaths, and short follow-up duration may not be sufficient to find a possible correlation between MPV levels.

What are the implications of these findings for clinical practice? As pointed out by Hakki et al.,[9] MPV is an easily obtained, simple, and inexpensive laboratory test that has been readily incorporated into clinical practice. However, it would be premature to conclude that measurement of the MVP should be routinely applied for risk stratification of stable HF outpatients in terms of HF-related hospitalizations. We need sufficient evidence indicating that measuring the marker will benefit patients. Proof that MPV is causally linked with future CV risk or cardiac decompensating requires demonstration that the association is modifiable, for example, by showing that additional antiplatelet therapies provide a superior clinical benefit than does standard HF therapy in patients with high MPV.

The availability to rapidly and routinely measure MPV presents an opportunity for intensified research into the mechanisms by which elevated MPV confers increased CV risk and HF-related hospitalization. The findings by Hakki et al.[9] first need to be replicated with additional patients to obtain more robust estimates of the magnitude of the association between MPV and the risk for CV death/HF hospitalization. Affected patient populations can then be studied through interventions with antiplatelet agents with the aim of reducing CV risk.

CONFLICT OF INTEREST

None.

REFERENCES

1. Davì G, Patrono C. Platelet activation and atherothrombosis. *N Engl J Med* 2007;357:2482-94.
2. Coppinger JA, Cagney G, Toomey S, et al. Characterization of the proteins released from activated platelets leads to localization of novel platelet proteins in human atherosclerotic lesions. *Blood* 2004;103:2096-104.
3. Price MJ, Berger PB, Teirstein PS, et al. Standard- vs. high-dose clopidogrel based on platelet function testing after percutaneous coronary intervention: the GRAVITAS randomized trial. *JAMA* 2011;305:1097-105.
4. Trenk D, Stone GW, Gawaz M, et al. A randomized trial of prasugrel versus clopidogrel in patients with high platelet reactivity on clopidogrel after elective percutaneous coronary intervention with implantation of drug-eluting stents: results of the TRIGGER-PCI (Testing Platelet Reactivity In Patients Undergoing Elective Stent Placement on Clopidogrel to Guide Alternative Therapy With Prasugrel) study. *J Am Coll Cardiol* 2012;59:2159-64.
5. Bonello L, Tantry US, Marcucci R, et al. Consensus and future directions on the definition of high on-treatment platelet reactivity to adenosine diphosphate. *J Am Coll Cardiol* 2010;56:919-33.
6. Karpatkin S. Heterogeneity of human platelets. VI. Correlation of platelet function with platelet volume. *Blood* 1978;51:307-16.
7. Bath PM, Butterworth RJ. Platelet size: measurement, physiology and vascular disease. *Blood Coagul Fibrinolysis* 1996;7:157-61.
8. Chu SG, Becker RC, Berger PB, et al. Mean platelet volume as a predictor of cardiovascular risk: a systematic review and meta-analysis. *J Thromb Haemost* 2010;8:148-56.
9. Kaya H, Yıldırımlı MK, Kurt R, et al. Mean platelet volume as a predictor of heart failure related hospitalizations in stable heart failure outpatients with sinus rhythm. *Acta Cardiol Sin* 2017;33:292-300.
10. Bath PM. The routine measurement of platelet size using sodium citrate alone as the anticoagulant. *Thromb Haemost* 1993;70:687-90.
11. Dastjerdi MS, Emami T, Najafian A, Amini M. Mean platelet volume measurement, EDTA or citrate? *Hematology* 2006;11:317-9.
12. Gosselaar PH, van-Dijk AJ, de-Gast GC, et al. Transferrin toxin but not transferrin receptor immunotoxin is influenced by free transferrin and iron saturation. *Eur J Clin Invest* 2002;32 Suppl 1:61-9.