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EDITORIAL COMMENT

Immature Platelet Count

Part of the Cardiologist's Complete Blood Count?*

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Clinicians have had a longstanding interest in the use of immature cell counts as a diagnostic and prognostic tool. Methods for measuring immature red cells (*reticulocytes*) are widely available, and an elevated reticulocyte count is routinely used as a marker of increased red cell production (e.g., hemolysis). Alterations in the immature platelet count (IPC) offer similar potential for insight into platelet disorders, but advances in this area have been limited by the lack of simple, widely applicable laboratory methods to measure IPC.

The recent advent of automated whole blood methods has stimulated interest in the measurement of the IPC (1). Following the addition of nucleic acid-specific dyes to whole blood and sorting by cell size and ribonucleic acid content, IPC can be calculated by multiplying the percentage of immature platelets by the platelet count. Most of the research using automated IPC methods has focused on assessing platelet turnover in different types of thrombocytopenia, but multiple reports also have indicated that increased IPC is associated with a reduced response to antiplatelet therapy (2–4).

In this issue of the *Journal*, Ibrahim et al. (5) report the results of a prospective study examining the association between IPC and the risk for subsequent major adverse cardiovascular events (MACE), defined as a composite of death, myocardial infarction, unplanned revascularization, or recurrent angina, in 93 adults with coronary artery disease (CAD) receiving oral antiplatelet therapy (5). The 30 patients who experienced MACE during the median follow-up of 31 months had a significantly greater mean baseline IPC value than did the 59 who did not experience MACE (10,507 vs. 6,322 platelets/μl; $p = 0.002$). Moreover, 60% of patients in the upper tertile of IPC experienced MACE compared with 24.1% in the intermediate tertile and 16.7% in the lower tertile ($p < 0.001$). Time-dependent receiver operating characteristic curve analysis demonstrated that a cut point of 7,632 platelets/μl was 70.7% sensitive and 82.1% specific for MACE, and the Cox proportional hazards analysis demonstrated that after adjustment for potential confounding variables, IPC >7,632 platelets/μl remained associated with a >4-fold increased risk for MACE (hazard ratio: 4.65; 95% confidence interval: 1.78 to 12.16; $p < 0.002$).

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Why might a higher IPC be associated with greater risk for MACE in patients with CAD receiving antiplatelet therapy? Several possible explanations should be considered (**Figure 1**). First, immature platelets are larger and enzymatically and metabolically more active, and have a higher thrombotic potential than smaller platelets (6). Consistent with this conclusion, greater mean platelet volume has been linked with the future risk for cardiovascular events in healthy subjects, in patients with cardiovascular risk factors, and in those with a history of myocardial infarction (7).

Second, a reduced response to antiplatelet therapy in patients with increased IPC could explain the link with the risk for MACE. Aspirin inhibits

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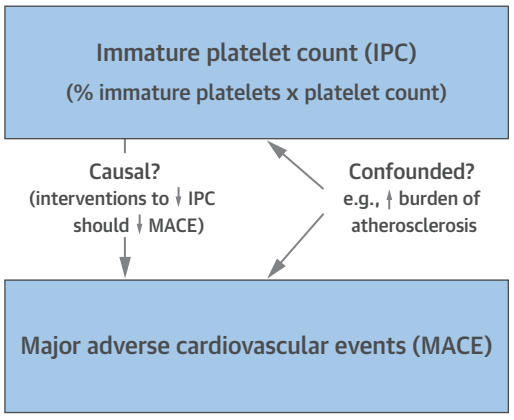

FIGURE 1 Possible Explanations for the Association Between IPC and the Risk for MACE

If the association is causal, interventions that target immature platelet count (IPC) might lower the risk for major adverse cardiovascular events (MACE), whereas if the association is confounded, interventions that target IPC cannot be expected to affect the risk for MACE.

platelet activation by irreversibly acetylating platelet cyclooxygenase (COX)-1, thereby preventing the formation of thromboxane A_2, a powerful platelet agonist and vasoconstrictor. Although aspirin itself has a half-life of only 20 min, it produces near-complete inhibition of thromboxane A_2 synthesis for 24 h when given once daily because platelets are anucleate and unable to regenerate COX-1 (8). In most patients receiving long-term, once-daily aspirin, platelet COX-1 activity is restored at a rate of approximately 10% per day, reflecting the 10-day platelet life span and the entry into the circulation of 10% of newly formed platelets. The inhibition of at least 90% of circulating platelets is sufficient to maintain complete suppression of platelet function. In situations of increased platelet turnover, however, a significant proportion of platelets are unaffected by aspirin and thus retain the capacity to produce thromboxane and to aggregate. Similarly, a significant proportion of platelets are unaffected by clopidogrel in patients with increased platelet turnover.

Third, the association between IPC and MACE might be explained by confounding. In the study by Ibrahim et al. (5), patients who experienced MACE might have had more advanced atherosclerosis and higher blood levels of inflammatory markers than those who did not experience MACE. Elevated blood levels of inflammatory markers have been linked with increased blood levels of thrombopoietin, the primary regulator of platelet turnover (9). Thus, the increase in IPC might be a consequence of more advanced atherosclerosis rather than playing a causal role.

What are the implications of these findings for clinical practice? As pointed out by Ibrahim et al. (5), IPC is an easily obtained, simple, and inexpensive laboratory test that has the potential to be readily incorporated into clinical practice. However, we think it would be premature to conclude that measurement of the IPC is ready for routine application to cardiovascular risk prediction or to therapeutics. Numerous biochemical markers (e.g., D-dimer, mean platelet volume, homocysteine) are independently predictive of future cardiovascular events, but before being introduced into practice, we need evidence that measuring the marker will benefit patients. Proof that IPC is causally linked with future cardiovascular risk requires demonstration that the association is modifiable, for example, by showing that more frequently administered or more potent antiplatelet therapies produce greater and more sustained platelet blockade than does standard therapy in patients with high platelet turnover, and that this translates into a reduction in cardiovascular events. Preliminary studies have demonstrated that twice-daily compared with once-daily aspirin administration produces greater platelet inhibition in patients with diabetes and increased platelet turnover (10), but whether this translates into superior cardiovascular protection remains to be demonstrated. A more immediate clinical application of IPC outside of the cardiovascular realm is for the workup of thrombocytopenia to distinguish decreased marrow production from increased peripheral destruction as a cause for low platelet count.

Although routine IPC measurement is not yet "ready for prime time," the ability to rapidly measure IPC presents an opportunity for intensified research into the mechanisms by which elevated IPC confers increased cardiovascular risk. The findings by Ibrahim et al. (5) first need to be replicated with larger numbers of patients to obtain more robust estimates of the magnitude of the association between IPC and the risk for MACE. We also need to explore other clinical settings in which the potential exists for increased platelet turnover and reduced response to antiplatelet therapy. Affected patient populations can then be studied with interventions that reduce the IPC or more effectively suppress immature platelets with the aim of reducing cardiovascular risk.

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