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EDITORIAL

Toward a guided approach to platelet activation in diabetes

M. D. Linden

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Diabetes is associated with substantially poorer cardiovascular outcomes. Furthermore, people with diabetes are at greatly increased risk of not responding to standard antiplatelet therapy for acute coronary syndromes, leading to higher mortality and stent thrombosis [1]. Poor glucose control likely contributes to these cardiovascular events through changes in platelet membrane fluidity and signalling, increased production of platelets leading to a greater fraction of younger and more reactive platelets not yet exposed to antiplatelet therapy, and increased triggering of platelet activation arising from an underlying thrombo-inflammatory milieu [2].

While patients with higher thrombotic risk may be prospectively identified through laboratory identification of elevated blood glucose or HbA1c [3], the approach to treatment for diabetic platelet hyper-responsiveness remains unclear. Options such as increasing frequency of antiplatelet therapy, additional and more aggressive antiplatelet therapy or more intensive glucose control have been suggested (Fig. 1). However, the data to support these are limited and, particularly where more aggressive antiplatelet therapy is proposed, must be measured against the potential for increased bleeding risk in patients with hyperglycemia.

In patients with type-2 diabetes, Capodanno et al. [4] demonstrated enhanced inhibition of platelet function when patients took 81 mg of aspirin twice per day compared with 81 mg daily. Spectre et al. [5] showed greater inhibition of platelet function with 75 mg twice per day when compared to 75 mg daily in patients with type-2 diabetes and vascular complications. In a recent study Rocca et al. [6] showed that increasing frequency of dose better attenuated platelet activation over 24 h in both diabetic and non-diabetic patients. Therefore increasing the frequency of antiplatelet therapy dosing represents an appealing strategy in patients with diabetes and poor glycemic control. However, the clinical effectiveness of this approach on cardiovascular outcome, as well as the net benefit against increased bleeding risk remains to be investigated. Similarly, the addition of more aggressive antiplatelet therapy, such as newer ADP receptor antagonists with greater potency and bioavailability, or emerging thrombin receptor antagonists have been suggested [2]. The use of these must be weighed against the potentially increased risk of bleeding.

While altering antiplatelet therapy strategies in patients with diabetes and poor glycemic control is an appealing avenue for further clinical investigation, a potential alternative or complimentary approach might be to achieve improved glycemic control in order to attenuate platelet activation. Several studies have assessed the ability of infused insulin in patients with diabetes to attenuate platelet function and improve cardiovascular outcome in acute coronary syndromes [7]. While evidence of improvement in cardiovascular outcome is variable, intensive treatment with insulin in patients with diabetes may attenuate platelet activation relative to conventional approaches to glycemic control [8].

In this issue of the *Journal of Thrombosis and Thrombolysis*, Vivas et al. [9] explore whether tight glycemic control with insulin infusion attenuates platelet reactivity in patients with an acute coronary syndrome and hyperglycemia at admission. In a post hoc analysis of the prospective, randomized, open-label CHIPs study, 67 patients with poor glycemic control (as measured by HbA1c > 6.5 %) were

M. D. Linden (✉)
Centre for Microscopy, Characterisation and Analysis, M510, University of Western Australia, 35 Stirling Highway, Nedlands, WA 6009, Australia
e-mail: matthew.linden@uwa.edu.au

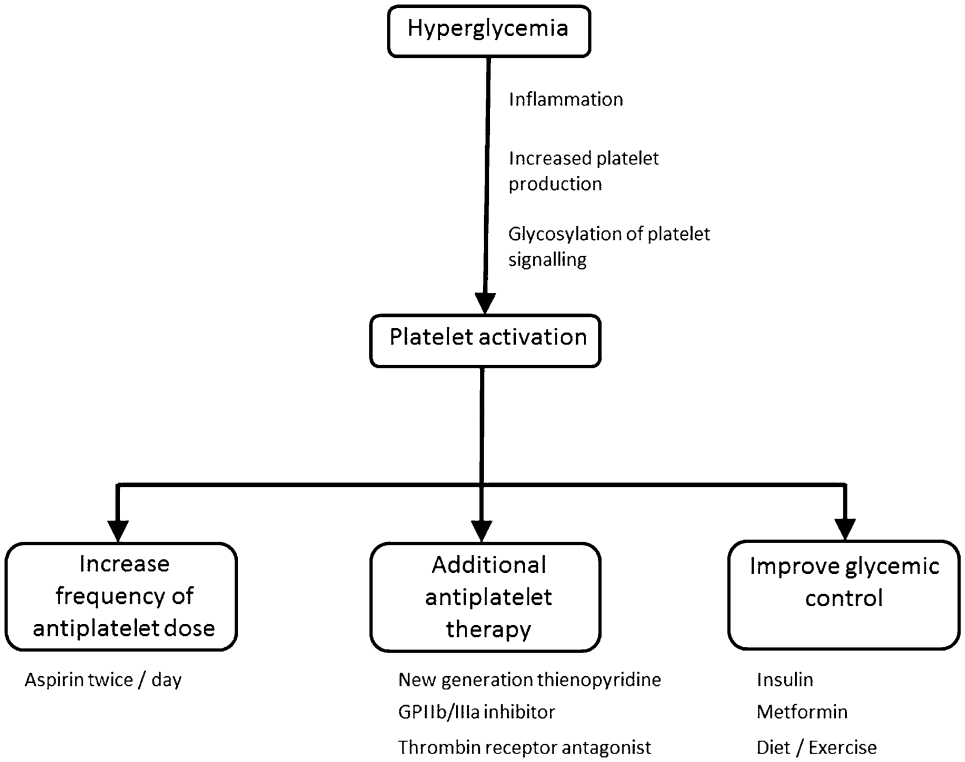

Fig. 1 Contributing mechanisms and potential approach to treatment of diabetes associated platelet activation

randomized to either an intensive glucose control group ($n = 37$) or conventional treatment group ($n = 30$). Patients in the intensive group received an insulin infusion during the first 24 h of admission followed by daily subcutaneous ultra-slow insulin and additional rapid acting insulin for meals to achieve a glucose target of 80–120 mg/dL ($n = 37$). Conversely, patients in the conventional group received rapid-acting insulin only to achieve a glucose target of <180 mg/dL. Parameters of platelet aggregation, activation and reactivity were measured at admission prior to commencement of insulin therapy, 24 h after commencement of treatment and at hospital discharge. While all patients showed greater platelet activation in response to chemical agonists at discharge compared to the measurement taken at admission, the increase in platelet function was attenuated in the intensive group, resulting in significantly reduced parameters of platelet function at discharge for those randomized to intensive insulin. No difference in patient characteristics, including in-hospital antiplatelet therapy between groups existed, suggesting this phenomenon was due to the insulin intervention. This important, preliminary finding supports the potential benefit of intensive glucose control strategies to improve cardiovascular protection by attenuating platelet function in patients with hyperglycaemia, acute coronary syndromes and poor glucose control at admission. Investigation of cardiovascular events and clinical outcome in patients randomized to this treatment strategy is warranted.

While significant platelet activation might be expected in this cohort, the magnitude of platelet activation (e.g. ~45 % P-selectin expression at admission) reported by Vivas et al. is higher than previously reported for acute coronary syndromes [10]. This may reflect pre-analytical variables resulting from the challenges of platelet function testing in the clinical setting. However, the magnitude of difference in parameters of platelet reactivity between conventional and intensive treatment groups was quite substantial (e.g. 14.3 % higher 20 μM ADP stimulated platelet aggregation in the conventional group) and likely to be of clinical significance.

The mechanism by which better control of hyperglycemia contributes to attenuated platelet function in this study are unclear and likely to be multifactorial. It is hypothesised that stimulation of the IRS-1 receptor may be involved, and this is suggested by Vivas et al. However, these data show augmentation of responsiveness to chemical stimulation with conventional therapy, rather than elevated circulating platelet activation by IRS-1. However, this may reflect a lack of statistical power to demonstrate a difference in unstimulated PAC-1 or CD62P, rather than an absence of effect.

Of interest, in a separate analysis of 42 patients also with acute coronary syndrome and hyperglycemia at admission, but better glucose control (as measured by HbA1c < 6.5 %), Vivas et al. report no improvement in parameters of platelet function at discharge with intensive glucose control strategy

($n = 20$) when compared to the conventional treatment ($n = 22$). The effect size between HbA1c > 6.5 % and HbA1c < 6.5 % groups was not directly compared and consequently the data is insufficient to support a conclusion of a difference between platelet response to insulin therapy between those with and without elevated HbA1c. Nevertheless, this paper highlights the potential benefit of tailored therapy in response to laboratory monitoring. This paper further underscores the need for clinical research evaluating a guided approach to the management of platelet function through tighter glucose control in subsets of patients on the basis of laboratory assessment of elevated HbA1c. While preliminary, the research presented by Vivas, et al. therefore represents an important seminal finding which will likely inform further prospective studies of this guided approach to therapy. Future investigation should focus on whether the improvements in platelet reactivity achieved by adjusting approaches to antiplatelet or glucose limiting therapies translates to improved clinical outcomes.

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