

**Editorial Focus**

# Thrombin as a common downstream target blocking both platelet and monocyte activation

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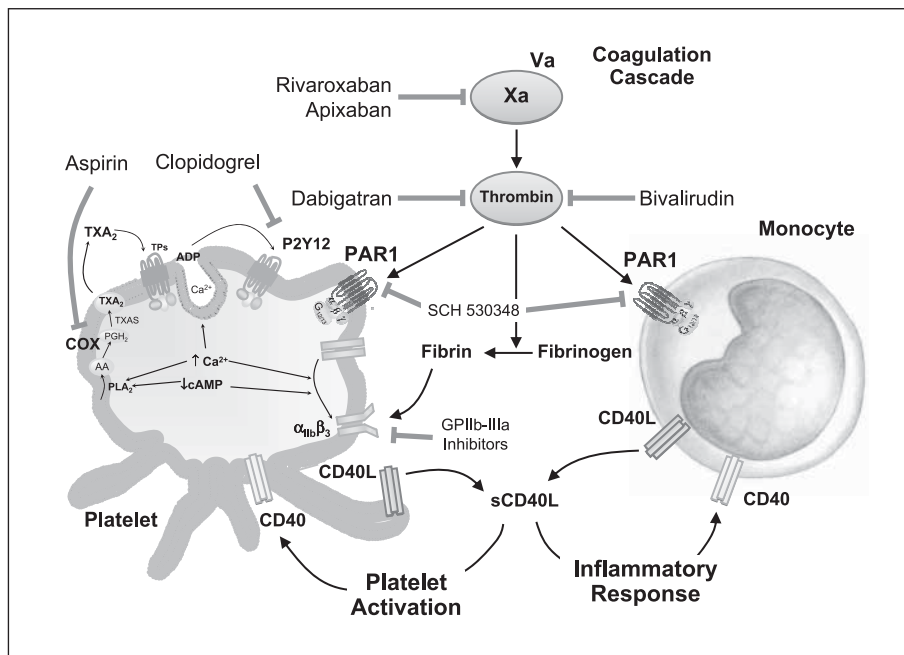
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**P**latelets play a pivotal role in the pathogenesis of thrombotic complications after percutaneous coronary interventions (PCI) (1). The use of optimal antiplatelet therapy is critical in reducing adverse events in this setting. Despite the efficacy of dual antiplatelet therapy in patients undergoing PCI, thrombo-ischaemic events and, in particular, stent thrombosis are frequent complications (2). High post-treatment platelet reactivity is associated with cardiovascular outcome after PCI (3) and coronary stent implantation (4).

Different agents are currently in use for adjunctive anticoagulant treatment on top of adequate antiplatelet regimen during PCI. Traditionally, unfractionated heparin (UFH) has been the standard anticoagulant administered during coronary intervention. Enhanced platelet activation *in vivo* and *ex vivo* has been shown after UFH treatment (5, 6). Moreover, heparin does not

suppress the transient increase in thromboxane biosynthesis associated with coronary angioplasty (7). Low-molecular-weight heparin (LMWH), in contrast, does not affect platelet activation *in vivo* and *ex vivo* after PCI (5, 8).

Recently bivalirudin, a short-acting direct thrombin inhibitor, has been shown to be effective and safe in patients undergoing PCI (9), with reduced bleeding as compared with heparin. Reduced inhibition of adenosine diphosphate (ADP)-induced platelet aggregation at the time of PCI is associated with an increased risk for adverse thrombotic complications (10). Bivalirudin, given during PCI in patients pretreated with 600 mg of clopidogrel, is unlike UFH associated with further inhibition of platelet aggregation (11). A similar effect by bivalirudin was previously described on platelet P-selectin (12). Moreover, bivalirudin alone or coupled with clopidogrel may significantly down-



**Figure 1: Thrombin, generated at the site of vascular damage by extrinsic and intrinsic coagulation cascades, is a potent agonist for both platelet and monocyte activation through the protease-activated receptors (PAR). Any antiplatelet drug targeting the thrombin receptor on platelet (PAR-1) or thrombin inhibitors, either parenteral (bivalirudin), or oral (dabigatran), as well as oral factor Xa inhibitors (rivaroxaban), has the potential to suppress residual platelet/leukocyte and inflammatory activation escaped to dual antiplatelet therapy.**

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regulate platelet-derived soluble CD40 ligand (6). Interestingly, in patients with acute coronary events accelerated systemic thrombin generation is strictly associated with markedly increased release of soluble CD40L from platelets as well as with higher interleukin (IL)-6 levels (13). Soluble CD40L is considered as a biomarker of platelet-mediated inflammation (14) in clinical settings such as athero-thrombosis or cancer.

Interestingly, in their article published in the current issue of *Thrombosis and Haemostasis* Busch et al. (15) examined the effects of bivalirudin compared to UFH on both platelet activation, measured as ADP-induced surface expression of P-selectin and PAC-1, and on monocyte activation, as a marker of systemic inflammation.

Thrombin, the most powerful physiological platelet agonist, activates protease-activated receptors (PAR-1 and PAR-4) inducing both platelet activation (1) and leukocyte activation (16), thus promoting inflammation. LMWH and UFH induce a downregulation of inflammation, decreasing systemic proinflammatory cytokines and nuclear factor- $\kappa$ B in lipopolysaccharide-stimulated monocytes. Bivalirudin inhibits the two- to three-fold increase in myeloperoxidase release from neutrophils (17) as well as formation of platelet-leukocyte aggregates (12) occurring after PCI. The additional reduction in ADP-induced platelet activation experienced with bivalirudin is consistent with the pre-

viously documented interaction between thrombin-induced, PAR-mediated and ADP-induced activation of platelets (18) and enforces the concept that multi-target therapy is needed to fully inhibit platelets. In this light, bivalirudin, because of its favorable safety profile, appears to be a valid candidate as adjunctive therapy at least in the setting of elective PCI (Fig. 1).

The results of clinical trials on the use of anticoagulant agents (19) shed light on the involvement of inflammation, endothelial dysfunction, activation of monocytes and of the coagulative cascade in orchestrating thrombus formation and amplification *in vivo* (20), as well as in restenosis (21). Understanding this previously unappreciated scenario may explain at least in part the proportion of clinical treatment failure under dual antiplatelet therapy and paves the way for additional therapeutic tools possibly acting downstream such a detrimental cascade.

Thus, thrombin may be a common downstream target blocking platelet activation, monocyte activation and systemic inflammation that together may be responsible for further ischaemic events despite dual antiplatelet therapy. If so, antiplatelet drugs targeting PAR-1 on platelet or thrombin inhibitors, either parenteral such as bivalirudin, or oral such as dabigatran, as well as oral factor Xa inhibitors such as rivaroxaban, may effectively suppress residual platelet/leukocyte and inflammatory activation escaped during dual antiplatelet therapy.

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