Platelet Protagonist/Antagonist: Understanding the Distinguishing Characteristics of Anticoagulants

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Clinical coagulation laboratory tests do not accurately reflect hemostasis and thrombosis in vivo. Thrombin generation in vivo occurs in 3 overlapping phases: initiation, priming, and propagation. During initiation, injury to the vessel wall exposes the cells to tissue factors, which lead to the production of small amounts of thrombin. During priming, the thrombin that is generated initially binds to platelets and activates them through protease-activated receptors. During the propagation phase, factor X is activated by the factor IXa/VIIIa complex that is assembled on the activated platelet surface. Subsequent formation of factor Xa/Va complexes on the platelet surface leads to a burst of thrombin and fibrin formation. Pharmacologic concentrations of a direct thrombin inhibitor, bivalirudin, inhibit thrombin-induced activation of platelets to a greater extent than pharmacologic concentrations of unfractionated heparin.
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An improved understanding of the mechanisms of thrombosis highlights the critical interplay between platelets and thrombin. This interaction and its implications for anti-thrombotic therapy will be discussed.

Mechanisms of Thrombosis: The Role of Thrombin and Platelets

The coagulation cascade has been traditionally depicted as 2 somewhat independent pathways that converge to a common pathway, with thrombin generation as the endpoint of the reactions (Figure 1). Although this depiction

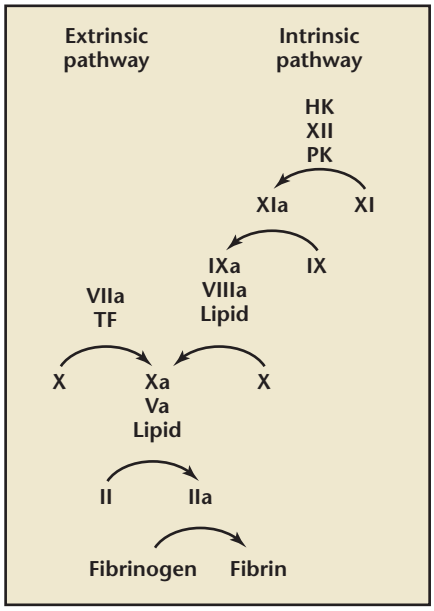
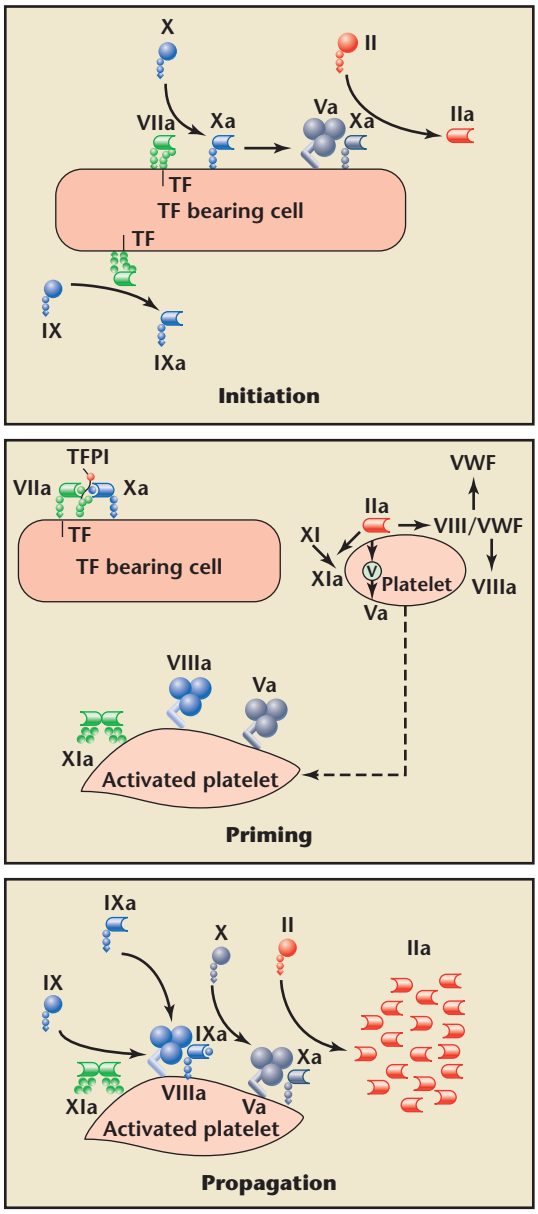


Figure 1. *Cascade model of coagulation. Traditional model of coagulation divided into the intrinsic and extrinsic pathways. Reproduced with permission from Monroe DM et al.*[1]

Figure 2. *Cell-based model of coagulation. An updated model of coagulation that highlights the role of platelets and better characterizes thrombosis in vivo. TF, tissue factor; TFPI, tissue factor pathway inhibitor; VWF, von Willebrand factor. Reproduced with permission from Monroe DM et al.*[1]



reflects the processes observed in clinical coagulation laboratory tests (the prothrombin time measures the "extrinsic pathway" and the activated partial thromboplastin time measures the "intrinsic pathway"), it is an inaccurate reflection of hemostasis and thrombosis in vivo.[1,2] Activation of the coagulation cascade and thrombin generation do not occur physiologically in solution but are localized to a phospholipid surface.[1,2] In part, this localization confines the reaction to the specific site of injury. Not all phospholipid surfaces are the same. Platelets support thrombin generation in a manner that is not completely mimicked by other phospholipid surfaces.[3]

The model depicted in Figure 2 more accurately reflects our current understanding of thrombin generation in vivo.[4] In this model, coagulation occurs in 3 overlapping phases: initiation, priming, and propagation. Injury to the vessel wall exposes blood to cells with tissue factor on their surface. Tissue factor may be derived from extravascular sources, such as fibroblasts, or may be derived from sources in blood that have been referred to as protected and include that supplied by the interaction between platelets and leukocytes, which is mediated by CD62 (P-selectin) and CD15 (P-selectin glycoprotein [GP] ligand 1). Factor VII binds to tissue factor and is rapidly activated. The factor VIIa/tissue factor complex activates factor X and factor IX. Factor Xa and other proteases activate factor V. The combination of factor Xa plus factor Va on the phospholipid surface cleaves prothrombin to produce small amounts of thrombin.[5] The small amount of thrombin that is produced leads to an explosive increase in the generation of thrombin.[6]

Injury to the vessel wall leads to adherence of platelets, which is mediated by collagen and von Willebrand factor.[7] This adherence leads to the activation of platelets, which is increased during priming when the small amount of thrombin that is generated initially binds to platelets and activates them through protease-activated receptors (PARs). Platelets may be pivotal in the initial generation of thrombin because their activation results in degranulation that releases partially active factor V from α-granules.[8] Collagen and thrombin act in synergy to activate platelets to a greater extent than that seen with either agonist alone.[9] Thrombin cleaves the partially activated factor V to a fully active form. Thrombin also cleaves factor VIII, releasing it from von Willebrand factor and activates factor XI bound to the platelet surface. The result of this stage is a primed activated platelet that rapidly binds the cofactors Va and VIIIa as well as factor XIa.[10]

Platelets may be pivotal in the initial generation of thrombin because their activation results in degranulation that releases partially active factor V from α-granules.

During the propagation phase, factor X is activated by the factor IXa/VIIIa complex that is assembled on the activated platelet surface. Subsequent formation on the platelet surface of factor Xa/Va complexes leads to a burst of thrombin and fibrin formation.

Platelets contribute to thrombosis in multiple ways. Adherence of platelets after vascular injury contributes to the formation of a hemostatic plug and initiates activation.[11] Activation of platelets contributes to thrombosis through: 1) the formation of platelet-platelet aggregates mediated by GP IIb/IIIa[12] and platelet-leukocyte aggregates mediated by P-selectin[13]; 2) the release of granular products[14] that support generation of thrombin (such as calcium, factor V, and fibrinogen), recruitment of additional activated platelets (through release of thromboxane and adenosine diphosphate [ADP]), and stimulation of vasoconstriction (through release of serotonin and other vasoactive peptides); 3) formation of thrombin, promoted by the phospholipid surface on which coagulation factor complexes form[1,10]; and 4) change in the shape of the platelet with pseudopod extension.[15] Thus, platelet activation and thrombin generation are intimately intertwined. Platelets are pivotal in thrombin generation and thrombin is a powerful agonist for platelet activation.

Thrombin and Platelet Activation

Because thrombin is a powerful platelet agonist, we characterized the effect of pharmacologic concentrations of bivalirudin, unfractionated heparin (UFH), and the combination of UFH plus eptifibatide (UFH+E) on thrombin-induced activation of platelets.[16] This type of characterization had not been performed previously because thrombin-induced fibrin polymerization interferes with most assays of platelet function. Thrombin receptor agonist peptide (TRAP) has been used to mimic the effects of thrombin by activating the protease-activated receptor.[17] Direct thrombin inhibitors such as bivalirudin inhibit cleavage of the tethered ligand (TRAP) of the protease-activated receptor but do not inhibit binding of TRAP. Thus, the antiplatelet effects of bivalirudin can only be assessed when thrombin is

Table 1
Platelet Activation in the Absence of Added Agonist

Anti-thrombotic	Platelets Binding PAC-1 (%)	Platelets With Surface Expression of P-selectin (%)
UFH 1.2 U/mL (ACT = 258 ± 13 sec)	0.9 ± 0.3	0.9 ± 0.3
UFH 2.0 U/mL (ACT = 618 ± 31 sec)	3.2 ± 0.5*	1.6 ± 0.5
Bivalirudin 8 μg/mL (ACT = 348 ± 9 sec)	0.5 ± 0.1	0.8 ± 0.3
Bivalirudin 14 μg/mL (ACT = 384 ± 5 sec)	0.2 ± 0.1	0.8 ± 0.4
UFH 1.2 U/mL + E 1.7 μg/mL (ACT = 348 ± 9 sec)	0.3 ± 0.1	2.0 ± 0.5

For PAC-1, ANOVA, $P < .001$.
*UFH 2.0 U/mL is greater than other treatments ($P < .05$).
UFH, unfractionated heparin; ACT, activated clotting time; E, eptifibatide.
Adapted from Schneider DJ et al.[16]

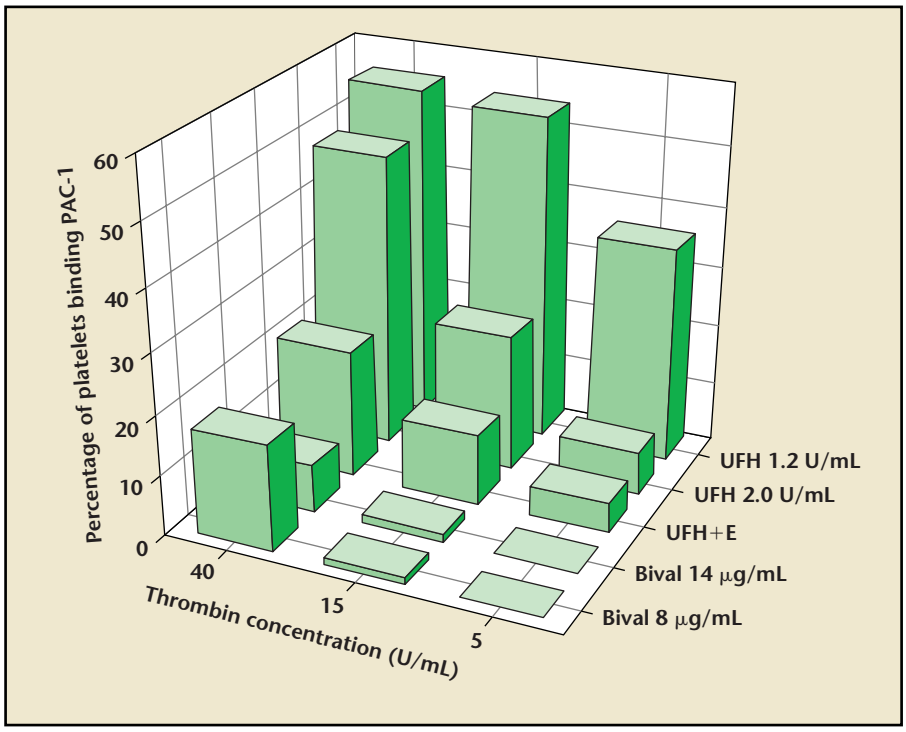


Figure 3. *Platelet activation with respect to the activation of GP IIb/IIIa. Blood was taken from patients (n = 12) with symptomatic coronary artery disease at the time of cardiac catheterization and spiked with UFH alone (1.2 and 2.0 U/mL) and in combination with E (E 1.7 μg/mL + UFH 1.2 U/mL) or bival (8 and 14 μg/mL). After 15 minutes, platelet function was assessed with the use of flow cytometry. Fibrin polymerization was inhibited with the peptide GPRP, and activation of GP IIb/IIIa was identified by the binding of the antibody PAC-1. Platelet activation was induced with thrombin. Values are means. Bival inhibited thrombin-induced PAC-1 binding more effectively than UFH alone or in combination with E (P < .05). UFH, unfractionated heparin; E, eptifibatide; bival, bivalirudin; GP, glycoprotein. Adapted from Schneider DJ et al.*[16]

used as the agonist. We were able to modify our flow cytometry–based assay of platelet function to enable us to test the relative effects of UFH and bivalirudin on thrombin-induced activation of platelets.

Blood was taken from patients undergoing clinically indicated cardiac catheterization and spiked in vitro with anti-thrombotic regimens that are used in vivo. Anti-thrombotic effects were characterized by assay of the activated clotting time (ACT, Table 1), and platelet function was assessed with the use of flow cytometry (Table 1, Figures 3 and 4). All patients had been treated previously with aspirin and clopidogrel but no patient had been treated with an anticoagulant.

Our results demonstrated that pharmacologic concentrations of the direct thrombin inhibitor, bivalirudin, more effectively inhibit thrombin-induced activation of platelets than either UFH alone or in combination with the GP IIb/IIIa antagonist eptifibatide in blood from patients with coronary artery disease who had been treated previously with aspirin and clopidogrel (Table 1, Figures 3 and 4). Although eptifibatide inhibited binding of PAC-1 to the activated conformer of GP IIb/IIIa, bivalirudin more effectively prevented activation of GP IIb/IIIa and hence PAC-1 binding than did the combination of UFH plus eptifibatide (Figure 3). As expected, eptifibatide did not inhibit P-selectin expression (Figure 4) and thus would not be expected to prevent formation of platelet-leukocyte aggregates. These results are consistent with the similar (statistically non-inferior) incidence of ischemic cardiac events that was seen in the Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events (REPLACE-2) study.[18] Moreover, they support the hypothesis that greater limitation of thrombin activity by bivalirudin may have contributed to the trend toward a greater reduction in mortality after 1 year than that seen in the REPLACE-2 study.[19]

Heparin and Platelet Function

My colleagues and I[16] and others[20] have found that UFH activates platelets (Table 1). Greater concentrations of UFH were associated with greater activation of platelets in the absence of agonist in blood from patients with coronary artery disease who were undergoing cardiac catheterization (Table 1). Activation of platelets was apparent with respect to activation of GP IIb/IIIa (PAC-1 binding), an observation consistent with the previously reported binding of UFH to GP IIb/IIIa that mediates activation of platelets.[20] Accordingly, although UFH may limit thrombin generation, it increases activation of platelets. This effect is likely to be counterproductive and potentiate thrombosis.

Activation of platelets in response to agonists other than thrombin is increased when blood has been treated with UFH.[21-23] The activation of platelets by ADP was greater when blood was exposed to greater concentrations of UFH[21] and that the activation of platelets was greater when anticoagulated with UFH compared with a direct thrombin inhibitor, hirudin (Figure 5). Similarly, blood from patients with coronary artery disease that was spiked with pharmacologic concentrations of UFH exhibited greater activation than blood spiked with bivalirudin (Figure 6).

To determine whether effects seen in vitro would be apparent in vivo,

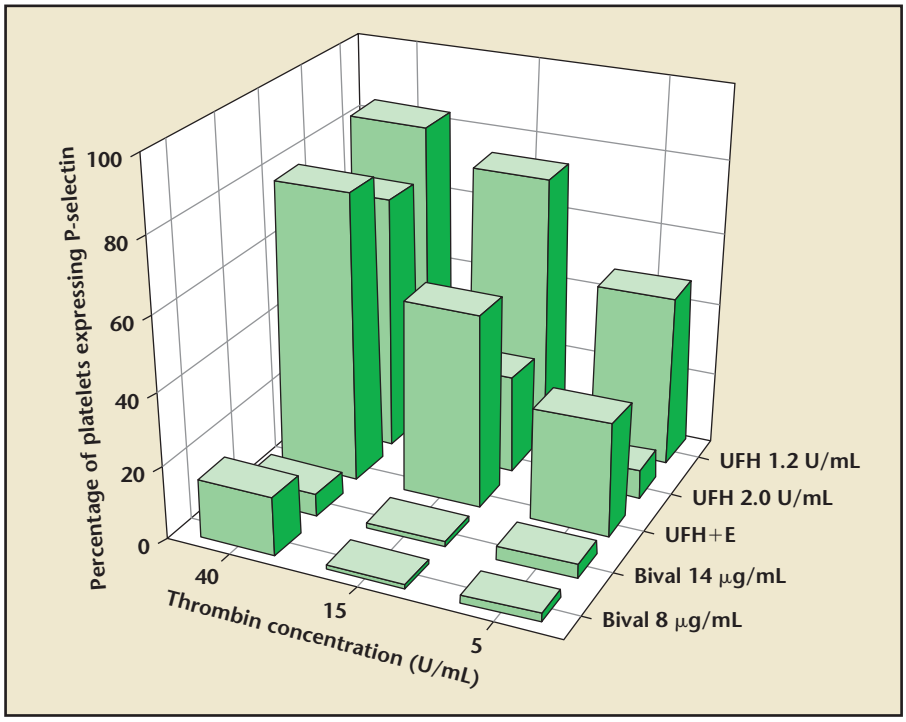


Figure 4. *Platelet activation with respect to the platelet surface expression of P-selectin. Blood was taken from patients (n = 12) with symptomatic coronary artery disease at the time of cardiac catheterization and spiked with UFH alone (1.2 and 2.0 U/mL) and in combination with E (E 1.7 μg/mL + UFH 1.2 U/mL) or bival (8 and 14 μg/mL). After 15 minutes, platelet function was assessed with the use of flow cytometry. Fibrin polymerization was inhibited with the peptide GPRP, and platelet surface expression of P-selectin was identified by the binding of the antibody anti-CD62. Platelet activation was induced with thrombin. Values are means. Bival inhibited thrombin-induced P-selectin expression more effectively than UFH alone or in combination with E (P < .05). UFH, unfractionated heparin; E, eptifibatide; bival, bivalirudin. Adapted from Schneider DJ et al.*[16]

we characterized platelet function in patients undergoing percutaneous coronary intervention (PCI) who were treated with either bivalirudin or UFH plus eptifibatide.[24] We obtained blood from the guide catheter placed in the coronary ostium and used it to characterize platelet reactivity ex vivo, the formation in vivo of platelet-leukocyte aggregates, and leukocyte activation in vivo reflected by myeloperoxidase release. Coronary ostial blood was taken because we have shown previously that it reflects the downstream milieu with respect to thrombin activity, platelet reactivity, and inflammation.[25,26]

In this comparison in vivo of UFH+E and bivalirudin, we observed, consistent with our previous work in vitro, greater agonist-induced expression of P-selectin in whole blood samples obtained before PCI from patients treated with UFH+E (Figure 7). A functional significance of the increased platelet reactivity was supported by an increased prevalence in vivo of platelet-leukocyte aggregates (Figure 8) and evidence of greater activation of leukocytes in those treated with UFH+E compared with bivalirudin (Figure 9). Consistent with the duration of exposure to UFH (bolus only), differences in platelet reactivity and platelet-leukocyte formation were apparent shortly (10 minutes) after initiation of treatment. Underscoring the potential significance of even transient increases in platelet reactivity and the formation of platelet-leukocyte aggregates, the concentration of myeloperoxidase continued to be significantly greater in the UFH+E group 30 minutes after initiation of treatment in the post-PCI sample.

Treatment with eptifibatide was associated with a decreased capacity of platelets to bind fibrinogen in response to ADP.[24] Thus, because multiple agonists activate platelets, formation of platelet aggregates mediated by GP IIb/IIIa would be expected to be inhibited to a greater extent in patients treated with UFH+E. Accordingly, use of a GP IIb/IIIa antagonist would be expected to decrease the prevalence of platelet aggregates but not to inhibit the formation of platelet-leukocyte

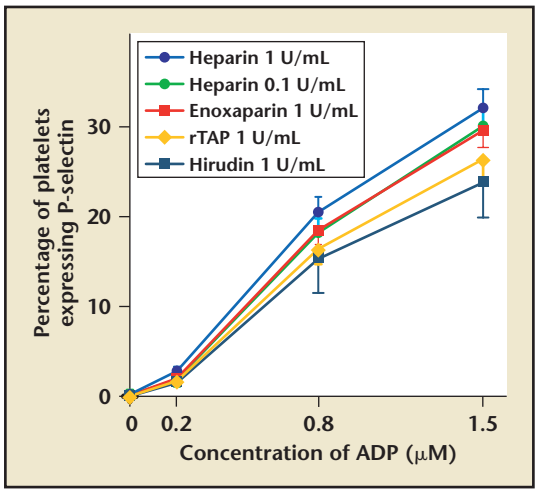


Figure 5. *ADP-induced activation of platelets determined based on detection of platelet surface expression of P-selectin by flow cytometry in whole blood anticoagulated with unfractionated heparin (anti-IIa/Xa = 1 and 0.1 U/mL blood), enoxaparin (anti-Xa = 1 U/mL of blood), a direct Xa inhibitor, tick anticoagulant protein (rTAP, anti-Xa = 1 U/mL of blood), and direct thrombin inhibitor, hirudin (anti-IIa = 1 U/mL of blood). Results are means ± SEM in blood from 12 subjects. Assays for each subject under each set of conditions were performed in triplicate. Differences between heparin 1 U/mL and heparin 0.1 U/mL and between heparin 1 U/mL and other anticoagulants were significant (P < .05) as determined by the Wilcoxon signed rank test with respect to all concentrations of ADP used. ADP, adenosine diphosphate. Adapted from Schneider DJ et al.*[21]

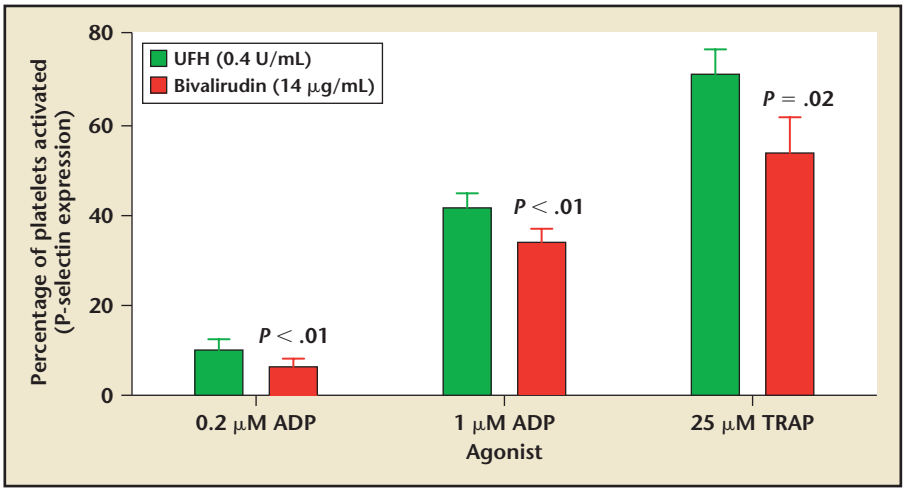


Figure 6. *Platelet surface expression of P-selectin (activation) in response to 0.2 μM ADP, 1 μM ADP, and 25 μM TRAP. Blood from patients with coronary artery disease undergoing cardiac catheterization was spiked in vitro with UFH (0.4 U/mL) or bivalirudin (14 μg/mL). Greater platelet reactivity was seen in blood treated with UFH than bivalirudin (P ≤ .01 bivalirudin compared with UFH). UFH, unfractionated heparin; ADP, adenosine diphosphate; TRAP, thrombin receptor agonist peptide. Adapted from Aggarwal A et al.*[22]

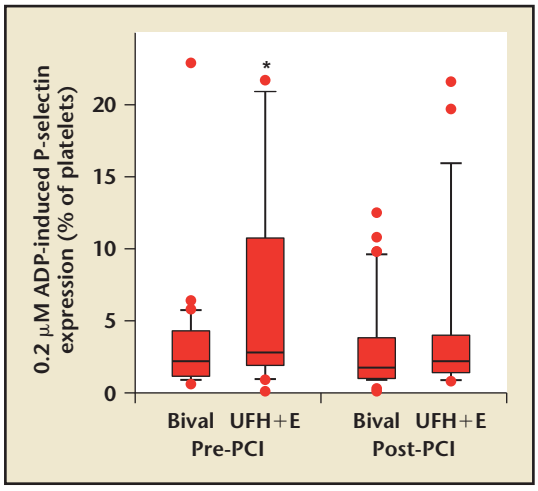


Figure 7. *Platelet surface expression of P-selectin in response to 0.2 μM ADP before and after PCI in blood from patients treated with bival or UFH+E. Blood was taken from the coronary artery of the culprit vessel approximately 10 minutes (pre-PCI) and 30 minutes (post-PCI) after treatment with B or UFH+E. Activation of platelets was induced in vitro with 0.2 μM ADP and assessed with the use of flow cytometry. In the plot, the box is the 25th and 75th percentiles, the error bars are the 10th and 90th percentiles, and the horizontal line is the median. Solid circles are results below the 10th percentile and above the 90th percentile. *P < .05; ADP, adenosine diphosphate; bival, bivalirudin; UFH, unfractionated heparin; E, eptifibatide; PCI, percutaneous coronary intervention. Adapted with permission from Keating FK et al.*[24]

aggregates induced by UFH. The design of the study does not, however, permit determination of whether UFH, eptifibatide, or the combination of both was responsible for the observed transitory increase in platelet reactivity, platelet-leukocyte formation, and leukocyte activation compared with bivalirudin.

Interaction Between Platelet Agonist Receptors

ADP and thrombin activate platelets through 7 transmembrane G-protein–coupled receptors expressed on the platelet surface. Thrombin induces a unique and specific proteolysis of protease-activated receptors (PARs). Proteolysis of PARs by thrombin exposes a tethered ligand at the extracellular N-terminus of the receptor that induces activation.[27] Two of the 4 known PARs, PAR1 and PAR4, are expressed on human platelets.[28] PAR1 has a higher affinity for thrombin than PAR4, and a sequential activation mechanism by thrombin has been proposed.[28,29] ADP is a weaker agonist than thrombin, is stored in dense granules of the platelet, and is released during activation. Thus, exposure of platelets to thrombin leads to the release of ADP that contributes to the activation of platelets. ADP activates 2 G-protein–coupled receptors on the surface of the platelet, $P2Y_1$[30] and $P2Y_{12}$.[31]

Inhibition of both thrombin- or ADP-induced activation of platelets is greater with the combination of a direct thrombin inhibitor and an ADP antagonist than with either agent alone.[32] Synergy has been identified with the use of established criteria.[32] We have found that the combination of pharmacologic concentrations of a direct thrombin inhibitor (bivalirudin) plus a $P2Y_{12}$ antagonist (cangrelor) inhibits thrombin-induced and ADP-induced activation of platelets to a greater extent than pharmacologic concentrations of UFH plus cangrelor (Figure 10). These results are consistent with the synergistic interaction previously identified and suggest that a direct thrombin inhibitor but not UFH will exhibit synergy.

Properties of Direct Thrombin Inhibitors

Direct thrombin inhibitors (DTIs) can be categorized into those that interact solely with the active (catalytic) site of thrombin (univalent DTI) or those that interact with the active site plus the fibrinogen-binding site (exosite 1, bivalent DTI) (Table 2). DTIs contrast with heparins that are indirect thrombin inhibitors and require an endogenous cofactor, antithrombin. Bivalent inhibitors, particularly hirudin and its derivatives, exhibit a very high affinity and specificity for thrombin.[33] By contrast, the binding affinity of univalent DTIs (eg, argatroban, melagatran) is substantially (1000-fold) less.[34]

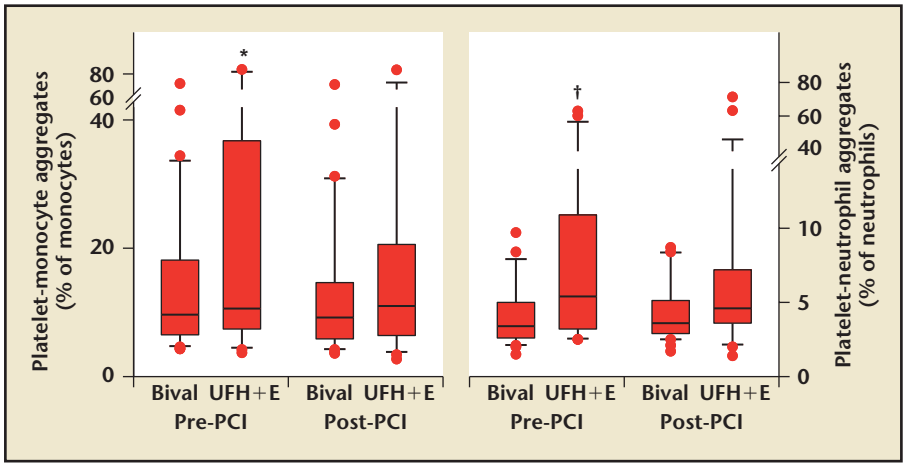


Figure 8. *Formation in vivo of PMA and PNA in blood from patients treated with bival or UFH+E. Blood was taken from the coronary artery of the culprit vessel approximately 10 minutes (pre-PCI) and 30 minutes (post-PCI) after treatment with B or UFH+E. Formation in vitro of PMA and PNA was inhibited by the addition of anti-CD62. The percentage of monocytes or neutrophils associated with platelets was assessed with the use of flow cytometry. In the plot, the box is the 25th and 75th percentile, the error bars are the 10th and 90th percentiles, and the horizontal line is the median. Solid circles are results below the 10th percentile and above the 90th percentile.* *P < .05; †P < .01. *Bival, bivalirudin; UFH, unfractionated heparin; E, eptifibatide; PCI, percutaneous coronary intervention; PMA, platelet-monocyte aggregates; PNA, platelet-neutrophil aggregates. Adapted with permission from Keating FK et al.[24]*

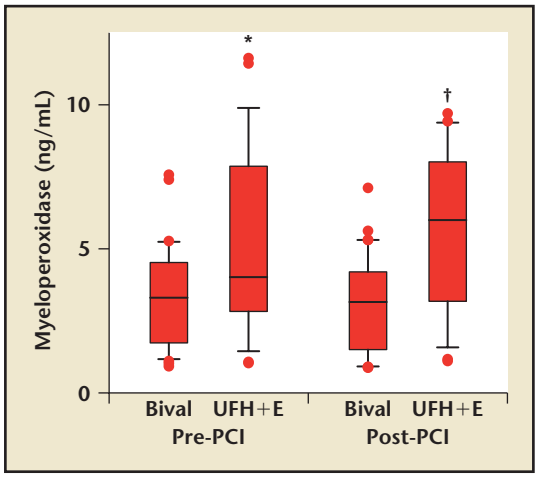


Figure 9. *The concentration of myeloperoxidase in blood from patients treated with bival or UFH+E. Blood was taken from the coronary artery of the culprit vessel approximately 10 minutes (pre-PCI) and 30 minutes (post-PCI) after treatment with bival or UFH+E. The concentration of myeloperoxidase was determined with the use of enzyme-linked immunosorbent assay. In the plot, the box is the 25th and 75th percentile, the error bars are the 10th and 90th percentiles, and the horizontal line is the median. Solid circles are results below the 10th and above the 90th percentiles.* *P < .01; †P = .0001. *Bival, bivalirudin; UFH, unfractionated heparin; E, eptifibatide; PCI, percutaneous coronary intervention. Adapted with permission from Keating FK et al.[24]*

Accordingly, the univalent DTIs exhibit relative thrombin selectivity and hirudin derivatives exhibit marked thrombin specificity. DTIs bind in a non-covalent manner to thrombin, whereas heparin-catalyzed binding of antithrombin to thrombin is covalent. Because of the marked affinity, hirudin forms an essentially irreversible complex with thrombin.

Hirudins are produced by leeches and have a characteristic structure that consists of a single polypeptide chain of 65 amino acids with 3 disulfide bridges. Two synthetic preparations of r-hirudin are available: lepirudin and desirudin. They have minor structural and pharmacologic differences. Only lepirudin is available for clinical use in North America. During intravascular infusion, lepirudin distributes into the extravascular space. Thus, particularly after extended treatment, hirudin redistributes from the extravascular compartment into the intravascular compartment and a prolonged anticoagulant effect can be anticipated. Hirudin and hirudin–thrombin complexes are cleared primarily by the kidneys and their half-life increases greatly in patients with renal insufficiency. In individuals with normal renal function, the terminal elimination half-life of lepirudin is about 80 minutes. Hirudins are immunogenic, and antihirudin antibodies form between 1 and 4 weeks after beginning treatment with r-hirudin. Immunization rates are similar with lepirudin and desirudin.

Bivalirudin unites a C-terminal dodecapeptide derived from native hirudin (residues 53-64) with an active-site-binding N-terminal tetrapeptide (D-Phe1-Pro2-Arg3-Pro4), and 4 glycine residues bridge the 2 segments. Bivalirudin exhibits lower affinity for thrombin than does hirudin. The affinity of bivalirudin for thrombin is comparable to that of univalent DTIs; however, its specificity for thrombin appears to be greater than that of univalent DTIs.[33] The binding of bivalirudin to thrombin is reversible because bivalirudin is a substrate of thrombin and proteolysis occurs at its arg3-pro4 bond.[35] Accordingly, the lower affinity and the proteolysis of bivalirudin lead to a reversible inhibition of thrombin. The elimination half-life of bivalirudin is approximately 25 minutes.[36] Metabolism (by enzymes in blood) accounts for nearly 80% of the clearance of bivalirudin. Thus, recommended initial dose reductions in patients with moderate and severe renal insufficiency are from 20% to 60%. Bivalirudin is less immunogenic than hirudin.

Currently, only one univalent DTI, argatroban, is available for use in North America. Pharmacologic features of argatroban include reversible inhibition of thrombin, a half-life of

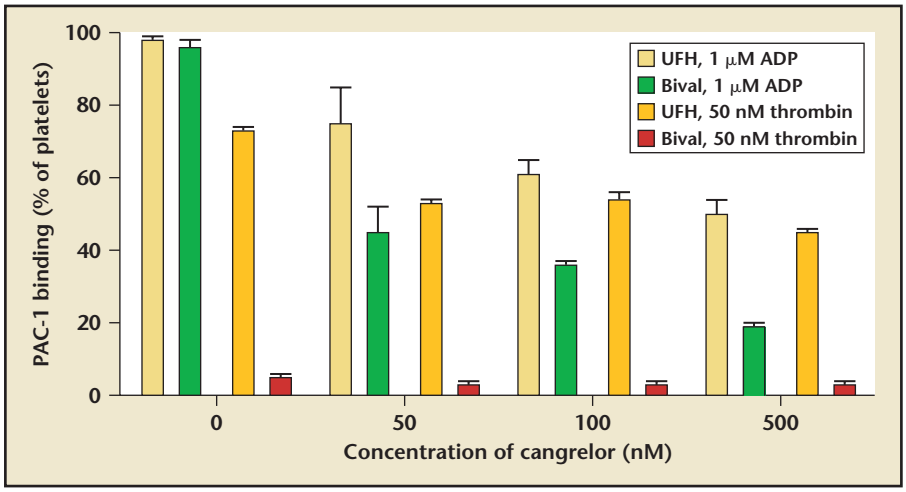


Figure 10. *Platelet activation with respect to the activation of GP IIb/IIIa. Blood was spiked with UFH alone (1.2), bival alone (8 μg/mL), or the combination of either UFH or bival plus increasing concentrations of cangrelor. After 15 minutes, platelet function was assessed with the use of flow cytometry. Fibrin polymerization was inhibited with the peptide GPRP and activation of GP IIb/IIIa was identified by the binding of the antibody PAC-1. Platelet activation was induced with thrombin (50 nM) and ADP (1 μM). Values are means ± SD. Bival inhibited thrombin-induced PAC-1 binding greater than UFH alone (P < .05). The combination of bival plus cangrelor inhibited ADP-induced PAC-1 binding greater than UFH plus cangrelor (P < .05). UFH, unfractionated heparin; bival, bivalirudin; GP, glycoprotein; ADP, adenosine diphosphate.*

Table 2
Properties of Direct Thrombin Inhibitors

Property	Lepirudin	Argatroban	Bivalirudin
Bivalent	yes	no	yes
Reversible	no	yes	yes
Half-life	1.3 h	45 min	25 min
Indication	HIT	HIT	PCI
Reduced bleeding	no	yes	yes
Reduced ischemia	yes	no	yes
Caution in renal patients	yes	no	no
Caution in liver patients	no	yes	no
Antibodies	yes	no	no
Hypersensitivity	yes	no	no

HIT, heparin-induced thrombocytopenia; PCI, percutaneous coronary intervention.

40 to 50 minutes, clearance by hepatobiliary metabolism, and a lack of immunogenicity. Argatroban is also approved in the United States for PCI in patients in whom heparin is contraindicated because of heparin-induced thrombocytopenia.

Summary

Platelets are pivotal in the generation of thrombin, and thrombin is a key agonist of platelet activation. Pharmacologic concentrations of a direct thrombin inhibitor, bivalirudin, inhibit thrombin-induced activation of platelets to a greater extent than pharmacologic concentrations of UFH. UFH activates platelets and potentiates the activation of platelets by agonists such as ADP. This effect has been observed in vitro and confirmed in vivo. Activation of platelets by thrombin and ADP appears to be linked, and the combination of pharmacologic concentrations of a direct thrombin inhibitor plus a $P2Y_{12}$ antagonist (cangrelor) inhibits thrombin-induced and ADP-induced activation of platelets to a greater extent than pharmacologic concentrations of UFH plus cangrelor. Because of its great affinity, hirudin irreversibly inhibits thrombin. By contrast, bivalirudin and argatroban reversibly inhibit thrombin generation and have shorter half-lives of approximately 25 minutes for bivalirudin and 40 to 50 minutes for argatroban. Clinical experience in patients undergoing PCI is greater with bivalirudin than with argatroban. ■

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Main Points

- An improved understanding of the mechanisms of thrombosis highlights the critical interplay between platelets and thrombin, with certain implications for anti-thrombotic therapy.
- Because thrombin is a powerful platelet agonist, the effect of pharmacologic concentrations of bivalirudin, unfractionated heparin (UFH), and the combination of UFH plus eptifibatide on thrombin-induced activation of platelets was assessed.
- Pharmacologic concentrations of the direct thrombin inhibitor, bivalirudin, more effectively inhibit thrombin-induced activation of platelets than either unfractionated heparin alone or in combination with a glycoprotein IIb/IIIa antagonist eptifibatide in blood from patients with coronary artery disease who had been treated previously with aspirin and clopidogrel.