Anticoagulation for Acute Coronary Syndromes: From Heparin to Direct Thrombin Inhibitors

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The anticoagulant properties of heparin were discovered in 1916, and by the 1930s researchers were evaluating its therapeutic use in clinical trials. Treatment of unstable angina with unfractionated heparin (UFH), in addition to aspirin, was introduced into clinical practice in the early 1980s. UFH was combined with aspirin to suppress thrombin propagation and fibrin formation in patients presenting with acute coronary syndromes (ACS) or patients undergoing percutaneous coronary intervention (PCI). However, UFH stimulates platelets, leading to both activation and aggregation, which may further promote clot formation. Clinical trials have demonstrated that newer agents, such as the low-molecular-weight heparins (LMWHs), are superior to UFH for medical management of unstable angina or non–ST-segment elevation myocardial infarction. Increasingly, the LMWHs have been used as the anticoagulant of choice for patients presenting with ACS. For patients undergoing PCI, LMWH provides no substantial benefit over UFH for anticoagulation; however, direct thrombin inhibitors (DTIs) have demonstrated safety and efficacy in this setting. UFH is likely to be replaced by more effective and safer antithrombin agents, such as DTIs. DTIs have antiplatelet effects, anticoagulant action, and most do not bind to plasma proteins, thereby providing a more consistent dose-response effect than UFH. The FDA has approved 4 parenteral DTIs for various indications: lepirudin, argatroban, bivalirudin, and desirudin. The antiplatelet, anticoagulant, and pharmacokinetic properties of bivalirudin support its use as the anticoagulant of choice for both lower- and higher-risk patients, including those undergoing PCI.

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In 1916, Jay McLean, a 26-year-old medical student at Johns Hopkins University, proclaimed his discovery of "antithrombin" to his physiology professor, William Howell. In fact, he had discovered heparin.[1] Then, Charles Best, in 1928, organized a team of chemists, physiologists, and surgeons in Toronto to focus on the development of heparin for commercial use. This

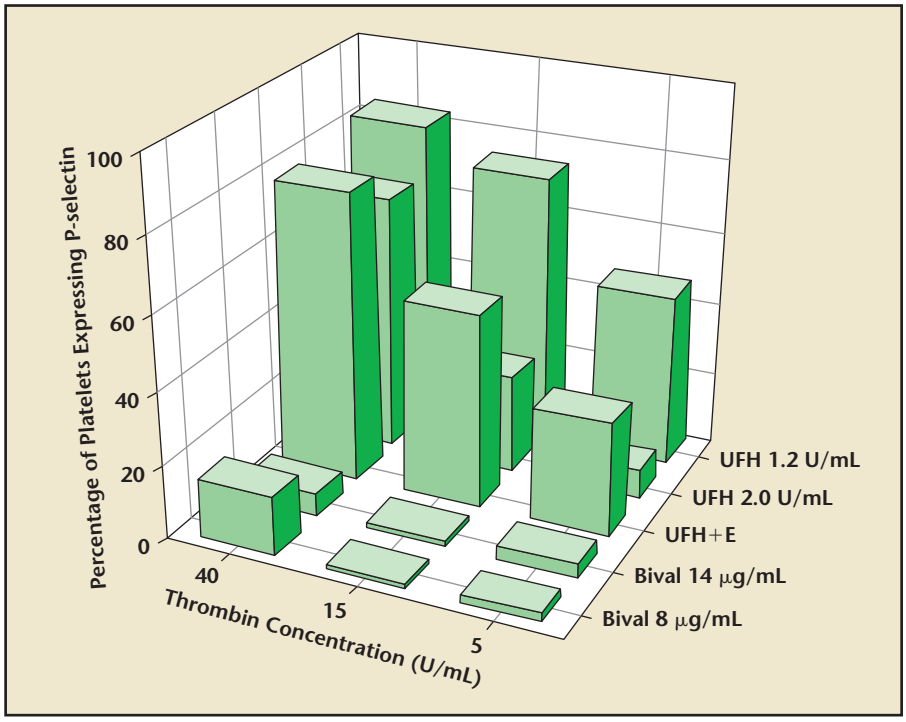
group determined animal tissues that were the best source of heparin, performed purification and identification, and determined the pharmacologic properties of heparin in vitro. By 1935, these researchers had initiated human clinical trials with heparin and by 1941 reported a series of 700 patients treated with heparin.

The therapeutic use of unfractionated heparin (UFH) in addition to aspirin compared with aspirin alone for the treatment of unstable angina was introduced into clinical practice in the early 1980s. The efficacy of UFH in addition to aspirin was supported by the meta-analysis by Oler and colleagues, which showed a 33% reduction in death and myocardial infarction (MI).[2] The overall relative risk (RR) of MI or death during randomized treatment was 0.67 (95% confidence interval [CI], 0.44-1.02) with UFH plus aspirin. Historically, UFH has been combined with aspirin to suppress thrombin propagation and fibrin formation in patients presenting with acute coronary syndromes (ACS) and for percutaneous coronary interventions (PCI); however, its effectiveness has been recently questioned in these settings.[3] Unlike newer anticoagulant alternatives, UFH paradoxically stimulates platelet activation and aggregation, which may further promote clot formation. In addition, obtaining a valid therapeutic activated partial thromboplastin time (aPTT) in cardiology patients is a major challenge, and dosing is complex. Due to substantial variation in reagents and instruments, target aPTT ranges for UFH in ACS clinical trials cannot be extrapolated to individual institutions. Further, the risk of ischemic events is greater shortly after abrupt discontinuation of UFH compared with alternative agents with longer half-lives and less stimulation of platelet aggregation. Key clinical trials, however, have not demonstrated that UFH is inferior to newer low-molecular-weight heparins (LMWHs) as a medical treatment for unstable angina or non–ST-segment elevation myocardial infarction (UA/NSTEMI). Consistent with this evidence, the most recent practice guidelines for UA/NSTEMI from the American College of Cardiology and the American Heart Association give both UFH and the LMWH enoxaparin Class IA recommendations in patients with ACS.[4] In patients with STEMI receiving the fibrinolytic agent tenecteplase as reperfusion therapy, enoxaparin has also been shown to be superior to UFH in combination. In PCI procedures, newer direct (bivalirudin) antithrombins have demonstrated safety and efficacy. There is little doubt that as we move forward in optimizing adjunctive anticoagulation in the cardiology setting, UFH use will largely be replaced by more effective and safer antithrombin agents.

Unfractionated Heparin as a Platelet Activator

Despite its effect on inhibiting thrombin, UFH has been shown to activate platelets; higher concentrations of heparin led to greater platelet activation. In an analysis by Schneider and colleagues, 2 measures of platelet activation were made: the percentage of platelet binding PAC-1 and the platelet surface expression of P-selectin (Figure 1).[5] PAC-1 is a monoclonal antibody that binds to the fibrinogen binding site on the activated

Figure 1. *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.*[5]



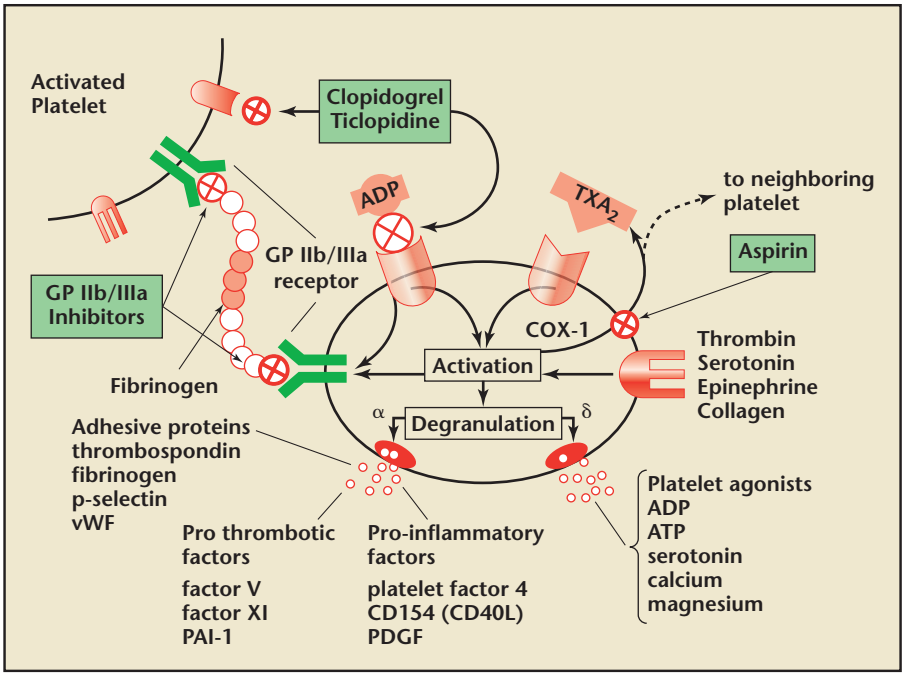
glycoprotein (GP) IIb/IIIa receptor. P-selectin (CD62P) is constitutively expressed in the alpha granule membrane of platelets and, following platelet activation, is expressed on the platelet surface where it mediates the adhesion of activated platelets to other platelets as well as to endothelial cells and leukocytes.

UFH led to a concentration-dependent increase in both measures of platelet activation, whereas no such effect was observed with the direct thrombin inhibitor (DTI) bivalirudin. Interestingly, the addition of eptifibatide to UFH actually led to an increase in the expression of P-selectin. This observation is consistent with the known effects of the GP-IIb/IIIa inhibitors, which only block platelet *aggregation* but do not generally inhibit the constellation of events associated with platelet *activation*—thrombosis, inflammation, and vasoconstriction—that lead to amplification of the platelet activation process (Figure 2).[6]

Additionally, UFH has the undesirable effect of increasing the release of von Willebrand factor from vessel walls, which is associated with platelet activation and an increase in cardiac thrombotic outcomes.[7] UFH also stimulates platelet activation through its interaction with platelet factor 4.[8]

The implications of these findings are compounded by the observation that UFH predisposes to greater platelet aggregation compared with LMWH in patients with ACS (Figure 3) and in normal patients compared with enoxaparin and the DTI argatroban (Figure 4).[9] Platelet aggregation increased 2-fold during the infusion of UFH. Enoxaparin also increased platelet aggregation; however, the increase was modest and not statistically significant. Argatroban actually led to a nonsignificant reduction of platelet aggregation induced by the platelet-activating compound adenosine diphosphate (ADP).

Figure 2. *The series of events that occur with platelet activation. Platelet activation involves: 1) a shape change in which the platelet membrane surface area is greatly increased; 2) the secretion of pro-inflammatory, prothrombotic, adhesive, and chemotactic mediators (release reaction) that propagate, amplify, and sustain the atherothrombotic process; and 3) the activation of the glycoprotein (GP) IIb/IIIa receptor from its inactive form. Multiple agonists, including thromboxane A_2 (TXA_2), adenosine diphosphate (ADP), thrombin, serotonin, epinephrine, and collagen, can activate the platelet and thus contribute toward establishing the environmental conditions necessary for atherothrombosis to occur. Aspirin inhibits the production of thromboxane A_2 by its effect on the enzyme cyclo-oxygenase (COX) 1. The ADP receptor antagonists clopidogrel and ticlopidine prevent the binding of ADP to its receptor. The effect of combining aspirin and clopidogrel is synergistic in preventing platelet aggregation. Antithrombins such as unfractionated or low-molecular-weight heparin, hirudin, or bivalirudin are important in interfering with both thrombin-induced platelet activation and coagulation. The GP IIb/IIIa receptor antagonists act at a later step in the process by preventing fibrinogen mediated cross-linking of platelets, which have already become activated. ATP, adenosine triphosphate; PAI, plasminogen activator inhibitor; PDGF, platelet-derived growth factor; vWF, von Willebrand factor. Reproduced with permission from Mehta SR, Yusuf S.*[6]



Low-Molecular-Weight Heparins

Increasingly, the LMWHs have been used as the anticoagulant of choice for patients presenting with ACS. On the other hand, acceptance of the use of LMWHs for patients undergoing PCI has been limited by lack of a standardized protocol for following the anticoagulant effects in the catheterization laboratory and the long half-life delaying vascular sheath removal and possibly leading to a greater incidence of access-site-related bleeding.

The Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-wave Coronary Events (ESSENCE) trial compared the effectiveness of the LMWH enoxaparin administered subcutaneously (1 mg/kg twice daily for 2 to 8 days; mean of 2.6 days) with UFH in patients with ACS.[10] At 14 days the composite endpoint (death, MI, or recurrent angina) was significantly lower for patients assigned to enoxaparin than those assigned to UFH (16.6% vs 19.8%; P = .019). At 30 days, the composite endpoint remained significantly lower in the enoxaparin group (19.8% vs 23.3%; P = .016). However, the incidence of bleeding was significantly higher in the enoxaparin group (18.4% vs 14.2%; P = .001), primarily because of ecchymosis at injection

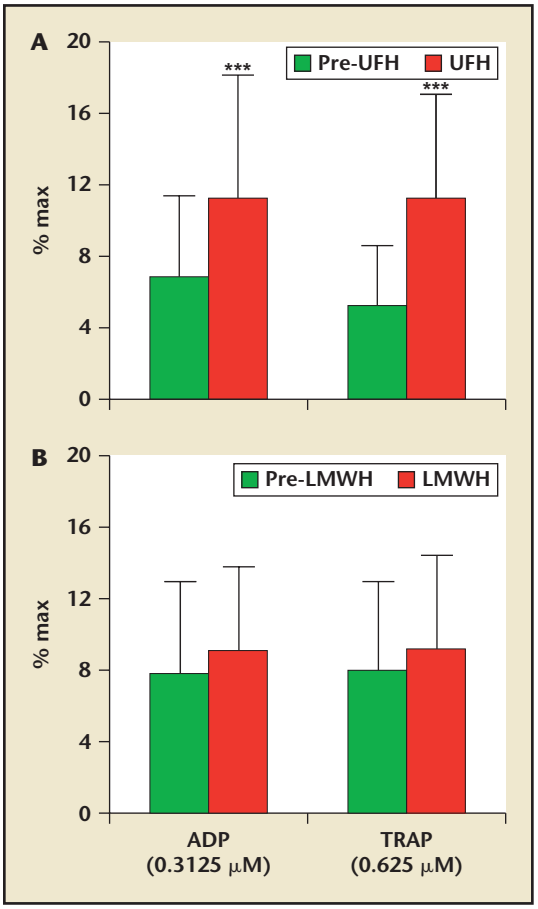


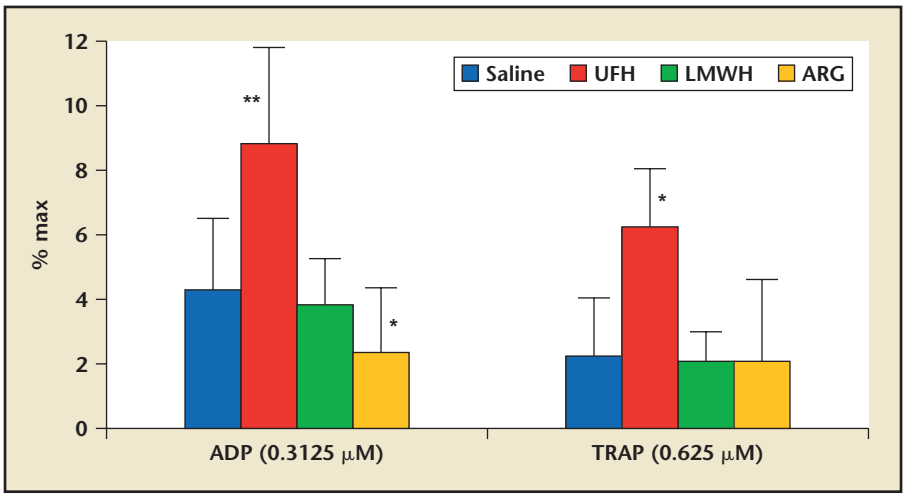
Figure 3. *Platelet aggregation (% maximum [max]) to ADP and to TRAP in patients with unstable angina before and during the infusion of UFH* **(A)** *and of enoxaparin (LMWH)* **(B)**. ****P < .001 vs before UFH. ADP, adenosine diphosphate; LMWH, low-molecular-weight heparin; TRAP, thrombin receptor agonist peptide; UFH, unfractionated heparin. Reprinted with permission from Xiao Z, Théroux P.*[9]

sites. The Thrombolysis in Myocardial Infarction (TIMI)-11B trial randomized patients with unstable angina or non–Q-wave MI to enoxaparin or UFH. There was a significant relative risk reduction (23.8%) in the composite endpoint (death, MI, or urgent revascularization) for patients in the enoxaparin group compared with patients in the UFH group.[11]

The Superior Yield of the New Strategy of Enoxaparin, Revascularization, and Glycoprotein IIb/IIIa inhibitors (SYNERGY) trial evaluated the safety and efficacy of subcutaneous enoxaparin compared with intravenous UFH in high-risk patients with non–ST-segment elevation (NSTE) ACS.[12] Among high-risk patients treated with an invasive management strategy, enoxaparin was noninferior compared with UFH for the risk of death or MI at 30 days, but TIMI major bleeding was elevated with enoxaparin. The primary endpoint of death or nonfatal MI at 30 days occurred in 14.0% of patients in the enoxaparin arm and 14.5% in the UFH arm (odds ratio [OR] 0.96; 95% CI, 0.87-1.06). Major bleeding per TIMI criteria was higher in the enoxaparin arm (9.1% vs 7.6%; $P = .008$). The lack of increased efficacy and increased risk of bleeding seems to have tempered the enthusiasm for using enoxaparin in patients with ACS destined to undergo urgent PCI.

The Fraxiparine in Ischemic Syndromes (FRAXIS) trial compared the LMWH nadroparin with UFH in unstable angina or non–Q-wave MI. There was no significant benefit of this LMWH over UFH in major adverse cardiac event rate but there was a significant excess of bleeding in patients treated with nadroparin.[13] The Enoxaparin Versus Tinzaparin in Non-ST-Segment Elevation Acute Coronary Syndromes (EVET) trial compared the efficacy of 2 different LMWHs, enoxaparin versus tinzaparin, in patients

Figure 4. *Maximum (max) platelet aggregation in PRP in normal individuals after the addition in whole blood of normal saline (control), UFH, enoxaparin (LMWH), and argatroban (ARG). Platelet aggregation to low concentrations of ADP and TRAP is significantly increased in the presence of UFH. *P < .05, **P < .01 vs control. ADP, adenosine diphosphate; LMWH, low-molecular-weight heparin; PRP, platelet-rich plasma; TRAP, thrombin receptor agonist peptide; UFH, unfractionated heparin. Reprinted with permission from Xiao Z, Théroux P.*[9]



with NSTE ACS. The primary composite 7-day endpoint (recurrent angina, MI, or death) was lower in the enoxaparin arm compared with the tinzaparin arm (12.3% vs 21.1%; P = .015).[14] Results from this head-to-head trial emphasize the point that there does not seem to be a "class effect" among the LMWHs.

The Fragmin in Unstable Coronary Artery Disease (FRIC) trial compared the efficacy and safety of weight-adjusted subcutaneous dalteparin with UFH in the acute treatment of unstable angina or non–Q-wave MI and the value of prolonged dalteparin compared with placebo in those initially anticoagulated.[15] There were no significant differences between the UFH and dalteparin groups in the 6-day incidence of the primary composite endpoint of death, MI, or recurrent angina (7.6% vs 9.3%; RR 1.18; 95% CI, 0.84-1.66). The results of the FRIC trial provide another example of the heterogeneity of effects of the LMWH class.

Another shortcoming of the heparins, including LMWH, is the rebound in thrombin activity that occurs following cessation of therapy. This rebound may contribute to a hypercoagulable state following cessation of therapy and predispose patients to thrombotic events. Cessation of enoxaparin in patients with ACS results in a rapid increase of coagulation activity that can occur as early as 3 hours after the loss of therapeutic anticoagulation levels (Figure 5).[16] Despite platelet inhibition with aspirin, this rebound state still develops, but it can be partially inhibited with the addition of clopidogrel. The depletion of natural anticoagulants, such as tissue factor pathway inhibitor, or decreased activity in the protein C pathway are among the mechanisms that might account for the rebound activation in coagulation after discontinuation of heparin.

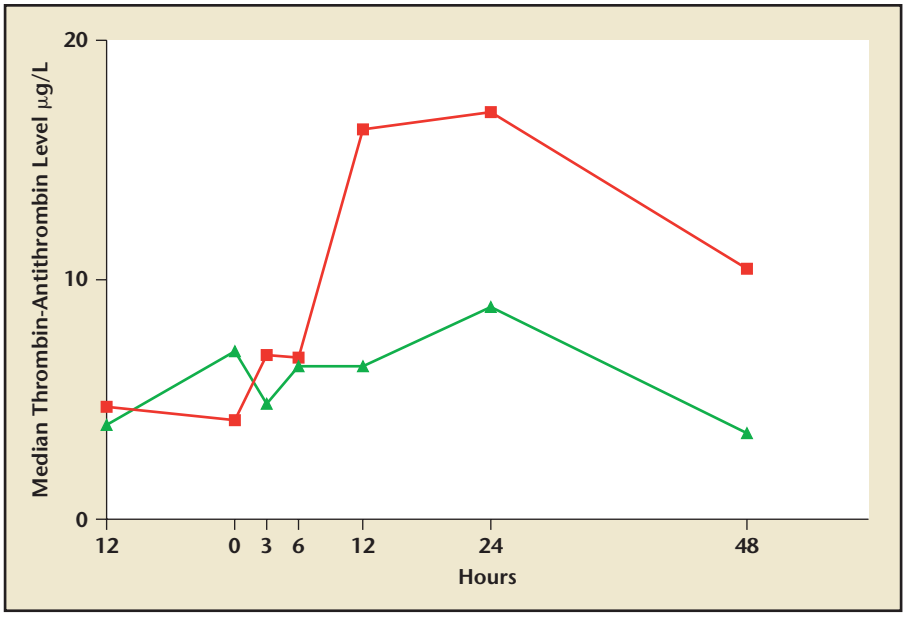


Figure 5. *Median thrombin-antithrombin levels at different time points during and after heparin treatment.* ***Squares*** *= no clopidogrel;* ***triangles*** *= clopidogrel. Hour 0 = 12 h after last enoxaparin dose. Reprinted with permission from Di Nisio M et al.*[16]

These data suggest significant in-class heterogeneity between the effectiveness of the individual LMWHs compared with UFH for patients with ACS. These differences may be related to the relative specificity of the specific LMWH to antagonize factor X versus factor II as well as other pharmacokinetic characteristics including half-life and metabolism. There seems to be no evidence that LMWH provides a substantial benefit over UFH for anticoagulation during PCI.

Fondaparinux

Fondaparinux is the first of a new class of synthetic antithrombotic agents that has been assessed in patients presenting with ACS in both ST-segment elevation myocardial infarction (STEMI) and non–ST-segment elevation myocardial infarction (NSTEMI). The identity and sequence of the 5 monomeric sugar units contained in fondaparinux are identical to a sequence of 5 monomeric sugar units that can be isolated after either chemical or enzymatic cleavage of the polymeric glycosaminoglycans heparin and heparan sulfate. This monomeric sequence is thought to form the high-affinity binding site for the anticoagulant factor antithrombin III. One potential advantage of fondaparinux over LMWH or UFH is that the risk for heparin-induced thrombocytopenia is substantially lower. However, renal excretion precludes its use in patients with significant renal dysfunction.

The goal of the Fifth Organization to Assess Strategies in Acute Ischemic Syndromes (OASIS-5) trial was to evaluate treatment with fondaparinux compared with enoxaparin among high-risk patients with unstable angina or NSTEMI.[17] There was no difference in the primary endpoint of death, MI, or refractory ischemia at day 9, which occurred in 5.7% of the enoxaparin group and 5.8% of the fondaparinux group (hazard ratio [HR], 1.01; 95% CI, 0.90-1.13). Major bleeding events by day 9 were lower in the fondaparinux group compared with enoxaparin

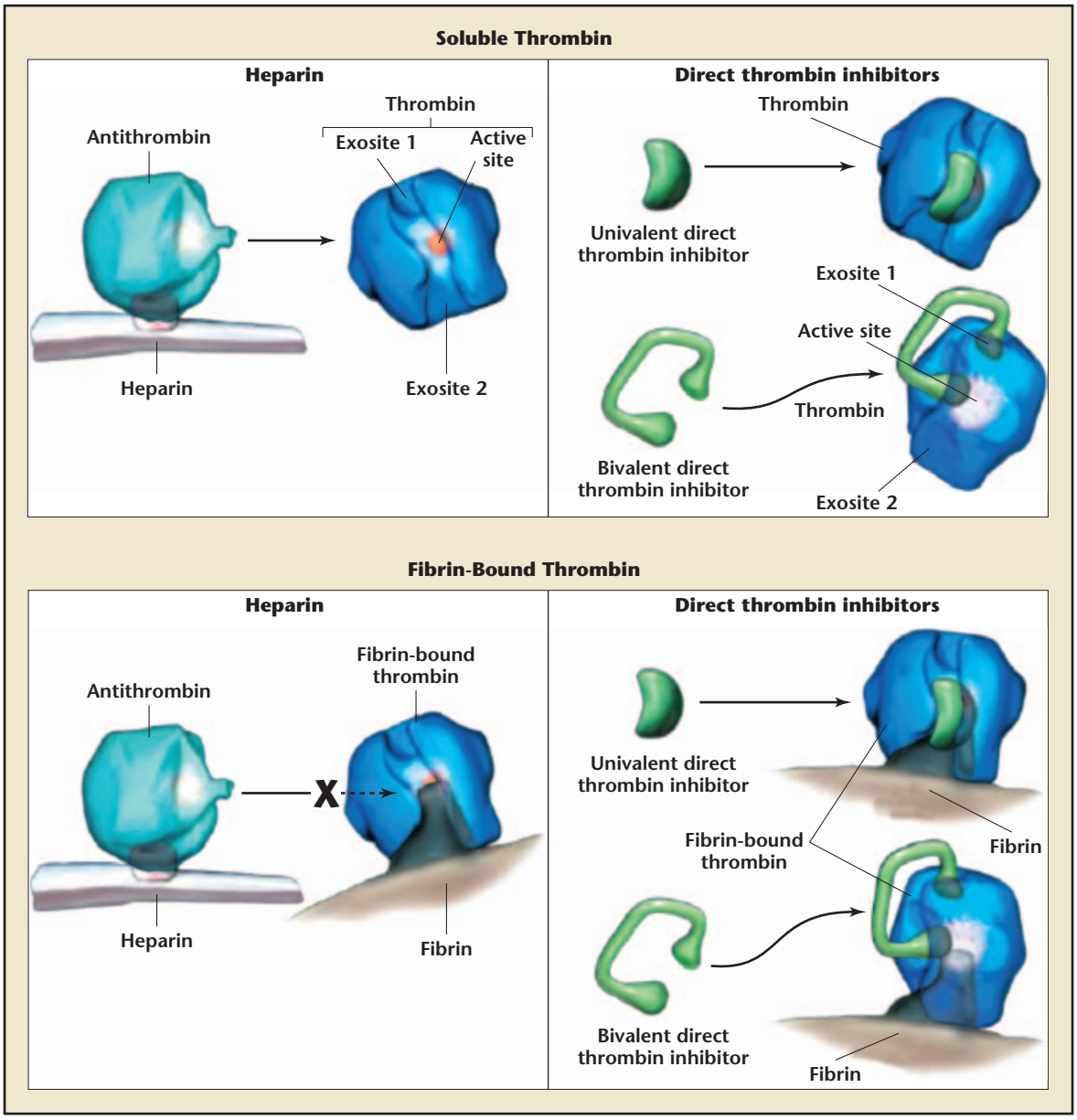


Figure 6. *Differences in the mechanism of binding thrombin-heparin versus direct thrombin inhibitors (univalent and bivalent). In the absence of heparin, the rate of thrombin inactivation by antithrombin is relatively low, but after conformational change induced by heparin, antithrombin irreversibly binds to and inhibits the active site of thrombin. Thus, the anticoagulant activity of heparin originates from its ability to generate a ternary heparin–thrombin–antithrombin complex. The activity of DTIs is independent of the presence of antithrombin and is related to the direct interaction of these drugs with the thrombin molecule. Although bivalent DTIs simultaneously bind the exosite 1 and the active site, the univalent drugs in this class interact only with an active site of the enzyme. In the lower panel, the heparin–antithrombin complex cannot bind fibrin-bound thrombin; whereas given their mechanism of action, DTIs can bind to and inhibit the activity of not only soluble thrombin but also thrombin bound to fibrin, as is the case in a blood clot. Reprinted with permission from Di Nisio M et al.*[19]

(2.2% vs 4.1%; HR, 0.52; 95% CI, 0.44-0.61; $P < .001$). In patients who underwent PCI, there was no difference in death or MI (6.2% for fondaparinux vs 5.8% for enoxaparin; P = NS), but bleeding was lower in the fondaparinux group (2.3% vs 5.1%; $P < .001$). Of concern was the occurrence of thrombus formation on indwelling coronary catheters during PCI, which occured more frequently in the fondaparinux group (n = 29 vs n = 8; RR, 3.59; 95% CI, 1.64-7.84; $P = .001$).

In OASIS-6, patients with STEMI were randomized to either the fondaparinux group (2.5 mg/day for up to 8 days or hospital discharge;

n = 6036) or the control group (placebo or UFH; n = 6056).[18] The primary endpoint of death or MI at 30 days was lower in the fondaparinux group compared with the control group (9.7% vs 11.2%; HR, 0.86; 95% CI, 0.77-0.96; $P = .008$). The reduction in death or MI at 30 days in the fondaparinux group was driven by comparison to the subset of the control group in whom UFH was not indicated, where death or MI occurred in 11.2% of the fondaparinux group versus 14.0% of the control group (HR, 0.79; $P < .05$). When compared with the control patients who did receive UFH, there was no difference between fondaparinux and the control group. Similar to the observation in OASIS-5, there was increased coronary guide-catheter-related thrombosis with fondaparinux in patients undergoing primary PCI.

Direct Thrombin Inhibitors

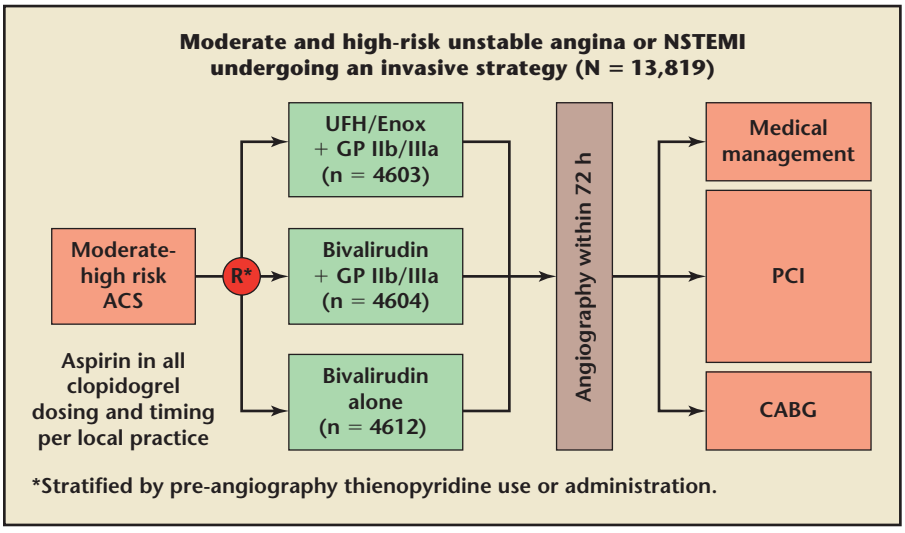
The US Food and Drug Administration has approved 4 parenteral DTIs: lepirudin and argatroban for heparin-induced thrombocytopenia, bivalirudin as an alternative to heparin for patients undergoing PCI, and desirudin for prophylaxis against deep venous thrombosis in patients undergoing hip replacement. The activity of DTIs, as opposed to heparin, is independent of the presence of antithrombin as they act directly on the thrombin molecule. Bivalent DTIs (hirudin, bivalirudin, lepirudin, and desirudin) interact with the active site of thrombin and the exosite 1, whereas the univalent DTIs (argatroban) bind only to the active site (Figure 6).[19] Compared with heparin, the mechanism of action of the DTIs allows for binding and inactivating both soluble and fibrin-bound thrombin. By directly inactivating thrombin and thereby reducing the thrombin-mediated activation of platelets, DTIs have antiplatelet effects in addition to their anticoagulant action. With the exception of argatroban, the DTIs do not bind to plasma proteins and therefore provide a more consistent dose-response effect than that observed with UFH.

In a meta-analysis published by the Direct Thrombin Inhibitor Trialists' Collaborative Group, 35,970 patients were randomized to either a DTI or UFH. Treatment with DTIs reduced the incidence of the composite outcome of death or MI.[20] As a group, the DTIs were also found to be associated with a reduced risk of bleeding.

The Hirulog Early Reperfusion/Occlusion (HERO) trial compared the effectiveness of the DTI hirulog (currently referred to as bivalirudin) versus UFH for achieving early and complete flow of the infarct-related artery in patients with acute myocardial infarctions (AMIs) receiving streptokinase and aspirin. There was no difference in the primary outcome of 30-day mortality between the 2 groups, although there was a reduction in reinfarction within 96 hours for patients receiving hirulog.[21]

Two more recent trials have evaluated the safety and efficacy of bivalirudin in both lower- and higher-risk patients, many of whom would undergo PCI. The Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events (REPLACE)-2 trial compared the use of bivalirudin with UFH and planned GP IIb/IIIa inhibitor use during elective or urgent PCI.[22] The trial was designed to test the hypothesis that bivalirudin alone was noninferior compared with UFH plus planned GP IIb/IIIa inhibitor use during PCI for the quadruple composite endpoint of 30-day death, MI, urgent revascularization, or in-hospital major hemorrhage. The quadruple endpoint occurred in 10.0% of patients in the UFH plus GP IIb/IIIa arm compared with 9.2% in the bivalirudin arm (OR = 0.917; 95% CI, 0.772-1.089; $P = .32$). A reduction of major bleeds from 4.2% to 2.4% was observed with bivalirudin. Results from the REPLACE-2 trial established bivalirudin as a safe and effective replacement for UFH plus GP IIb/IIIa in lower-risk patients, which led to

Figure 7. *ACUITY trial design. ACS, acute coronary syndrome; ACUITY, Acute Catheterization and Urgent Intervention Triage Strategy Trial; CABG, coronary artery bypass graft; Enox, enoxaparin; GP, glycoprotein; NSTEMI, non–ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; UFH, unfractionated heparin. Data from Stone GW et al.*[23]



greater utilization of this agent for patients undergoing PCI.

The Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial compared the effectiveness of bivalirudin, with and without a GP IIb/IIIa inhibitor, to heparin (UFH or LMWH), with routine GP IIb/IIIa inhibition, in patients presenting with unstable angina and NSTEMI (Figure 7).[23,24] The primary net clinical benefit was significantly improved in the bivalirudin alone group compared with the heparin plus GP IIb/IIIa group (10.1% vs 11.7%; $P = .015$ for superiority). Major bleeding was significantly lower in the bivalirudin alone group compared with the heparin plus GP IIb/IIIa group (3.0% vs 5.7%; $P < .001$ for superiority) and drove the net clinical benefit, which takes into account both thrombotic and hemorrhagic complications. Interestingly, the addition of a GP IIb/IIIa inhibitor to bivalirudin did not yield a significant improvement in the net clinical benefit over bivalirudin alone.

Bivalirudin with provisional GP IIb/IIIa inhibitor is indicated for use as an anticoagulant in patients undergoing PCI. It is intended for use with aspirin. The most common adverse events associated with the drug in clinical trials comparing bivalirudin and heparin were back pain, pain, nausea, headache, and hypotension. The incidence of these adverse events was comparable in both the bivalirudin and heparin groups. An unexplained fall in blood pressure or hematocrit, or any unexplained symptom, should lead to serious consideration of a hemorrhagic event and cessation of administration. Bivalirudin is contraindicated in patients with active major bleeding or hypersensitivity to the drug or its components.

Conclusions

The selection of anticoagulants for medical management of ACS as well as prevention of thrombotic complications with PCI has clearly evolved away from the use of UFH. A host of unattractive characteristics including its platelet activating effect, inconsistent dose-response effect, inability to inhibit clot-bound thrombin, rebound hypercoagulable state with cessation of therapy, and association with heparin-induced thrombocytopenia makes UFH less appealing as a first-line anticoagulant for patients with ACS or patients undergoing PCI.

The LMWHs are a heterogenous family of compounds with a range of efficacy and safety, with enoxaparin showing some benefits over UFH in the medical treatment of ACS. However, these benefits do not seem to exist when comparing the effect of enoxaparin to UFH in patients undergoing PCI. Fondaparinux seems to be superior to UFH as a medical therapy for ACS, but its association with catheter-related thrombosis makes it unlikely to be used in patients undergoing PCI. In large clinical trials, bivalirudin has been shown in both lower- and higher-risk patient subsets undergoing PCI to be associated with less major bleeding without any significant increase in thrombotic complications compared with heparin use in combination

Main Points

- Clinical trials have demonstrated that unfractionated heparin (UFH) is inferior to newer agents, such as low-molecular-weight heparins (LMWHs) and direct thrombin inhibitors (DTIs), for medical management of unstable angina or non–ST-segment elevation myocardial infarction. Newer agent bivalirudin has similar prevention of ischemic complications with less bleeding (as shown in the ACUITY study), and enoxaparin has similar prevention of ischemic complications with greater bleeding (SYNERGY).
- Increasingly, LMWH has been used as an anticoagulant for patients presenting with acute coronary syndrome. However, acceptance of the use of LMWH for patients undergoing percutaneous coronary intervention (PCI) has been limited.
- In patients undergoing PCI, LMWH provides no substantial benefit over UFH for anticoagulation; however, DTIs have demonstrated safety and efficacy in this setting.
- UFH is likely to be replaced by more effective and safer antithrombin agents, such as DTIs.
- DTIs have antiplatelet effects, anticoagulant action, and do not bind to plasma proteins, thereby providing a more consistent dose-response effect than UFH.
- The FDA has approved 4 parenteral direct thrombin inhibitors: lepirudin, argatroban, bivalirudin, and desirudin.
- The antiplatelet, anticoagulant, and pharmacokinetic properties of bivalirudin support its use as the anticoagulant of choice for both lower- and higher-risk patients undergoing PCI.

with GP IIb/IIIa inhibition. The antiplatelet, anticoagulant, and pharmacokinetic properties of bivalirudin that account for the benefits observed in clinical trials support its use as the anticoagulant of choice for both lower- and higher-risk patients, including those undergoing PCI. ■

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