

Table 34.5. Comparison of Low-Molecular-Weight Heparins to Unfractionated Heparin

Characteristic	Unfractionated Heparin	LMW Heparins
Composition	Heterogenous mixture of polysaccharides; molecular weight 3000-30,000 Daltons	Homogenous glycosaminoglycans; molecular weight 4000-6000 Daltons
Mechanism of anticoagulation	Activates antithrombin III*; equivalent activity against factor Xa and thrombin; releases TFPI from endothelium; unable to inactivate clot-bound thrombin or FDP; inactivates fluid-phase thrombin	Less activation of antithrombin III; greater activity against factor Xa than thrombin; releases TFPI from endothelium; unable to inactivate clot-bound thrombin or FDP; weaker inactivation of fluid-phase thrombin
Pharmacokinetics	Variable binding to plasma proteins, endothelial cells, and macrophages leads to unpredictable anticoagulant effects (less available to interact with antithrombin III); half-life is short	Minimal binding to plasma proteins, endothelial cells, and macrophages leads to predictable anticoagulation; longer half-life
Laboratory monitoring	Essential because of unpredictable anticoagulant effects; use aPTT or ACT	Unnecessary except in renal failure or body weight < 50 kg or > 80 kg; use anti-factor Xa levels
Clinical uses	Prevention of venous thrombosis; treatment of venous thrombosis, unstable angina, acute MI, ischemic stroke. Routinely used during percutaneous intervention.	At least as effective as heparin for prevention of venous thrombosis in surgery and trauma patients, and for treatment of unstable angina, venous thrombosis, ischemic stroke. No definite advantage over heparin during percutaneous intervention.
Neutralization	Protamine neutralizes antithrombin activity	Protamine neutralizes antithrombin activity but only partially reverses anti-factor Xa activity.
HIT-2	Should not be used in patients with a history of HIT-2	Should not be used in patients with a history of HIT-2
Cost	Inexpensive	10-20 times more expensive than unfractionated heparin

Abbreviations: ACT = activated clotting time; aPTT = activated partial thromboplastin time; HIT = heparin-induced thrombocytopenia; TFPI = tissue factor pathway inhibitor; FDP = fibrin degradation products

* Antithrombin III is now commonly referred to as antithrombin

Table 34.6. Features of Heparin-Induced Thrombocytopenia (HIT)

	Type I HIT	Type II HIT
Incidence	10%	Rare
Mechanism	Direct platelet aggregating effect of heparin	Autoantibody (IgG or IgM) directed against platelet factor IV-heparin complex
Onset	Early (1-5 days)	Later (> 5 days); may occur sooner if prior heparin exposure
Platelet count	50,000/mm ³ - 150,000/mm ³	< 50,000/mm ³
Duration	Transient; often improves even if heparin is continued	Requires discontinuation of ALL heparin; gradual recovery in platelet count over 1-5 days in most patients
Clinical course	Benign	Recalcitrant venous and arterial thromboses and thromboembolism; may be fatal
Heparin substitute	UFH or LMWH may be continued	Argatroban (Acova) and lepirudin (Refludan) are FDA-approved

Abbreviations: UFH = unfractionated heparin; LMWH = low-molecular-weight heparin

LOW-MOLECULAR-WEIGHT HEPARINS

Low-molecular-weight (LMW) heparins are fragments of commercial grade heparin with potent antithrombotic properties. LMW heparins have numerous features distinct from unfractionated heparin (UFH), including a more predictable anticoagulation effect, lack of inhibition by platelet factor-4, lack of need for monitoring, and a lower risk of HIT (Table 34.7). In contrast to UFH, LMW heparins have less antithrombin activity and do not prolong the aPTT; their anticoagulant effect is mediated primarily by inhibition of Factor Xa (thrombin generation) (Table 34.5). LMW heparins have been used to prevent deep venous thrombosis and pulmonary embolism,⁶² and the randomized ESSENCE⁶³ and TIMI-11b⁶⁴ trials demonstrated better event-free survival for enoxaparin vs. UFH in non-ST-elevation acute coronary syndromes (Table 34.8). However, studies during coronary intervention suggested little or no benefit over UFH (Table 34.9). Although ENTICES⁶⁵ and REDUCE⁶⁶ suggested a significant reduction in early ischemic events with enoxaparin or reviparin compared to UFH, these observations were not confirmed in ERA,⁶⁷ ATLAST,⁶⁸ or ENOXAPARIN⁶⁹ (Table 34.9). Likewise, some studies reported less bleeding with LMW heparin (ENTICES,⁶⁵ ATLAST⁶⁸), while others did not (ERA,⁶⁷ ENOXAPARIN,⁶⁹ REDUCE⁶⁶). Local delivery of enoxaparin showed a reduction in angiographic restenosis after stenting (POLONIA⁷⁰ trial), but other trials showed no difference in restenosis or late MACE between LMW heparin and UFH. LMW heparin has also been evaluated for extended therapy in high-risk post-stent patients: In ATLAST,⁶⁸ overall event rates were low, and there was no incremental benefit for enoxaparin compared to standard

antiplatelet therapy. In fact, bleeding complications were more frequent after enoxaparin. More recently, observational studies of enoxaparin with (NICE-4)⁷¹ and without (NICE-1)⁷² platelet glycoprotein IIb/IIIa receptor antagonists for routine procedural anticoagulation have been completed. These studies and others⁷³ suggest that enoxaparin is safe and effective, and may be a reasonable alternative to UFH for procedural anticoagulation in the interventional setting. The recently completed NICE-3 study⁷⁴ demonstrated that patients with acute coronary syndromes receiving a IIb/IIIa antagonist and subcutaneous enoxaparin could safely undergo percutaneous revascularization without UFH. In ACUTE II,⁷⁵ a randomized trial of enoxaparin vs. UFH in interventional patients receiving tirofiban, safety and efficacy endpoints were similar between groups. Future data from INTERACT and CRUISE will help clarify the role of LMW heparin and IIb/IIIa antagonists in the cath lab. For now, LMW heparins are reasonable alternatives to UFH for procedural anticoagulation, but are not superior to UFH during percutaneous intervention in terms of reducing ischemic complications.

Table 34.7. Low-Molecular-Weight Heparin Preparations*

Preparation	Indications
Dalteparin (Fragmin)	Venous thrombosis, unstable angina (120 U/kg SQ BID; max. 10,000 U)
Enoxaparin (Lovenox)	Venous thrombosis, unstable angina (1 mg/kg SQ BID); PTCA (1 mg/kg IV)
Tinzaparin (Innohep)	Venous thrombosis (175 anti-Xa IU/kg SQ QD)
Ardeparin (Normiflo)	Venous thrombosis (50 U/kg SQ BID)
Danaparoid (Orgaran)**	Venous thrombosis (750 anti-Xa units SQ BID)
Nadroparin (Fraxiparin)	Not established
Reviparin (Clivarine)	Not established
Certoparin (Sandoparin)	Not established

Abbreviations: BID = twice daily; SQ = subcutaneous; QD = once daily

* Different preparations are not interchangeable; each is classified as a distinct drug by the FDA

** Low-molecular-weight heparinoid

Table 34.8. Major Clinical Trials of Low-Molecular-Weight Heparins for Unstable Angina

Study	Drug	Setting	Endpoint	Results
FRISC ²¹⁶ (n = 1506)	ASA, β -blockers for all patients; dalteparin (120 IU/kg SQ BID) vs. placebo	UA, non-Q-MI	Death, MI at 6 days	Risk reduction 68% (1.8% vs. 4.7%, $p < 0.01$) for dalteparin; more minor bleeding (7.9% vs. 0.3%) but similar major bleeding; less death, MI at 40 days (5.0% vs. 11%, $p = 0.07$)
FRIC ²¹⁷ (n = 1482)	Dalteparin vs. standard heparin for 6 days	UA, non-Q-MI	Death, MI, revascularization at 45 days	No difference in outcome (14% vs. 12.9%) or bleeding (1.1% vs. 1%) for dalteparin
FRISC-Troponin ²¹⁸ (n = 971)	ASA, β -blockers for all patients; dalteparin (120 mcg/kg BID for 5-7 days, or 7500 U QD for 5 weeks) vs. placebo	High-risk UA with elevated troponin-T, non-Q-MI	Death, MI at 45 days	Short- and long-term dalteparin superior to placebo
ESSENCE ⁶³ (n = 3171)	Enoxaparin vs. standard heparin	UA, non-Q-MI	Death, MI, recurrent angina at 14 days	Enoxaparin superior to heparin (19.8% vs. 23.3%, $p < 0.02$); 16% relative risk reduction
TIMI-11b ⁶³ (n = 3910)	Enoxaparin vs. standard heparin	UA, non-Q-MI	Death, MI, urgent revascularization at 8 days	Enoxaparin superior to heparin (12.4% vs. 14.5%, $p = 0.048$); 14% relative risk reduction
FRISC-II ²¹⁹ (n = 2267)	Dalteparin in all patients for 5 days; then dalteparin vs. placebo for 3 months	UA, non-Q-MI	Death, MI at 3 months	Dalteparin superior to placebo at 1 month (3.1% vs. 5.9%), but no differences at 3 months (6.7% vs. 8%). No difference in patients treated with PCI
Gurfinkel ²²⁰ (n = 219)	Nadroparin vs. heparin vs. placebo for 5-7 days	UA	Death, MI, angina, revascularization at 7 days	Nadroparin superior to heparin
FRAXIS ²²¹ (n = 3468)	Nadroparin (short and long duration) vs. heparin	UA, non-Q-MI	Death, MI, refractory angina at 14 days	Short- and long-term nadroparin similar to heparin
ACUTE-II ⁷⁵ (n = 525)	Enoxaparin plus tirofiban vs. UFH plus tirofiban	UA	Safety and clinical outcomes	Outcomes similar with UFH and enoxaparin
NICE-3 ⁷⁴ (n = 616)	Enoxaparin plus IIb/IIIa antagonist (observational)	UA	Safety (non-CABG major bleeding)	Comparable safety (1.9%) and clinical efficacy
SYNERGY (n~ 8000)	Enoxaparin vs. UFH (efficacy)	UA managed invasively	Death/MI at 30 days	[Ongoing]

Abbreviations: CABG = coronary artery bypass grafts; MI = myocardial infarction; PCI = percutaneous intervention; UA = unstable angina; UFH = unfractionated heparin

Acronyms: See Table 34.31, p. 803

Table 34.9. Major Trials of Low-Molecular-Weight Heparin for Coronary Intervention

Study	Drug	Setting	Endpoints	Results
ENTICES ⁶⁵ (n = 123)	Enoxaparin (30-60 mg BID x 10d) + ASA + ticlopidine vs. ASA + dipyridamole + warfarin	Elective stent	Markers of thrombin activity and platelet activation at 10 days	No differences in markers; enoxaparin group had fewer ischemic events (5% vs. 20%, p < 0.01) and bleeding complications (16% vs. 5%, p < 0.05)
ERA ⁶⁷ (n = 458)	Enoxaparin (for 1 month post-procedure)	PTCA	MACE and angiographic restenosis at 6 months	No difference in late MACE or restenosis
REDUCE ⁶⁶ (n = 625)	Reviparin (procedural IV and 28 days post-procedure SQ)	PTCA	Angiographic restenosis at 6 months	Reviparin group had a 52% reduction in early ischemic events (3.9% vs. 8.2%, p < 0.05); no difference in bleeding, restenosis, or late MACE
ENOXAPARIN ⁶⁹ (n = 60)	Enoxaparin (procedural only; IV)	PTCA/stent	Anticoagulation level (anti-Xa); procedural success	Similar anticoagulation effects, success, and complications
Diez ⁷³ (n = 70)	Enoxaparin (procedural only; IV)	PTCA/stent	Procedural success	Comparable success
NICE-1 ⁷² (n = 812)	Enoxaparin (procedural only IV without IIb/IIIa antagonists)	PTCA/stent (observational)	Safety	Low risk of bleeding and early MACE; comparable results to NICE-4
NICE-4 ⁷¹ (n = 857)	Enoxaparin (procedural only IV with IIb/IIIa antagonists)	PTCA/stent (observational)	Safety	Low risk of bleeding and early MACE; comparable results to NICE-1
ATLAST ⁶⁸ (n = 1121)	Enoxaparin (for 1 month post-procedure)	High-risk or suboptimal stent	Death, MI, or urgent revascularization at 30 days	Study stopped because of low event rates (placebo 2.7% vs. enoxaparin 1.8%, p = NS); more bleeding with enoxaparin
POLONIA ⁷⁰ (n = 100)	Locally delivered enoxaparin via transport catheter vs. systemic UFH	Stent	Late lumen loss; loss index	Both endpoints significantly reduced
NICE-3 ⁷⁴ (n = 616)	Enoxaparin plus IIb/IIIa antagonist	ACS (PCI in 292 patients)	Safety (major bleeding)	Comparable bleeding (1.9% overall, 1.0% in PCI patients) and success
SYNERGY (n ~ 8000)	Enoxaparin vs. UFH (IIb/IIIa strongly encouraged)	ACS managed invasively	Death/MI	[Ongoing]

Summary: Compared to unfractionated heparin, LMW heparins have distinct advantages, including ease of administration and lack of need for intensive monitoring (primarily due to less protein binding). However, in patients undergoing percutaneous intervention, LMW heparins have not yet been shown to be superior to unfractionated heparin; cost is a clear disadvantage of LMW heparins. Further studies as adjuncts to platelet IIb/IIIa inhibitors are in progress.

Abbreviations: ACS = acute coronary syndrome; MACE = major adverse cardiac events; PCI = percutaneous coronary intervention; UFH = unfractionated heparin

Acronyms: See Table 34.31, p. 803

DIRECT THROMBIN INHIBITORS

Direct thrombin inhibitors are generally classified as polypeptide or low-molecular weight inhibitors⁷⁶ (Table 34.10). Polypeptide inhibitors such as hirudin (recombinant hirudin is lepirudin) and bivalirudin (hirulog) inactivate circulating thrombin via the active binding site and clot-bound thrombin via exosite-1. Low-molecular weight inhibitors such as argatroban also inactivate circulating thrombin via the active binding site, but do not inactivate clot-bound thrombin. Unlike heparin, direct thrombin inhibitors such as hirudin and bivalirudin do not require antithrombin for anticoagulant effect, form highly stable noncovalent complexes with circulating *and* clot-bound thrombin, and are not inhibited by platelet factor 4 (Tables 34.11, 34.12). Although a pilot study reported that bivalirudin was similar to heparin in decreasing ischemic complications after PTCA,⁷⁷ a subsequent study reported fewer ischemic and bleeding complications with bivalirudin in high-risk patients with post-infarction angina.⁷⁸ In the Hirudin European Trial versus Heparin in the Prevention of Restenosis after PTCA (HELVETICA),⁷⁹ PTCA patients with unstable angina had fewer early ischemic events after hirudin, but no difference in restenosis. A higher incidence of intracranial hemorrhage has been reported in three trials combining hirudin and thrombolytic therapy (GUSTO IIa,⁸⁰ TIMI 9A,⁸¹ HIT-III⁸²). The ongoing CACHET and REPLACE trials are evaluating the efficacy of bivalirudin (with “rescue” IIB/IIIa antagonist if necessary) vs. unfractionated heparin with routine IIB/IIIa antagonist during coronary intervention (Table 34.13). In the United States, lepirudin (Refludan, a recombinant hirudin) and argatroban (Acova, a small molecule active site inhibitor) are approved for use in patients with heparin-induced thrombocytopenia who require IV anticoagulation. In such patients, lepirudin is administered as an initial bolus of 0.4 mg/kg (maximum 44 mg) over 15-20 seconds, followed by a continuous infusion of 0.15 mg/kg/hr (maximum rate 16.5 mg/hr). Monitoring is accomplished using the same aPTT guidelines as for UFH. Bivalirudin (Angiomax) has recently been approved for procedural anticoagulation in unstable angina.

Table 34.10. Direct Thrombin Inhibitors

Polypeptide Inhibitors

Hirudin (Lepirudin)*⁺
Bivalirudin (Hirulog)

Low-Molecular-Weight Inhibitors
Noncovalent

Argatroban (Acova)⁺
Napsagatran
Inogatran
Melogatran

Reversible-covalent

Efegatran
Boro-arginine derivatives

* Hirudin is derived from medicinal leech saliva. It is available by recombinant DNA technology as lepirudin (Refludan)

+ FDA-approved for patients with HIT-2 who require anticoagulation

Table 34.11. Comparison of Unfractionated Heparin and Direct Thrombin Inhibitors*

	Unfractionated Heparin	Direct Thrombin Inhibitors
Effect on clot-bound thrombin, FDP	None	Inactivation
Effect on antithrombin	High-affinity interaction; inhibits thrombin and factor Xa	High affinity interaction
Effect on factor Xa bound to platelets	None	Inactivation
Binding to endothelium and plasma proteins	High; results in less heparin availability to activate antithrombin	None
Binding to PF-4	High affinity	None
Anticoagulant effects	Highly variable	Predictable
Laboratory monitoring	Essential	May be unnecessary with bivalirudin

Summary: Direct thrombin inhibitors have biologic and pharmacokinetic advantages compared to heparin. The biologic advantage reflects their ability to inactivate clot-bound thrombin via exosite 1 (polypeptide inhibitors), whereas the pharmacologic advantages produce more predictable anticoagulant effects without the need for intensive laboratory monitoring (especially bivalirudin), by less binding to endothelial and plasma proteins. Bivalirudin may block procoagulant activity associated with eptifibatid and tirofiban.

Abbreviations: FDP = fibrin degradation products; PF-4 = platelet factor-4

* Hirudin, bivalirudin

Table 34.12. Comparison of Direct Thrombin Polypeptide Inhibitors

	Hirudin	Bivalirudin
Source	Saliva of medicinal leech; now available by recombinant technology*	Semisynthetic
Composition	65-amino acid polypeptide	20-amino acid polypeptide
Inhibition of thrombin	Slowly reversible, highly selective	Transient, reversible
Safety margin	Narrow	Wide
Dose range	Narrow	Wide
Effect on Protein C	Inhibits activation	Promotes activation and enhances anticoagulation
Laboratory monitoring	Necessary	Probably not necessary

Summary: Compared to hirudin, bivalirudin has potential safety advantages (shorter half-life, transient reversible thrombin inhibition) and efficacy (wider dose range, promotes activation of protein C). Despite the theoretical advantages of direct thrombin inhibitors compared to heparin, clinical trials of hirudin as adjuncts to thrombolytic therapy or PTCA have not demonstrated better efficacy than heparin. Bivalirudin may be safer and more effective than hirudin; further study is needed.

* Recombinant hirudin is available as lepirudin (Refludan)

Table 34.13. Major Trials of Thrombin Antagonists for Coronary Intervention

Study	Drug	Setting	Endpoint	Results
Van den Bos ²⁰⁴ (n = 113)	Hirudin vs. heparin	PTCA	Safety	More reliable aPTTs with hirudin; comparable clinical outcomes
HELVETICA ⁷⁹ (n = 1141)	Hirudin vs. heparin	PTCA	Death, MI, TVR, ARS at 6 months	No difference in outcome
Hirulog Pilot ⁷⁷ (n = 291)	Hirulog (bivalirudin)	PTCA	Dose ranging (feasibility)	Less abrupt closure with higher doses
Hirulog Angioplasty Study ⁷⁸ (n = 4098)	Hirulog vs. heparin	PTCA	Death, MI, abrupt closure, rapid clinical deterioration in hospital	Hirulog with less bleeding (3.8% vs. 9.8%, $p < 0.001$) and fewer events in post-MI patients (9.1% vs. 14.2%, $p = 0.04$), but no difference overall (11.4% vs. 12.2%, $p = \text{NS}$)
CACHET Pilot ²⁰⁵ (n = 210)	Bivalirudin (with rescue abciximab) vs. heparin/abciximab	PTCA/Stent	Clinical outcomes and bleeding	Reduction in composite events with bivalirudin
REPLACE	Bivalirudin (with rescue abciximab) vs. heparin/abciximab	PCI	Clinical outcomes	[Ongoing]

Abbreviations: ARS = angiographic restenosis; MI = myocardial infarction; TVR = target vessel revascularization; PTCA = percutaneous transluminal coronary angioplasty; PCI = percutaneous coronary intervention

Acronyms: See Table 34.31, p. 803

ANTIPLATELET THERAPY

Oral antiplatelet therapy is the cornerstone of pharmacotherapy during percutaneous coronary intervention (Table 34.14). Aspirin alone (PTCA, laser, atherectomy) and aspirin plus clopidogrel (stents) are the standard regimens in the interventional setting.

A. ASPIRIN. Aspirin blocks the formation of prostaglandin endoperoxides and thromboxane A₂ by inhibiting prostaglandin G/H synthase and the cyclooxygenase pathway. This effect is transient in nucleated cells but is permanent for the life of anucleate platelets. Aspirin also exerts antiplatelet effects which are independent of its effects on thromboxane.^{83,84} Preprocedural aspirin reduces the risk of abrupt coronary occlusion by 50-75% and is standard therapy for all coronary interventional procedures.^{85,86} Other beneficial effects include prevention of coronary artery disease and stroke, improved outcome in chronic stable angina, unstable angina, and acute MI,⁸⁷⁻⁹² and maintenance of saphenous vein graft patency after coronary bypass surgery.⁹³ Aspirin increases the risk of bleeding complications^{94,95} and has no impact on restenosis.⁹⁶