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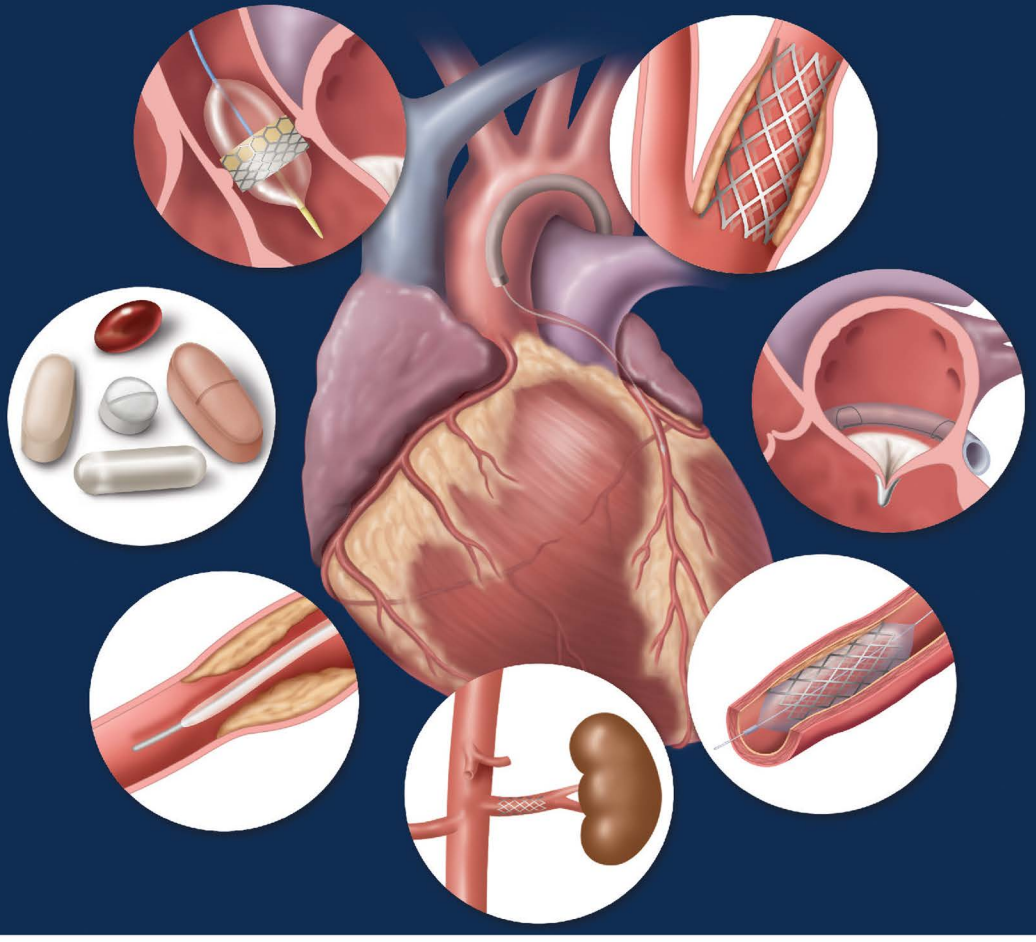
Textbook of Interventional CARDIOLOGY

A Global Perspective



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CHAPTER 4

Antithrombotics

Grant W Reed, A Michael Lincoff

EDITORIAL COMMENT

Antithrombin therapy was well recognized as an important factor in reducing peri-procedural ischemic events early in the development of percutaneous coronary intervention. With the evolution of interventional techniques, the goals of therapy have also evolved to including mitigation of the bleeding complications. Dr Grant Reed is a Fellow in the Department of Cardiovascular Medicine, Cleveland Clinic, Cleveland, USA, and Professor A Michael Lincoff is a Professor of Medicine, Cleveland Clinic Lerner College of Medicine and the Director of Cleveland Clinic Coordinating Center for Clinical Research, Cleveland, USA. In this chapter, Dr Reed and Professor Lincoff establish the basic pharmacology of the anti-thrombin therapies currently available, provide a comprehensive review of the clinical trial experience with these agents, and discuss the important aspects of the clinical use of these therapies.

INTRODUCTION

Patients undergoing percutaneous coronary intervention (PCI) are at risk for thrombosis, both due to the underlying pathology necessitating the procedure [e.g. acute coronary syndrome (ACS)], as well as from iatrogenic causes (e.g. endothelial disruption and plaque injury during the procedure). Recognition of this risk has led to the widespread adoption and refinement of antithrombotic therapies immediately before and during PCI, which has substantially reduced associated thromboembolic and cardiovascular events. As such, a comprehensive understanding of periprocedural antithrombotic therapy is sine qua non for the interventionist to limit both thrombotic as well as bleeding risk during the procedure.

The term "antithrombotic agent" is broad, referring to any agent that may limit or prevent arterial or venous thrombosis, and can be broken down into three components: anticoagulant, antiplatelet, and fibrinolytic agents. Anticoagulant agents specifically target the soluble coagulation cascade, which consists of proteins essential for the formation of a fibrin clot. Anticoagulation, in combination with antiplatelet therapy, is effective in reducing the short-term risk of death or myocardial infarction (MI) in the setting of ACS caused by coronary artery disease (CAD). The focus of this chapter will be on *anticoagulant* agents, as antiplatelet agents were covered in Chapters 2 and 3, and fibrinolytics is covered in Chapter 5.

MECHANISM OF ACTION

Knowledge of the coagulation cascade, as well as its interactions with platelets and the vascular endothelium, is necessary to understand the mechanisms of action of the common anticoagulants used in the catheterization laboratory.

Platelet Activation

In ACS, rupture of a vulnerable atherosclerotic plaque causes disruption of the underlying vascular endothelium. Exposure to collagen and von-Willebrand's factor causes platelets to adhere to the subendothelium and, along with the thrombogenic contents released during plaque

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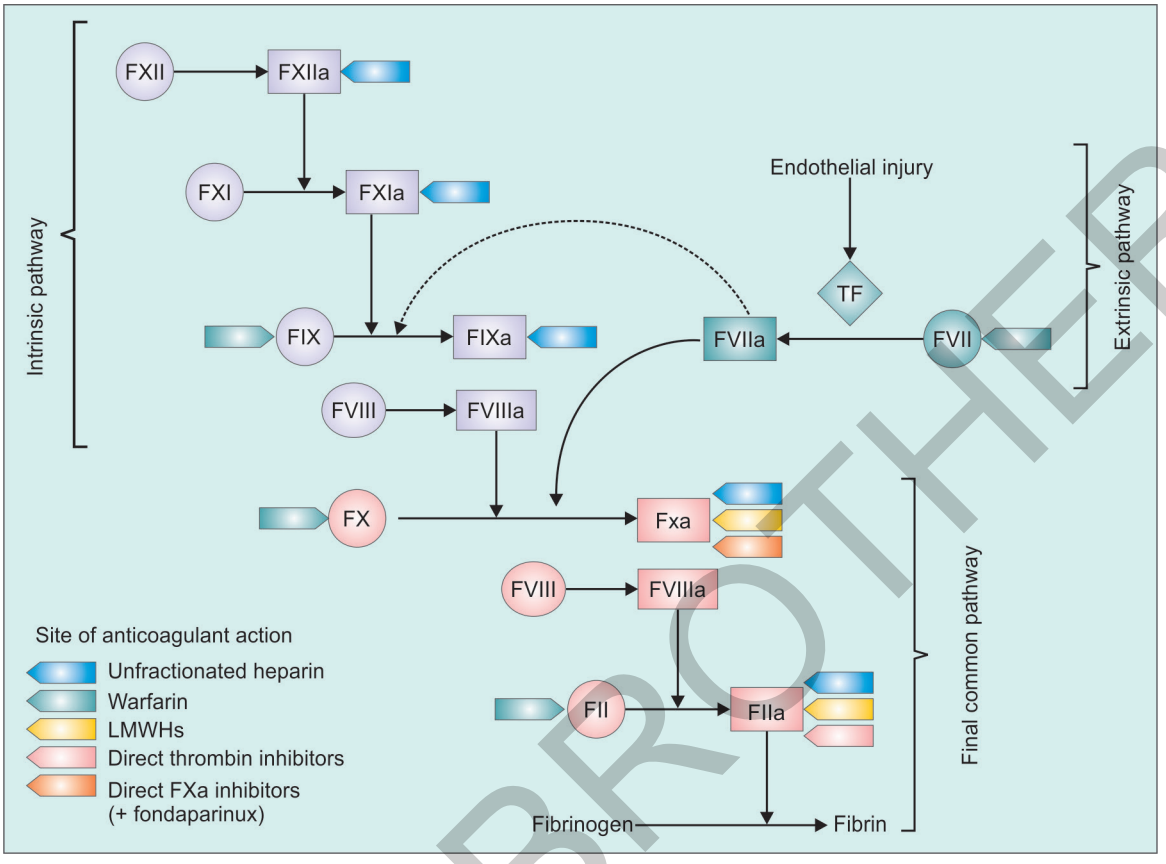

Fig. 4.1: Coagulation cascade and therapeutic targets of common anticoagulants. (LMWHs: Low molecular weight heparins).

rupture, promote platelet activation. Activated platelets release granules containing substances that promote additional platelet activation [such as adenosine diphosphate (ADP), thromboxane A2 (TXA_2), and serotonin (5HT)] and aggregation. Platelets also undergo conformational changes, promoting platelet aggregation via glycoprotein (GP) IIb/IIIa receptors on the platelet's surface, which cross-link via thrombin, integrating with the coagulation system, further discussed below. Platelet activation and antiplatelet medications are discussed more fully in Chapters 2 and 3, and ACS is covered more fully in Chapters 13 and 14.

Overview of the Coagulation Cascade

Coagulation factors are soluble serine proteases, which mechanistically act by cleaving other proteases in downstream sequence, eventually resulting in fibrin formation. The coagulation cascade is further broken down into three pathways; the extrinsic (tissue factor) pathway and the intrinsic (contact activation) pathway, which converge to activate the common pathway of fibrin formation.

The coagulation cascade is visually depicted in Figure 4.1. Briefly, in the extrinsic pathway, endothelial injury causes Factor (F) VII to leave the circulation, which then binds tissue factor (aka TF, FIII, or thromboplastin), a protein typically expressed on stromal fibroblasts and leukocytes. The activated TF-FVIIa complex then activates FX to FXa, initiating the common pathway. Conversely, the intrinsic pathway consists of several coagulation factors, beginning with the conversion of FXII to FXIIa by kallikrein, and ending with the activation of FX and the common pathway (*see* Fig. 4.1). The common pathway begins with activation of FX, which then acts to convert prothrombin (FII) to thrombin (FIIa), which subsequently acts to convert fibrinogen (FI) to fibrin (FIa), which further cross-links and forms a fibrin-clot.

Iatrogenic Promotion of Thrombosis during Intervention

In addition to the mechanisms described above with ACS, wire and catheter manipulation may cause endothelial

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injury, exposure of TF, and activation of the extrinsic coagulation cascade. Further, alterations in fluid stasis and shear stress from wire and catheter manipulation may activate platelets and promote a prothrombotic state. Additionally, catheter and wire materials themselves can be intrinsically thrombogenic, either transiently (i.e. equipment that is removed), or permanently (i.e. implanted stents). Likewise, angioplasty and stent deployment both cause platelet activation and disruption of the coronary artery endothelium, promoting thrombosis.

SUMMARY OF CLASSIFICATION OF ANTICOAGULANT AGENTS

Figure 4.1 summarizes the mechanistic targets of the four classes of common anticoagulants, which will be the focus of the remainder of the chapter.

Heparins

Overview

An understanding of the structure, function, and pharmacology of unfractionated heparin (UFH) and its derivatives is important for the practicing interventional cardiologist, as heparin is the most widely used anticoagulant in the catheterization laboratory today.

Structure and Function

Heparin molecules are highly sulfated glycosaminoglycans, and are divided into three subgroups based on unique aspects of their chemical structure: UFH, low molecular weight heparins (LMWHs) (i.e. enoxaparin, dalteparin, and nadroparin), and fondaparinux. All heparins contain an "essential pentasaccharide" sequence, which is common to all of the drugs in this class. This sequence binds to antithrombin (previously known as "antithrombin III") (AT), causing a conformational change in AT that increases its affinity for its substrates. Antithrombin can inactivate several coagulation factors, particularly FXa and thrombin (FIIa); this activity is increased ~1000-fold when bound to heparin.

The length of the saccharide chain determines the relative affinity of each heparin derivative (Figs 4.2A and B). A chain length of at least 18 units (U) is required for the heparin-AT complex to bind to thrombin, while binding FXa is independent of chain length and occurs with the essential pentasaccharide complex alone. As UFH is a mixture of molecules with different chain lengths (both short and long), UFH-AT complexes bind to and inactivate both FXa and FIIa. Conversely, LMWHs are smaller molecules (4,000–5,000 kDa), enriched for short chains, and thus LMWH-AT complexes inhibit FXa preferentially (depending on the ratio of short/long chain molecules in the specific LMWH used). Fondaparinux is a synthetic version of the essential pentasaccharide only, and fondaparinux-AT complexes exclusively inhibit Xa. Thus, while both enoxaparin and fondaparinux act primarily via their anti-Xa activity, they are derivatives of heparin, and are not classified as direct FXa inhibitors.

Pharmacokinetics and Dosing Considerations

The use of heparin in the catheterization laboratory holds several advantages, including a well-established efficacy profile for preventing periprocedural thrombosis, ease of use, short half-life, and low cost. Table 4.1 describes the pharmacokinetics of the common agents, and Table 4.2 provides their common dosing (based on recommendations from current American Heart Association (AHA)/American College of Cardiology (ACC)/Society of Coronary Angiography and Interventions (SCAI) guidelines).[1-4] The risk/benefits of each agent from clinical trial data are described in the evidence review later in this chapter.

Important Considerations and Limitations of Heparinoid Use

Certain limitations are true of the entire heparin class. Specifically, the heparin-AT complex is unable to bind clot-bound thrombin or platelet-bound FXa. Conversely, certain limitations are dependent to the saccharide chain length of the heparin molecule. The pharmacokinetics of UFH hold certain disadvantages, as only ~33% of UFH binds to AT, and the rest binds variably to different plasma proteins, accounting for a wide range of efficacy among individuals. The efficacy and safety of UFH can be improved weight-based dosing and close monitoring of laboratory parameters, such as the activated clotting time (ACT) and activated partial thromboplastin time (aPTT) (discussed later in this chapter). One important side effect is that UFH may directly activate platelets. Additionally, UFH binds to a platelet factor (PF) 4, which not only blunts its efficacy, but IgG antibodies to UFH-PF4 complexes may target platelets, leading to heparin-induced thrombocytopenia (HIT), a prothrombotic state. Treatment of HIT requires immediate discontinuation of all heparin products and administration of another anticoagulant (typically bivalirudin or argatroban) to prevent or treat thrombosis.

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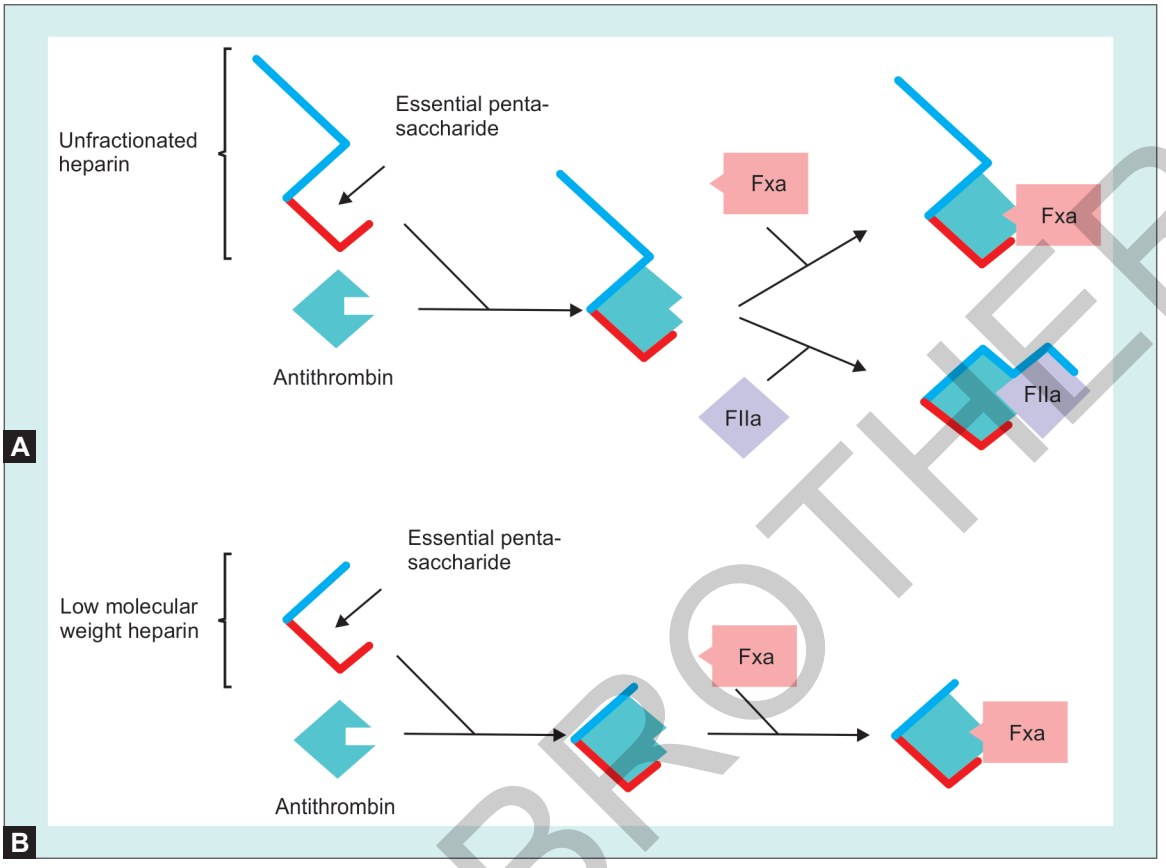

Figs. 4.2A and B: Mechanism of action of different heparinoid agents. (A) Unfractionated heparin contains a mixture of long- and short-chain saccharides, which enhance antithrombin's affinity for both FXa and FIIa. (B) Low molecular weight heparin contains predominantly short-chain saccharides, and thus preferentially increases antithrombin's inactivation of FXa. Fondaparinux consists of the essential pentasaccharide only, and thus selectively enhances antithrombin's inhibition of FXa.

Table 4.1: Pharmacokinetics of common anticoagulants.[1-4]

Agent	*Onset/peak*	*Half-life/duration*	*Metabolism/clearance*
Heparins			
Long-chain			
Unfractionated heparin	IV: immediate* SQ: 20–30 minutes*	Dose dependent; 25 U/kg: 30 minutes 100 U/kg: 60 minutes 400 U/kg: 150 minutes	Metabolism: hepatic; partially by RES Clearance: renal†
Low molecular weight heparins			
Enoxaparin	IV or SQ – Onset: 30 minutes Peak: 3–5 hours	Dose-independent; 12 hours	Metabolism: hepatic Clearance: renal‡
Dalteparin	Onset: 1–2 hours Peak: 4 hours	Dose-independent; ≤ 12 hours§	Metabolism: hepatic Clearance: renal‡
Essential pentasaccharide only			
Fondaparinux	SQ: 2–3 hours*	Dose-independent; 17–21 hours	Metabolism: unknown Clearance: renal‡

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Agent	*Onset/peak*	*Half-life/duration*	*Metabolism/clearance*
Direct thrombin inhibitors			
Bivalirudin	Immediate*	25 minutes; total duration 1 hour	Metabolism: proteolysis Clearance: renal‡
Argatroban	Immediate*	50 minutes	Metabolism: hepatic Clearance: feces

Data obtained from Lexicomp, drug package inserts. All listed agents follow linear (first order) kinetics.
(DTI: Direct thrombin inhibitor; IV: Intravenous; LMWH: Low molecular weight heparin; RES: Reticuloendothelial system; SQ: Subcutaneous; UFH: Unfractionated heparin).
Notes: *Onset and peak are same.
†At therapeutic doses, elimination is rapid via nonrenal mechanisms.
‡Dosage adjustment recommended in renal insufficiency.
§Anti-Xa activity 2–5 hours; prolonged in renal insufficiency 3.7–7.7 hours.

Table 4.2: Recommended dosing for anticoagulants during PCI.[1-4]

Agent	*Received initial therapy*	*No initial therapy*
Heparins		
UFH	GPI planned: Using UFH, target ACT 200–250 seconds No GPI: target ACT 250–300 seconds (HemoTec), 300–350 seconds (Hemochron)	GPI planned: 50–70 U/kg, target ACT 200–250 seconds No GPI: 70–100 U/kg, target ACT 250–300 seconds (HemoTec), 300–350 seconds (Hemochron)
Enoxaparin	Last SC dose > 8 hours prior: no therapy Last SC dose < 8 hours prior: 0.3 mg/kg IV bolus	IV bolus: 0.5–0.75 mg/kg
Dalteparin*	GPI planned: Using UFH, target ACT 200 seconds No GPI: Using UFH, target ACT 250–300 seconds (HemoTec), 300–350 seconds (Hemochron)	GPI: IV bolus UFH 60–70 U/kg No GPI: IV bolus UFH 100–140 U/kg
Fondaparinux†	IV bolus UFH 50–60 U/kg	IV bolus UFH 50–60 U/kg
Direct thrombin inhibitors		
Bivalirudin	IV bolus: 0.5–0.75 mg/kg IV MD: Increase to 1.75 mg/kg/h	IV bolus: 0.5–0.75 mg/kg IV MD: 1.75 mg/kg/h
Argatroban	IV bolus: 200 mcg/kg IV MD: 15 mcg/kg/min	IV bolus: 350 mcg/kg IV MD: 15 mcg/kg/min

(ACT: Activated clotting time; GPI: Glycoprotein IIb/IIIa inhibitor; IV: Intravenous; PCI: Percutaneous coronary intervention; SC: Subcutaneous; UFH: unfractionated heparin).
Notes: *Dalteparin was evaluated for the treatment of UA/NSTEMI prior to the widespread use of $P2Y_{12}$ inhibitors, GPIs, and stents, and thus its efficacy and safety in the contemporary era is not well established.
†Not recommended as sole anticoagulant during PCI. Contraindicated for CrCl < 30 mL/min.

As LMWH contains a higher ratio of short:long chain saccharides, and fondaparinux is the essential pentasaccharide only, they carry certain advantages over UFH, including greater bioavailability (>95%), less protein binding, and more predictable kinetics. While UFH requires frequent monitoring of aPTT, this is not needed for LMWH or fondaparinux (though FXa activity can be monitored if desired). Additionally, while UFH must be given intravenously (IV) due to its short half-life, LWH and fondaparinux have longer half-lives, and may be given more conveniently in subcutaneously (SQ) in twice daily dosing (Table 4.1). Importantly, both LMWH, and (especially) fondaparinux, cause less direct platelet activation, bind PF4 much less, and thus carry a much lower risk of causing HIT.

Certain patient populations deserve special consideration when choosing between heparin products. In patients with renal failure, UFH dosing does not have to be adjusted, whereas patients on LMWH, or FXa inhibitors must have their dose reduced, and if GFR is <30 mL/min, these agents must be avoided entirely. Additionally, one advantage of UFH is that it is easily reversible with protamine sulfate, while LMWH and fondaparinux are not.

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Clinical Trials and Evidence

Unfractionated heparin—overview: Unfractionated heparin is as a "legacy drug," as although its use in ACS and in the setting of PCI has been ubiquitous for the past 20 years, the evidence base supporting its use is weak, and would likely be considered inadequate by contemporary standards. In general, the level of evidence supporting UFH periprocedurally varies by indication. With regard to ACS, for unstable angina (UA), data are limited to a few small randomized controlled trials (RCTs) and meta-analyses; for acute MI there are no RCTs of UFH versus placebo, but only observational data from trials of other agents plus adjunctive UFH (i.e. fibrinolytics, $P2Y_{12}$ inhibitors, and PCI). Similarly, for PCI, there are no RCTs of heparin versus placebo, as it is unethical to perform such trials based on experiential data associating thrombosis with wire and catheter use during PCI. However, retrospective analyses of UFH use during PCI have been performed in an attempt to identify optimal UFH dosing targets, and some small RCTs have compared conventional UFH dosing to weight-based UFH and low-dose UFH in selected populations.

Unfractionated heparin—use in ACS: Several small RCTs from the 1990s evaluated the addition of UFH + ASA versus ASA alone for the secondary prevention of MI or mortality after UA. The meta-analysis by Oler et al. of six RCTs included patients who had received 2–7 days of UFH + ASA versus ASA alone within 48 hours of the onset of UA, with aPTT titrated to 1.5–2x normal.[5] Overall, UFH + ASA reduced the risk of MI or death over ASA alone during the treatment period by 33% [relative risk (RR), 0.67; 95% confidence interval (CI), 0.55–1.02]. However, the risk of MI and death did not differ between the end of the treatment period and 12 weeks. These findings were confirmed by the RISC trial,[6] a double-blind, placebo controlled trial of 796 people with UA/non–ST-segment elevation myocardial infarction (NSTEMI). RISC randomized patients to ASA 75 mg/daily and/or intermittent IV UFH for 5 days. The risk of MI and death were reduced by ASA at 5 days (RR, 0.43; 95% CI, 0.21–0.91), 1-month (RR, 0.31; 95% CI, 0.18–0.53), and 3 months (RR, 0.36; 95% CI, 0.23–0.57). While the addition of UFH did not significantly lower the event rate, the group given ASA + UFH had the lowest number of events at 5 days. Thus, data from meta-analyses as well as the RISC trial suggest that UFH stabilizes patients with ACS while administered, but does not yield a sustained benefit in the absence of revascularization.

Unfractionated heparin—ACT: The anticoagulant effect of UFH may be monitored within minutes in the catheterization laboratory by checking the ACT. Activated clotting time is a point-of-care test in which whole blood is added to a tube containing a negatively charged surface activator. This triggers the intrinsic pathway, and the time to clot formation is then measured, with a higher ACT indicating more anticoagulated blood. Although intended to monitor the anticoagulant effect of UFH, ACT is altered by other anticoagulants, coagulation factor deficiencies, platelet count, platelet function, aprotinin use, and other variables. There are several manufacturers of different ACT assays, each with unique surface activators. Thus, the "normal range" differs among assays, and target ACT also depends on the indication for anticoagulation.

Early studies demonstrated a strong inverse relationship between ACT and ischemic events during PCI. In a study of 1,469 patients, Ferguson et al. showed that an ACT < 250 seconds was associated with increased rates of in-hospital death and revascularization after PCI.[7] Similarly, Narins et al. matched 62 patients who had abrupt vessel closure during PCI to 162 patients without, and found that ACT was lower in patients with abrupt vessel closure than those without (median 350 vs 380 seconds, respectively; $p = 0.004$).[8] Additionally, there was a strong linear relationship between ACT and the probability of abrupt vessel closure, and higher ACT was not associated with bleeding complications.[8] A large meta-analysis of six RCTs including 5,216 patients found that an ACT 350–375 seconds provided the lowest composite ischemic event rate of 6.6%, or a 34% relative risk reduction at 7 days post-PCI compared to an ACT between 171 and 295 seconds ($p = 0.001$).[9] In contrast, in a separate meta-analysis of four large, contemporary PCI trials (CREDO, CAPTURE, REPLACE 1, and REPLACE 2), containing 9,974 patients, higher ACT did not correlate with a reduction in ischemic outcomes, but was associated with a small increase in minor bleeding (OR, 1.04; 95% CI, 1.02–1.07, $p = 0.01$), and lower doses of UFH (<5,000 U) did not compromise efficacy, but were safer.[10]

Unfractionated heparin—dosage adjustments with weight and glycoprotein IIb/IIIa inhibitors: There are no trial data directly comparing weight-adjusted UFH to a fixed bolus UFH strategy, although weight-adjusted dosing is recommended based on results from GPI (glycoprotein IIb/IIIa inhibitor) trials. The EPIC trial investigated the addition of a GPI to standard of care in patients undergoing PCI at high risk for ischemic events, and demonstrated that routine high-dose UFH (10,000 U) was associated with

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Table 4.3: Guideline recommendations for choice of anticoagulants at time of PCI.[1-4]

Agent	*Class*	*LOE*	*Considerations*
Heparins			
Unfractionated heparin	I	C	• Dosing is based on if a GPI is given.
Enoxaparin	IIb	B	• An additional dose of 0.3 mg/kg IV should be given at time of PCI in patients who have received < 2 therapeutic doses, or if the last dose was > 12 hours before PCI (Class I; LOE B). • Patients treated w/ SC enoxaparin within 12 hours of PCI should not be given additional UFH (i.e. avoid "stacking") (Class III, LOE B)
Fondaparinux	III	C	• Should not be the only anticoagulant used during PCI given risk of catheter-associated thrombosis.
Direct thrombin inhibitors			
Bivalirudin	I	B	• Lower bleeding rates with bivalirudin than with UFH + GPI; benefit disappears when bivalirudin is used with a GPI.

(GPI: Glycoprotein IIb/IIIa inhibitor; IV: Intravenous; LOE: Level of evidence; PCI: Percutaneous coronary intervention; SC: Subcutaneous; UFH: Unfractionated heparin).

high rates of bleeding after PCI.[11] Building on this, the EPILOG trial randomized patients undergoing PCI to the GPI abciximab + standard weight-based UFH (100 U/kg), abciximab + low-dose UFH (70 U/kg), or placebo + low-dose UFH (70 U/kg), and found that while abciximab reduced ischemic events at 30 days, the combination of abciximab + standard dose UFH was associated with increased bleeding.[12] Further, the ESPIRIT trial randomized patients undergoing elective PCI + stenting to the GPI eptifibatide or placebo, and found that ischemic events did not increase with a lower ACT, at least to 200 seconds. While bleeding events did increase with the addition of a GPI, an ACT of 200–250 seconds provided a reasonable balance of safety and efficacy in patients on a GPI.[13]

Unfractionated heparin—summary: Tables 4.2 and 4.3 provide a summary of the current AHA/ACC/SCAI recommended dosing and guidelines on the use of UFH during PCI. In short, for use in primary PCI for STEMI without a GPI, while there is limited evidence on UFH dosing, typical usage is an initial bolus of 70–100 U/kg, titrated to an ACT of 250–300 seconds. For PCI with a GPI (or if being conservative due to increased bleeding risk), there is more evidence to guide decision making (i.e. EPIC, EPILOG, and ESPIRIT trials), and one should use a reduced initial bolus of 50–70 U/kg, titrated to an ACT of 200–250 seconds. Guidelines for use in UA/NSTEMI are roughly the same (as they are derived from much of the same data).

LMWHs—Overview

The evidence base supporting the use of LMWH during PCI is summarized in Figure 4.3. Most trials of LMWH use during PCI have been with patients with ACS, and evidence is much weaker for patients undergoing elective PCI. The early trials demonstrating a benefit of LMWH over UFH in ACS were all carried out among patients managed medically, without routine revascularization. The longer duration of therapy in these trials may have helped show benefit of LMWH over UFH in medically managed ACS, whereas results have been somewhat different in contemporary trials done in the era of early invasive management.

Trials of LMWH in ACS without routine early revascularization: The major early trials of LMWH in ACS were of patients with UA/NSTEMI managed medically. The FRISC trial randomized 1,506 patients with UA/NSTEMI to either SQ dalteparin (120 IU/kg—maximum 10,000 IU) twice daily for 6 days, then 7,500 IU once daily for 35–45 days) + aspirin or aspirin alone, and found that during the first 6 days the rate of death and new MI was 63% lower in the dalteparin group (1.8% vs 4.8%; RR, 0.37; 95% CI, 0.20–0.68).[14] The FRAXIS trial randomized 3,468 patients with UA/NSTEMI to UFH for 6 days, nadroparin for 6 ± 2 days, or nadroparin for 14 days. While it found that nadroparin was noninferior to UFH for prevention of ischemic events at 6 or 14 days, use of nadroparin for 14 days was not superior to UFH and led to increased risk of major bleeding (3.5 vs 1.6%; $p = 0.0035$).[15]

Enoxaparin was evaluated in the ESSENCE trial, in which 3,171 patients with UA/NSTEMI were randomized to enoxaparin 1 mg/kg SQ twice daily or UFH for 2–8 days (median 2.6 days). In ESSENCE, enoxaparin resulted in a 16% relative reduction in the risk of death, MI, or recurrent angina at 14 days (16.6% vs 19.8%; $p = 0.019$), and 15% at 30 days (19.8% vs 32.2%; $p = 0.016$). The need for

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revascularization procedures was also lower at 30 days in the enoxaparin group (27.1% vs 32.2%; $p = 0.001$), and there were no differences in bleeding.[16] The thrombolysis in myocardial infarction (TIMI) 11B trial randomized 3,910 patients with UA/NSTEMI to UFH or enoxaparin (30 mg IV bolus followed by SQ injections of 1 mg/kg twice daily) for 3–8 days (median 4.6 days).[17] There was an additional outpatient arm to the study, in which the enoxaparin group received enoxaparin for 43 days, and the UFH group received SQ placebo. The TIMI 11B found that enoxaparin provided a 24% reduction in death, MI, or urgent revascularization at 48 hours over UFH (7.3% vs 5.5%; $p = 0.026$), and a persistent 15% reduction at 14 days (16.7% vs 14.2%; $p = 0.029$). At follow-up at 43 days, the risk reduction was maintained, but major bleeding increased.[17] Benefits of enoxaparin seemed dependent upon underlying patient risk as assessed by the TIMI risk score; enoxaparin was superior to UFH if TIMI risk score was ≥4, whereas no difference was seen if <4.[18] Similar results were observed when validated in the ESSENCE cohort.[19]

Integrating the above, enoxaparin appears superior to UFH among high-risk patients with UA/NSTEMI receiving medical management, while nadroparin and dalteparin appear equivalent to UFH. However, there have been no head-to-head comparisons of these different LMWH agents in ACS; so definitive conclusions cannot be made. Further, as mentioned, all of these early trials were of conservative management, and none included patients treated with PCI while on study drug.

Trials of LMWH in an early invasive approach: While the more recent, contemporary trials of LMWH for ACS have included a mix of conservative and invasive approaches, most have incorporated other medications such as antiplatelet agents as well. In the setting of STEMI, the open-label ATOLL trial randomized 910 patients to primary PCI with adjunct IV enoxaparin or IV UFH. ATOLL found similar bleeding rates but a lower rate of composite death, recurrent ACS, or urgent revascularization with enoxaparin compared to UFH (7% vs 11%; RR, 0.59; 95% CI, 0.38–0.91; $p = 0.015$).[20] The SYNERGY trial was the only adequately-powered trial to investigate a strategy of enoxaparin versus UFH in patients with high-risk NSTEMI managed with an early invasive approach. In total, 9,978 patients were randomized to either weight-based UFH or enoxaparin 1 mg/kg every 12 hours periprocedurally, superimposed upon standard guideline approved therapies (aspirin, clopidogrel, and/or GPI), and PCI was performed at least 6–8 hours after the last enoxaparin dose. Enoxaparin was noninferior to UFH in the prevention of ischemic events at 30 days. However, enoxaparin did cause an increase in TIMI major bleeding (9.1% vs 7.6%; $p = 0.008$), although GUSTO severe bleeding and transfusions were not significantly different.[21]

Further insight into the proper role of LMWH during PCI can be gained from GPI trials. The INTERACT trial randomized 746 patients with high-risk NSTEMI to the GPI eptifibatide + weight-based UFH versus enoxaparin. Approximately, 29% of patients underwent PCI. Major bleeding was lower in the enoxaparin group at 4 days (1.8% vs 4.6%; $p = 0.03$). Additionally, enoxaparin reduced ischemic events at 48 hours and reduced death or MI at 30 days (5% vs 9%; $p = 0.031$),[22] although subgroup analysis was not performed for the PCI group. In the A–Z trial, which randomized 3,987 patients with UA/NSTEMI to the GPI tirofiban + weight-based UFH versus tirofiban + enoxaparin, approximately 43% of patients had PCI within 2 days, and 60% had PCI within 4.5 days. Overall, enoxaparin was found to be noninferior to UFH for the prevention of ischemic events and did not increase bleeding. Subgroup analysis suggested that enoxaparin produced better outcomes in patients managed conservatively (ischemic event rate 7.7% vs 10.6%; p = not specified), but was noninferior in the early invasive strategy.[23]

Given the above, enoxaparin appears to be a safe and as effective as UFH when used in patients with ACS undergoing an early-invasive strategy, both with and without a GPI. However, the convenience of using LMWH must be balanced with a potentially higher bleeding risk, given the results of the SYNERGY trial.

Trials of LMWH in an elective PCI: Two large trials compared the use of LMWH as an alternative to UFH for elective PCI. The REDUCE trial randomized 612 patients with single-lesion CAD treated with balloon angioplasty to reviparin (7,000 U fixed-dose bolus, followed by a 10,500 U over the next 24 hours) versus UFH (10,000 U fixed-dose bolus, followed by 24,000 U over the next 24 hours). Patients were also given 3,500 U SQ reviparin for 28 days, or placebo injections. REDUCE found that while the requirement for bailout intervention was reduced with reviparin (2.0% vs 6.9%; $p = 0.003$), the composite of death, MI, and need for repeat intervention was not reduced at 30 days, and risk of major bleeding was the same.[24] This study was followed by the STEEPLE trial, which randomized 3,528 patients undergoing elective PCI to enoxaparin (one of two doses—0.5 or 0.75 mg/kg) or UFH (adjusted for ACT), with use of a GPI at the discretion of the primary operator. STEEPLE

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found that enoxaparin 0.5 mg/kg reduced composite major and minor bleeding over UFH by 31% at 48 hours (5.9% vs 8.5%; $p = 0.01$), whereas bleeding with the higher dose enoxaparin 0.75 mg/kg dose did not differ from UFH (6.5% vs 8.5%; $p = 0.051$). Importantly, enoxaparin was associated with a fourfold increase in patients achieving therapeutic anticoagulation levels (79% for enoxaparin 0.5 mg/kg, 92% for 0.75 mg/kg, and only 20% for UFH; $p < 0.001$), and ischemic outcomes did not differ (although the trial was underpowered to assess this).[25]

A recent meta-analysis compared the efficacy and safety of enoxaparin and UFH during PCI, both for ACS as well as elective PCI.[26] The study included 30,966 patients; 33.1% had primary PCI for STEMI, 28.2% had secondary PCI after fibrinolysis, and 38.7% had PCI for non–ST-segment elevation (STE) ACS or elective PCI. Enoxaparin was associated with significant reductions in death (RR, 0.66; 95% CI, 0.57–0.76; $p < 0.001$), composite death or MI (RR, 0.68; 95% CI, 0.57–0.81; $p < 0.001$), and a reduction in major bleeding (RR, 0.80; 95% CI, 0.6–0.85; $p < 0.001$). Looking at subgroup analysis, the mortality benefit from enoxaparin was driven by patients with STEMI (RR, 0.62; 95% CI, 0.48–0.79; p = not specified), as although there was a trend toward lower mortality in patients with non-STE ACS and elective PCI, this did not reach statistical significance. However, the reduction in major bleeding was observed consistently among STEMI and non-STE ACS and elective PCI cases.

LMWH—summary: Tables 4.2 and 4.3 provide a summary of the current AHA/ACC recommendations regarding dosing and use of LMWH during PCI. Figure 4.4 summarizes the evidence above. Based on the evidence, LMWH appear at least as effective as UFH in the prevention of ischemic events after PCI, may yield a mortality benefit in patients with high-risk ACS over UFH in results from pooled analyses. While RCT data would suggest there is a small increased risk of bleeding with enoxaparin when used in an early invasive approach, results from meta-analysis suggest enoxaparin is likely about as safe as UFH when used during PCI.

In clinical practice, a single 1 mg/kg SQ dose of enoxaparin inhibits factor Xa levels within 30 minutes, and provides effective anticoagulation for 8–12 hours after injection. Thus, in ACS patients who have received enoxaparin, PCI can be safely performed within this 8-hour window, and if within an 8–12-hour window, an additional 0.3 mg/kg IV injection should be given. Elderly patients and those with renal function should be preferentially given UFH.

Fondaparinux—Overview

Two large RCTs have evaluated the role of fondaparinux for the treatment of ACS, including patients treated with PCI.

Trials on Use of Fondaparinux in PCI: The OASIS-5 trial randomized 20,078 patients with UA/NSTEMI to either fondaparinux (2.5 mg daily) or enoxaparin (1 mg/kg twice daily), with or without adjunctive GPI administration.[27] Fondaparinux was noninferior to enoxaparin in reducing the primary endpoint of composite death, MI, or refractory ischemia at both 9 and 30 days. However, fondaparinux significantly reduced major bleeding at 9 days (2.2% vs 4.1%; HR, 0.52; 95% CI, 0.44–0.61; $p < 0.01$), and reduced long-term mortality at both 30 and 180 days. Approximately 40% of patients underwent PCI, and in this population the primary endpoint did not differ at any point during follow-up. While there was a decrease in PCI-related bleeding complications, there was an increase in guide-catheter thrombosis with fondaparinux (0.9% vs 0.3%).[27] These results were largely consistent with the OASIS-6 trial, which focused on a higher risk population, and randomized 12,092 patients with STEMI to fondaparinux (2.5 mg daily) for 8 days or UFH for 48 hours (for patients in whom anticoagulation was felt be indicated) or no anticoagulation.[28] Glycoprotein administration was allowed, and fondaparinux and UFH dosing was adjusted. OASIS-6 found that fondaparinux reduced the primary endpoint of composite death or reinfarction at 30 days [9.7% vs 11.2%; hazard ratio (HR), 0.86; 95% CI, 0.77–0.96; $p = 0.008$], with benefits observed as early as 9 days, and benefits persisted up to 3–6 months. However, similar to OASIS-5 trial, fondaparinux was not superior to UFH in the 29% of patients who underwent primary PCI. Additionally, there was a higher rate of guide catheter thrombosis (0 vs 22 events; $p < 0.001$), and more coronary complications (abrupt vessel closure, new angiographic thrombus, catheter thrombus, no reflow, dissection, or perforation; 225 vs 270 events; $p = 0.04$) with fondaparinux.[28]

Given these findings, the FUTURA/OASIS-8 trial investigated the addition of low-dose versus standard-dose UFH to fondaparinux during PCI for the reduction of catheter-associated thrombosis.[29] FUTURA randomized 2,026 patients with NSTEMI undergoing PCI initially treated with fondaparinux to either low-dose UFH (50 U/kg, regardless of GPI use) or standard-dose UFH (85 U/kg, reduced to 60 U/kg with GPI use), adjusted by ACT level. There was no difference in the primary outcome of

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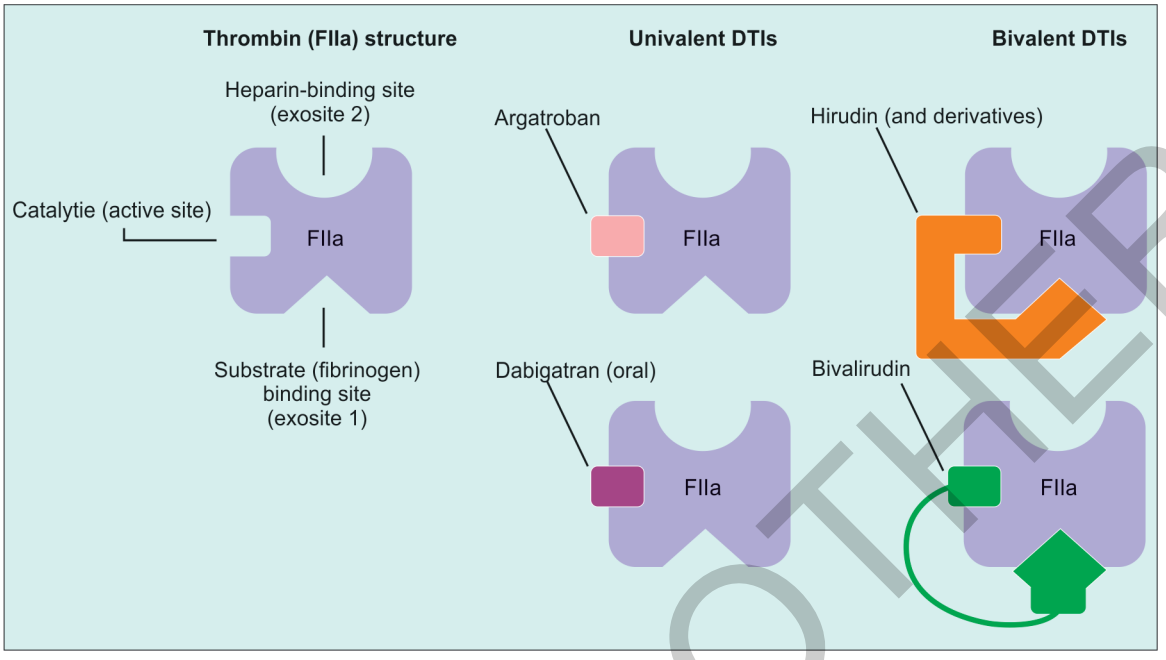

Fig. 4.3: Structure of the commonly used direct thrombin inhibitors (DTIs). Thrombin (FIIa) has a catalytic (active) site, a substrate binding site (exosite 1), as well as a heparin binding site (exosite 2). Univalent DTIs bind the catalytic site alone, while bivalent DTIs also bind the substrate binding site.

composite major bleeding, minor bleeding, or access site complications between the low- and standard-dose groups (4.7% vs 5.8%; OR, 0.80; 95% CI, 0.54–1.19; $p = 0.27$) or in the key secondary outcomes of composite major bleeding at 48 hours or death, MI, or target vessel revascularization (TVR) within 30 days (5.8% vs 3.9%; OR, 1.51; 95% CI, 1.00–2.28; $p = 0.05$). Importantly, catheter thrombosis rates were lower than in the OASIS-5 and OASIS-6 trials, but were not statistically different between UFH dosing groups (0.5% vs 0.1%; $p = 0.15$).

Fondaparinux—summary: Tables 4.2 and 4.3 summarize the current AHA/ACC dosing recommendations regarding the use of fondaparinux during PCI. Given the above data, it appears that the major benefit of fondaparinux is in patients medically managed, and it is not superior to UFH or enoxaparin in patients undergoing PCI. Moreover, although catheter thrombosis occurred more frequently in the fondaparinux group in the OASIS-5 and OASIS-6 trials, catheter thrombosis was not consistently reported in trials LMWH agents, and it is possible that this may complicate other agents, as well. Regardless, given the data, fondaparinux is not recommended for use as the sole anticoagulant during PCI, and UFH or another agent with anti-factor IIa activity should be administered as well to avoid the potential hazard of catheter thrombosis.

Direct Thrombin Inhibitors

Overview

Direct thrombin inhibitors (DTIs; FIIa inhibitors) are agents that inhibit both free and fibrin-bound thrombin. They have several important advantages over UFH, as described in the sections below.

Structure and Function

There are two types of DTIs, dependent on their molecular interactions with thrombin (Fig. 4.3). *Bivalent DTIs* bind to both the catalytic site on thrombin and the substrate recognition site (exosite 1), and consist of hirudin and its derivatives bivalirudin, lepirudin, and desirudin. *Univalent* DTIs bind to one or the other of the active or substrate recognition sites, and consist of argatroban, ximelagatran, and dabigatran. Allosteric inhibitors of thrombin are a third class of drugs that are currently in development but have yet to reach the clinical trial stage. The most common DTI used today is bivalirudin, which is a synthetic 20-amino acid peptide analog of hirudin, which demonstrates linear kinetics, allowing for a direct correlation between dose and anticoagulation activity.

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Pharmacokinetics, Dosing Considerations, and Limitations of Use

Pharmacokinetic and dosing considerations for bivalirudin are provided in Table 4.1. Direct thrombin inhibitors have several important conceptual and practical advantages over UFH and LMWH during PCI. Direct thrombin inhibitors bind directly to both free and fibrin-bound thrombin, do not require a cofactor (such as AT), and have no known natural inhibitors (such as PF4). Further, DTIs do not bind to plasma or tissue proteins and thus have more predictable biophysical availability and are not subject to the steric hindrance of the heparin-AT complex that prevents inhibition of clot-bound thrombin. While UFH directly activates platelets and can cause HIT, DTIs do not.

Another important advantage of bivalirudin is unlike with UFH, ACT levels do not correlate with bleeding or ischemic events, and as such there is no merit to continuous monitoring. Periprocedural ACT only needs to be checked once to assure the drug is in the system (and not infiltrated or still in the infusion bag). Emerging tests, such as the ecarin clotting time, can measure the effect of hirudin and its derivatives (discussed at the end of the chapter).

Bivalirudin is cleared by a combination of proteolysis and renal elimination, and approximately 25% can be cleared by hemodialysis. As such, dosing adjustments are recommended in patients with moderate-to-severe renal dysfunction, and it should be avoided in patients with end-stage renal disease. Further patients with extremes of body weight may have an altered volume of distribution, and patients at extreme age were not included in clinical trials, and as such caution should be used when dosing bivalirudin in such patients.

Clinical Trials and Evidence

DTIs—overview: Bivalirudin has been the most widely studied DTI in clinical trials to date. The RCT evidence supporting DTI use during PCI is summarized in Figure 4.4.

EARLY TRIALS OF HIRUDIN VERSUS UFH

The early trials of DTI use in ACS were performed with hirudin, which has since been replaced largely by bivalirudin in clinical use. The HELVETICA trial randomized 1,141 patients with UA treated with balloon angioplasty to fixed-dose UFH for 24 hours, hirudin for 24 hours, or hirudin for 24 hours followed by SQ dosing for 3 days. While hirudin reduced early cardiac events within 96 hours (RR, 0.61; 95% CI, 0.41–0.90; $p = 0.023$), it had no benefit over UFH over longer term follow-up.[30]

In contrast, the OASIS-2 trial randomized 10,141 patients with UA/NSTEMI to IV UFH or hirudin for 72 hours. In OASIS-2 trial, hirudin did reduce the composite cardiovascular death, MI, or refractory angina compared to UFH at 7 days (5.6% vs 6.7%, RR, 0.82, $p = 0.0125$), but increased major bleeding requiring transfusion (1.2% vs 0.7%, $p = 0.01$).[31] Likewise, the GUSTO IIa trial evaluated a strategy of 3–5 days of UFH adjusted to PTT versus hirudin for the prevention of ischemic events, but was stopped early due to an increase in intracerebral hemorrhage with hirudin in patients treated with fibrinolysis.[32] In a different approach in which adjunctive anticoagulation doses were reduced with fibrinolysis, GUSTO IIb randomized 12,142 patients to UFH or hirudin (at a lower dose than in the GUSTO IIa trial), and found that hirudin reduced the risk of composite death or MI at 24 hours (1.3% vs 2.1%, $p = 0.001$) but not 30 days, and did not increase the risk of major bleeding.[33] It is important to note that no patients in the OASIS-2 or GUSTO IIa/b trials were treated with adjunctive antiplatelet agents (such as $P2Y_{12}$ inhibitors or GPI agents) other than aspirin, and few had PCI; their results are difficult to generalize to the contemporary era.

Early trials of bivalirudin versus UFH: Data from the first clinical trials of evaluating bivalirudin use in clinical practice suggested that bivalirudin was as effective in the prevention of ischemic events as UFH, but may be associated with less bleeding. The first large-scale randomized trial to evaluate bivalirudin versus UFH during PCI was the Bivalirudin Angioplasty Study, which randomized 4,098 patients undergoing balloon angioplasty for UA or postinfarction angina to high-dose UFH or bivalirudin.[34,35] In the overall study population, bivalirudin was noninferior for the prevention of in-hospital death or ischemic outcomes, but did reduce bleeding versus UFH (3.8% vs 9.8%, $p < 0.001$). However, in a reanalysis of a more complete dataset of the trial, bivalirudin was found to significantly reduce death, MI, or repeat revascularization at 7 days and 90 days, and there was a trend toward reduced events at 180 days as well.[35] Importantly, however, no patients received GPI agents or had coronary stenting in this trial, and thus it is difficult to generalize these results to contemporary patient care.

A more recent trial, ISAR-REACT 3 randomized 4,570 patients with stable angina or UA undergoing PCI treated with 600 mg clopidogrel to bivalirudin or high-dose UFH (140 U/kg initial bolus).[36] In ISAR-REACT 3, there was no difference in the composite of death, MI, or urgent TVR

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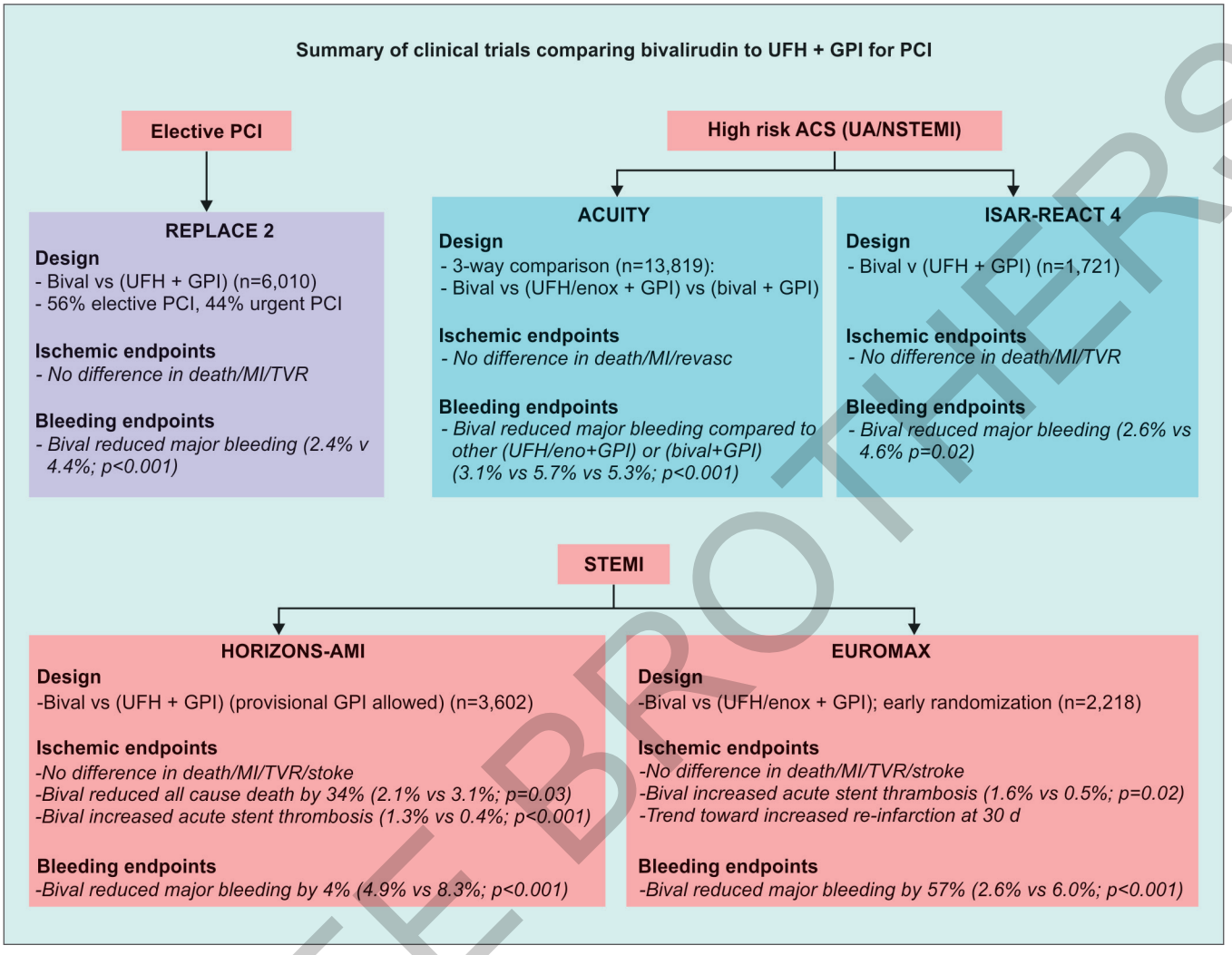

Fig. 4.4: Summary of clinical trials comparing bivalirudin to UFH + GPI for PCI. All endpoints reproted above are at day. Endopints of TVR or revasc were for urgent intervention. See reference list for study citations and acronyms. (UFG: Unfractionated heparin; GPI: Glycoprotein IIb/IIIa inhib itor; PCI: Percutaneous coronary intervention; Bival: Bivalirudin; MI: Myocardial infarction; TVR: Target vessel revascularizatio; enox: Enoxaparin; revasc: Revascularization).

between bivalirudin and UFH (5.9% vs 5.0%; p = 0.23). However, major bleeding was lower with bivalirudin (3.1% vs 4.6%; RR, 0.66; 95% CI, 0.49–0.90; p = 0.008).[36] Taken together, these early trials suggest that bivalirudin is as effective as UFH in preventing recurrent ischemic events in UA/NSTEMI treated with PCI in the absence of GPI use, and may cause less bleeding than UFH. However, these bleeding findings have since been challenged by preliminary data from the NAPLES III and HEAT-PPCI trials, which are discussed in the "Contemporary Trials of Bivalirudin versus UFH" section later in this chapter.

Trials of bivalirudin versus UFH + GPI: *Overview*: Most of the recent trials of bivalirudin have compared this agent to heparin regimens including a GPI and are summarized in Figure 4.4. The available data suggest no difference in ischemic event rates and reduced bleeding event rates with bivalirudin alone versus heparin + GPI, regardless of whether used in an elector urgent settings. Trials performed among the highest risk patients with STEMI, however, have consistently suggested an increased risk of early stent thrombosis (ST) with bivalirudin.

Elective PCI: Bivalirudin compared with UFH + GPI in the setting of elective or urgent PCI (without MI) was tested among 6,010 patients in the large scale REPLACE-2 trial.[37] Patients were treated with aspirin and approximately 85% received a thienopyridine prior to PCI. With GPI used

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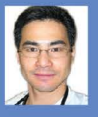

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