



Anticoagulants and Primary PCI

9

Fahim H. Jafary

9.1 Introduction

Percutaneous coronary interventions (PCI) mandate usage of anticoagulants to facilitate a successful and safe procedure. This chapter reviews commonly used anticoagulant regimens used for PCI with tailored guidance for the acute setting, in particular primary PCI for ST-elevation myocardial infarction (STEMI).

9.2 Rationale for the Use of Anticoagulant Therapy

PCI involves a variety of events that cumulatively increase the risk of intra and post procedure thrombosis. These include balloon-induced injury and dissection with exposure of the subendothelial tissue to blood, activation of platelets and the coagulation cascade and implantation of a potentially thrombogenic foreign body (stent) in the coronary circulation. These effects are, of course, more pronounced during PCI for acute coronary syndromes (ACS) where the thrombotic milieu is already “hot” at the outset. Therefore, anticoagulation with antiplatelet and antithrombotic therapy during PCI is considered obligatory. Of note, no placebo-controlled trials of antithrombotic therapy in PCI have ever been conducted, nor will there ever be such a trial. Indeed, the 2017 European Society of Cardiology (ESC) guidelines [1] give anticoagulation (antithrombotic therapy) a class I indication for routine use during STEMI PCI.

F. H. Jafary
Tan Tock Seng Hospital, Singapore, Singapore
e-mail: fahim_haider_jafary@ttsh.com.sg

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9.3 Classes of Anticoagulant

Several classes of anticoagulant regimens are available. Each of these is discussed in detail below.

9.3.1 Unfractionated Heparin and STEMI

Unfractionated heparin (UFH) has been available since the 1930s, and there is, therefore, an extensive generational physician experience with this drug in a variety of clinical settings. Derived from porcine intestine, a bag of UFH contains a heterogeneous mix of polysaccharides with a wide variety of molecular weights (Table 9.1). Only a third of the UFH molecules are biologically active as a result of possessing a key pentasaccharide sequence that is able to bind to antithrombin (AT) [2]. UFH attaches to AT to form a tertiary complex that binds to and inhibits

Table 9.1 Comparative chart of characteristics of various anticoagulants used in the primary PCI setting

Drug	UFH	LMWH	Fondaparinux	Bivalirudin
Molecular weight (kDa)	3–30 (mean 15)	2–10	1.7	2.2
Action	Binds to AT, inhibits IIa and Xa	Binds to AT, inhibits Xa	Binds to AT, inhibits Xa	Directly binds to thrombin
Xa:IIa ratio	1:1	4:1	Pure Xa	Pure IIa
Plasma proteins binding	Extensive	Low	None	
T $\frac{1}{2}$ after dose	Variable (dose dependent) ^a			25 min
PCI dose	70–100 U/kg (no GPI planned) 50–70 U/kg IV (GPI planned). Target to therapeutic ACT	0.5 mg/kg IV bolus		0.75-mg/kg IV bolus, then 1.75-mg/kg/h infusion
Activates platelets	+++	+	–	–
HIT	0.5%	<0.1%	Negligible	Negligible
Monitoring	ACT ^b	Anti Xa levels ?ACT	Anti Xa levels ^c	ACT ^d
Reversal	Protamine	Protamine (partial)	None	None

AT antithrombin, ACT activated clotting time, HIT heparin-induced thrombocytopenia

^aHalf-life increases with dose

^bACT reflects therapeutic effect

^cNo point-of-care options

^dACT does *not* reflect therapeutic effect, only reflects delivery of drug

both factor Xa and as IIa (thrombin), thereby inhibiting production and action of thrombin. As UFH inhibits both molecules, its anti Xa:IIa activity ratio is 1:1. In contrast, low molecular weight heparins (LMWH) by virtue of their predominantly shorter chains are only able to bind to AT and hence have primarily anti-Xa activity (Table 9.1).

Some well-known limitations of UFH include its inability to penetrate and bind to clot-bound thrombin, extensive binding by plasma proteins which limit bioavailability, an inherent platelet-activating effect of heparin and complex pharmacokinetics which make the anticoagulation response to a given dose somewhat unpredictable [2]. Despite these limitations unfractionated heparin remains the most widely used antithrombotic agent during PCI, and both the ACCF/AHA [3] and ESC [1] guidelines give UFH a class I recommendation in primary PCI.

There are no comparative dosing trials of UFH in primary PCI and dosing recommendations are somewhat arbitrary. The 2017 ESC guidelines [1] recommend an UFH dose of 70–100 IU/kg intravenous bolus when no glycoprotein IIb/IIIa inhibitor is planned and 50–70 IU/kg bolus with planned glycoprotein IIb/IIIa inhibitor use. It remains unclear whether STEMI patients, given the ongoing thrombotic milieu, should receive the higher end of the dose spectrum of UFH.

9.3.2 Low-molecular Weight Heparins and STEMI

Unlike UFH, LMWH consist of a relatively more homogeneous mix of molecules and have better bioavailability and longer half-life. As a result, LMWH have the advantage of more predictable and consistent anticoagulation compared to UFH. Although extensively studied in the ACS population, there is limited data in the context of STEMI. In the randomized ATOLL trial [4], 910 STEMI patients were randomized to an intravenous bolus of 0.5 mg/kg enoxaparin or standard dose UFH. Although the trial had a strong trend towards benefit favouring enoxaparin (17% relative risk reduction; $p = 0.068$), it failed to meet the primary endpoint. Moreover, it should be recognized that this was an open label trial, and while a per-protocol analysis that excluded 13% of the study group (for protocol violations) suggested that enoxaparin was statistically superior to UFH, this can be regarded as hypothesis generating at best. Furthermore, > 70% of the study population received a glycoprotein IIb/IIIa inhibitor; therefore it is difficult to extrapolate the data to patients not receiving additional glycoprotein IIb/IIIa inhibitor therapy. Nevertheless, these results do imply that enoxaparin is at least as safe as UFH in the primary PCI setting. The ACCF/AHA guidelines make no recommendations on enoxaparin, but the 2017 ESC guidelines [1] give it a class IIa recommendation (level of evidence A) (Table 9.2). Both the ACCF/AHA [3] and ESC guidelines recommend against the use of fondaparinux, a synthetic pentasaccharide LMWH, during primary PCI given a higher risk of ischemic events and catheter thrombosis in the OASIS-6 trial [5].

Table 9.2 Summary of major societal guidelines on the use of various antithrombotic agents in primary PCI

Drug	ACCF/AHA		ESC	
	Rec.	LOA:	Rec.	LOA
UFH	I	C	I	C
Enoxaparin	No recommendation		IIa	A
Fondaparinux	III	B	III	B
Bivalirudin	I	B	IIa I ^a	A C

ACCF/AHA American College of Cardiology Foundation/American Heart Association, ESC European Society of Cardiology, Rec recommendation, LOA level of evidence

^aIn patients with heparin-induced thrombocytopenia

Table 9.3 Summary of randomized trials of bivalirudin vs. heparin in primary PCI

Trial	Year	Treatment	Control	Radial	MACE	Bleeding	ST
HORIZONS-AMI [13]	2007	Bival + pGPI	Heparin + GPI	6%	↓	↓	↑
EUROMAX[14]	2013	Bival ^a	Heparin	~50%	↓	↓	↑
HEAT-PPCI [15]	2014	Bival	Heparin	80%	↑	No diff	↑
BRIGHT [16]	2015	Bival ^a	Heparin or heparin + GPI	78%	No diff	↓	No diff
VALIDATE-SWEDEHEART[17]	2017	Bival ^a	Heparin	90%	No diff	No diff	No diff

Bival bivalirudin, pGPI provisional GP IIb/IIIa inhibitor, MACE major adverse cardiac events, ST stent thrombosis

^aBivalirudin infusion continued post PCI

9.3.3 Direct Thrombin Inhibitors and STEMI

The most widely studied and used direct thrombin inhibitor (DTI) is bivalirudin. Bivalirudin binds reversibly to the catalytic site of thrombin and acts as a competitive inhibitor. Unlike heparins, bivalirudin can bind to clot-bound thrombin, is not bound by plasma proteins and, therefore, has excellent bioavailability. Bivalirudin also blocks thrombin-induced platelet aggregation. The dosing schedule of bivalirudin for STEMI patients undergoing PCI is outlined in Table 9.1. Despite its numerous theoretical advantages, recent randomized trials have failed consistently to demonstrate unequivocal superiority of bivalirudin over unfractionated heparin in the STEMI setting (Table 9.3). The studies do suggest a lowered risk of major bleeding, driven at least partially by reduced access site bleeding. Of note, several trials suggested an increased risk of early stent thrombosis (possibly ameliorated by prolonging the bivalirudin infusion post PCI).

Given the lack of superiority and significantly higher costs, the role of bivalirudin in STEMI remains questionable. This is of particular importance in the current era of using more potent P2Y₁₂ inhibitors (e.g. ticagrelor and prasugrel) and transradial access (which all but eliminates access site bleeding). Society guidelines are somewhat discordant, with the ACCF/AHA guidelines [3] awarding bivalirudin a class IB recommendation in STEMI, while the more updated 2017 ESC guidelines [1] give it a IIa recommendation unless there is a history of heparin-induced thrombocytopenia (class Ib).

9.4 Monitoring of Intensity of Anticoagulation in the Cardiac Catheterization Laboratory

9.4.1 Unfractionated Heparin

The anticoagulation response of UFH is variable and unreliable. Therefore, monitoring the level of anticoagulation using a point-of-care testing device is inherently attractive. The most widely used test to measure the anticoagulant effect of high doses of heparin (levels at which the aPTT would be “immeasurable”) is the activated clotting time (ACT) which has a linear dose-response to heparin concentrations in the very high 1–5 U/mL range and is available as a point-of-care assay. That said, there is lack of robust data to suggest that ACT testing and monitoring is necessary and beneficial. Several studies have questioned the relationship between ACT levels achieved and ischemic complications [6, 7]. Despite its limitations, ACT remains widely used in the cardiac catheterization laboratory to gauge the intensity of heparinization. Indeed, the ACCF/AHA guidelines [3] give monitoring ACT levels and titrating UFH dosing during primary PCI a class I recommendation, though the ESC guidelines are silent on the subject. The ACCF/AHA/SCAI PCI guidelines [8] recommend titrating UFH dosing to target ACT levels (Table 9.4) although these “targets” are largely based on consensus and experience rather than systematic study.

Table 9.4 Effect of various antithrombotic drugs on activated clotting time

Drug	Xa:IIa activity	Effect on ACT	Target ACT (s)
UFH	1:1	Linear ↑	GPI, 300–350 (Hemochron), 250–300 (HemoTech) No GPI, 200–250 (any device)
Enoxaparin	4:1	Modest ↑	None defined ^a
Fondaparinux	Pure Xa	No effect	No recommendation
Bivalirudin	Pure IIa	Disproportionate ↑	No recommendation ^b

UFH unfractionated heparin, ACT activated clotting time, GPI glycoprotein IIb/IIIa inhibitor

^aSee text for recommendations

^bACT levels do not correlate with therapeutic efficacy; only an indicator of drug delivery

9.4.2 Low Molecular Weight Heparin

Monitoring anticoagulation with enoxaparin is difficult because the ACT does not follow a linear dose-response unlike with UFH. The most definitive assay of enoxaparin's anticoagulant effect (measuring anti factor Xa activity) is not a readily available laboratory or point-of-care assay. Nevertheless, enoxaparin does moderately prolong the ACT, and several authors have suggested a role of ACT testing to guide enoxaparin therapy in the cardiac catheterization laboratory. One group has proposed a target ACT of 175 s for PCI performed with and 200 s for PCI performed without a glycoprotein IIb/IIIa inhibitor [9]. They also propose that every additional 0.1 mg/kg bolus of intravenous enoxaparin may be expected to increase the ACT by 10 s [10]. Of note, this has not been systematically studied for outcomes and remains a rough guide at most.

9.4.3 Bivalirudin

Bivalirudin raises the ACT usually in the “super therapeutic” range (often >300 s). However, studies with bivalirudin have reproducibly demonstrated no relationship between ACT levels and either bleeding or ischemic complications, quite in contrast to heparin. Thus, it may be reasonable to check an ACT once following the bolus of bivalirudin to confirm that the drug was delivered, thereby avoiding inadvertent failure of drug administration (e.g. intravenous line occlusion and other errors which may easily occur in the emergency setting). However, there is no role of sequentially testing ACT for the above-mentioned reasons. It is important to note, though, that the pivotal bivalirudin trials gave an additional dose of 0.3 mg/kg bolus if the post bolus ACT was <225 s. However, the ACCF/AHA or ESC guidelines do not specifically recommend this practice.

9.5 Approach to the Patient Who Has Received Anticoagulation Prior to Primary PCI

Although relatively unusual for a patient to receive parental anticoagulation prior to arrival to the cardiac catheterization laboratory for primary PCI, historically, some emergency room (ER) physicians have routinely administered UFH in the ER to STEMI patients. Also, in a “rescue” or “salvage” PCI setting, a patient may have received full-dose thrombolytic therapy prior to arriving to the laboratory. Furthermore, a situation may arise in which a patient admitted with an acute coronary syndrome “heats up” and progresses to STEMI despite receiving some sort of anticoagulation therapy. Table 9.5 shows the therapeutic options for the patient who arrives to the cardiac catheterization laboratory with anticoagulant therapy on board. Table 9.6 summarizes the approach to dosing if prior therapy has been administered.

Table 9.5 Therapeutic options for anticoagulation during primary PCI based on pretreatment status

Pretreatment	Therapeutic options during primary PCI
None	UFH Enoxaparin Bivalirudin
UFH ^a	UFH Bivalirudin
Enoxaparin	Enoxaparin ^a
Fondaparinux	UFH
GPI	UFH—check ACT and adjust dose (see Table 9.1)
Thrombolytic ^b	UFH—check ACT and adjust dose

UFH unfractionated heparin, GPI glycoprotein IIb/IIIa inhibitors

^aNo good “formula” to convert dosing of UFH to enoxaparin and vice versa

^b“Salvage” PCI setting

Table 9.6 Dosing of anticoagulation therapy in the cardiac catheterization laboratory in patients receiving anticoagulation prior to arrival

Drug	On treatment	Not on treatment
UFH	Check ACT on arrival “Top-up” UFH according to ACT	70–100 U/kg (no GPI planned) 50–70 U/kg IV (GPI planned). Target to therapeutic ACT
Enoxaparin	Last SC dose <8 h—no additional ^a Last SC dose >8 h—additional bolus 0.3 mg/kg IV bolus	0.5 mg/kg IV bolus
Fondaparinux	70–100 U/kg (no GPI planned) 50–70 U/kg IV (GPI planned) Target to therapeutic ACT [18]	
Bivalirudin	0.5 mg/kg bolus; ↑ drip to 1.75 mg/kg/h	0.75 mg/kg bolus; 1.75 mg/kg/h drip

ACT activated clotting time, UFH unfractionated heparin, SC subcutaneous, GPI glycoprotein IIb/IIIa inhibitor

^aIf patient received <2 doses, assume no steady state and administer additional bolus

As a rule of thumb, if a patient has been on therapy, then a “booster” dose of the anticoagulant is recommended. On the other hand, if a patient has received no prior therapy, then the full dose of the anticoagulant should be administered. It is important to note that “on therapy” for these purposes assumes a steady state of the drug. For enoxaparin, which is commonly used in the acute coronary syndrome setting, this means at least two doses have been administered. Hence if a patient arrives to the cardiac catheterization laboratory after receiving one dose of enoxaparin in the ward, it is safer to administer an additional dose of enoxaparin (Table 9.6). Note that no good “formula” exists to switch previous therapy with UFH to enoxaparin and vice versa when a patient arrives to the cardiac catheterization laboratory.

9.6 Role of Anticoagulation Following Successful PCI

By and large, anticoagulation should be stopped after a successful procedure. Data suggests that extending the anticoagulation with post procedure UFH or LMWH does not reduce ischemic complications but does increase bleeding risks [11, 12]. Therefore barring some compelling indication (very high thrombus burden or left ventricular thrombus) UFH or LMWH should not be continued after primary PCI. Similarly routine ACT check post procedure likely has little cumulative value other than to determine when the access sheath may be removed in the case of femoral access. In the case of bivalirudin, trials have suggested an increased risk of acute stent thrombosis following drug cessation at the end of the procedure (Table 9.3). This may be related to the very short half-life of the drug with a rapid wash-out. Prolonging the infusion may help mitigate that risk, although the data shows mixed results.

9.7 Summary

Anticoagulation with an antithrombotic drug is considered mandatory during PCI. UFH remains the most widely used antithrombotic agent during primary PCI and ideally should be dosed to a target therapeutic ACT. Enoxaparin may be a reasonable alternative in primary PCI, although advantage for this over heparin is debatable. Bivalirudin has many theoretical advantages over the heparins; however, trials in the primary PCI setting have failed to show superiority of bivalirudin for ischemic events, although bleeding events (driven partially by access site bleeding) are reduced. Furthermore, acute stent thrombotic events may be increased with bivalirudin, and consequently use of this drug is less widespread. Anticoagulation dosing in the cardiac catheterization laboratory needs to be tailored according to prior therapy and titrated (at least in the case of UFH) either empirically or to a therapeutic ACT where monitoring is available.

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