
UNFRACTIONATED HEPARIN

Unfractionated heparin is a heterogeneous polysaccharide which binds to antithrombin to potentiate the inhibition of thrombin and factor Xa. In the cath lab, heparin effect is measured by the activated clotting time (ACT), which is the time for whole blood to form a firm, grossly-apparent clot in response to kaolin (HemoTec ACT) or diatomaceous earth (HemoChron ACT).^{18,19} For the same heparin concentration, a higher ACT is obtained using the HemoChron system.²⁰ Intravenous heparin is virtually always employed during intervention to reduce the risk of abrupt closure.²¹

A. PROCEDURAL HEPARIN WITHOUT GLYCOPROTEIN IIb/IIIa INHIBITORS. There are no objective standards to identify the optimal level of anticoagulation during intervention; “therapeutic” levels have been empirically derived from the early cardiac surgery experience and from other observations.²²⁻³⁶ Common practice is to maintain the HemoChron ACT at 300-350 seconds and the HemoTec ACT at 250-300 seconds, although some interventionalists prefer higher values. The average heparin dose required to achieve an ACT > 300 seconds varies with the anginal syndrome,^{37,38} but a common initial weight-adjusted^{39,40} dose is 100 U/kg. Lower doses of heparin (5000 U bolus) have been used in some low-risk patients,^{41,42} but this practice is not recommended since the ACT level during PTCA may be inversely related to the risk of abrupt closure.^{35,43} Ischemic complications after PTCA were higher in patients with a HemoTec ACT < 250 seconds compared to those with an ACT > 300 seconds.³² The requirements for high levels of anticoagulation are not as stringent with stents, but minimum safe levels for ACT have not been established. Since the risk of bleeding increases with higher ACT levels, the ideal therapeutic ACT “window” may be relatively narrow. Patients who require larger doses of heparin to achieve a “therapeutic” ACT and the 30% of patients with elevated fibrinopeptide A levels despite “therapeutic” ACTs and high heparin levels (reflecting heparin resistance and residual thrombin activity) may have worse outcomes than other patients.⁴⁵ Unfortunately, there are no readily available bedside assays to identify these high-risk patients.

B. PROCEDURAL HEPARIN WITH GLYCOPROTEIN IIb/IIIa INHIBITORS. The precise recommendations for heparin administration during percutaneous intervention are somewhat ambiguous (Table 34.4, Figure 34.1). For planned abciximab, the recommended heparin bolus is 70 U/kg to achieve a target ACT of 200-250 seconds. Although the current FDA-approved labeling of eptifibatid and tirofiban includes a recommendation for a heparin dose of 100 U/kg to achieve an ACT of 300-350 seconds, most interventional cardiologists (including ourselves) recommend a heparin bolus of 70 U/kg to achieve an ACT 200-250 seconds, as with abciximab. In ESPRIT, in which patients were treated with a double bolus followed by an infusion of eptifibatid, the heparin bolus was 60 U/kg to achieve a target ACT of 200-300 seconds. For patients already receiving heparin, the guidelines are more confusing; one suggested approach is described in Figure 34.1. In our practices, the target ACT and heparin dose are identical for patients treated with abciximab, eptifibatid, or tirofiban.

- C. POSTPROCEDURAL HEPARIN.** In recent years the routine use of post-procedure heparin has declined after several studies⁴⁶⁻⁵⁰ suggested no value for preventing ischemic events and increased risk for bleeding and vascular complications. In situations when post-procedural heparin may be recommended (e.g., patients requiring an IABP), meticulous monitoring of anticoagulation is required to prevent bleeding; bedside aPTT (Biotrack 523 Portable aPTT machine, Ciba-Corning Diagnostics, Medfield, MA) has improved the safety of heparin anticoagulation. Since rebound thrombin generation⁵¹ and abrupt closure⁵² may be temporally associated with discontinuation of prolonged heparin infusions, heparin should be tapered slowly over 6-24 hours rather than abruptly stopped.
- D. LIMITATIONS OF HEPARIN.** Heparin catalyzes the inactivation of thrombin and activated factor Xa, but must bind with antithrombin III to exert its anticoagulant effect. Heparin's antithrombotic activity is limited by its inability to inactivate clot-bound thrombin,⁵³ neutralization by platelet factor IV from platelet-rich thrombi, and inactivation by fibrin II monomers, which are formed by the action of thrombin on fibrinogen (Table 34.5). Accordingly, "therapeutic" concentrations of heparin may not prevent propagation of thrombus.^{45,54} In addition, prolonged heparin infusions may deplete antithrombin III and potentially increase the risk of thrombosis.^{55,56}
- E. ADVERSE EFFECTS.** The major adverse effect of heparin is bleeding, which is generally proportional to the heparin dose, ACT level, and use of concomitant antiplatelet and thrombolytic therapy. An infrequent but important complication of heparin therapy is heparin-induced thrombocytopenia (HIT) (Table 34.6) (Chapter 25).^{57,58} Type-I HIT is due to direct (non-immune-mediated) platelet activation, results in mild thrombocytopenia, and has a benign clinical course. In contrast, Type-II HIT is due to immune-mediated platelet activation, results in moderate or severe thrombocytopenia, and is associated with serious thromboembolic complications. Platelet transfusions should not be used to treat patients with HIT due to the increased risk of thrombotic complications. An infusion of the prostacyclin analog Iloprost (Berlex laboratories) titrated to eliminate in-vitro heparin-induced platelet activation (infusion rates of 10-48 ng/kg/min) was successful in preventing recurrent HIT-2 in patients requiring cardiovascular surgery.^{57,58} Anticoagulation in HIT-2 patients has also been achieved with defibrinating viper venoms like Ancrod or Reptilase, and with the heparinoid Org 10172.⁵⁸ Low-molecular-weight heparin may reduce^{59,60} but not eliminate⁶¹ the risk of HIT-1, but is absolutely contraindicated in patients with prior HIT-2. Recently, the direct-acting thrombin antagonists lepirudin (Refludan) and argatroban (Acova) have become commercially available as alternatives to heparin (see below). Heparin-induced thrombocytopenia is discussed in greater detail in Chapter 25.

Table 34.2. Antithrombotic and Antiplatelet Agents for Coronary Intervention**Antithrombotic Therapy**

- Heparin (unfractionated)
- Low-molecular-weight heparin
- Direct thrombin inhibitor
 - Polypeptide inhibitors (hirudin [Lepirudin], bivalirudin [Hirulog])
 - Low-molecular-weight inhibitors (argatroban [Acova])

Antiplatelet Therapy

- Aspirin
- Clopidogrel
- Ticlopidine
- Dipyridamole
- Platelet GP IIb/IIIa antagonists
 - Abciximab
 - Eptifibatide
 - Tirofiban
- Other antiplatelet agents

Table 34.3. Antithrombotic Therapy for Coronary Intervention: Effects, Indications, and Dose

Drug	Effect on Abrupt Closure	Indication and Dose
Aspirin	↓	Elective PTCA: 325 mg/d at least one day prior to procedure; continue indefinitely. Urgent PTCA: 4 chewable baby aspirins (total: 325 mg)
Dipyridamole	-	Not used
Ticlopidine	↓	Aspirin-intolerant or allergic patient: 250 mg PO BID starting 3-5 days prior to intervention. Stents: 250 mg BID x 2-4 weeks. Used less frequently now that clopidogrel is available
Clopidogrel	↓	Aspirin-intolerant, allergic, or resistant patient: 75 mg PO QD. Stents: 300 mg oral loading dose, then 75 mg PO QD x 2-4 weeks. Radiation therapy for in-stent restenosis: Aspirin plus clopidogrel for at least 9 months following the procedure
Heparin	↓	See Table 34.4 and Figure 34.1
LMW heparin	↓	Alternative to unfractionated heparin for procedural anticoagulation: Enoxaparin 1 mg/kg IV
Thrombolytics	-	Dissolution of intracoronary thrombus: Streptokinase (250,000 units IC) or tPA (10-20 mg IC) over 5-45 minutes
Dextran	-	Not recommended
GP IIb/IIIa inhibitors	↓	See Table 34.4 and Figure 34.1

↓ Most data suggest a decreased incidence

- No effect or unknown effect

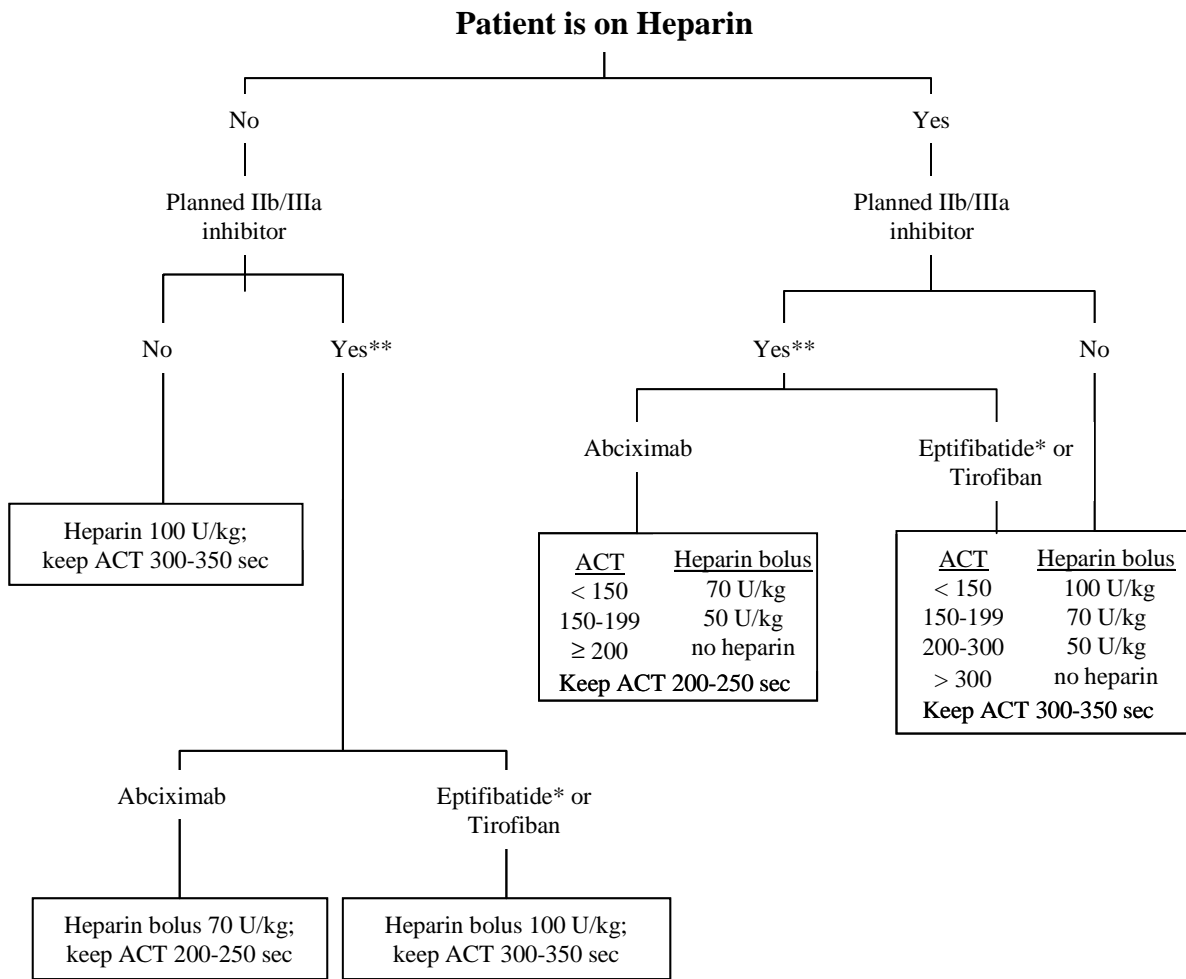


Figure 34.1. Approach to Heparin Administered During Percutaneous Intervention

* In ESPRIT, the recommended initial heparin dose was 60 U/kg to achieve a target ACT 200-300 seconds

** In practice, many interventionalists use the same heparin and target ACT guidelines for tirofiban or eptifibatide as recommended for abciximab

Table 34.4. Platelet Glycoprotein IIb/IIIa Antagonists for Coronary Intervention

	Abciximab	Eptifibatide	Tirofiban								
Dose for PCI	0.25 mg/kg IV bolus plus 0.125 mcg/kg/min (maximum 10 mcg/min) IV infusion for 12 hours. Low-dose heparin and early sheath removal to minimize bleeding (Table 34.24). For patients with unstable angina planning to undergo PCI within 24 hours, bolus plus infusion abciximab (PCI dose) can be started up to 24 hours prior to PCI and continued at the same rate until one hour after the procedure	Acute coronary syndromes (PURSUIT dose): 180 mcg/kg IV bolus plus 2.0 mcg/kg/min IV infusion. If arrive in cath lab > 4 hours after initiating therapy, no additional bolus is required. Percutaneous intervention (ESPRIT dose): 2 x 180 mcg/kg/min IV bolus 10 minutes apart, plus 2.0 mcg/kg/min IV infusion for 18-24 hours	10 mcg/kg IV bolus (over 3 minutes) immediately prior to PCI followed by an infusion of 0.15 mcg/kg/min for 18-24 hours. Patients with creatinine clearances < 30 cc/min should receive half the usual infusion rate								
Heparin (unfractionated)	Maintain ACT at 200-250 seconds to minimize bleeding. Initial IV heparin dose based on ACT: <table border="0"> <tr> <td><u>ACT (sec)</u></td> <td><u>Heparin (bolus)</u></td> </tr> <tr> <td>< 150</td> <td>70 U/kg</td> </tr> <tr> <td>150-199</td> <td>50 U/kg</td> </tr> <tr> <td>≥ 200</td> <td>no additional</td> </tr> </table> Discontinue heparin immediately after PCI	<u>ACT (sec)</u>	<u>Heparin (bolus)</u>	< 150	70 U/kg	150-199	50 U/kg	≥ 200	no additional	100 U/kg bolus, titrate to ACT 300-350 seconds. May also consider lower doses, as recommended for abciximab. In ESPRIT, the recommended initial heparin dose was 60 U/kg to achieve a target ACT of 200-300 seconds	100 U/kg bolus, titrate to ACT 300-350 seconds. May also consider lower doses, as recommended for abciximab
<u>ACT (sec)</u>	<u>Heparin (bolus)</u>										
< 150	70 U/kg										
150-199	50 U/kg										
≥ 200	no additional										
Aspirin	325 mg started at least 1 day prior to PCI and continued indefinitely; 4 chewable baby aspirin (325 mg total) for urgent intervention. For stents, add clopidogrel 300 mg oral load, then 75 mg PO daily for 2-4 weeks	See abciximab	See abciximab								

Abbreviations: ACT = activated clotting time; PCI = percutaneous coronary intervention