

# The Use and Limitations of Unfractionated Heparin

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**Abstract:** Despite the development of newer anticoagulants, unfractionated heparin remains an indispensable agent in the treatment of thrombotic disorders. Heparin exerts its major effect via antithrombin, converting antithrombin to a more efficient inhibitor of circulating thrombin (factor IIa), factor Xa, factor IXa, factor XIIa, and kallikrein. However, due to the multiple anticoagulant mechanisms of heparin, differential molecular weight-based clearance, issues of heparin resistance, and patient-specific characteristics (age, weight, gender, and tobacco), attaining therapeutic anticoagulation is complicated. As a result, a minority of patients in major clinical trials achieve an activated partial thromboplastin time within the target window in an appropriate time-frame despite the use of weight-based titration nomograms. The resultant under- or over-therapeutic anticoagulation is associated with increased risks of ischemic and bleeding complications, suggesting the importance of maintaining heparin anticoagulation within a relatively narrow therapeutic range. In this review we discuss the mechanisms of heparin action, clinical ramifications of incorrect dosing in major trials, and attempts to improve the achievement of therapeutic anticoagulation.

**Key Words:** unfractionated heparin, heparin mechanism, heparin dosing, AutoHep

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Heparin (derived from the Greek *hēpar*, or liver) is a potent anticoagulant initially isolated from canine livers in 1916 and first used in clinical trials in 1935.<sup>1</sup> Despite the advent of newer anticoagulants, heparin remains a mainstay for the treatment of patients with acute coronary syndrome (ACS), venous thromboembolic disease, atrial fibrillation, and in numerous other clinical scenarios.<sup>2–5</sup> However, the optimal dosing and titration system for heparin infusion remains elusive; almost 75% of patients fail to achieve the target activated partial thromboplastin time (aPTT) at 24-hour<sup>6,7</sup> (Fig. 1). Furthermore, this variable anticoagulant effect increases the risk of thrombotic and bleeding complications.<sup>13</sup>

In this review, we will discuss heparin's pharmacologic mechanisms, methods to optimize its use, the clinical ramifications of inaccurate dosing, and new strategies to achieve therapeutic anticoagulation.

## MECHANISM OF ACTION

Unfractionated heparin (UFH) exerts its effect by binding and inducing a conformational change in antithrombin (AT), converting AT to a more efficient inhibitor of circulating thrombin (factor IIa), factor Xa, factor IXa, factor XIIa, and kallikrein (Fig. 2).<sup>14–17</sup> Contributing to its efficiency, heparin can dissociate from the thrombin: AT complex and catalyze the activity of other AT molecules.<sup>18</sup> Furthermore, at high concentrations heparin binds heparin cofactor

II to create an AT-independent thrombin inhibitor, but also binds platelets and induces their aggregation.<sup>19–21</sup> Another minor anticoagulant effect of heparin is its induction of tissue factor pathway inhibitor release by endothelial cells, which abrogates the response to activated tissue factor (factor VIIa).<sup>22</sup>

Heparin is a heterogenous mixture of glycosaminoglycans of varying molecular weight (mean, 15,000 days; range, 3000–30,000 days), only one-third of which possess the high-affinity binding site for AT—the “essential pentasaccharide” sequence.<sup>23,24</sup> The varying size of heparin molecules in a preparation of unfractionated heparin is important to its anticoagulant properties. Inactivation of factor Xa requires only the binding of AT by heparin, but thrombin inactivation requires the formation of a ternary complex between heparin, AT, and thrombin.<sup>25</sup> Therefore, smaller heparin molecules are able to catalyze the inactivation of factor Xa, while larger molecules (consisting of at least 18 saccharide units) to effect the binding of both AT and thrombin are required to inactivate thrombin. As a result, the majority of molecules in the low-molecular-weight compounds (mean weight, 5000 days; range, 1000–10,000 days) have antifactor Xa activity, while only 25% to 50% have AT activity.<sup>23,26</sup>

The clearance of heparin is dependant on size. In vivo, the higher molecular weight moieties are more rapidly cleared, resulting in a differential accumulation of the low-molecular weight species. As a result, there may be a substantial anticoagulant effect through the inhibition of factor Xa, with less effect on aPTT due to a lesser effect on thrombin (factor IIa) activity.<sup>23</sup> Therefore, routine monitoring may not reflect the true degree of anticoagulation.

“Heparin resistance” describes the situation in which patients require >35,000 units of heparin over 24 hours to achieve a therapeutic aPTT ratio, and is seen in almost one-fifth of patients undergoing cardiopulmonary bypass.<sup>27,28</sup> The mechanisms of heparin resistance include AT deficiency and increased heparin binding by plasma proteins.<sup>29,30</sup> Patients with ACS or venous thromboembolism display a decreased anticoagulant effect of heparin, possibly due to an increased plasma level of heparin binding proteins in the acute phase, and Rich et al demonstrated that heparin resistance increases with the severity of ACS.<sup>31,32</sup> As discussed below, inadequate heparin dosing is associated with worse clinical outcomes, and the phenomenon of heparin resistance underscores the need for vigilant monitoring of anticoagulant effect in this high-risk group of patients.<sup>33</sup>

An “apparent,” or artifactual, heparin resistance may be seen with elevated factor VIII levels (in conditions such as pregnancy or burn injury).<sup>34,35</sup> In this situation, the subtherapeutic aPTT does not reflect the true degree of anticoagulation, which may be better assessed using an anti-factor Xa assay (along with demonstration of elevated factor VIII levels). Failure to recognize this entity could result in heparin over-dosing and the inherent complications therein.

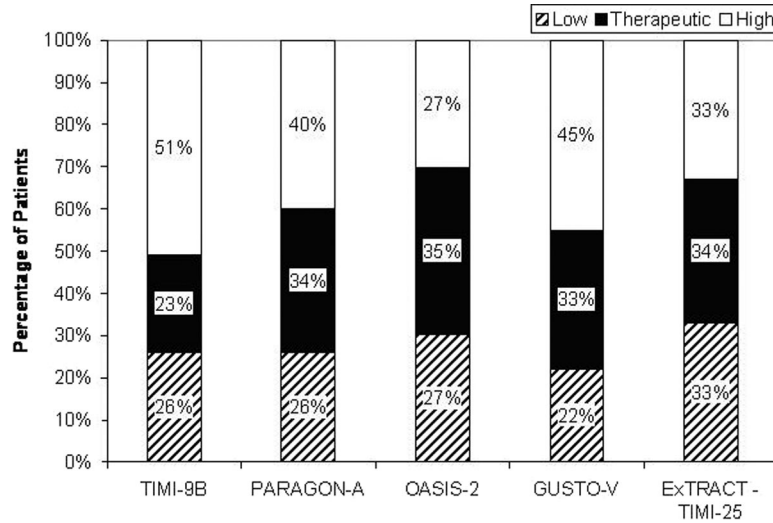
Taken together the multiple anticoagulant mechanisms of heparin, differential molecular weight-based clearance, and issues of heparin resistance all influence its therapeutic dosing. Patient-specific characteristics such as age, weight, gender, and tobacco use also affect aPTT levels and further complicate the attainment of optimal anticoagulation. To date, only weight-based nomograms (discussed below) have shown improved results over traditional bolus-dosing regimens; strategies for titration based upon age and gender have not been formulated.

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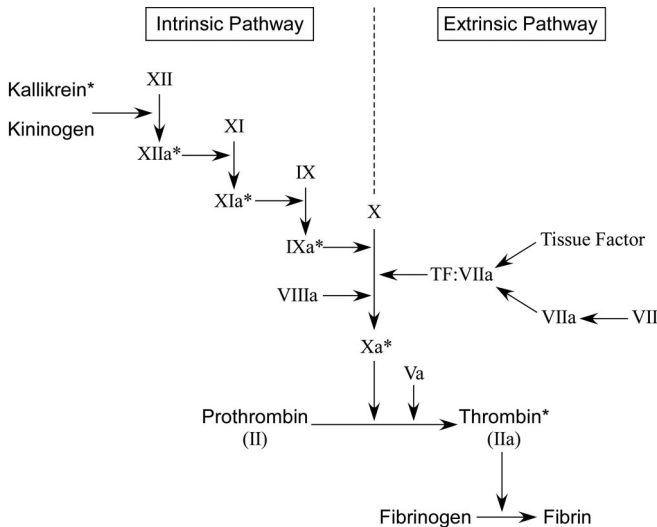
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**FIGURE 1.** Distribution of initial aPTT ratios in major trials utilizing unfractionated heparin for the treatment of acute coronary syndrome.<sup>8–12</sup>



**FIGURE 2.** The coagulation cascade. \*Targets of unfractionated heparin.

**ACHIEVING THERAPEUTIC ANTICOAGULATION**

The aPTT has been established as a useful tool in measuring the effects of anticoagulation on the intrinsic and common pathways.<sup>36</sup> Due to the variable effects of heparin discussed previously, fixed dosing is ineffective and achieving appropriate anticoagulation requires titration based upon the aPTT to a goal of 1.5 to 2.5 times control. This “therapeutic range” is largely based upon an old study which showed an increased risk of recurrent venous thromboembolism in patients who failed to achieve an aPTT ratio of at least 1.5.<sup>37</sup>

Strategies for heparin use have evolved from empiric bolus dosing to the application of standard weight-based titration nomograms which provide greater accuracy in predicting heparin requirements.<sup>38–40</sup> Current recommendations for the initiation and maintenance of a heparin infusion vary based upon the clinical setting and the use of concomitant anticoagulants (Table 1).<sup>41–44</sup> After the initial dose is given, the aPTT is measured every 6 hours and nomogram-based titrations are performed to maintain an aPTT ratio

**TABLE 1.** Initial Recommended Dose of Unfractionated Heparin

Clinical Situation	Initial Heparin Dose
NSTEACS <sup>41</sup>	Bolus: 60 units/kg (maximum 4000 units) Infusion: 12 units/kg/h (maximum 1000 units) Goal PTT: 1.5–2.0 times control (corresponding to anti-factor Xa level of 0.2–0.5 units/mL [laboratory-specific])
STEMI with fibrinolysis <sup>42</sup>	Bolus: 60 units/kg (maximum 4000 units) Infusion: 12 units/kg/h (maximum 1000 units) Goal PTT: 1.5–2.0 times control (corresponding to anti-factor Xa level of 0.2–0.5 units/mL [laboratory-specific])
STEMI without fibrinolysis <sup>42</sup>	Bolus: 60–70 units/kg (maximum 4000 units) Infusion: 12–15 units/kg/h (maximum 1000 units) Goal PTT: 1.5–2.0 times control (corresponding to anti-factor Xa level of 0.2–0.5 units/mL [laboratory-specific])
PCI with GP IIb/IIIa inhibitor <sup>43</sup>	Bolus: 50–70 units/kg Additional bolus: dose as needed Goal ACT: >200 s
PCI without GP IIb/IIIa inhibitor <sup>43</sup>	Bolus: 60–100 units/kg Additional bolus: dose as needed Goal ACT: 250–300 s
Venous thromboembolic disease <sup>44</sup>	Bolus: 80 units/kg (maximum 4000 units) Infusion: 18 units/kg/h Goal PTT: 1.5–2.5 times control (corresponding to anti-factor Xa level of 0.3–0.7 units/mL [laboratory-specific])

NSTEACS indicates non-ST-segment elevation acute coronary syndrome; STEMI, ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; GP IIb/IIIa, glycoprotein IIb/IIIa; PTT, partial thromboplastin time; ACT, activated clotting time.

of 1.5 to 2.5. After 2 consecutive therapeutic levels are measured, monitoring can be reduced to every 24 hours.

In addition to the variability of heparin response discussed previously, there are well-recognized limitations to aPTT monitoring, such as the inconsistency between different coagulometers and reagents. For instance, at a given therapeutic heparin concentration (gauged by anti-factor Xa level), aPTT ratios may range from 1.6 to 6.2 depending on the reagent used.<sup>4,5</sup> Nevertheless, aPTT-based titration remains the conventional standard, and it is recommended that laboratories establish specific therapeutic ranges for each machine and set of reagents.<sup>4,5,46</sup>

### CLINICAL RAMIFICATIONS OF INCORRECT DOSING

The use of heparin invariably results in a substantial risk for bleeding complications (Table 2).<sup>47–54</sup> Furthermore, the proportion of patients who fail to achieve appropriate levels of anticoagulation with heparin is staggering, and multiple investigators have demonstrated an increased rate of adverse events associated with incorrect heparin dosing.<sup>55</sup> Menon et al analyzed the major thrombolytic trials in which patients received UFH as an adjunctive therapy.<sup>56</sup> They found that as the therapeutic level for UFH dosing was increased, the rate of intracranial hemorrhage also increased, even prompting the early termination of the thrombolysis in myocardial infarction-9A and GUSTO-I (Global Use of Strategies to Open Occluded Coronary Arteries)-IIA trials. This was especially true in elderly patients, who present the highest risk for bleeding with UFH. They also reported similar trends in patients with MI or undergoing percutaneous coronary intervention receiving heparin alone. Similarly, in their analysis of 29,656 patients treated with thrombolysis for acute MI in the GUSTO-I (Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries) trial, Granger et al demonstrated that an aPTT ratio higher than 70 seconds was associated with a higher likelihood of mortality, stroke, bleeding, and reinfarction.<sup>57</sup> Conversely, an aPTT of 50 to 70 seconds at 12 hours was associated with the lowest 30-day risk of mortality, stroke, and bleeding.

Anand et al performed a subgroup analysis of 5058 patients enrolled in the Organization to Assess Strategies for Ischemic

Syndromes-2 trial of UFH versus hirudin for non-ST-segment elevation acute coronary syndrome.<sup>8</sup> At all measured time-points within 72 hours, a maximum of only 50% of patients had achieved a therapeutic aPTT ratio, and a substantial percentage of patients who were initially therapeutic fell out of the range. The occurrence of major bleeding was significantly higher for patients with an aPTT >100 versus <100 seconds (odds ratio [OR] 1.48 [95% CI, 1.01–2.17;  $P = 0.04$ ]). Similarly, the rate of ischemic complications was significantly greater for patients with aPTT <60 versus >60 seconds, with a risk ratio of 1.54 (95% CI, 1.10–2.15;  $P = 0.01$ ) for recurrent CV death, myocardial infarction, and refractory angina. These findings suggested the importance of maintaining heparin anticoagulation within a relatively narrow therapeutic range of aPTT values.

More recently, Cheng et al evaluated 6055 patients receiving UFH and thrombolysis for STEMI in the EXTRACT (Enoxaparin and Thrombolysis in Reperfusion for Acute Myocardial Infarction Treatment)-thrombolysis in myocardial infarction-25 trial.<sup>9</sup> As observed in previous studies, only 33.8% of patients achieved a therapeutic aPTT ratio at 8 hours, despite adherence to the ACC/AHA weight-based nomogram for heparin dosing. Patients with a markedly high aPTT (defined as an aPTT ratio >2.75) had a significantly increased risk of major or minor bleeding (OR, 2.11; 95% CI, 1.27–3.53;  $P = 0.004$ ). A markedly low aPTT (<1.25) was associated with a strong trend toward recurrent MI (OR, 2.19; 95% CI, 0.98–4.91;  $P = 0.057$ ). Even aPTT ratios that were not substantially subtherapeutic (1.25–1.49) were associated with a trend toward increased risk of MI (OR, 2.06; 95% CI, 0.99–4.30;  $P = 0.054$ ).

Patients with venous thromboembolic disease face similarly untoward outcomes with suboptimal heparin dosing. Multiple investigators have demonstrated an increased risk of recurrent VTE in patients who failed to achieve a therapeutic aPTT.<sup>37,58,59</sup> Certainly, not all adverse events would be avoided with strict adherence to a therapeutic heparin dosing regimen. However, the data provided suggests that these complications would be reduced if sub- and supra-therapeutic aPTT ratios were minimized. This concept is becoming exceedingly important, especially as newer generation anticoagulants suggest an improvement in both thrombotic and bleeding events when compared with heparin.<sup>47,50,60–62</sup>

**TABLE 2.** Rates of Major Bleeding in Contemporary Trials Using Intravenous Heparin During an Invasive Strategy for the Management of Patients With Acute Coronary Syndrome

Trial	Adjunctive Anticoagulation	Major Bleeding (%)
ACUITY <sup>47</sup>	GP II/IIIa inhibitor	5.7
ASSENT-4 PCI <sup>48</sup>	GP IIb/IIIa inhibitor in 50%	4.4
FRISC II <sup>49</sup>	None	3.1
HORIZONS-AMI <sup>50</sup>	GP IIb/IIIa inhibitor	5
PRISM PLUS <sup>51</sup>	None	3
PROTECT-TIMI-30 <sup>52</sup>	GP IIb/IIIa inhibitor	3.2
REPLACE-2 <sup>53</sup>	GP IIb/IIIa inhibitor	4.5
SYNERGY <sup>54</sup>	None	2.5

ACUITY indicates Acute Catheterization and Urgent Intervention Triage Strategy; ASSENT-4 PCI, Assessment of the Safety and Efficacy of a New Treatment Strategy for Acute Myocardial Infarction with Percutaneous Coronary Intervention; FRISC II, Fragmin and fast Revascularization during InStability in Coronary artery disease; HORIZONS-AMI, Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction; PRISM PLUS, Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms; PROTECT-TIMI-30, Trial to Evaluate the Relative Protection Against Post-PCI Microvascular Dysfunction and Post-PCI Ischemia Among Anti-platelet and Anti-thrombotic Agents - Thrombolysis in Myocardial Infarction-30; REPLACE-2, Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events; SYNERGY, Superior Yield of the New Strategy of Enoxaparin, Revascularization, and Glycoprotein IIb/IIIa Inhibitors.

### ATTEMPTS TO IMPROVE DOSING

In one of the first published articles of heparin treatment for venous thromboembolic disease, Basu et al began a fixed dose of 1000 units/h.<sup>37</sup> This was clearly ineffective, with an important number of patients failing to achieve a therapeutic aPTT with resultant recurrence of disease. A considerable improvement was made with the publication of a titration nomogram by Cruickshank et al, followed shortly by Hull et al.<sup>63,64</sup> In comparison with patients receiving “intuitive” dosing, a larger percentage of the groups treated via nomogram-based titration achieved therapeutic anticoagulation. However, much of the focus in these studies was the need to exceed the “therapeutic threshold” to reduce the rate of recurrent venous thromboembolism, without an emphasis on the number of patients who achieved supra-therapeutic aPTT ratios.

Given the concern of excessive anticoagulation leading to bleeding complications, Raschke et al further refined the use of nomograms with the comparison of a weight-based system to a standard nomogram.<sup>39</sup> Patients whose dose was titrated based upon body-weight were more likely to exceed the therapeutic threshold of aPTT >1.5 at 6 hours (86% vs. 32%,  $P < 0.001$ ), and achieved a stable therapeutic range in a more rapid fashion (14.1 hours vs. 22.3 hours,  $P < 0.001$ ). As importantly, many fewer patients manifested a supra-therapeutic value at the 24-hour point, and there were no

episodes of major bleeding reported (in comparison with the 6.5% reported by Hull et al for standard nomogram use).<sup>64</sup> Weight-based nomograms have been similarly validated in larger clinical trials, lending credence to the conclusions made in the initial study.<sup>38,40</sup> However, despite the improvements seen with weight-based dosing, a majority of patients still fail to achieve therapeutic anticoagulation in a safe or efficient manner as shown in Figure 1.<sup>9</sup> In addition to the inherent variabilities in heparin action, adherence to published nomograms is poor, laboratory-based testing of aPTT levels is inefficient, and medication errors are common.

A noteworthy percentage of health-care practitioners do not adhere to recommended dosing strategies for heparin use. Alexander et al evaluated UFH dosing in 13,298 patients with non-ST-segment elevation acute coronary syndrome enrolled in the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the American College of Cardiology/American Heart Association Guidelines) registry.<sup>65</sup> They found that less than one-third of patients received guideline-recommended dosing of UFH, with a similar number of patients being under- or over-dosed. Additionally, patients who are thinner, elderly, and/or women (all groups with higher bleeding rates in multiple trials) are more likely to receive excess heparin dosing due to a nonadherence to published dosing guidelines.

Another important consideration is the time required for centralized laboratory aPTT testing, which has been observed to be as high as 180 minutes in large trials.<sup>40,66</sup> There are a number of factors that contribute to this delay, including the time required for phlebotomy, transfer of the blood sample to the laboratory, batched analysis, reporting of aPTT results, and ultimately adjustment of the UFH drip by the nursing staff. In contrast, the use of a point-of-care testing apparatus has been shown to decrease this time period to as little as 14.5 minutes.<sup>66</sup> Given the number of blood draws required and the duration of anticoagulation in patients receiving heparin, bedside testing would likely decrease this treatment lag by many hours overall.

Zabel et al evaluated the use of a bedside aPTT monitor (CoaguCheck Plus, Boehringer-Mannheim, Indianapolis, IN) versus standard laboratory measurement in a subgroup of 1713 patients in the GUSTO-1 trial.<sup>6</sup> A greater number of patients in the bedside group achieved an aPTT ratio in the therapeutic window (15% vs. 17% and 20% vs. 23% at 6- and 12-hour follow-up, respectively). Providing evidence for a clinical benefit to this strategy, bedside-monitored patients demonstrated a significant decrease in bleeding, recurrent ischemia, and red blood cell transfusion, as well as non-significant trends toward decreased mortality and stroke.

The AutoHep device is a novel system for optimizing heparin treatment. Briefly, the device is attached to 2 peripheral IVs, one for heparin infusion and the other for automated venous blood sampling. A computer algorithm determines heparin dosing and titration in response to aPTT values, and automatically makes changes in the infusion rate. An added benefit to the automated system is the minimization of medication errors, which is an unfortunate reality of medical practice.<sup>67</sup> In a small feasibility trial of the device, the investigators demonstrated therapeutic levels in a remarkable 100% of patients at the 6-hour point, and patients maintained the therapeutic window for 46 of 48 hours of the trial.<sup>7</sup> The device is not yet approved for clinical use.

## CONCLUSIONS

Due to complicated pharmacodynamics and patient-specific characteristics, anticoagulation with heparin is unpredictable. Furthermore, complexities in aPTT monitoring, as well as logistical difficulties in obtaining and responding to those values in a timely

fashion, introduce significant impediments to appropriate and effective heparin therapy. The resultant under- or over-anticoagulation has clinical ramifications, such as recurrent thrombosis or significant bleeding. Despite the use of standard nomograms for heparin titration, efficient heparin dosing remains elusive. Though alternative anticoagulants are available, the use of heparin remains a mainstay in the treatment of various thrombotic disorders. Therefore, future research and development of computer-aided algorithms, bedside aPTT monitoring, and automated infusion devices is encouraged to optimize patient outcomes and safety.

## DISCLOSURES

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