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Anti-factor Xa activity is not the whole truth, and aPTT is actually sensitive to low molecular weight heparins

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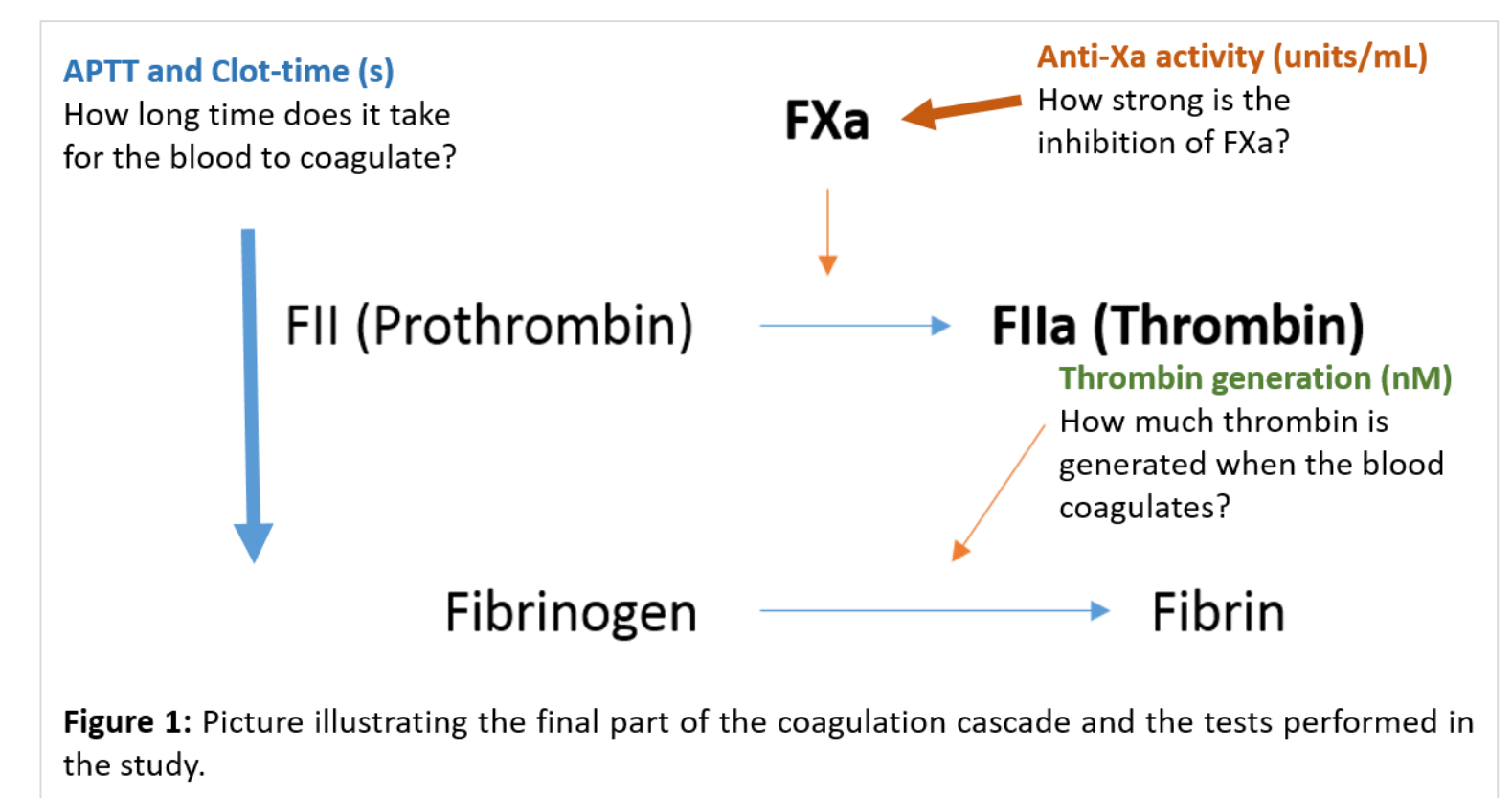
Introduction: Low molecular weight heparins (LMWHs) such as enoxaparin (Klexane®) and tinzaparin (Innohep®) are widely used for perioperative thrombosis prophylaxis. Although monitoring is not routine, it is recommended when accurate dosing is especially important, such as in the context of renal impairment, hypercoagulable states or at extremes of weight or age[1].

aPTT (activated partial prothrombin time) is generally not considered sensitive to LMWHs while anti-factor Xa (anti-FXa) activity, which has been shown to correlate well to the concentration of LMWH in the blood [2], is the gold standard for measuring 'heparin activity' despite LMWHs' varying degrees of anti-thrombin (anti-FIIa) activity (Table 1).

Agent	Trade name in Sweden	Mean molecular mass	Anti Fxa/FIIa (IU/mg)	Anti-Fxa/FIIa ratio
Unfractionated heparin (UFH)	Heparin	15 kDa	193/193	1
Tinzaparin	Innohep	6.8 kDa	90/45	2.0
Dalteparin	Fragmin	6.0 kDa	130/52	2.5
Enoxaparin	Klexane	4.2 kDa	100/25	3.9
Fondaparinux	Arixtra	1.7 kDa	930/0	∞

Table 1: Table displaying the different pharmacokinetic and pharmacodynamic properties of various commonly used LMWHs[1,2]. Heparins with longer molecular fragments display a higher anti-FIIa activity relative to the anti-Fxa activity. This property can be expressed as the anti-Fxa/FIIa ratio.

Method: We present two studies which compare various laboratory tests' (Figure 1) responses to enoxaparin and tinzaparin added in vitro to blood in concentrations of 0 to 1.5 anti-FXa units/ml. Blood in the first study was sampled from healthy individuals and tested aPTT using four different techniques (free-oscillation rheometry (FOR), Hemochron Jr® and a chromogenic assay using two different reagents), thrombin generation (TG) using two different reagents and



anti-FXa activity. The second study used blood sampled at the time of withdrawing epidural catheters from patients who had undergone major surgery and the time of clot initiation was measured with two viscoelastic assays: FOR and thromboelastometry (ROTEM) using reagents activating intrinsic coagulation.

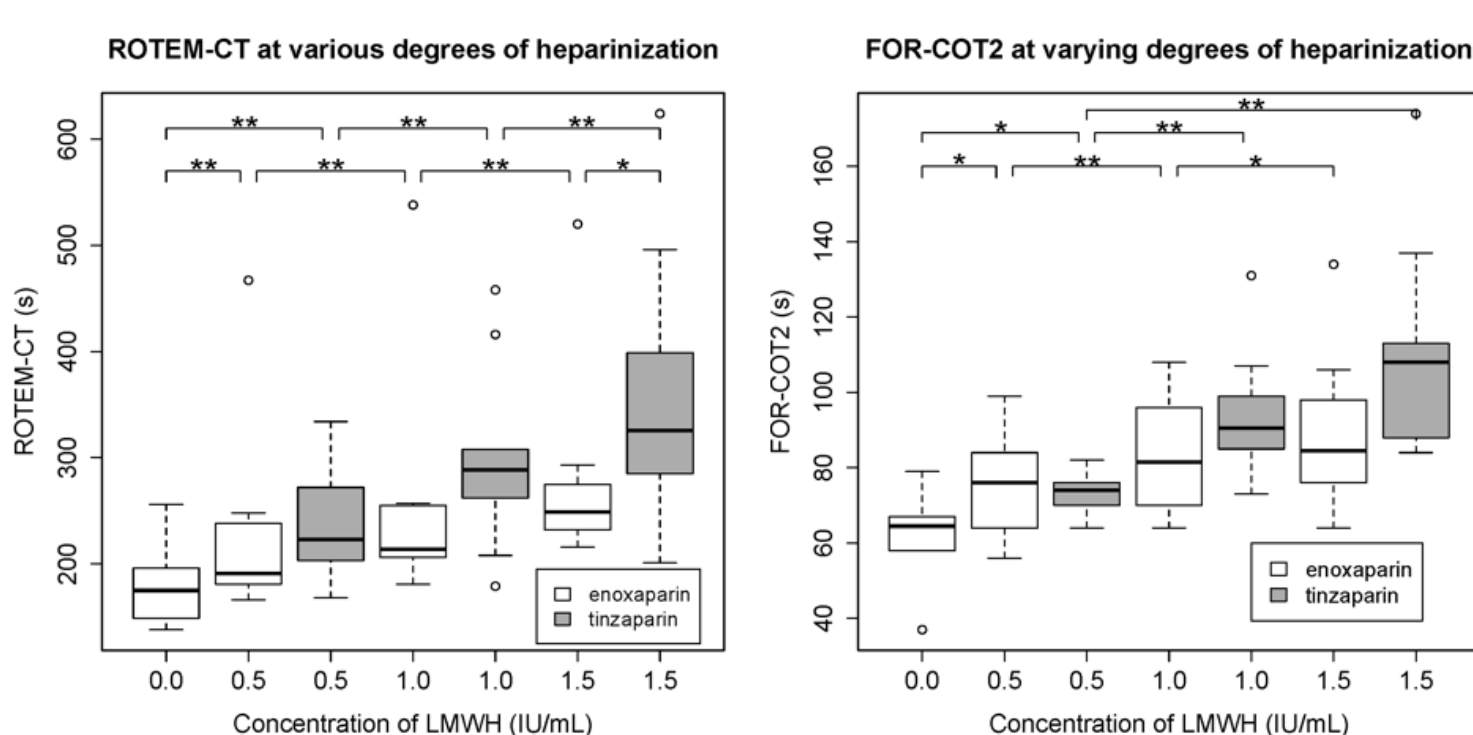
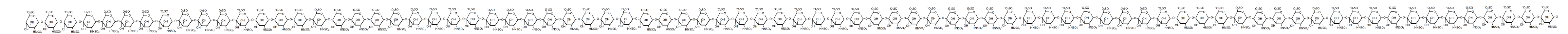


Figure 2: Boxplots showing the thromboelastic responses to various concentrations of LMWH. Increasing concentrations of both LMWHs significantly prolonged the clot time (ROTEM-CT and FOR-COT2) assayed by both ROTEM and FOR.

Results and discussion: Measures of clot initiation with both ROTEM and FOR showed significant dose-responses to increasing concentrations of LMWH, however there was significant inter-individual variation (Figure 2). This also applied aPTT but not measures of clot stability: aPTT correlated well to the concentration of LMWH with correlation coefficients (R_s) ranging from 0.81 to 0.93 for the different methods tested (Figure 3). The various methods and reagents for measuring aPTT do, however, give differing results. In our study the aPTT's produced by the ActinFSL reagent were lower than the other methods while the patient-near test Hemochron Jr had slightly lower correlation to the anti-Xa activity. Tinzaparin prolonged the clot time (Figure 4) and aPTT (Figure 5) and inhibited TG more than enoxaparin at equivalent levels of anti-FXa

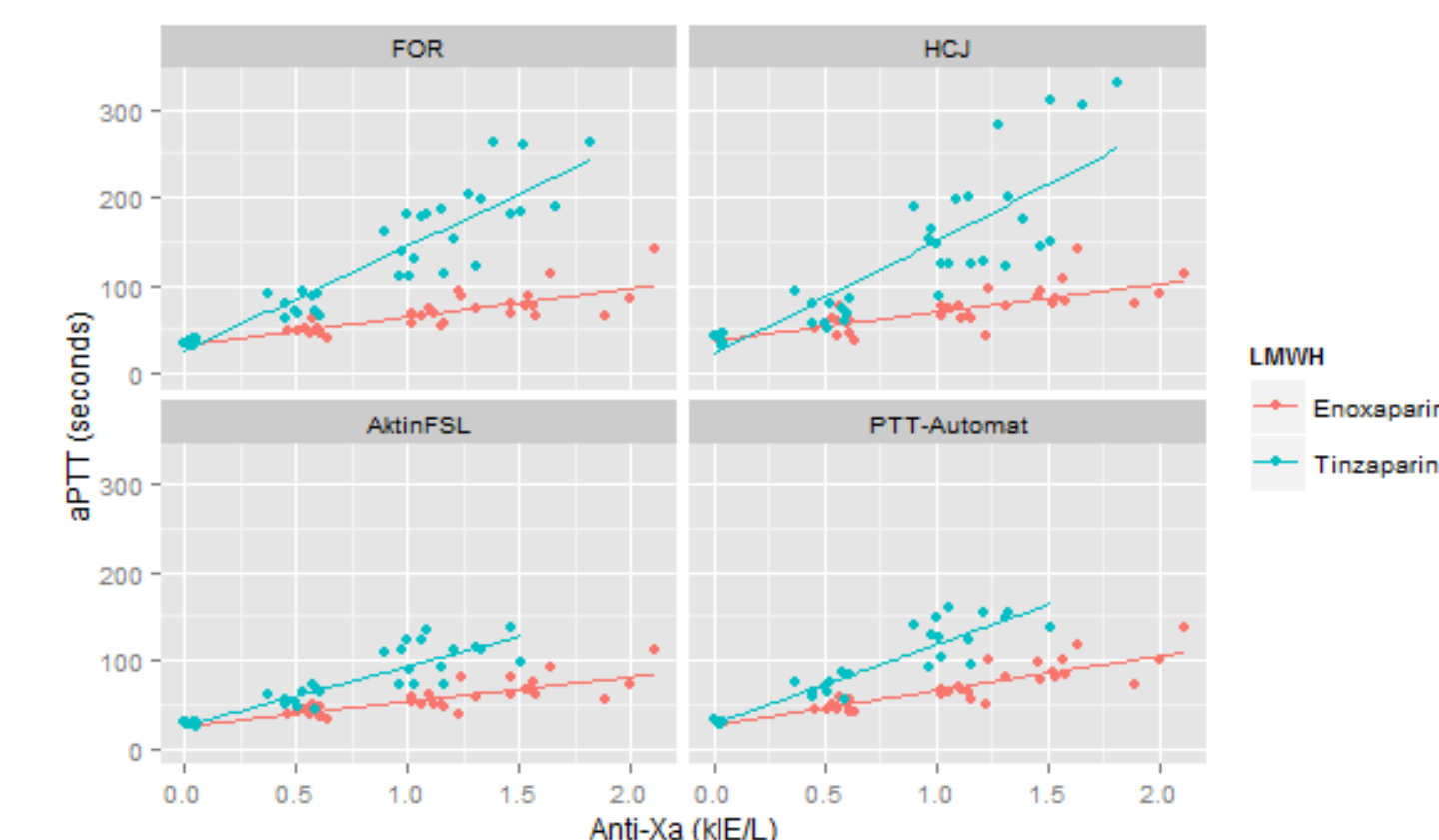


Figure 3: Correlations between aPTT and anti-FXa using various reagents and methods for measuring aPTT. Anti-FXa activity reflects the concentration of LMWH and the aPTT correlated well to this measure. The correlation for Hemochron Jr is slightly weaker than for the other reagents.

activity. This has been observed in previous studies[3] and would appear to be due to tinzaparin's stronger anti-FIIa activity and FIIa being downstream of FXa in the coagulation pathway.

Conclusions: Contrary to popular belief, aPTT is sensitive to LMWH, correlating well to anti-FXa activity. Clinicians must understand that anti-FXa does not measure anti-FIIa activity and, while it correlates well with the concentration of LMWH in the blood, it does not give the whole truth about the anticoagulative effect. This is reflected in Tinzaparin's greater prolongation of global coagulation tests such as aPTT and clot initiation, as compared to Enoxaparin. As anti-FXa measures LMWH activity upstream of FIIa, it underestimates whole-blood coagulation in less

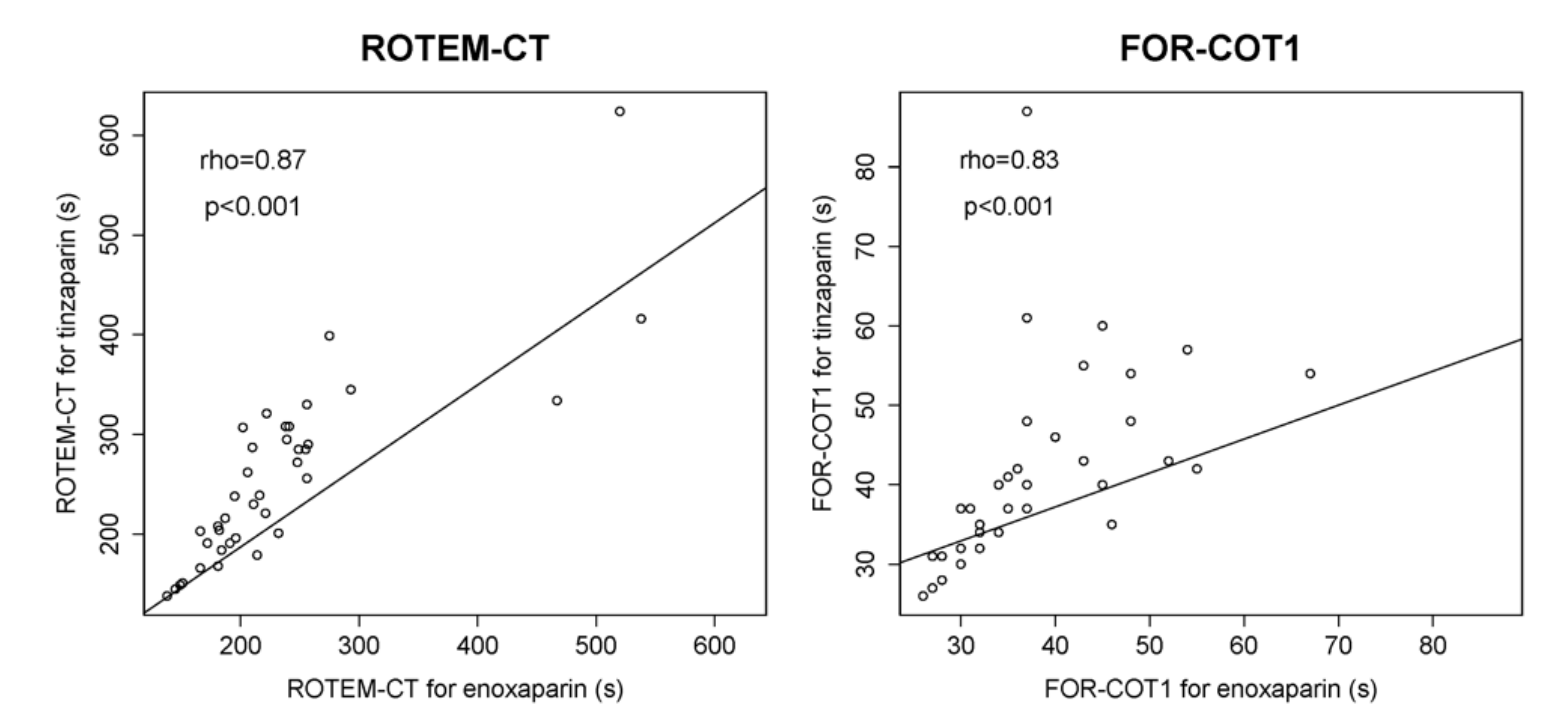


Figure 4: Scatter plot comparing the clot time (ROTEM-CT and FOR-COT1) at corresponding doses of enoxaparin and tinzaparin. The results are significantly correlated but tinzaparin prolongs the clot time to a larger extent.



Figure 5: Comparison of enoxaparin and tinzaparin's relative effects on aPTT. Bland-Altman plot showing that the aPTT's induced by tinzaparin ranged from on average 49% more than the mean (when measured using the PTT-Automat reagent) to 66% more than the mean (when measured using the MRX931 reagent (FOR: free oscillation rheometry)).

FXa specific LMWH's in this order: tinzaparin (Innohep®) > dalteparin (Fragmin®) > enoxaparin (Klexane®) > fondaparinux (Arixtra®) (See Table 1). TG is therefore an interesting option that needs further investigation.

Articles presented:

- Thomas O, Lybeck E, Strandberg K, Tynngård N, Schött U. Monitoring Low Molecular Weight Heparins at Therapeutic Levels: Dose-Responses of, and Correlations and Differences between aPTT, Anti-Factor Xa and Thrombin Generation Assays. PLoS One. 2015;10(1):e0116835. doi:10.1371/journal.pone.0116835
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