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Anti-IIa for monitoring unfractionated heparin in children: results of the HEARTCAT study

Short title: Anti-IIa for UFH in children

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Essentials

- Unfractionated heparin has variable effects in children and therefore, monitoring is essential.
- A randomized controlled trial substudy investigating an anti-IIa assay in children was conducted.
- Anti-IIa values are lower in younger children, an effect more pronounced at low-dose heparin.
- Heparin effect on Xa and IIa is not equal, particularly in infants and after high-dose heparin.

Abstract

Background: Unfractionated heparin (UFH) is used for prophylaxis and treatment of thrombosis in children. Laboratory monitoring of UFH is needed to prevent over- or under-anticoagulation.

Objectives: Study objectives were to investigate i) the association between UFH dose and UFH effect as monitored by anti-IIa, ii) the relationship of anti-IIa and anti-Xa effects, and iii) the influence of patients' age and other factors on UFH effect.

Patients and methods: Randomized controlled trial in children during cardiac catheterization, comparing high-dose UFH (100 units/kg bolus) versus low-dose UFH (50 units/kg bolus). Blood samples were drawn at baseline, after 30, 60 and 90 minutes. For the purpose of this study, 49 children and 117 blood samples were evaluated.

Results: The anti-IIa assay discriminated well between high and low-dose UFH. Multiple regression demonstrated a significant influence of UFH dose and age on anti-IIa levels. Younger children had lower anti-IIa levels than older children, an effect more pronounced at low-dose UFH. Anti-Xa/anti-IIa ratios were equal at low-dose UFH. However, anti-Xa levels were relatively increased over anti-IIa in infants and after high-dose UFH bolus.

Conclusion: The UFH effect on anti-IIa levels is lower in infants compared to older children. This influence of age appears to be dose-dependent, more pronounced at low-dose UFH. Anti-Xa versus anti-IIa levels are not equal, particularly in infants and after high dose UFH. Monitoring UFH using solely anti-Xa assays may not be sufficient in children and the anti-IIa assay may provide important complementary information.

KEY WORDS: children – drug monitoring - factor IIa - heparin – infant

INTRODUCTION

Unfractionated heparin (UFH) is the most commonly used anticoagulant for primary prophylaxis of thrombotic events (TE) in children.[1, 2] Due to its complex pharmacodynamic and pharmacokinetic mechanisms, there is significant inter-individual variation of the anticoagulant effect of UFH which is especially relevant in children.[3-7] Therefore, to prevent over- and under-anticoagulation, laboratory monitoring of the UFH effect is important.

While several studies investigated the use of the activated partial thromboplastin time (aPTT), the activated clotting time (ACT) and the anti-Xa assay for monitoring UFH in children, there is only limited information of the use of anti-IIa assays. [8-22] In contrast to low molecular weight heparins, whose anticoagulant effect is mainly mediated by inhibiting factor Xa, UFH inhibits both factor Xa and factor IIa.[23] Based on the assumption that the UFH effect on both factors is about equal, the use of the anti-Xa assay for UFH monitoring seems justified. However, until recently this assumption has never been tested in children, even though important differences of the coagulation system in children compared to adults are well known.[6] The work by Newall et al. has indicated that UFH has different effects on factor Xa versus factor IIa in children, and that this relationship is age-dependent.[15, 19, 24] This raises the question whether the anti-IIa assay provides additional information for monitoring UFH **levels** in children to the widely used anti-Xa assay.

HEARTCAT (***Hep***arin ***A***nticoagulation ***R***andomized ***T***rial in Cardiac ***Cat***heterization) was a parallel-cohort randomized controlled trial comparing two UFH dose protocols for primary prevention of TE in children undergoing cardiac catheterization.[25] Results on laboratory monitoring of UFH with aPTT, ACT, and anti-Xa have previously been reported.[22] The present manuscript reports the results of anti-IIa monitoring of UFH in children. The specific study objectives were to investigate (i) the association between UFH dose and UFH anticoagulant effect as monitored by anti-IIa, ii) the relationship of anti-IIa and anti-Xa effects, and iii) the influence of patients' age and other factors on UFH **levels**.

METHODS

Study design

The study design was a single-centre, double-blinded parallel-cohort randomized controlled trial (RCT) of consecutive children undergoing cardiac catheterization comparing a high-dose UFH protocol (100 units/kg body weight bolus for all children followed by continuous infusion of 20 units/kg/h for children older than one year or 28 units/kg/h for infants) versus a low-dose protocol (50 units/kg bolus). Patients with no consent for randomization received UFH as per standard-of care and were followed in a parallel cohort (50 units/kg for venous diagnostic catheterization, 100 units/kg for arterial diagnostic and any interventional catheterization). Patients in the cohort study consented to clinical outcome assessment and laboratory testing. All patients were treated with UFH (UFH "Immuno", 1000 international units/ml, EBEWE Pharma, Austria) intravenously during cardiac catheterization. The study protocol was approved by the ethics committee of the Medical University of Vienna and registered as a clinical trial in EudraCT, registration number 2005-004150-27 (https://clinicaltrialsregister.eu). The study design has previously been described in detail.[25] The laboratory substudy presented here was planned *a priori*.

Study population

The study population consisted of patients, 0 to 18 years of age, requiring diagnostic or interventional cardiac catheterization at the Division of Paediatric Cardiology, Medical University of Vienna. Written informed consent was obtained from parents and patients of appropriate age. Exclusion criteria were pre-existing anticoagulation or antiplatelet therapy.

Study outcomes

To monitor UFH during cardiac catheterization, blood samples were taken to measure anti-factor-Xa (anti-Xa), activated partial thromboplastin time (aPTT), activated clotting time (ACT), anti-factor-IIa (anti-IIa), and antithrombin levels. The results of anti-Xa, aPTT and ACT have already been reported in a separate manuscript.[22]

Clinical efficacy outcome was a thromboembolic event at puncture site diagnosed by screening with vascular ultrasonography, safety outcome was bleeding at the puncture site or other locations as previously described in more detail.[25]

Blood sample acquisition

Blood samples were drawn directly from cardiac catheters or vascular sheaths. To avoid UFH contamination, UFH was strictly administered via an additional peripheral venous line. A baseline sample was obtained immediately after the insertion of the femoral venous or arterial sheath and before the administration of UFH in every patient. Thereafter, blood samples were taken during the procedure at predefined time points (30 minutes, 60 minutes and 90 minutes after UFH administration, and at the end of the procedure). The ACT was measured immediately, the rest of the blood samples were collected in tubes containing 3.8% sodium citrate in a proportion of 9:1. Platelet poor plasma was prepared by double centrifugation at 1300g for 10 minutes each, aliquoted and frozen at -80°C for batch analysis. The methods used for testing anti-Xa, aPTT and ACT have previously been reported. [22]

Anti-Factor-IIa assay

The anti-IIa assay used for this study was an in-house assay developed by Summerhayes and Newall and is a modified version of a commercial assay from Biophen.[26] The original Biophen aIIa assay is a two stage chromogenic method developed for measuring UFH concentration in human citrated plasma, where the tested heparin binds to exogenous antithrombin added in excess. This heparin-antithrombin complex inhibits thrombin as a first step. The residual thrombin then binds to a thrombin specific chromogenic substrate, which releases paranitroalanine (pNA) from the substrate as a second step. The amount of pNA released therefore indicates the residual thrombin activity and is inversely proportional to the UFH concentration in the plasma sample. In contrast to the Biophen assay, the modified assay is performed without exogenous antithrombin. The non-antithrombin-supplemented anti-IIa assay was used with the intention to reflect the effects of age-specific antithrombin levels in plasma.

Statistical analysis

Statistical analysis was performed using SPSS 22.0 for Windows (Chicago, Ill). Continuous variables are presented as median, minimum and maximum values, categorical variables as absolute frequencies and percentages. Figures display medians with 95% confidence intervals. Linear mixed regression modelling was performed to assess the influence of UFH dose, body weight, age, sex, baseline anti-IIa level and baseline antithrombin level on the UFH anticoagulant response assessed by anti-IIa assay. Various models with UFH dose or age either as continuous variable or as categorical variable (low dose versus high dose group; infants versus children) were calculated and the best fitting model according to AIC (Akaike information criterion) values was chosen as the final model which is presented in the results section. No significant differences in UFH levels over time could be observed between the high-dose group of the RCT (receiving a UFH bolus followed by continuous infusion) and the high dose group of the cohort study (high dose UFH bolus only). Therefore, the results of the RCT and the cohort study were combined. To test whether UFH effects were associated with clinical outcomes, logistic regression modelling was performed with TE or bleeding complications as dependent variables and anti-IIa (30 min post-UFH samples) as independent variables, without and with inclusion of co-variables such as dose and age.

RESULTS

Study population

The flow of participants in the HEARTCAT study has been described in detail in the publication reporting clinical outcomes.[25] Of 227 children enrolled in the overall study, 163 had blood samples taken for UFH monitoring. The blood samples of 14 patients could not be evaluated for various, mostly technical, reasons (e.g. clotted sample, no heparin administered). Therefore, the final cohort of the laboratory study evaluating anti-Xa, aPTT and ACT consisted of 149 patients.[22] For this substudy, anti-IIa results of 117 blood samples of 49 consecutive patients were available.

Patient demographics

Median age was 5.6 years (minimum 0.01; maximum 18) and median body weight was 17.0 kg (3.1; 66.9). There were 12 (24%) infants, 14 (29%) children 1-5 years, 11 (23%)

6-10 years, and 12 (24%) 11-18 years of age. Twenty-five (51%) patients were female. Overall, 23 (47%) patients were in the low-dose and 26 (53%) in the high-dose UFH group. Twenty-nine (59 %) patients were enrolled in the RCT, and 20 (41%) patients in the parallel cohort receiving UFH as per standard-of-care.

Timing of blood samples

Samples obtained during cardiac catheterization were taken at the predefined time points of 30, 60, 90 minutes after UFH administration. However, the final samples at completion of catheterization were taken at variable times, as the duration of the procedure varied considerably, sometimes ending even before 30 minutes. As a result, the actual timing of sampling was somewhat heterogeneous. For the purpose of analysis, samples obtained within defined time bands were assigned to the predefined time points (baseline=0min, n=49; 20-44=30min, n=40; 45-74=60min, n=15; 75-104=90min, n=10). Because only three samples were collected beyond 104 minutes after UFH administration, these were not used for the analysis.

Time course of anti-IIa

Figure 1, panel A, shows the time course of median anti-IIa values at baseline and after administration of UFH. At all time points, there was a clear discrimination between high and low dose.

Factors influencing anti-IIa

Table 1 shows the results of a linear mixed regression model analysing the influence of various parameters on anti-IIa levels over time following UFH administration. The best fitting model is presented including only significant determinants ($p<0.05$). Anti-IIa levels were significantly associated with UFH dose group, age, baseline antithrombin level, sample time point, and female sex (table 1). For example, anti-IIa levels increased by an average of 0.03 unit/ml for every year of age, and by 0.05 unit/ml per 0.1 unit/ml higher baseline antithrombin levels. In the overall study cohort, median antithrombin at baseline was 0.85 units/ml (minimum 0.52; maximum 1.16), and 30% of patients had antithrombin levels below respective age-specific reference values.[7] Female sex was associated with higher anti-IIa values.

Influence of age on anti-IIa

Figure 2 shows median anti-IIa values after UFH administration by age groups, separate for dose groups and combined for all time points. Anti-IIa values were lowest in infants and steadily increased over age groups 1-5 years, 6-10 years, and 11-18 years in the high-dose group, while this increase was somewhat less steady in the low dose group. In the regression model for anti-IIa, there was a strong trend (p=0.082) for an interaction of age and dose, i.e. the differences between age groups were more prominent in the low dose group compared to the high dose group.

Comparing anti-IIa and anti-Xa

Although anti-Xa values from this study have previously been reported [22], the time course of anti-Xa values for this subcohort is displayed in figure 1, panel B, for the purpose of comparison. Anti-Xa values showed a similarly shaped time course but were generally higher compared to anti-IIa values.

Figure 3 shows the results of anti-IIa plotted versus anti-Xa (panel A), aPTT (panel B), and ACT (panel C), respectively, for all samples after UFH administration. While anti-IIa and anti-Xa corresponded well at low values (mostly children with low-dose UFH), anti-Xa were disproportionally increased over anti-IIa at higher values (exclusively patients with high dose UFH). The correlations of anti-IIa with ACT and APTT were poor.

To further evaluate the differential effects of UFH on coagulation factors, ratios of anti-Xa to anti-IIa values were calculated for each individual sample. These ratios were assessed in relation to time after UFH administration, UFH dose, and patient's age. Figure 4 shows the time course of median anti-Xa/anti-IIa ratios for samples after UFH administration, separate for UFH dose groups. In the high-dose group, median ratios were 1.7 and 1.5 at 30 and 60 minutes, respectively, declining to a ratio of approximately 1 at 90 minutes. In the low-dose group, anti-Xa/anti-IIa ratios were around 1 at all time points. Thus, at higher UFH levels, there was a stronger effect on factor Xa than on factor IIa which resolved with decreasing UFH levels over time.

Figure 5 shows anti-Xa/anti-IIa ratios for different age groups, separate for UFH dose groups and combined for all time points after UFH. Infants had higher anti-Xa/anti-IIa ratios compared to older children, an effect more prominent at high-dose UFH. Median anti-Xa/anti-IIa ratios for infants were 2.1 after high-dose UFH and 1.2 after low-dose

UFH. Linear mixed regression with anti-Xa/anti-IIa ratio as dependent variable found significant influences of UFH dose group, age group, and baseline antithrombin levels (table 1), corroborating the visual impressions from figure 4 and 5. Although the differences in ratios between age groups appeared to be dose-dependent, a test for interaction did not reach statistical significance. Interestingly, patients with higher baseline antithrombin levels had lower anti-Xa/anti-IIa ratios.

Association of anti-IIa with clinical outcome

As previously reported, HEARTCAT did not find a significant relationship between UFH dose group and the incidence of TE and bleeding complications of cardiac catheterization.[25] Moreover, UFH effects achieved in plasma as measured by anti-Xa, aPTT and ACT were not associated with clinical outcome.[22] In the present analysis, logistic regression similarly revealed no significant association between anti-IIa values and TE or bleeding complications.

DISCUSSION

HEARTCAT was the first large randomized controlled trial comparing high-dose versus low-dose UFH during cardiac catheterization in children using objective outcome assessment by ultrasound. The results on clinical outcome and on monitoring the UFH effect by aPTT, anti-Xa, and ACT have previously been reported.[22, 25] In the present substudy, we investigated the value of an anti-IIa assay for monitoring UFH therapy in children. The anti-IIa assay discriminated well between the two different UFH dose protocols. Anti-IIa levels were significantly lower in younger children compared to older children and the influence of age on the anti-IIa levels tended to be dose-dependent. Anti-Xa/anti-IIa ratios were increased in infants compared to older children and increased in patients after high-dose UFH bolus.

While several studies assessed various assays (aPTT, ACT, anti-Xa) for monitoring UFH therapy in children, only three studies were prospective and none compared different dose protocols.[17-20] Generally, agreement between various laboratory assays is poor in children.[11, 13, 18, 22] UFH effects have been shown to be age-dependent but target therapeutic ranges are not well established.[11, 15, 19, 22] Together with previous work

by Newall et al., HEARTCAT provides the only data on the anti-IIa effects of UFH in children.[15, 19] HEARTCAT study adds to the existing information by the randomized comparison of different UFH dose regimens. Moreover, HEARTCAT had a larger proportion of infants, the age-group showing the largest differences in UFH effects.

HEARTCAT investigated primary UFH prophylaxis in clinically stable children undergoing elective cardiac catheterization. The study setting can be taken as model situation, even if it cannot fully be extrapolated to other clinical situations. A limitation of the study was that most patients received a single UFH bolus and only a proportion of patients in the high-dose group received a continuous UFH infusion. Therefore, the data do not reflect steady state heparinization. An important limitation is that the study could not demonstrate an association of **UFH levels** in plasma with clinical outcome such as thrombosis or bleeding, as these events were rare, which does not allow to define appropriate target levels for anti-IIa. Finally, the sample size for this substudy was relatively small and, given the somewhat variable timing of samples, the data structure was simplified by defining time bands for better display. Therefore, the analyses can only be considered explorative**.**

HEARTCAT is the first study in children to systematically assess the effect of two different UFH doses on anti-IIa. In a previous study of children undergoing cardiac catheterization, Newall et al. evaluated anti-IIa levels after an UFH bolus.[19] As all children received the same UFH dose (100 u/kg), the authors compared anti-IIa values in samples taken at 15 minutes versus 120 minutes after UFH administration, using the later time point as a surrogate for lower UFH concentrations. Interestingly, they did not find a significant decrease of anti-IIa levels between the two sample time points. In HEARTCAT, the anti-IIa assay discriminated well between high-dose and low-dose UFH, and anti-IIa values decreased over time in both dose groups. The multiple regression model confirmed high UFH dose and earlier sample time point to be significantly associated with higher anti-IIa levels.

HEARTCAT demonstrated a significant influence of age on anti-IIa **levels** with younger children having lower levels compared to older children. This finding is in accordance with two previous studies by Newall et al., one study assessing patients receiving UFH during intensive care [15], and the study in cardiac catheterization mentioned above.[19]

Both studies similarly showed that younger children had lower anti-IIa levels compared to older children.

Importantly, HEARTCAT showed a trend for interaction between age and UFH dose, i.e. the differences in anti-IIa levels between age groups were more pronounced at low UFH dose. A similar age-dose interaction was shown for anti-Xa and similar trends for APTT and ACT, as reported.[22] Therefore, there is increasing evidence that the age-specific differences of UFH effects **on anti-IIa and anti-Xa levels** in children's plasma are dose-dependent and more relevant at low UFH dose.

The observed differences in time-courses of anti-IIa between the high-dose and low-dose UFH groups are likely related to dose-dependent clearance of UFH reaching saturation at higher doses, consistent with reports from the literature that the half-life of UFH increases with dose.[27] The differences in anti-IIa (and anti-Xa levels) between age groups may also, in part, be related to increased UFH clearance at younger ages. Since age-dependent differences were most prominent early after the UFH bolus, this would be related to the early phase of rapid clearance resulting from UFH binding to cells and plasma components.[28] The less pronounced age-specific differences of UFH **levels** at high-dose can be interpreted by saturation effects at higher dose.

The relationship of anti-Xa and anti-IIa was assessed to investigate whether UFH exerts differential **activities** against these coagulation factors dependent on dose, time after UFH administration, age, or other factors. In vitro, the effect of UFH on factor Xa and thrombin is about equal (anti-Xa/anti-IIa ratio of 1) but little is known on this relationship after in-vivo UFH infusion.[28] Newall et al. has shown that anti-Xa/anti-IIa ratios were two-fold increased in infants 15 minutes after receiving a high-dose UFH bolus, but decreased to a ratio of 1 after 120 minutes.[19] They concluded that the UFH concentration had an impact on the anti-Xa/anti-IIa ratio, with greater effect in infants than in older children. HEARTCAT similarly showed significantly increased anti-Xa/anti-IIa ratios in children receiving high-dose UFH which decreased over time, while ratios were around 1 in the low dose group at all time points. Moreover, infants had significantly higher anti-Xa/anti-IIa ratios compared to older children. Again, there was a suggestion of age-dose interaction, with differences between age-groups tending to be more pronounced at high UFH dose. We previously reported that anti-Xa levels were

decreased in infants compared to older children.[22] Therefore, since both anti-Xa and anti-IIa levels were lower in infants compared to older age groups, there appears to be a relatively increased UFH effect on **anti-Xa assay** compared to **anti-IIa assay** in infants.

We can only speculate on the reasons for these differential UFH activities as assessed by anti-Xa and anti-IIa assay that may be related to differences in clearance mechanisms. The higher molecular weight fractions of UFH have been reported to be cleared more rapidly from the circulation, leading to relative accumulation of lower molecular-weight fractions that have a higher anti-Xa versus anti-IIa activity.[28] **This effect of UFH clearance may be more pronounced in infants as compared to older children or adults, as infants have a shorter half-life of heparin plasma levels than older patients.[29]** Moreover, the effect was mainly seen at high UFH doses, maybe because clearance reaches saturation at different concentrations for high molecular-weight versus low molecular weight fractions. However, differences in clearance do not explain well our finding that these differential effects were most pronounced early after the UFH bolus but subsided over time.

Our results show that after UFH infusion in children, particularly in infants receiving high-dose UFH, the assumption of an equal UFH effect on factor Xa and factor IIa is not valid. Thus, monitoring UFH using solely anti-Xa assays may not be sufficient in children and the anti-IIa assay may provide important complementary information on the overall UFH **activity.** At the same weight-based UFH bolus dose, the overall UFH effect was lower in infants compared to older children. In addition, anti-IIa **levels** were even lower than anti-Xa **levels** in infants**.** Whether these differential **levels** affect the anti-thrombotic effect or risk of bleeding of UFH remains to be explored. This is especially important as infants had a higher risk of both thrombotic and bleeding complications compared to older children.[21, 25] Thus, the results raise an important issue that warrants further studies correlating the different UFH effects in infants and children with clinical outcomes.

HEARTCAT used an anti-IIa assay without exogenous excess antithrombin supplementation as described by Summerhayes et al..[26] Regression analysis showed that patients' antithrombin at baseline were significantly positively associated with anti-IIa levels. **The results are in accordance with an in-vitro study by Mitchell et al. showing for various anti-Xa and anti-IIa assays that measurement of UFH spiked**

into plasma was dependent on endogenous antithrombin levels.[30] Whether antithrombin levels affect the measurement of UFH in the assay only, or this reflects the physiological dependence of UFH on the patient's antithrombin level in vivo is still a matter of debate.[12, 31] As antithrombin was an independent determinant of anti-IIa **levels** in addition to the influence of age, the lower anti-IIa response seen in infants is partially, but not exclusively explained by lower antithrombin levels in this age group. As previously reported, antithrombin levels were also positively associated with anti-Xa levels, which were also based on a non-supplemented assay.[22] However, antithrombin levels were inversely associated with anti-Xa/anti-IIa ratios. Apparently, the **anti-IIa assay** is relatively more sensitive to plasma antithrombin levels compared to **the anti-Xa assay.**

As previously reported for the aPTT [22], anti-IIa values were associated with female sex. As the study population predominantly consisted of prepubertal children, this may well be a chance finding.

In conclusion, HEARTCAT demonstrated that the anti-IIa assay discriminated well between high and low dose UFH in children. Infants had lower anti-IIa levels but higher anti-Xa/anti-IIa ratios compared to older children. The age-specific differences in UFH **levels,** both for anti-IIa and anti-Xa, appear to be dose-dependent, more pronounced at low UFH dose. The results show that UFH effects on factor Xa and factor IIa are not equal in children, particularly in infants and high-dose UFH. Consequently, measuring anti-IIa may provide important complementary information for monitoring the UFH **levels** in children. Future studies are required to establish age-appropriate targets for anti-IIa based on clinical outcome.

AUTHORSHIP CONTRIBUTION

A. Hanslik designed the study, analysed data and wrote the manuscript. E. Kitzmüller and K. Thom collected data and contributed substantially to writing the manuscript. H. Karapetian, N. Prutsch and J. Voitl collected blood samples and data, and performed laboratory analyses. U. Tran performed statistical analyses and critically revised the manuscript. I. Michel-Behnke provided valuable support for performing the study and

critically revised the manuscript. F. Newall contributed to data analysis and critically revised the manuscript. C. Male designed the study, participated in data analysis and contributed substantially to writing the manuscript.

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DISCLOSURE OF CONFLICTS OF INTERESTS

The authors state that they have no conflict of interest.

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Table 1. Linear mixed regression models of factors influencing anti-IIa values and anti-Xa/anti-IIa ratio.

b, unstandardized partial correlation coefficient; CI, confidence interval; AT, antithrombin.

	determinant	**b**	**95% CI**	p
anti-IIa, units/ml	UFH dose group (high versus low)	0.12	(0.02; 0.23)	0.022
	age (per year)	0.03	(0.01; 0.04)	<0.001
	Baseline antithrombin (per 0.1 units/ml)	0.05	(0.03; 0.08)	<0.001
	Sample time point (30 vs 90 minutes)	0.14	(0.08; 0.21)	<0.001
	sex (female)	0.08	(0.01; 0.14)	0.033
anti-Xa/anti-IIa ratio	UFH dose group (high versus low)	0.65	(0.25; 1.05)	0.002
	age (infants versus older children)	0.55	(0.03; 1.07)	0.038
	baseline antithrombin (per 0.1 units/ml)	-0.21	(-0.37; -0.05)	0.014

Figure 1. Time course of anti-IIa (A) and anti-Xa (B) values (median, 95% confidence interval) comparing the high-dose versus the low-dose UFH group. (------ high dose group, ── low dose group).

Figure 2. Stratification by age groups of anti-IIa values (median, 95% confidence interval) in samples after UFH administration comparing dose groups (high-dose versus low-dose). Black dots represent low dose, white dots high dose group.

Figure 3. Agreement of anti-Xa (A), aPTT (B) and ACT (C) with anti-IIa values of individual samples after UFH administration. Black dots represent low dose, white dots high dose group.

Figure 4. Time course of anti-Xa/anti-IIa ratio values (median, 95% confidence interval) comparing dose groups (high-dose versus low-dose). (------ high dose group, ── low dose group)

Figure 5. Stratification by age groups of anti-Xa/antiIIa ratio values (median, 95% confidence interval) in samples after UFH administration comparing dose groups (high-dose versus low-dose). Black dots represent low dose, white dots high dose group.

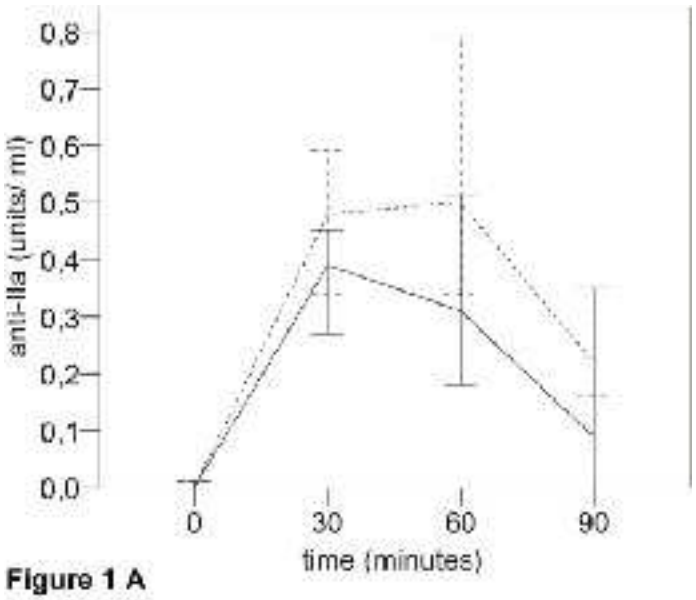

Figure 1 A

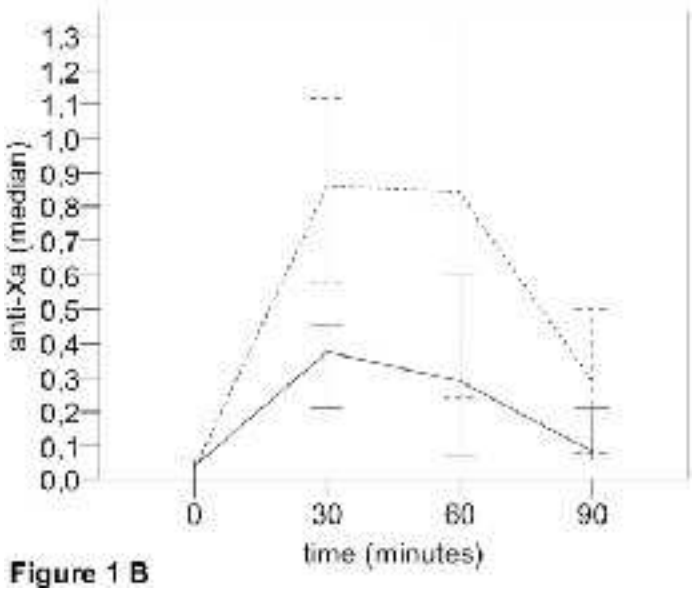

Figure 1 B

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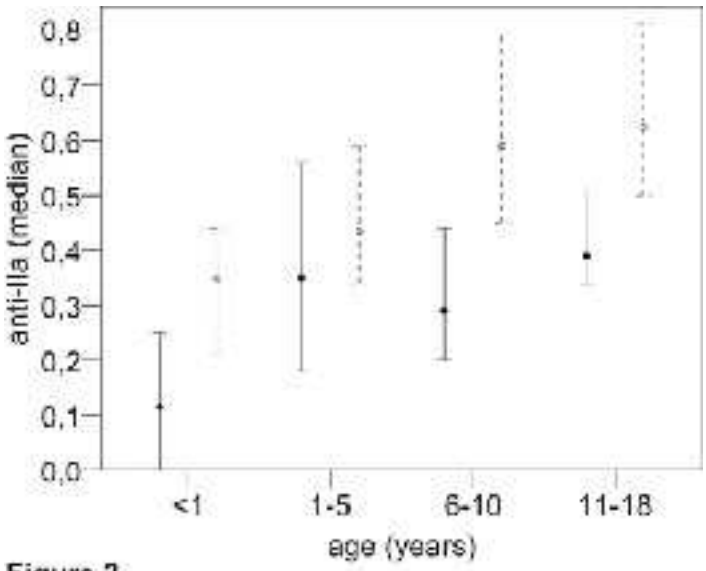

Figure 2

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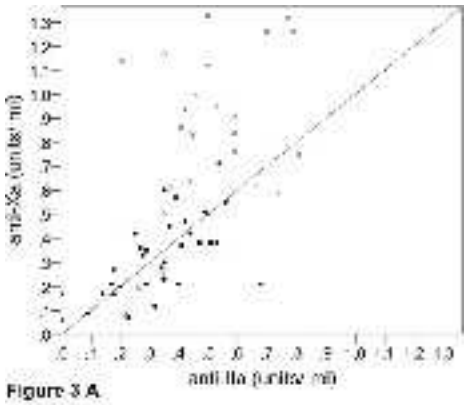

Figure 3 A

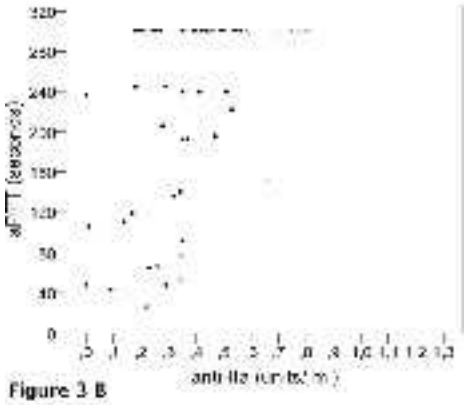

Figure 3 B

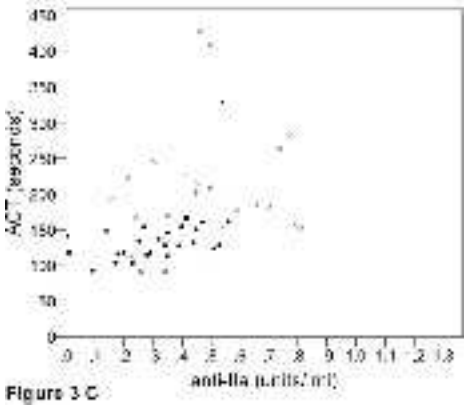

Figure 3 C

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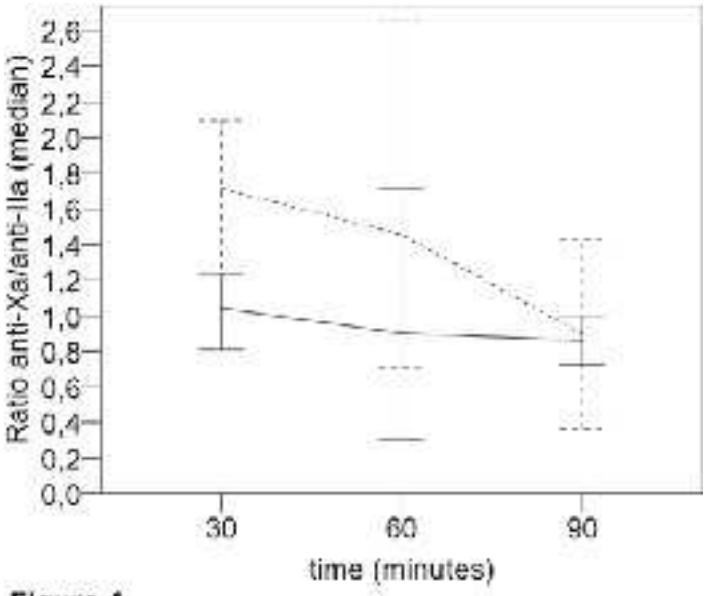

Figure 4

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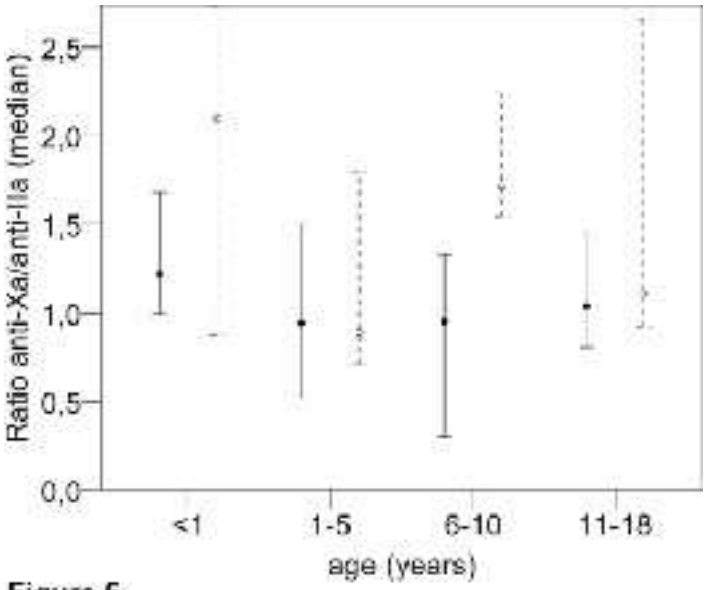

Figure 5

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